HIGHLY CONFIDENTIAL

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical Technologies Advisory Committee – Thursday 18 July 2024

Transcatheter heart valves for transcatheter aortic valve implantation in people with aortic stenosis

The following documents are made available to the Committee:

1. **Final Scope**

2. **Assessment Report Overview**

3. **Updated External Assessment Report** produced by Newcastle External Assessment Centre

4. **External Assessment Report consultation comments and responses**

5. **User Preference Report**

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Late Stage Assessment

Transcatheter heart valves for transcatheter aortic valve implantation in people with aortic stenosis

Final scope

Remit/evaluation objective

To assess the incremental clinical, economic and non-clinical benefits of transcatheter aortic valve implantation devices for people with severe aortic stenosis to justify price variation and inform procurement decisions.

Background

Aortic stenosis occurs when the aortic valve thickens or stiffens and doesn't open properly. Extra force is needed to pump blood through the valve, which puts strain on the heart. A recent study has estimated the overall prevalence of severe aortic stenosis among people over 55 years in the UK to be almost 1.5%, equal to around 300,000 people living with the condition at any one time.[1] Among those people, just under 200,000 were estimated to have symptomatic disease, which would require treatment. However, the system is severely strained. During the COVID-19 pandemic, cardiac surgery was limited to emergency cases. As a result, by March 2023 there were more than 380,000 people on cardiac waiting lists.[2] Long waiting times are a significant issue, because they have a negative impact on clinical outcomes.[3,4] Furthermore, the prevalence of aortic stenosis is projected to increase in the upcoming years as the British population ages.[5] People with aortic stenosis often have comorbidities, such as hypertension, coronary disease, atrial fibrillation, and renal dysfunction.

Current care pathway

For people with severe aortic stenosis the diseased valve can be replaced. Replacement of the aortic valve can be by either surgery or transcatheter intervention. Decision-making about the most appropriate intervention happens at a multidisciplinary team meeting. Medical history, treatment wait times, and planning for future interventions are considered. Transcatheter Aortic Valve Implantation (TAVI) is a minimally invasive procedure that avoids the need for a cardiopulmonary bypass and sternotomy. It involves the implantation of an artificial aortic valve, which is passed through a catheter inserted in a blood vessel in the upper leg or chest. TAVI is recommended for people who are at high surgical risk or if surgery is unsuitable (NICE guideline 208, NICE interventional procedure guidance 586). In February 2023, NHS England published a position statement that to alleviate the pressures on local systems, TAVI should also be considered as a treatment option for eligible people at an intermediate and low-surgical risk (NHS England, 2023). TAVI is also recommended as a less invasive treatment option if a previous

bioprosthetic valve has failed (NICE interventional procedure guidance 653). This procedure is referred to as valve-in-valve (ViV) TAVI.

The 2021 GIRFT National Cardiology Report has recommended the reorganisation of valve disease services (NHS England, 2021). A number of optimisation measures for aortic valve disease services have been implemented across the NHS. These include the use of local anaesthesia with sedation in the vast majority of procedures, a move towards preferentially using the transfemoral route, making refinements in the delivery equipment, having a single point of contact to co-ordinate patient care and consideration of same day discharge when appropriate. TAVI performed under local anaesthesia with sedation has comparable patient outcomes to those done under general anaesthetic.[6] Pre-procedural assessment and the TAVI procedure are done in highly-specialised heart valve clinics. Recent research has shown that shifting the pre-procedural workup to a local centre has the potential to significantly reduce wait times for TAVI.[7]

Population

TAVI is recommended for people with severe aortic stenosis who are at high surgical risk or for whom surgery is unsuitable (NICE guideline 208). People with severe aortic stenosis who are at low or intermediate surgical risk should also be considered for TAVI (NHS England, 2023).

The technology

An artificial aortic valve is implanted during a TAVI procedure. The device comprises of an expandable stent frame that suspends animal tissue leaflets.[8] The leaflets can be bovine or porcine and can have intra-annular or supra-annular position. The position may influence the hemodynamics of the valve and may impact future heart treatment. The stent frame can be made from a cobalt-chromium or a nickel-titanium (Nitinol) alloy. The valve is passed through a catheter and when positioned it can expand autonomously (self-expanding valve) or using a balloon in the catheter tip. TAVI devices come in different sizes, ranging from 20mm to 34mm.

Incremental innovations

Innovative features have been added to newer generation devices. These include the availability of smaller delivery sheaths, advances in deployment and anchoring and the ability to reposition or recapture a device in a case of suboptimal positioning. Newer devices also offer the opportunity to preserve coronary access, a range of sizes and specific designs to improve valve hemodynamics and procedural specification.

The following TAVI devices will be included in this assessment:

- Acurate Neo2 (Boston Scientific)
- Allegra (Biosensors)
- Evolut R, Evolut Pro+, Evolut FX (Medtronic) Evolut Pro excluded
- Hydra (SMT)

- Myval Octacor (Meril)
- Navitor (Abbott)
- Sapien 3, Sapien 3 Ultra (Edwards Lifesciences)
- Trilogy (Jenavalve). Trilogy not excluded

Intervention	Transcatheter heart valve for Transcatheter Aortic Valve Implantation (TAVI)
Population	Adults with symptomatic severe aortic stenosis who have been identified as suitable for valve replacement
Subgroups	The following subgroups will be considered: • People who are at high surgical risk or for whom surgery is unsuitable • People who are at low surgical risk • People who are at intermediate surgical risk • People with a failed previous bioprosthetic valve.
Comparators	Heart valve for Surgical Aortic Valve Replacement (SAVR) Alternative transcatheter heart valves for Transcatheter Aortic Valve Implantation (TAVI)
Outcomes	Clinical outcome measures relevant to the comparison with SAVR or alternative TAVI, can include but are not limited to: • mortality • length of hospital stay, including ICU stay • reintervention rate • heart failure • stroke • vascular complications • atrial fibrillation • acute kidney injury • endocarditis • pacemaker implantation rate • paravalvular leak • conversion to surgery • health-related quality of life. User preference and non-clinical outcome measures will be based on the prioritisation of outcomes as part of the multi-criteria decision analysis.

Economic analysis	The economic analysis will inform the benchmark price and the additional value of the incremental differences between the available technologies. The economic analysis will be based on the health economic model developed for NICE Guideline 208. Any analyses will be in accordance with the NICE reference case: • Time horizon of sufficient length to reflect all important differences in costs or outcomes between the technologies being compared • Costs will include the cost of the technology, accessories, training, staff and any treatment or (post)-procedural costs, including capacity constraints; costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	The separation of transcatheter heart valves into discrete categories, for example, with regards to the mechanism of expansion or indication, will be considered where appropriate. Assessment of TAVIs available to the NHS will include the value of innovative features of individual TAVIs as part of the comparison of alternative TAVIs. The impact of incremental innovations of TAVIs on access to care, treatment options, capacity and waiting lists, and the clinical care pathway may be considered as part of the comparison of alternative TAVIs. The prevalence of aortic stenosis rises with age. The associated mortality is also higher in older age groups. There may be sex-related differences in the prevalence, pathophysiology and natural history of aortic stenosis and the clinical outcomes of treatment. Geographical inequalities with regards to access to heart valve clinics exist. Cultural preferences and religious beliefs may influence the acceptability of some devices in certain societal groups.
Related NICE guidance	**Related NICE guidelines:** Heart valve disease presenting in adults: investigation and management (2021) NICE guideline 208. **Related interventional procedures:** Transcatheter aortic valve implantation for aortic stenosis (2017) NICE interventional procedures guidance 586 Sutureless aortic valve replacement for aortic stenosis (2018) NICE interventional procedures guidance 624 Balloon valvuloplasty for aortic valve stenosis in adults and children (2004) NICE interventional procedures guidance 78 Valve-in-valve TAVI for aortic bioprosthetic valve dysfunction (2019) NICE interventional procedures guidance 653

	Percutaneous insertion of a cerebral protection device to prevent cerebral embolism during TAVI (2019) Interventional procedures guidance 650 Aortic valve reconstruction with glutaraldehyde-treated autologous pericardium for aortic valve disease (2023) Interventional procedures guidance 769
Related National Policy	NHS England (2023) Position Statement on Transcatheter Aortic Valve Implantation (TAVI) and Surgical Aortic Valve Replacement (SAVR) for symptomatic, severe aortic stenosis (adults) to support elective performance NHS England (2021) GIRFT Programme National Specialty Report South Tees NHS Foundation Trust (2023) Optimising the Transcatheter Aortic Valve Implantation Pathway: a delivery guide NHS England (2022) Delivery Plan for Tackling the COVID-19 Backlog of Elective Care The NHS Long Term Plan (2019) NHS Long Term Plan Department of Health and Social Care (2016) NHS Outcomes Framework 2016-2017: Domains 1,2 Department of Health and Social Care (2023) Major Conditions Strategy (in development)

References

1. Strange, G.A., Stewart, S., Curzen, N. et al. (2022). Uncovering the treatable burden of severe aortic stenosis in the UK. *Open Heart*, 9:e001783. doi:10.1136/openhrt-2021-001783

2. British Heart Foundation. (2023). Heart care waiting list rises by 63 per cent in three years in England. Available at: https://www.bhf.org.uk/what-we-do/news-from-the-bhf/news-archive/2023/may/heart-care-waiting-list-rises-by-63-per-cent-in-three-years

3. Roule, V., Rebouh, I., Lemaitre, A. et al. (2022). Impact of wait times on late postprocedural mortality after successful transcatheter aortic valve replacement. *Sci Rep*, 12:5967. doi:10.1038/s41598-022-09995-z

4. Généreux, P., Stone, G., O'Gara, P. et al. (2016). Natural History, diagnostic approaches, and therapeutic strategies for patients with asymptomatic severe aortic stenosis. *J Am Coll Cardiol,* 67:263–2288. doi:10.1016/j.jacc.2016.02.057

5. d'Arcy, J.L., Coffey, S., Loudon, M.A. et al. (2016). Large-scale community echocardiographic screening reveals a major burden of undiagnosed valvular heart disease in older people: the OxVALVE Population Cohort Study. *Eur Heart J*, 37:3515-3522. doi:10.1093/eurheartj/ehw229

6. Fröhlich, G.M., Lansky, A.J., Webb, J. et al. (2014). Local versus general anesthesia for transcatheter aortic valve implantation (TAVR) – systematic review and meta-analysis. *BMC Med*, 12:41. doi.org/10.1186/1741-7015-12-41

7. Hewitson, L. J., Cadiz, S., Al-Sayed, S., et al. (2023). Time to TAVI: streamlining the pathway to treatment. *Open heart,* 10:e002170. doi:10.1136/openhrt-2022-002170

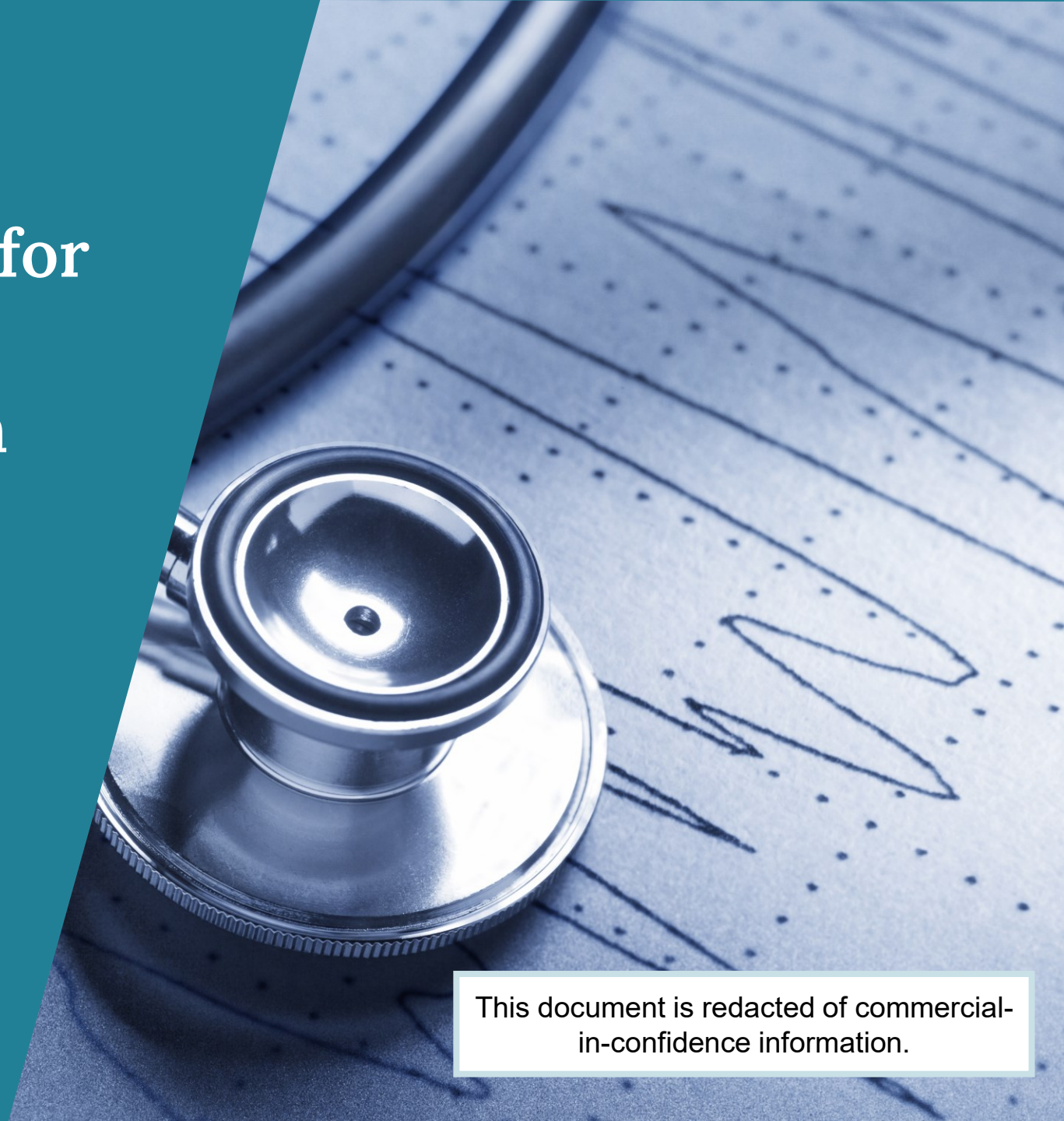
8. Steblovnik, K., Bunc, M. (2022). Technical aspects and development of transcatheter aortic valve implantation. *J Cardiovasc Dev Dis*, 9:282. doi:10.3390/jcdd9080282

Transcatheter heart valves for transcatheter aortic valve implantation in people with aortic stenosis [GID-HTE10027]

Late-Stage Assessment

Assessment Report Overview

NICE National Institute for Health and Care Excellence



This document is redacted of commercial-in-confidence information.

Background

NICE National Institute for Health and Care Excellence

The condition and current practice (1)

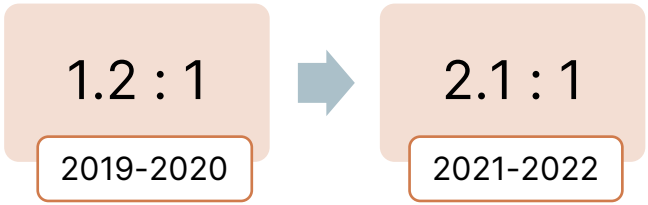
Aortic stenosis occurs when the aortic valve thickens or stiffens and doesn't open properly. The prevalence among people over 55 years in the UK is about 1.5% and is projected to increase in the upcoming years as the British population ages. Aortic stenosis can lead to heart failure and death if left untreated (see the Scope for this assessment).

Replacing the diseased valve through a catheter (transcatheter aortic valve implantation, TAVI) is an established treatment option, historically for those at high surgical risk (NICE guideline 208), but increasingly also in low and intermediate surgical risk groups (see NHS England's position statement, 2023). TAVI is also a treatment option if a previous bioprosthetic valve has failed (Interventional procedures guidance 653). Severe aortic stenosis can also be treated with surgical aortic valve replacement (SAVR). NICE Guideline 208 identified TAVI as cost-effective only for high surgical risk and inoperable people.

The procedure is carried out under general anaesthesia or under local anaesthesia with or without sedation and is predominantly undertaken electively with some centres conducting TAVI as a day-case procedure. The 2021 Getting It Right First Time (GIRFT) Report for Cardiology explicitly states that TAVI should be done under conscious sedation via a transfemoral route as the default.

The condition and current practice (2)

Ratio of people treated with TAVI and SAVR



Number of TAVI procedures and cost[1] to the NHS

The 2021 (GIRFT) Report for Cardiology acknowledged high levels of price variation across the speciality. Furthermore, GIRFT considered efficiency benefits between £35-40m per year could be achieved by ensuring procurement and NHS Supply Chain activities are clinically led and product choices are evidence-based with safety and outcomes unaffected by product change.

NHS England's position statement broadening access to TAVI for people at intermediate or low surgical risk aimed to alleviate pressures on local systems in supporting elective performance.

NICE

[1] Hospital Resource Group codes EY20A-B and EY21A-B; excludes the cost of the TAVI valve; GIRFT, Getting It Right First Time

The condition and current practice (3)

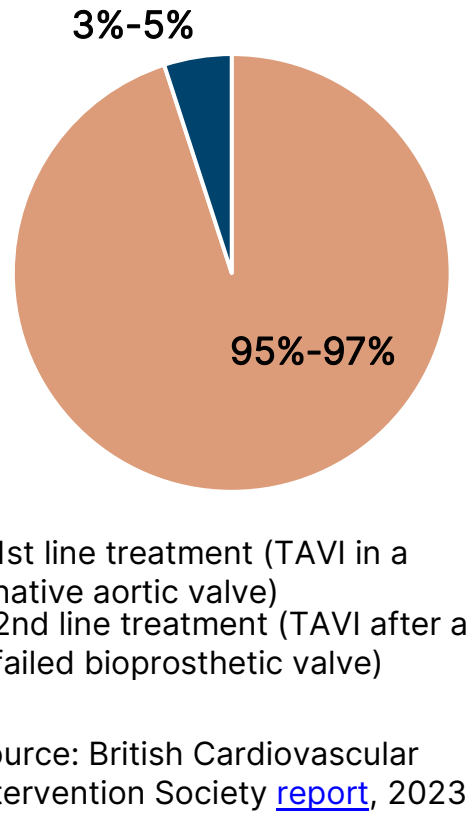
A clinical expert noted that with an increasing numbers of people undergoing TAVI (including people at lower surgical risk) and longer life expectancy, the rate of TAVI explants, a risky procedure, is rising.

The Society for Cardiothoracic Surgery in Great Britain & Ireland and the Royal College of Surgeons have expressed concerns that NHS England's position statement represents a policy change contrary to NICE guidance, which is not clinically appropriate and may increase patient risks.

However, most clinical experts contacted by the EAG confirmed that most TAVI procedures are still performed in high surgical risk people (between 40% to 80%, see Section 3 of the EAR).

Historically, valve-in-valve TAVI has represented 3%–5% of all TAVI procedures, but the expansion of TAVI use in low and intermediate surgical risk groups will likely result in an increase in this proportion.

Proportion of people undergoing first or second line TAVI, 2013 to 2022



Source: British Cardiovascular Intervention Society report, 2023

NICE

Abbreviations: EAG, External Assessment Group; EAR, External Assessment Report

Technologies under assessment

This late-stage assessment includes 11 TAVI valves from 8 manufacturers available on NHS Supply Chain's procurement framework.

The devices have valid CE certification as Class III implantable valves. There are differences in terms of the breadth of indication (see slide 8), but all devices are indicated for the 1st line treatment of people at high surgical risk. Clinical experts advised that cardiologists do not routinely score surgical risk in people undergoing TAVI.

The experts also advised that the specific choice of valve is based on patient anatomy, such as the native valve anatomy, the degree of calcification, and other considerations such as the vascular access, risk of pacemaker implantation, presence of a previous bioprosthetic valve and the patient's age (see Section 2 and Appendix G in the EAR).

The experts noted that there may be occasions where only 1 TAVI device is suitable, based on specific technology features and claimed benefits (see next slide). However, the clinical experts emphasized that most people can be treated with any TAVI device.

Abbreviations: EAG, External Assessment Group; EAR, External Assessment Report

Technology features

TAVI devices can have the following features:

- stent frame from either cobalt-chromium, cobalt-nickel, or nickel-titanium
- self- or balloon-expanding
- bovine or porcine pericardium tissue leaflets
- supra or intra-annular positioning
- an outer skirt or pericardial wrap (to reduce paravalvular leak)
- valve size between 20 mm and 34 mm
- anchors which fix onto native valve leaflets
- locators to support better alignment in the native aortic valve prior to deployment

Features of the delivery and loading systems:

- ability for recapture and reposition
- flexibility of the delivery sheath
- minimum vessel size for access

Further details can be found in Section 2 of the EAR.

Abbreviations: EAR, External Assessment Report

Technologies under assessment – key features

Key features of the technologies under assessment; see also Table 2 in the EAR

Manufacturer	Device	Expansion type	Tissue material	Supra- or Intra-annular	Valve sizes (mm)	High Surgical Risk	Intermediate Surgical Risk	Low Surgical Risk	TAVI-in-SAVR	TAVI-in-TAVI
Edwards Lifesciences	Sapien 3	Balloon	Bovine	Intra	20, 23, 26, 29	Yes	Yes	Yes	Yes	Yes
	Sapien 3 Ultra	Balloon	Bovine	Intra	20, 23, 26	Yes	Yes	Yes	Yes	Yes
Meril UK	Myval Octacor	Balloon	Bovine	Intra	20, 21.5, 23, 24.5, 26, 27.5, 29, 30.5, 32	Yes	Yes	Not contra-indicated	Not contra-indicated	Not contra-indicated
Abbott Medical	Navitor	Self	Bovine	Intra	23, 25, 27, 29	Yes	Not contra-indicated	Not contra-indicated	Not contra-indicated	Not contra-indicated
Biosensors International	Allegra	Self	Bovine	Supra	23, 27, 31	Yes	Not contra-indicated	Not contra-indicated	Yes	Not contra-indicated
Boston Scientific	ACURATE neo2	Self	Porcine	Supra	23, 25, 27	Yes	Yes	Yes	No	No
JenaValve	Trilogy	Self	Porcine	Supra	23, 25, 27	Yes	Not contra-indicated	Not contra-indicated	Not contra-indicated	Not contra-indicated
Medtronic	Evolut R	Self	Porcine	Supra	23, 26, 29, 34	Yes	Yes	Yes	Yes	Not contra-indicated
	Evolut Pro+	Self	Porcine	Supra	23, 26, 29, 34	Yes	Yes	Yes	Yes	Not contra-indicated
	Evolut FX	Self	Porcine	Supra	23, 26, 29, 34	Yes	Yes	Yes	Yes	Not contra-indicated
SMT	Hydra	Self	Bovine	Supra	22, 26, 30	Yes	Not contra-indicated	Not contra-indicated	No	No

Abbreviations: EAR, External Assessment Report; SAVR, Surgical Aortic Valve Replacement

Decision problem (1)

PICO	
Population	Adults with severe aortic stenosis who have been identified as suitable for valve replacement
Potential subgroups	• People with different levels of surgical risk (high, intermediate, low) • People with non-tricuspid valve morphology • People with a failed previous bioprosthetic valve
Interventions	Transcatheter heart valves for Transcatheter Aortic Valve Implantation (TAVI)
Comparator	Alternative transcatheter heart valves for TAVI
Outcomes	Key outcomes: mortality, stroke, vascular complications, length of hospital stay, reintervention rate, paravalvular leak User preference outcomes

For further details see the topic's Scope and the EAG's Assessment Protocol.

Abbreviations: EAG, External Assessment Group; PICO, Population, Intervention, Comparator, Outcomes

Decision problem (2)

The EAG assessed the suitability of Surgical Aortic Valve Replacement (SAVR) with a bioprosthetic valve as a comparator. It was excluded as a comparator for the following reasons:

- TAVI is the standard of care for people at high surgical risk and SAVR would be an appropriate comparator only for people at low or intermediate surgical risk.
    - However, clinical experts advised that clinical practice has remained largely consistent following the NHSE position statement in that the majority of TAVI procedures are still performed in people at high surgical risk. This is further confirmed by data from the National Adult Cardiac Surgery Audit.

- The audit has also provided evidence that the mortality rate of high surgical risk patients receiving isolated SAVR has dropped from over 9% (2020-2021) to 3.1% (2022-2023), which has been related to the increase in the uptake of TAVI. In addition, not all TAVI devices are indicated for use in low or intermediate surgical risk (see slide 8) and the definition of risk groups varies by manufacturer.
    - The EAG noted that the points above could lead to confounding that cannot be accounted for if SAVR data from either primary studies or a network meta-analyses are considered.

See Sections 2.4 and 3.1 in the EAG's Assessment Protocol for more details.

NICE

Abbreviations: EAG, External Assessment Group; SAVR, Surgical Aortic Valve Replacement

Clinical effectiveness

NICE National Institute for Health and Care Excellence

Approaches to clinical assessment

Clinical evidence was identified and assessed in order to:

- Review the clinical effectiveness of the TAVI devices in scope.
- Assess whether clinical equivalence can be assumed.
- Identify inputs for the economic model as part of the economic evaluation.

The EAG did not identify any systematic review or meta-analysis directly relevant to the decision problem. The following data sources were identified as suitable:

- UK TAVI Registry data
- Hospital Episode Statistics data
- Non-UK TAVI registries and peer-reviewed published evidence (for the clinical assessment of TAVI devices only)

Abbreviations: EAG, External Assessment Group

Summary of the sources of clinical data

Data source	Advantages	Limitations
UK TAVI Registry 01 April 2021 to 31 March 2023	• Representative of a UK NHS population. • In principle, includes all TAVI procedures from every centre across the UK.	• Captures 4 manufacturers only; quality and completeness of device model poorly reported. • Captures in-hospital outcomes only. • Several clinically important variables which determine choice of TAVI device are not recorded. • Around 14% of procedures are not entered into the registry. • Data are poorly reported for some fields.
Hospital Episode Statistics (HES) 01 April 2021 to 31 October 2023 with history to 01 April 2007	• Representative of a UK NHS population. • Contains additional outcomes, e.g. critical care stay and longer-term outcomes, e.g. aortic valve reintervention rate, mortality.	• Long-term evidence is restricted to older device generations. • Does not capture the specific TAVI device. • Lacks detailed clinical information such as medications, symptom scores and quality of life measures.
Published evidence	• Provides evidence when real world data are not available.	• Not identified through systematic methods. • Not necessarily representative of the UK NHS population. • Only 15 studies adjusted for population differences. • Variable study quantity per device and variable quality.

Abbreviations: HES, Hospital Episode Statistics; NHS, National Health Service

Approaches to clinical assessment

The EAG analysed data from the UK TAVI Registry and from HES. To obtain longer-term outcomes to inform the economic modelling, the EAG conducted linkage of HES and UK TAVI Registry data.

The EAG used targeted searches for non-UK TAVI registries and for peer-reviewed published evidence and long-term and comparative evidence requested from the companies for the devices which were not present in the UK TAVI Registry.

Due to the limitations of clinical data sources, the EAG considered a hierarchical approach to the evidence source when exploring device clinical efficacy and updating the clinical parameters in the economic model.

Technology	Primary source of evidence	Supplementary source of evidence
Sapien 3, Sapien 3 Ultra, Evolut R, Evolut Pro+, Navitor, ACURATE neo2	Linked UK TAVI Registry and HES data	Published evidence
Allegra, Evolut FX, Hydra, Myval Octacor, Trilogy	Published evidence	-

Abbreviations: EAG, External Assessment Group; HES, Hospital Episode Statistics

The UK TAVI Registry (1)

Workup

Patient-level data for all TAVI procedures undertaken between 01 April 2021 and 31 March 2023 were obtained.

The data included 4 manufacturers in scope (Abbott, Boston Scientific, Edwards Lifesciences and Medtronic). The TAVI device used was poorly completed and of low quality - close to 15% of the entries were not suitable for analysis. To address this the EAG extracted serial numbers from the data and requested verification from the companies. Following this, 7,409 procedures remained for analysis, comprising 7,119 native aortic valve procedures (96.1%), 263 TAVI-in-SAVR (3.5%), and 27 TAVI-in-TAVI (0.4%). See Section 4.1.1 and Appendix C1 in the EAR for further details on the cohort identification and data cleaning.

Analysis

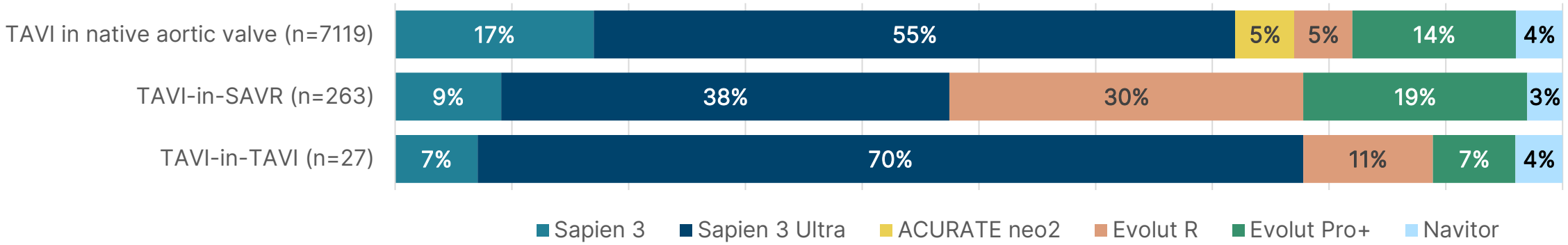
The EAG validated the TAVI Registry data (see Section 5.1.2 of the EAR) and investigated the differences between the native aortic valve, TAVI-in-SAVR and 27 TAVI-in-TAVI cohorts (see Appendix C6 in the EAR). Differences between the cohorts were observed for multiple characteristics, so the cohorts were analysed separately.

The EAG considered multiple imputation inappropriate for correction for missing data, because of potentially associated covariates and data not missing at random.

Abbreviations: EAG, External Assessment Group; EAR, External Assessment Report; SAVR, Surgical Aortic Valve Replacement

The UK TAVI Registry (2)

The use of devices as recorded in the UK TAVI Registry was unequal.



Only 3 TAVI procedures (0.04%) conducted with Evolut FX were recorded. They were excluded from the analysis as the EAG judged them to be too few for a meaningful statistical analysis.

EAG decision

Three hospitals reported using devices from 1 manufacturer, 21 hospitals used devices from 2 manufacturers, 3 hospitals used devices from 3 manufacturers, and 5 hospitals used devices from all 4 manufacturers. Most hospitals (90.6%) had access to at least 1 balloon expanding and 1 self-expanding TAVI device.

NICE

Abbreviations: EAG, External Assessment Group

The UK TAVI Registry (3)

The univariate analyses of patient characteristics showed statistical differences between people treated with each TAVI device, including age, sex, annual diameter, extensive calcification of ascending aorta, severe symptoms, poor left ventricular ejection fraction, valve size (see Table 13 in the EAR).

The univariate analyses also highlighted statistical differences across in-hospital outcomes between devices, including procedure duration, length of hospital stay, aortic regurgitation, major vascular complications, stroke before discharge, technical success (see Table 14 in the EAR).

Limitations

The EAG was aware of potential confounders which are not captured currently within the UK TAVI Registry, and therefore could not be adjusted for in the analysis, including surgical risk, anatomical characteristics such as challenging vascular access, tortuosity, aortic valve and left ventricular outflow tract calcium, medication prior to procedure, operator learning curve or level of experience.

The EAG highlighted that the analysis of observational real-world data from the UK TAVI Registry includes tests for associations between recorded variables but does not establish causality.

Abbreviations: EAR, External Assessment Report

Hospital Episode Statistics

An aggregated TAVI cohort (across all TAVI devices) identified from Hospital Episode Statistics (HES) was used to determine the coverage and representativeness of the UK TAVI Registry and to determine longer-term outcomes. It was based on 17,218 admissions following exclusions. See Sections 4.1.2 and 5.2.2 of the EAR for details on the cohort identification and cleaning and Appendix D3 in the EAR for details on the patient characteristics and longitudinal outcomes at 30 days, 1 year and 2 years for this cohort.

Limitations

- A key limitation is that HES does not record device manufacturer or model. Results may include devices used outside of their indications for use and potentially older devices no longer available in the NHS.
- HES lacks important patient characteristics and outcomes, including surgical risk, degree of calcification, haemodynamic performance (aortic valve mean gradient, aortic valve area).
- The EAG highlighted that analysis of observed real-world data includes tests for associations between recorded variables but does not establish causality.

Given the limitations, the EAG judged that HES cannot be used in isolation to determine longitudinal outcomes for the TAVI devices listed in the final scope.

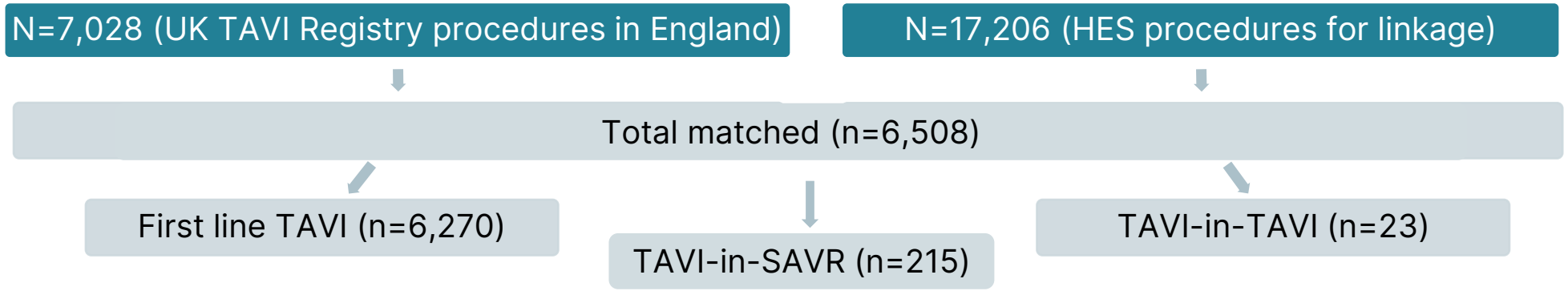
Abbreviations: EAR, External Assessment Report; HES, Hospital Episode Statistics; NHS, National Health Service;

Linkage of UK TAVI Registry and HES

Given the specific limitations of the UK TAVI Registry and HES data, the EAG linked data from both sources to obtain long-term outcomes specific to each device.

The two datasets were merged using NHS Trust code and an individual's sex, therefore creating a linked dataset where each row corresponded to a unique match on both fields, followed by additional steps when rules were applied to pull out rows containing potential matches. A small number of matches were done based on exact age and procedure date only if sex was missing. See Section 4.1.3 and Appendix E1 of the EAR for details on the matching steps.

In total, 6,508 out of 7,028 procedures in the UK TAVI Registry (92.6%) were successfully matched to a unique procedure in HES (see figure below and Figure 4 in the EAR).



NICE

Abbreviations: EAG, External Assessment Group; EAR, External Assessment Report; HES, Hospital Episode Statistics

Univariate analysis (1)

Univariable tests were undertaken to explore the relationship between covariates and TAVI device in the linked dataset. See table below for the key differences in patient characteristics (see Table 17 in the EAR for the full list).

Patient characteristics	Sapien 3	Sapien 3 Ultra	ACURATE neo2	Evolut R	Evolut Pro+	Navitor	p-value
Age, years: median [Q1,Q3]	81.0 [77.0 to 85.0]	82.0 [78.0 to 86.0]	83.0 [79.0 to 86.0]	81.0 [76.0 to 85.0]	82.0 [77.0 to 86.0]	83.0 [78.0 to 86.0]	<0.0001
Sex: (% male)	1,030/1,120 (92.0%)	1,818/3,584 (50.7%)	104/295 (35.3%)	172/246 (69.9%)	467/844 (55.3%)	72/169 (42.6%)	0.021
	The differing proportions were likely related to valve size availability. E.g. most people treated with Sapien 3 were male because it is available in a 29mm size while Sapien 3 Ultra is not. As sex is associated with height, weight and age, this may have a spillover effect.						
Weight, kg: median [Q1,Q3]	84.0 [74.0 to 95.7]	74.0 [64.0 to 85.5]	72.2 [63.6 to 86.8]	80.0 [67.0 to 92.0]	74.0 [64.2 to 86.0]	75.0 [64.5 to 83.7]	<0.0001
Annular diameter, mm: median [Q1,Q3]	27.5 [26.7 to 29.0]	24.0 [22.4 to 25.3]	23.0 [22.0 to 25.0]	26.0 [23.0 to 27.4]	24.0 [22.6 to 26.0]	24.3 [22.9 to 26.0]	<0.0001
Extensive calcification of ascending aorta: (%)	30/1,041 (2.9%)	89/3,362 (2.6%)	10/211 (4.7%)	19/239 (7.9%)	47/812 (5.8%)	3/158 (1.9%)	0.021
	If calcification of the ascending aorta was considered as a surrogate outcome of calcification of the aortic valve, these findings would support that self-expanding TAVI devices are used more frequently in calcified valves.						
CCSAS (any limitation of physical activity): (%)	235/1,083 (21.7%)	813/3496 (23.3,%)	45/268 (16.8%)	64/244 (26.2%)	170/805 (21.1%)	58/159 (36.5%)	0.021
Valve size, mm: median [Q1,Q3]	29.0 [29.0 to 29.0]	26.0 [23.0 to 26.0]	25.0 [23.0 to 27.0]	34.0 [29.0 to 34.0]	29.0 [26.0 to 29.0]	27.0 [25.0 to 29.0]	<0.0001
Use of cerebral circulation protection device(s): (%)	154/1,115 (13.8%)	349/3,566 (9.8%)	54/295 (18.3%)	27/243 (11.1%)	123/837 (14.7%)	17/168 (10.1%)	0.021
	There is an ongoing RCT investigating whether cerebral circulation protection reduces stroke in TAVI patients. Therefore, differences in stroke outcomes may be confounded by this additional treatment.						

Abbreviations: CCSAS, Canadian Cardiovascular Society Angina Status; EAR, External Assessment Report

Univariate analysis (2)

Several statistically different in-hospital outcomes between valves were identified in the univariate analysis (see table below and Table 18 in the EAR). However, no statistically significant differences were identified between TAVI devices across any of the long-term outcomes considered (see Table 19 and Figures 5-9 in the EAR).

In-hospital outcome	Sapien 3	Sapien 3 Ultra	ACURATE neo2	Evolut R	Evolut Pro+	Navitor	p-value
Length of procedure, mins: median [Q1,Q3]	60.0 [55.0 to 80.0]	60.0 [55.0 to 75.0]	80.0 [63.0 to 105.0]	93.0 [69.0 to 120.0]	75.0 [60.0 to 95.0]	69.0 [60.0 to 90.0]	<0.0001
LoHS, nights: median [Q1,Q3]	3.0 [2.0 to 8.0]	3.0 [2.0 to 9.0]	3.0 [2.0 to 5.0]	4.0 [2.0 to 13.0]	4.0 [2.0 to 11.0]	3.0 [2.0 to 10.0]	<0.0001
Peak PG, mmHg: median [Q1,Q3]	12.0 [9.0 to 18.0]	15.0 [10.0 to 22.0]	16.0 [11.0 to 22.0]	12.0 [8.0 to 19.0]	12.0 [8.0 to 17.0]	13.0 [9.0 to 18.0]	<0.0001
Mean PG, mmHg: median [Q1,Q3]	6.5 [5.0 to 10.0]	8.0 [5.0 to 12.0]	8.0 [5.0 to 11.0]	7.0 [4.0 to 11.0]	6.0 [4.0 to 9.0]	7.0 [4.0 to 9.0]	<0.0001
Valve area, cm2: median [Q1,Q3]	2.0 [1.6 to 2.5]	1.8 [1.5 to 2.1]	1.8 [1.5 to 2.0]	1.7 [1.5 to 2.1]	1.7 [1.5 to 2.0]	2.0 [1.8 to 2.4]	<0.0001
Aortic regurgitation	11/1,077 (1.0%)	33/3,442 (1.0%)	8/257 (3.1%)	12/239 (5.0%)	38/827 (4.6%)	6/162 (3.7%)	0.011
Malposition of valve	4/1,082 (0.4%)	14/3,446 (0.4%)	4/293 (1.4%)	5/237 (2.1%)	9/753 (1.2%)	3/167 (1.8%)	0.018
Use of post-implant balloon dilatation	52/1,078 (4.8%)	203/3,431 (5.9%)	26/292 (8.9%)	39/236 (16.5%)	128/744 (17.2%)	42/163 (25.8%)	0.011
Need for permanent pacing	79/1,061 (7.4%)	202/3,371 (6.0%)	15/256 (5.9%)	25/233 (10.7%)	95/746 (12.7%)	26/165 (15.8%)	0.011
Major vascular complications	12/1,051 (1.1%)	34/3,340 (1.0%)	7/244 (2.9%)	9/232 (3.9%)	12/724 (1.7%)	4/159 (2.5%)	0.025
Stroke before discharge	20/1,038 (1.9%)	38/3,316 (1.1%)	2/245 (0.8%)	5/227 (2.2%)	20/726 (2.8%)	6/147 (4.1%)	0.025

NICE

Abbreviations: EAR, External Assessment Report; LoHS, Length of Hospital Stay; PG, Pressure Gradient

Multivariate analysis (1): in-hospital outcomes

The EAG undertook multivariable analyses of TAVI in native aortic valve cohort only due to the limited number of procedures in the other cohorts. A Binary Logistic Regression (BLR) model was fitted for each in-hospital outcome trained on a selection of clinically relevant covariates (see Section 4.1.3 of the EAR).

The EAG made the following assumptions:

- Each model was trained on the same people (i.e. only complete datasets across all covariates and outcomes).
- A step-wise methods for variable selection was judged to be inappropriate in this case.
- In each model: observations were independent, there was no multicollinearity, and independent variables were linearly related to the log-odds of the event.
- Sapien 3 Ultra was used as the reference technology in each model, as the most used device.

EAG assumptions

BLR model results

The TAVI device was associated with in-hospital stroke, aortic regurgitation and permanent pacemaker implantation (see next slide and Table 20 in the EAR). Some patient characteristics were associated with increased odds of event (having general anaesthesia and frailty increased the odds of in-hospital death). Others reduced the odds of an event (male sex was protective against in-hospital stroke).

NICE

Abbreviations: BLR, Binary Logistic Regression; EAG, External Assessment Group, EAR, External Assessment Report

Multivariate analysis (2): in-hospital outcomes

Results of binary logistic modelling of UK TAVI Registry data (TAVI in native aortic valve) for each key in-hospital outcome (odds ratio [95% confidence interval])

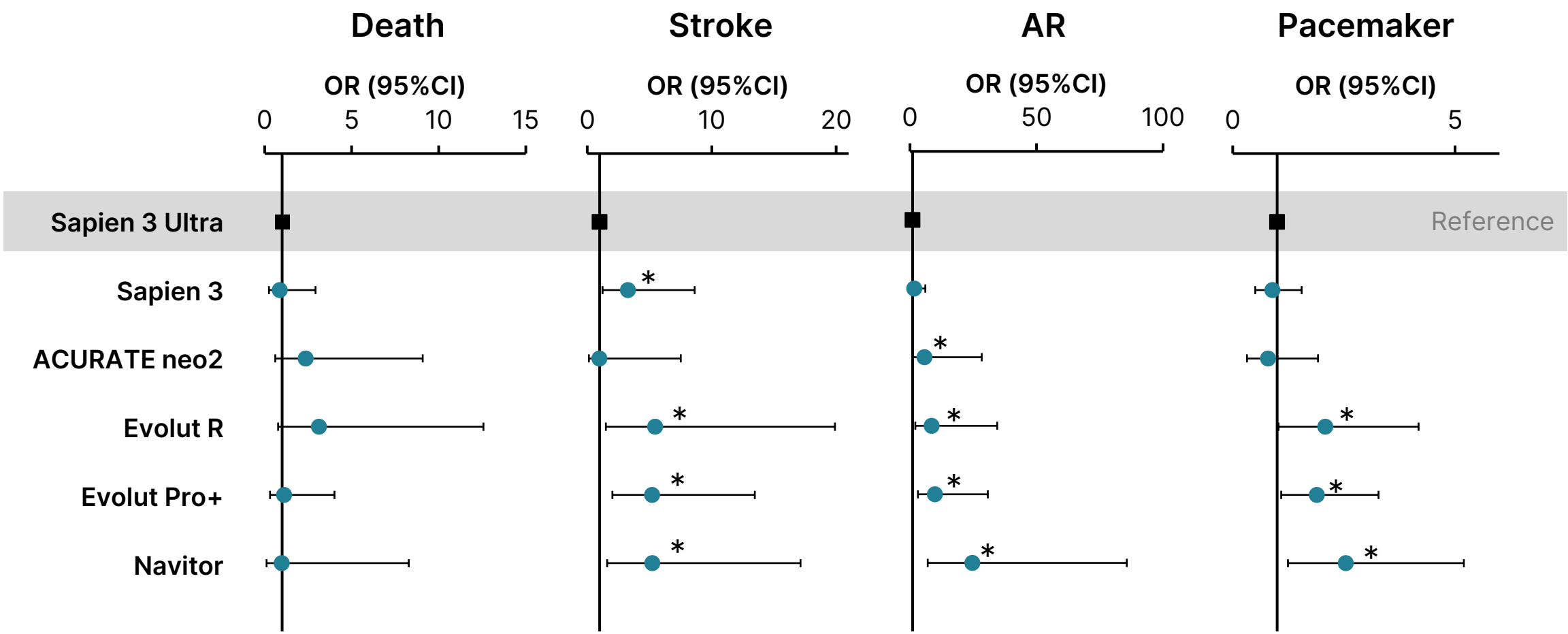
Parameter	Death	Stroke	Aortic regurgitation**	Permanent pacemaker implantation	Major bleeding	Major vascular complications	TAVI bailout/ reintervention before discharge	SAVR intervention
Incidence	47 events in 3,917 people	61 events in 3,910 people	46 events in 3,910 people	270 events in 3,913 people	47 events in 3,912 people	49 events in 3,913 people	23 events in 3,915 people	7 events in 3,915 people***
Sapien 3 Ultra	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Sapien 3	0.86 (0.25, 2.92)	**3.26 (1.23, 8.64)***	1.58 (0.41, 6.1)	0.89 (0.51, 1.55)	0.97 (0.28, 3.28)	0.60 (0.17, 2.17)	0.76 (0.11, 5.38)	0 (0, Inf)
ACURATE neo2	2.35 (0.61, 9.08)	0.97 (0.13, 7.51)	**5.60 (1.11, 28.32)***	0.79 (0.32, 1.92)	1.77 (0.48, 6.5)	3.10 (0.92, 10.39)	3.85 (0.74, 19.99)	0 (0, Inf)
Evolut R	3.11 (0.77, 12.57)	**5.44 (1.49, 19.91)***	**8.51 (2.1, 34.47)***	**2.08 (1.03, 4.18)***	0.77 (0.14, 4.15)	0.66 (0.11, 4.05)	2.28 (0.22, 24)	0 (0, Inf)
Evolut Pro+	1.11 (0.31, 4.01)	**5.21 (2.02, 13.46)***	**9.78 (3.11, 30.76)***	**1.89 (1.09, 3.28)***	0.41 (0.11, 1.52)	0.73 (0.2, 2.67)	3.28 (0.68, 15.86)	0 (0, Inf)
Navitor	0.97 (0.11, 8.28)	**5.22 (1.59, 17.15)***	**24.56 (7.04, 85.67)***	**2.54 (1.24, 5.2)***	1.07 (0.21, 5.3)	2.54 (0.62, 10.36)	0 (0, Inf)	0 (0, Inf)

*Statistically significant **The EAG identified that missing data had an impact on the aortic regurgitation outcome (see slide 29); this may have influenced the odds ratios for this outcome ***All interventions done with Sapien 3 Ultra

NICE

Abbreviations: SAVR, Surgical Aortic Valve Replacement

Multivariate analysis (3): in-hospital outcomes



47 events in 3,917 cases, 1.2%	61 events in 3,910 cases, 1.6%	46 events in 3,910 cases, 1.2%	270 events in 3,913 cases, 6.9%

NICE

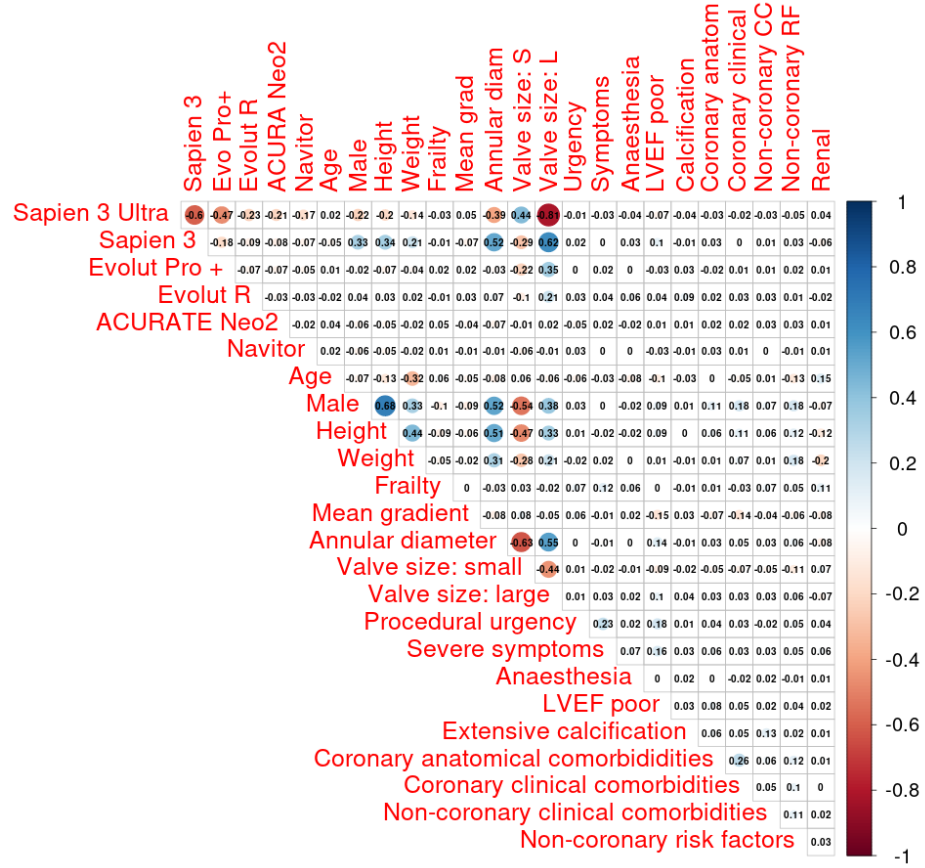
Abbreviations: AR, Aortic Regurgitation; OR, Odds Ratio; *Statistically significant

Multivariate analysis (4): in-hospital outcomes

BLR model results

The EAG identified a correlation between TAVI device and valve size:

- Sapien 3 Ultra showed a negative correlation with large valve size (-0.81) indicating more frequent use in small and medium valves, whereas Sapien 3 showed the opposite (0.62) indicating increased use in large valve sizes.
- Evolut Pro+ and Evolut R were positively correlated with large valve size (0.35 and 0.21 respectively).
- Notable correlations were also found between sex, height, weight, annular diameter and valve size, all of which were expected.



Correlation matrix for logistic model parameters for all outcomes

Abbreviations: BLR, Binary Logistic Regression; EAG, External Assessment Group

Multivariate analysis (5): long-term outcomes

A Cox Proportional Hazards (CPH) model was fitted for each long-term outcome (see Section 4.1.3 of the EAR).

CPH model covariates

The CPH model included the same covariates used in the BLR models, however, additional variables were introduced to look at the effect of in-hospital adverse events (during TAVI procedure) on long-term outcomes. This included in-hospital stroke's effect on death and subsequent stroke, aortic regurgitation's effect on re-admission for heart failure and in-hospital PPI's effect on subsequent pacemaker-related appointments (which reflected the need for ongoing maintenance and follow up related to the pacemaker).

CPH model results

TAVI device was not associated with any long-term outcomes (see next slide). Certain baseline characteristics were significantly correlated with differences in long term outcomes (e.g. age at discharge was correlated with increased risk of death post-discharge; see Table 21 in the EAR).

NICE

Abbreviations: BLR, Binary Logistic Regression; CPH, Cox Proportional Hazards; EAR, External Assessment Report; PPI, Permanent Pacemaker Implantation

Multivariate analysis (6): long-term outcomes

Results of the CPH models of UK TAVI Registry data (TAVI in native aortic valve) for each key outcome occurring post-discharge (hazard ratio [95% confidence interval]).

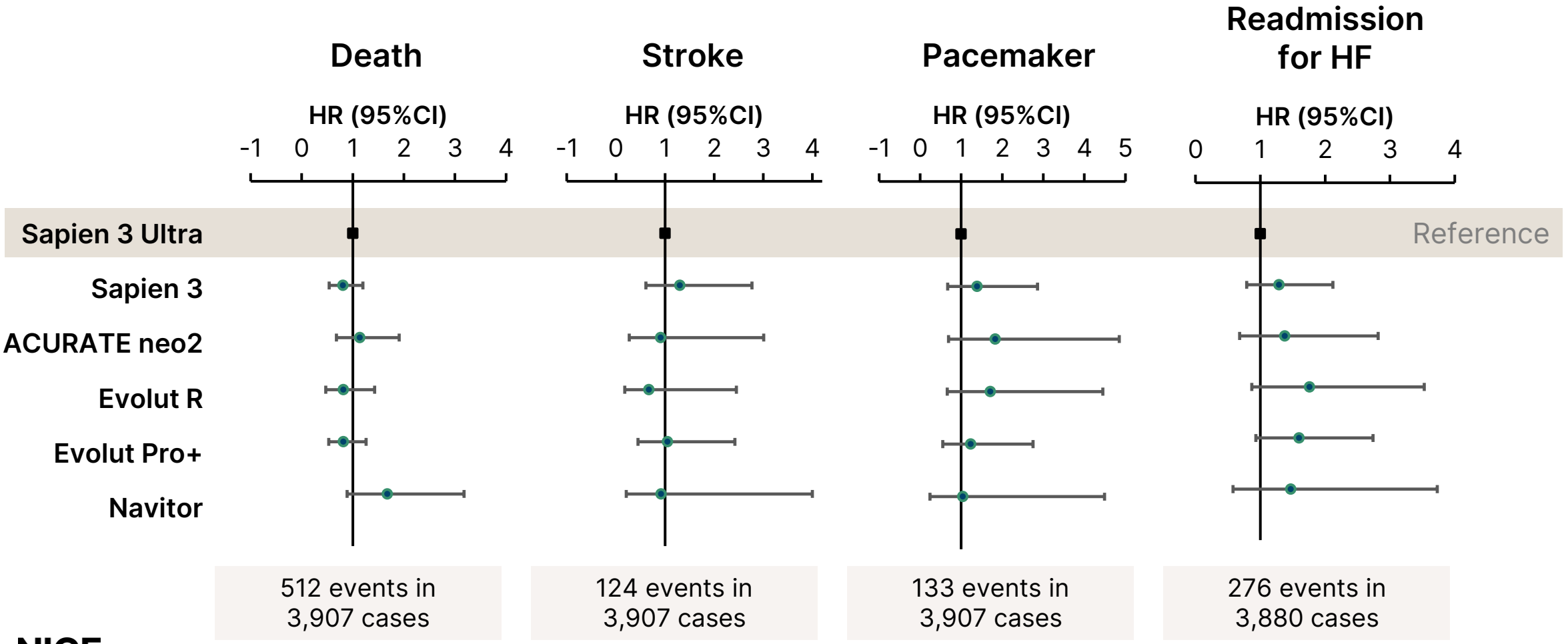
Parameter	Death	Stroke	Pacemaker	Aortic reintervention (TAVI or SAVR)	Readmission for heart failure
Incidence	512 events in 3,907 people	124 events in 3,907 people	133 events in 3,907 people	18 events in 3,907 people	276 events in 3,880 people
Sapien 3 Ultra	Reference	Reference	Reference	Reference	Reference
Sapien 3	0.81 (0.54, 1.2)	1.3 (0.61, 2.77)	1.39 (0.67, 2.86)	0 (0, Inf)	1.29 (0.79, 2.12)
ACURATE neo2	1.14 (0.68, 1.91)	0.91 (0.27, 3.01)	1.83 (0.69, 4.85)	0 (0, Inf)	1.38 (0.68, 2.82)
Evolut R	0.82 (0.47, 1.43)	0.67 (0.18, 2.45)	1.71 (0.66, 4.45)	0 (0, Inf)	1.76 (0.87, 3.53)
Evolut Pro+	0.82 (0.53, 1.26)	1.05 (0.45, 2.42)	1.23 (0.55, 2.75)	0 (0, Inf)	1.6 (0.93, 2.74)
Navitor	1.68 (0.89, 3.18)	0.92 (0.21, 4)	1.04 (0.24, 4.49)	0 (0, Inf)	1.47 (0.58, 3.73)

See next slide for a graphical representation of the results.

Abbreviations: CPH, Cox Proportional Hazards

Multivariate analysis (7): long-term outcomes

No statistically significant differences in long-term outcomes were observed.



NICE

Abbreviations: HF, Heart Failure; HR, Hazard Ratio

Multivariate analysis (8)

Model performance

Due to the relative low frequency of key outcomes, the confidence intervals for coefficients were often wide showing a degree of uncertainty in results. There was additional uncertainty stemming from the lower used of some technologies.

The proportions of people treated with Sapien 3 Ultra experiencing aortic regurgitation statistically differed before and after exclusion of incomplete cases (see Section 5.3.2 of the EAR). As Sapien 3 Ultra was used as the reference, the odds ratios observed for the other device types may have been influenced by this decrease, although it would not have influenced the relative differences between other devices.

In the assessment of in-hospital outcomes, the PPI model had a poor ability to discriminate between individuals who do and who don't experience an outcome (see Section 4.1.3 in the EAR); all other models were at acceptable levels. In the assessment of long-term outcomes, the models for death and pacemaker had low concordance (<0.7), which suggested that their predictive capability was lacking (see Table 21 in the EAR).

Multivariate analysis limitations

The EAG stressed that the multivariate analysis is limited by the availability and quality of the data, and by the presence of unmeasured potential confounders, such as surgical risk and valve calcification. Therefore, if clinicians tend to favour one model by default, the people treated with this device may more often have favourable characteristics or characteristics less likely to affect device choice.

EAG highlight

Abbreviations: EAG, External Assessment Group; EAR, External Assessment Report; PPI, Permanent Pacemaker Implantation

Multivariate analysis (9): self-expanding valves only

The EAG fitted the BLR and CPH models to data on the self-expanding devices only. Medtronic Evolut Pro+ was set as the reference (see Section 5.3.2 and Table 22 in the EAR).

In-hospital outcomes

ACURATE neo2 had statistically increased odds of major vascular complications when compared to Evolut Pro+. No other statistically significant differences for in-hospital outcomes between self-expanding TAVI devices were observed.

The EAG stated that this was a further indication that valves with different methods of expansion are used in different populations. For example, the odds of aortic regurgitation across self-expanding devices were not significantly different, while in the analysis including all devices the odds ratios of self-expanding valves ranged from 5 to 24 compared to a balloon-expanding valve.

EAG highlight

Long-term outcomes

The specific TAVI device was not significantly associated with any long-term outcome. Some patient characteristics and in-hospital outcomes affected long-term outcomes, largely in line with the observations in the analysis including all devices.

NICE

Abbreviations: BLR, Binary Logistic Regression; CPH, Cox Proportional Hazards; EAG, External Assessment Group, EAR, External Assessment Report

Published evidence

Identification

The EAG used published evidence to inform uncertainties in the clinical performance of the technologies in scope. Published evidence was identified through early scoping searches, targeted literature searches (based on device name) and evidence provided by the companies (see Section 4.1.4 in the EAR).

As data on newer generation devices were lacking, the EAG also considered comparative and long-term evidence from older generations.

Where there was a lot of evidence for a technology, the EAG prioritised studies in the UK setting, comparative evidence against devices in scope, longest follow-up data, largest sample size, most device comparisons or those reporting adverse events. Where no comparative evidence was available for a device (or its predecessor), non-comparative evidence was also considered.

Selection

The EAG prioritised studies including patient level data from an NHS setting where confounders could be adjusted for (i.e. systematic reviews with meta-regression, RCTs, observational studies with propensity matching or case-control studies) as key evidence.

Abbreviations: EAG, External Assessment Group; EAR, External Assessment Report; RCT, Randomised Controlled Trial

Key published evidence (1)

Forty-two peer-reviewed publications (including 30 comparative and 12 single arm studies) were considered key evidence for the 11 TAVI devices in scope (see table below).

Parameter	Total number of studies	Total number of people	Other comment
Myval Octacor	4 studies	576 people	Predecessor Myval was used in 5 studies including 419 people
Sapien 3/Sapien 3 Ultra	16 studies	155,054 people	Among the total, Sapien 3 Ultra in 5,519 people
Allegra	2 studies	206 people	-
ACURATE neo2	5 studies	3,194 people	Predecessor ACURATE neo was used in 8 studies and 8,192 people
Evolut R/Pro+/FX	20 studies	108,538 people	Among the total, Evolut FX in 681 people, Evolut Pro+ in 62,966 people
Hydra	1 study	157 people	-
Navitor	2 studies	257 people	Predecessor Portico in 8 studies including 4,264 people
Trilogy	1 study	1 person	Predecessor JenaValve in 2 studies, including 268 people

Key published evidence (2)

Only one study was undertaken exclusively in a UK. Among the remaining the majority were international multicentre studies (9) or studies conducted exclusively in the USA (8). Seven studies were conducted in Germany, 4 in multiple centres across Europe, 4 in Italy, 1 in the Netherlands and 1 in Switzerland. Two studies conducted in India and 1 in Brazil were included. Four systematic reviews did not report the locations of each included study.

Most of the publications were undertaken exclusively in people undergoing TAVI in a native aortic valve (N=26). Sample sizes ranged from single case reports to 99,725 in a systematic review and network meta-analysis.

Surgical risk was reported in all except 3 publications however, it was evaluated using different methods, including Society of Thoracic Surgeons (STS) score (N=28), EuroSCORE (N=4), EuroSCORE II (N=20), or MDT (N=4); with 12 studies reporting a combination of these. The studies also reported different thresholds to define surgical risk groups, making it difficult to quantify how many studies were undertaken in low, intermediate and high surgical risk groups. Nearly half of the studies included symptomatic patients and nearly half included only people undergoing transfemoral TAVI (see Section 5.4.1 in the EAR for further details on the key studies).

Abbreviations: EAR, External Assessment Report; MDT, Multidisciplinary Team; STS, Society of Thoracic Surgeons

Key published evidence (3)

Among the 42 key studies, only 15 accounted for population differences between arms within their study design or subsequent analysis:

- 1 systematic review with a meta-regression and subgroup analysis (Lerman et al. 2023).
- 2 RCTs (Baumbach et al. 2024; Herrmann et al. 2024).
- 10 observational studies with propensity score matching or adjustment (Baggio et al. 2023; Buono et al. 2022; Costa et al. 2022; Costa et al. 2024; Delgado-Arana et al. 2022; Forrest et al. 2020; Halim et al. 2023; Nazif et al. 2021; Pellegrini et al. 2023; Rudolph et al. 2024) using between 10 and 28 covariates during matching.
- 2 non-randomised studies reported multivariate analysis (Kim et al. 2022c; Tamm et al. 2021).

Critical Appraisal

The EAG critically appraised those 15 studies (see Appendix B2 in the EAR). Almost all studies were at high risk of bias, including the systematic review by Lerman et al. (2023) and the RCTs by Baumbach et al. (2024) and Herrmann et al. (2024).

Abbreviations: EAG, External Assessment Group; EAR, External Assessment Report; RCT, Randomised Controlled Trial

Published evidence – multi-device

Author (year); design, location	Intervention arms	Summary of key results and limitations
Santos-Martinez et al. (2022) Retrospective non-randomised Europe	Evolut R or Pro (n=298) Sapien 3 (n=290) ACURATE neo (n=180) Myval (n=135) Portico (n=125) Allegra (n=103)	Myval was the reference technology in the analyses in this study. It generally had favourable or non-inferior outcomes versus the other devices, which were statistically significant in some comparisons. The EAG noted that the study only reported in-hospital outcomes and did not adjust for differences in baseline characteristics between devices.
Yang et al. (2023) Systematic review and network meta-analysis of 79 studies	Sapien 3 (n=54,691) Evolut (n=35,339 including Evolut R and Evolut Pro) ACURATE (n=4,634 including ACURATE and ACURATE neo) Portico (n=2,001), DFM (n=450) and Lotus (n=2,610)	The best performing valve varied by the outcome of interest: procedural mortality (Portico), short-term mortality and no correct position (Sapien 3), stroke (DFM), PPI (ACURATE), moderate to severe PVL (Lotus), prothesis patient mismatch and mean aortic valve gradient (Evolut). The authors acknowledged that the analysis was restricted to short-term outcomes only, and that differences in patient anatomy between arms may have contributed to heterogeneity. Lack of data limited subgroup analysis on these factors, which limits generalisability of findings.
Rudolph et al. (2024) Non-randomised study with propensity score weighted analysis	Evolut R (n=7,028) Sapien 3 (n=13,296) ACURATE neo (n=2,922) Portico (n=878)	Sapien 3 showed statistically significantly better performance in the following outcomes when compared with the other valves: death (procedural, p=0.03), vascular complications (procedural, p<0.0001), dilatation (post-procedure, p<0.0001), paravalvular leak – grade II or higher (discharge, p<0.0001), transvalvular gradient (discharge, p<0.0001) and new pacemaker/implantable cardioverter defibrillators (1 year, p<0.0001).
Costa et al. (2022) Non-randomised study with propensity score matching Italy	Evolut R (n=1,125) Evolut Pro (n=337) Sapien 3 (n=768) ACURATE neo (n=290) Portico (n=208)	Evolut R showed statistically significantly better performance in the following outcomes when compared with the other valves (including Evolut Pro): PPI (in-hospital, p=0.002), moderate to severe paravalvular regurgitation (in-hospital, p<0.01), residual transvalvular gradients (in-hospital, p<0.01), ICU length of stay (discharge, p<0.001), post-procedural hospital length of stay (discharge, p<0.001) and PPI (1 year, p<0.01).

Abbreviations: ICU, Intensive Care Unit; PPI, Permanent Pacemaker Implantation; PVL, Paravalvular Leak

Published evidence – Myval Octacor

Author (year); design, location	Intervention arms	Summary of key results and limitations
Baumbach et al. (2024) Non-inferiority RCT International (N=16 countries)	Myval or Myval Octacor (n=379) Contemporary group; Evolut or Sapien series (n=377)	No statistical difference in the primary endpoint at 30 days or its components. No statistical difference in technical success, 30-day device success or early safety between arms. The EAG noted that the intervention arm included different generations of devices (both Myval Octacor and Myval). The comparator group included different manufacturer devices and generations. Both arms included crossover of intervention and comparator valves in analysis groups. Therefore, it is difficult to determine the incremental benefit of Myval Octacor, or generalisability of results from this study.
Delgado-Arana et al. (2022) Propensity matched Europe	Myval (n=103) Sapien 3 (n=103)	Statistically significantly better performance of Myval in the following outcomes: new permanent pacemaker implantation (30 days, p=0.020), peak aortic gradient (30 days, p<0.001), mean aortic gradient (30 days, p<0.001) and moderate prosthesis-patient mismatch (30 days, p=0.043).
Halim et al. (2023) Retrospective non-randomized cohort (propensity matched) The Netherlands	Myval (n=91) Evolut R or Pro (n=91)	Statistically significantly better performance of Myval on new permanent pacemaker implantation (30 days, p=0.01): Myval 4%, Evolut R or Pro, 15%.
Moscarella et al. (2024) Retrospective non-randomised cohort Italy	Evolut R (n=108) Myval (n=58)	Statistically significant better performance of Myval in the following outcomes: clinical efficacy (composite of freedom from all-cause mortality, all-stroke and cardiovascular hospitalisation) (2 years, p=0.006), cardiac hospitalisations (2 years, p=0.027) and pacemaker implantation (2 years, p=0.024). The EAG noted that reporting of baseline demographics between arms were lacking, and no adjustments were made to results to account for any difference in populations
Jose et al. (2023) Real-world observational India	Myval Octacor (n=123)	Technical success was 100% and device success rate at 30 days was 98.4%. At 30 days, overall mortality was 1.6%. AKI occurred in 1.6% of people and there was no incidence of stroke, bleeding (types 3 and 4), and major vascular complications.

Abbreviations: AKI, Acute Kidney Injury; RCT, Randomised Controlled Trial

Published evidence – Sapien 3/Ultra (1)

Sapien 3

Lerman et al. (2023): systematic review and meta-analysis of 21 studies comparing Sapien 3 (n=19,897) with Evolut R or Pro (n=15,351). Thirty-day mortality ($p<0.001$), permanent pacemaker implantation ($p<0.001$), bleeding ($p=0.02$), major vascular complications ($p=0.04$), moderate or severe aortic regurgitation ($p=0.001$), mean and peak transvalvular pressure gradients ($p<0.001$) were in favour of Sapien 3. No long-term mortality differences were identified.

Al-abcha et al. (2021): systematic review and meta-analysis of 9 studies comparing Sapien 3 (n=1,866) with Evolut R (n=1,576). Odds of having a permanent pacemaker ($p=0.0007$) or moderate to severe paravalvular regurgitation ($p=0.02$) lower for Sapien 3. No other outcomes differing.

Sapien 3 Ultra

Costa et al. (2024): non-randomised propensity matched analysis comparing Sapien 3 Ultra (n=587) to Evolut Pro or Pro+ (n=587). Statistically-significantly better performance of Sapien 3 Ultra for the following outcomes: permanent pacemaker implantation (in-hospital, $p<0.001$), new onset LBBB (in-hospital, $p<0.001$), major bleeding (in-hospital, $p=0.003$), effective orifice area, median (30 days, $p<0.001$), transprosthetic mean gradient, median (30 days, $p<0.001$), disabling stroke (in hospital $p=0.015$). No difference in all-cause mortality.

NICE

Abbreviations: LBBB, Left Bundle Branch Block

Published evidence – Sapien 3/Ultra (2)

Sapien 3 Ultra

Pellegrini et al. (2023): non-randomised propensity matched analysis comparing Sapien 3 Ultra (n=472) to ACURATE neo2 (n=472). Statistically better outcomes for Sapien 3 Ultra: post-dilation (procedural, p<0.001) and mean gradient (post-procedural, p<0.001). Statistically better outcomes for ACURATE neo2: device success (procedural, p<0.001) and severe patient-prosthesis mismatch (post-procedural, p<0.001). No difference in all-cause mortality.

Nazif et al. (2021): non-randomised propensity matched analysis comparing Sapien 3 Ultra (n=1,324) to Sapien 3 (n=1,324). Statistically better performance of Sapien 3 Ultra with regards to the following outcomes only: aortic valve area, mean (discharge, p<0.01) and paravalvular regurgitation (discharge, p<0.01; 30 days, p=0.02).

Combined Sapien 3/Ultra

Herrmann et al. (2024): RCT comparing Evolut Pro/Pro+/FX (n=355) to Sapien 3/Ultra (n=361) in people with small annuli. Statistically better performance of Evolut Pro/Pro+/FX for both composite co-primary endpoints, bioprosthetic-valve dysfunction in women (12 months; p<0.001), mean aortic gradient (12 months; p<0.001), effective orifice area (12 months; p<0.001), haemodynamic structural valve dysfunction (12 months; p<0.001) and moderate or severe prosthesis-patient mismatch (30 days; p<0.001).

NICE

Abbreviations: RCT, Randomised Controlled Trial

Published evidence – ACURATE neo2

Author (year); design, location	Intervention arms	Summary of key results and limitations
Baggio et al. (2023) Retrospective non-randomised (propensity matched) International	Evolut Pro or Pro+ (n=452) ACURATE neo2 (n=452)	Outcomes with a statistically-significant difference in favour of ACURATE neo2 included: mean and peak aortic gradient (discharge, p<0.001 and p=0.008), effective orifice area, mean (procedural, p<0.001), vascular complications (procedural, p=0.003), cardiac and vascular hospitalisation (30 day, p=0.038 and p=0.001), new permanent pacemaker implantation (30 day, p<0.001), intervention for cardiac structural complication (30 day, p=0.041) and AKI stage III or IV (30 day, p=0.002).
Buono et al. (2022a) Retrospective non-randomised (with propensity matching) Italy	ACURATE neo2 (n=205) ACURATE neo (n=205)	ACURATE neo2 achieved significantly better performance in the following outcomes: ICU stay, median (in-hospital, p=0.003) and moderate or severe paravalvular aortic regurgitation (discharge, p<0.001)
Kim et al. (2022c) Retrospective non-randomised Germany	ACURATE neo2 (n=810) ACURATE neo (n=2,055)	ACURATE neo2 performed significantly better on the following outcomes: paravalvular regurgitation (procedural; p=0.03) and bleeding, type 2 to 4 (procedural; p<0.01).
Kim et al. (2024) Post-market surveillance non-comparative study	ACURATE neo2 (n=250)	Longest follow-up data for ACURATE neo2. All-cause mortality was 0.8% at 30 days and 5.1% at 1 year. The 1-year rates for stroke and disabling stroke were 3.0% and 1.3%, respectively. Early haemodynamic improvements were maintained up to 1 year.

See also slides 35 and 38.

NICE

Abbreviations: AKI, Acute Kidney Injury; ICU, Intensive Care Unit

Published evidence – Evolut R/Pro+/FX

Comparative evidence for Evolut R and Evolut Pro+ against technologies by other manufacturers in scope has been presented in slides 35, 36, 37, 38 and 39. In addition, the EAG identified the following key studies:

Author (year); design, location	Intervention arms	Summary of key results and limitations
Merdler et al. (2023) Retrospective non-randomised cohort US	Evolut FX (n=100) Evolut Pro+ (n=100)	The Evolut FX valve demonstrated a statistically significant advantage in the following 30-day outcomes: aortic mean gradient (discharge, p=0.006) and aortic peak velocity (discharge, p=0.002). This was the longest-term evidence available for Evolut FX.
Zaid et al. (2023) Retrospective non-randomised US	Evolut FX (n=226) Evolut Pro+ (n=378)	The Evolut FX valve demonstrated a statistically significant advantage in the following in-hospital outcomes: commissural alignment (p<0.0001), left coronary cusp depth (p<0.001) and device recaptures (p=0.004).
Gozdek et al. (2023) Systematic review with meta-analysis (N=11 observational studies)	Evolut R (n=8,924) Evolut Pro (n=3,439)	The authors established statistically significant better performance of Evolut Pro in the following outcomes: more than one valve needed (procedural, p=0.02), moderate to severe PVL (timepoint NR, p=0.002) and major bleeding (timepoint NR, p=0.03).
Forrest et al. (2020) Retrospective non-randomised cohort	CoreValve (n=5,514) Evolut R (n=11,295) Evolut Pro (n=2,065)	Statistically significant lower rates of major bleeding (30 days, p=0.01) and moderate or severe aortic regurgitation (30 days, p=0.03) for Evolut R.

Abbreviations: EAG, External Assessment Group; PVL, Paravalvular Leak

Published evidence – Allegra

The longest available evidence for Allegra was reported in the single arm study reporting outcomes for 103 people extracted from the Swiss TAVI Registry from a single centre (Wolfrum et al. 2023). Kaplan Meier analysis was used to estimate 3-year all-cause mortality (31.4%) and cardiovascular mortality (18.8%).

Allegra was also included in Santos-Martinez et al. (2022), a large retrospective non-randomised study in Europe (see slide 35). Allegra and 4 other devices were compared to Myval (reference technology). Allegra was statistically significantly inferior with regards to the following outcomes: cerebrovascular events (in-hospital), major vascular complications (in-hospital), left bundle branch block (discharge), new permanent pacemaker implant (discharge) and mean aortic gradient (discharge). The EAG noted that the study only reported in-hospital outcomes and did not adjust for differences in baseline characteristics between devices.

NICE

Abbreviations: EAG, External Assessment Group

Published evidence – Hydra

The EAG did not identify any published comparative evidence for the Hydra TAVI device.

The longest follow-up was from Aidietis et al. (2022) that reported 30-day (n=146) and 1-year (n=114) outcomes in 157 people in 18 centres across Europe and Asia:

- 5 device-related deaths (3.2%; 95% CI 1.2% to 1.7%) at 30 days.
- Moderate or severe paravalvular leak was 5.3%, 6.3% and 6.9% at post-procedure, 30 days and 1-year timepoints.
- Improvements in mean gradient were observed post-procedure ($p<0.001$), which were sustained at 30 days ($p<0.001$) and 1 year ($p<0.001$).
- Improvements in effective orifice area were also observed post-procedure ($p<0.001$), 30 days ($p<0.001$) and sustained at 1 year.
- Pacemaker implantation was 10.8% and 11.5% at 30 days and 1 year. At 30 days, major bleeding (4.5%), major vascular complications (4.5%), stroke (0.6%), acute kidney injury (0.6%) were reported; no increase in these events was reported at 1 year. No myocardial infarction or transient ischaemic attack events occurred in the cohort.

NICE

Abbreviations: EAG, External Assessment Group

Published evidence – Navitor

Comparative evidence for Navitor against other devices in scope was not available. Eckel et al. (2023) compared Navitor to Abbott's previous generation device, Portico. The longest follow-up identified for Navitor was 1 year reporting outcomes for 120 people (Sondergaard et al. 2023), which included 2 UK centres (remaining in the US, Europe and Australia). The longest follow-up for device family (Portico) was 3 years, which included 803 people (Giordano et al. 2024). Evidence including Portico was presented in slide 35.

Author (year); design, location	Intervention arms	Summary of key results and limitations and EAG comment
Eckel et al. (2023) Retrospective non-randomised cohort Germany	Navitor (n=137) Portico (n=139)	Navitor was significantly better with regards to the following outcomes: paravalvular leak - greater than mild or trace or requiring SAVR or valve-in-valve (in-hospital, p=0.041), major vascular complication (in-hospital, p=0.036) and severe bleeding (in-hospital, p=0.005).
Sondergaard et al. (2023) Prospective single arm Multinational	Navitor (n=120)	At 30 days, the rate of all-cause mortality was 0%, and no subjects had moderate or greater PVL. The rate of disabling stroke was 0.8%, life-threatening bleeding was 2.5%, stage 3 acute kidney injury 0%, major vascular complications 0.8%, and new pacemaker implantation 15.0%. At 1 year, the rates of all-cause mortality, disabling stroke and moderate PVL were 4.2%, 0.8% and 1.0%, respectively.
Giordano et al. (2024) Retrospective non-randomized cohort Multinational	Portico (n=803)	The composite of death, stroke, myocardial infarction, and reintervention for valve degeneration occurred in 37.5% (95% confidence interval: 34.1-40.9%), with all-cause death in 35.1% (31.8-38.4%), stroke in 3.4% (1.3-3.4%), myocardial infarction in 1.0% (0.3-1.5%), and reintervention for valve degeneration in 1.1% (0.6-2.1%).

Published evidence – Trilogy

The EAG identified 1 German case report specific to the Trilogy device (Geyer et al. 2023), reporting outcomes to 1 month.

Comparative evidence was only available for a predecessor device (exclusively in transapical TAVI procedures):

- Seiffert et al. (2015) reported 1-year outcomes of transapical TAVI in people with aortic stenosis using JenaValve (n=88 people), Engager (Medtronic, n=50), and ACURATE (Symetis, n=62). Fluoroscopy and procedure time, use of contrast agent, all-cause mortality at 1 year were highest for those receiving JenaValve.

No between-generation comparative evidence was identified.

The EAG noted that most TAVI procedures in the UK are done via a percutaneous transfemoral delivery approach and that this is recommended as the default position by GIRFT. Therefore, the EAG considered that results from the published studies may not be generalisable to an NHS setting.

Clinical experts have advised that JenaValve would not be used in a person with aortic stenosis only and is more appropriate for use in people with aortic regurgitation.

Abbreviations: EAG, External Assessment Group, GIRFT, Getting It Right First Time; NHS, National Health Service

Ongoing studies

Study ID, location	Design	Intervention arms	Comment
NCT0444302 Denmark	Randomized controlled trial	Myval (including Octacor) and Sapien series	-
NCT04703699 International	Observational single-arm study	Myval valves	Meril valves only
NCT05989074 Unknown	Randomized controlled trial	Allegra valve compared to balloon-expandable valve systems	Mixed comparator arm; women only
NCT06049654 Spain	Randomized controlled trial	Allegra valve compared to Sapien 3/Ultra valves specifically for valve-in-valve indication	Valve-in-valve indication only
NCT02732691 International	Observational single-arm study	Trilogy valve	Active, but not recruiting
NCT04415047 USA	Single arm trial	Trilogy valve	Aortic regurgitation

Other evidence identified by the EAG

Adverse events

The EAG identified 6 publications reporting adverse events not directly captured within the economic modelling for 2 devices (ACURATE neo2, Evolut Pro+). The EAG acknowledged that capturing adverse events for TAVI devices is likely to be associated with breadth of use and that systematic searches for all devices in Scope of this late-stage assessment have not been undertaken. Therefore, the EAG considered these additional outcomes to be incidental findings relating to adverse events. See Section 5.4.3 in the EAR.

Usability

The EAG identified 2 conference abstracts reporting outcomes from clinician surveys investigating procedural technique outcomes and feedback with Evolut FX compared with Evolut Pro+. The abstracts overlapped in authorship, timepoint, setting and figure used. The authors noted that 79% of operators rated the Evolut FX as having a more predictable deployment than the Evolut Pro+.

Abbreviations: EAG, External Assessment Group

Clinical equivalence

The EAG identified extensive published evidence for differences in outcomes between TAVI devices in and out of scope, however, noted that:

- the quality and length of follow-up were generally low
- the indications for the included devices vary
- clinical experts have advised that patient characteristics inform the choice of which TAVI is most suitable.

The EAG identified published evidence comparing generations of devices from 4 manufacturers (Abbott, Boston Scientific, Edwards Lifesciences and Medtronic); see Section 5.4.6 in the EAR. Hydra (SMT) and Allegra (Biosensors) are first generation TAVI devices. No comparisons were identified that compared JenaValve Trilogy with an earlier JenaValve device, or Myval Octacor with Myval.

The EAG did not assume equivalence in clinical outcomes between the TAVI devices or between generations of a TAVI device by the same manufacturer.

EAG assumption

NICE

Abbreviations: EAG, External Assessment Group

Summary of the clinical evidence (1)

- The EAG considered the multivariate analysis of linked patient level data from the UK adjusting for recorded confounders to be the strongest source of evidence available.

  The analysis identified statistically significant differences across 6 TAVI devices from 4 manufacturers in in-hospital stroke, aortic regurgitation and permanent pacemaker implantation outcomes. It did not identify a statistical difference in long-term outcomes.

- The EAG's multivariate analysis accounted for recorded confounders but a number of clinically important variables (such as surgical risk, degree of valve calcification) were not available and could not be for. Many of them are used in practice to choose a particular TAVI device at the individual patient level.

- The EAG considered that the results may be confounded by the less frequent use of some devices in the NHS.

  Therefore, the EAG emphasized that the clinical significance of the observed differences is uncertain.

NICE

Abbreviations: EAG, External Assessment Group; NHS, National Health Service

Summary of the clinical evidence (2)

The EAG's assessment identified differences in outcomes between TAVI devices in the published literature, but noted significant limitations:

- Only 15 studies adjusted for population differences.
- Few included people recruited from a UK setting and there were limitations in length of follow up and reporting.
- Some results were from older trial data (with longer-follow-up) which can be less generalisable.
- Sometimes the differences were restricted to those between valve expansion types or at the manufacturer level only.
- There were methodological issues and conflicts of interest of authors in the studies.

Therefore, the EAG considered the published evidence to be at high risk of bias.

The EAG further noted that:

- Since there were technical differences between different TAVI devices and between generations of a device, clinical equivalence could not be assumed.
- The results from the multivariate analysis are not fully comparable to the results from the published literature.
- As with the multivariate analysis, the results may be confounded by the less frequent use of some devices in the NHS.

NICE

Abbreviations: EAG, External Assessment Group; NHS, National Health Service

Economic evaluation

NICE National Institute for Health and Care Excellence

Review of the literature and the NG208 economic model

Review of the economic literature

- The EAG reviewed economic evaluations or models published from 01 January 2020 to 28 November 2023.

No economic assessments were identified that compared different TAVI devices.

Review of the NG208 model

- The EAG assessed of the suitability of the NICE Guideline 208 (NG208) economic model. It critically appraised the model against the CHEERS 2022 checklist (see Appendix F1 in the EAR) and assessed the assumptions from the model to considered their appropriateness within the context of this late-stage assessment (see Appendix F2 in the EAR).

✓ The EAG confirmed that the NG208 economic model remained consistent with other economic evaluations for TAVI and was a suitable basis for the economic evaluation within this late-stage assessment.

The EAG made adjustments to the model due to some limitations of the NG208 economic model. Among them:

i. The EAG's model was adjusted to permitted multi-technology comparisons.
ii. The EAG's model added relevant and excluded irrelevant health states.
iii. The EAG broke down the costs obtained from Healthcare Resource Groups.

NICE

Abbreviations: CHEERS, Consolidated Health Economic Evaluation Reporting Standards; EAG, External Assessment Group; NG, NICE Guideline

EAG's economic model

The EAG's economic model was an adaptation of the NG208 model to allow comparison of multiple TAVI devices. It was built in *rdecision*.

General approach

- Discounting and the costing perspective were consistent with the NICE reference case.
- The time horizon was 15 years.
- Men and women were modelled separately.
- The model was probabilistic and was run 500 times for the base case analysis and in each scenario.
- Results were presented as Net Monetary Benefit (NMB) to allow comparison and ranking of more than 2 technologies.
- The willingness-to-pay (WTP) threshold was £20,000 per QALY.

NMB = QALYs x λ – Cost, where λ is the chosen willingness to pay (WTP) threshold.

Conversion to SAVR or subsequent SAVR during follow-up was treated as an outcome, and average cost and utility decrement (disutilities) associated with SAVR adverse events were obtained from the NG208 economic model output.

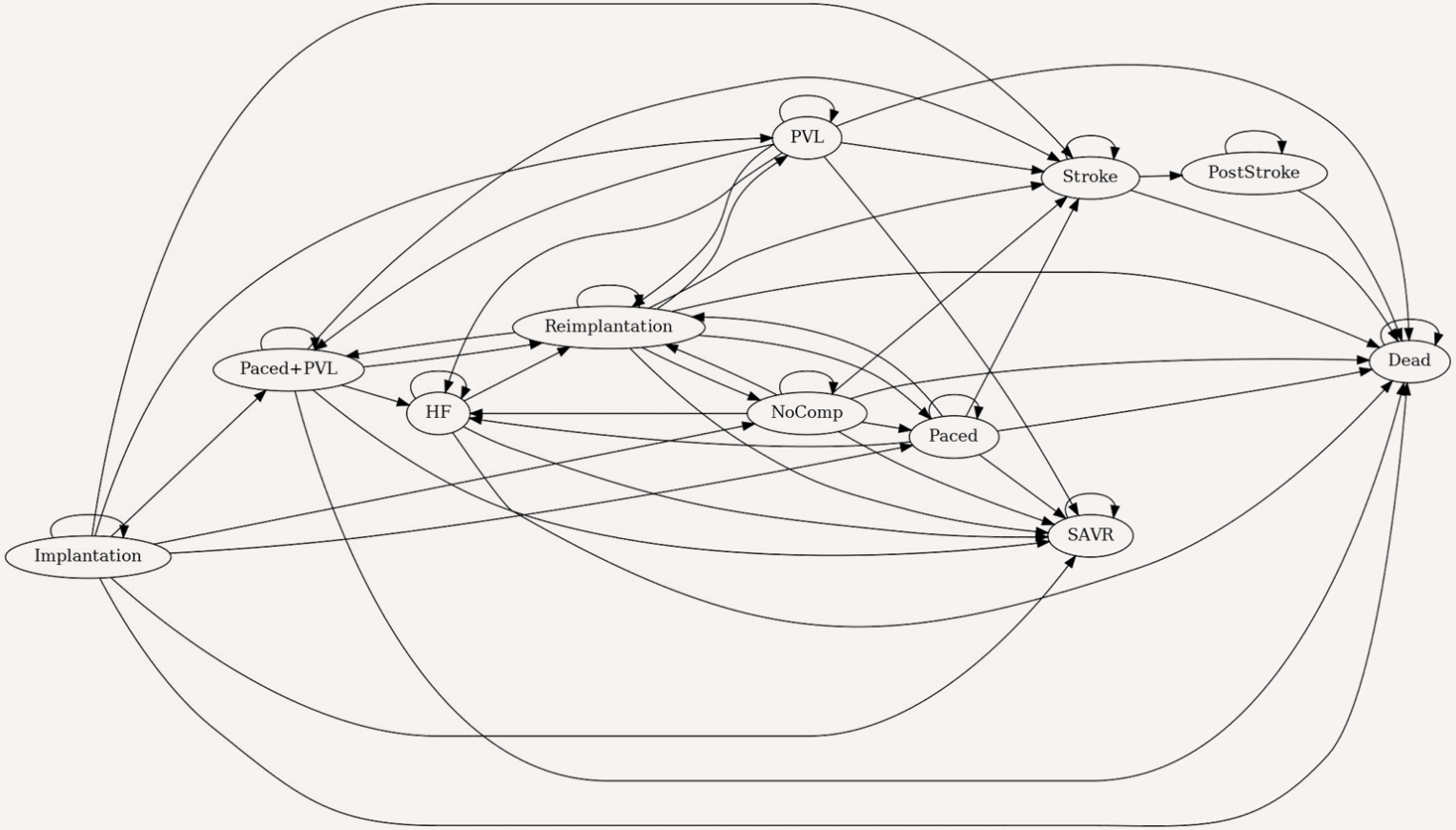
NICE

Abbreviations: EAG, External Assessment Group; NG, NICE Guideline; NMB, Net Monetary Benefit; QALY, Quality-Adjusted Life Year; WTP, Willingness-to-pay

Model structure

Modelled health states included:

- Death
- Aortic stenosis resolved by TAVI and having a stroke [Stroke]
- Aortic stenosis resolved by TAVI and having major or severe paravalvular leak [PVL]
- Aortic stenosis resolved by TAVI and having a pacemaker [Paced]
- Subsequent TAVI procedure [Reimplantation]
- Aortic stenosis resolved from surgical aortic valve repair, including bailout SAVR [SAVR]
- TAVI procedure and no adverse events [NoComp].



Some health conditions were combined into a single health state. For example, the states stroke + PVL, stroke + pacemaker and stroke + PVL + pacemaker were combined within the stroke state.

EAG assumption

Modelling assumptions

Assumption	EAG's reasoning
Only TAVI devices for which there are data within the UK TAVI Registry were included in economic modelling.	The EAG considered it inappropriate to use a combination of real-world evidence and trial data for the economic evaluation (see Section 6 of the EAR)
The cohort in the model represented the real-life case mix of people at different surgical risks	Most people would fall into the high surgical risk category Current proportion of people in each risk group is not known with certainty and it would not be feasible to generate a weighted average of risk group specific utility values
MI or need for renal replacement therapy as acute complications of TAVI were not included in the model	Rarity of events (0.3% and 0.1% respectively from the UK TAVI Registry and expert advice)
No modelling of technical success with VARC-3	VARC-3 includes freedom of surgery or intervention related to the device or major vascular or access-related or cardiac structural complication, so there is risk of double counting
The proportions of people opting for SAVR because of the TAVI waiting list applied equally across device arms	Clinical experts advise that waiting lists are not different between TAVI devices
The rate of people leaving the Implantation/Reimplantation state was set to ensure that 95% of people leave (are discharged) within 30 days	Avoidance of use of tunnel states
The rate at which people leave the stroke state (for the post-stroke state) was set to ensure that the mean occupancy time is 1 year	Avoidance of use of tunnel states
The EAG also considered the appropriateness of the assumptions from the NG208 economic model (see Appendix F1 in the EAR).	

Abbreviations: EAG, External Assessment Group; EAR, External Assessment Report; NG, NICE Guideline; VARC, Valve Academic Research Consortium

Model parameters (1)

Transition probabilities

- Transition probabilities between states for men and women separately were computed from transition rates using the UK TAVI Registry/HES linked dataset (see next slide).
- In the base case the starting population had the average characteristics derived from the UK TAVI Registry: 82 years of age, 57.4% male, undergoing a 70-minute procedure.
- The relative rates of transition to health states are given by the rate of leaving an implantation state multiplied by the absolute risk of having an event.

Cost parameters

- Cost parameters were updated using the most recent data from sources including NHS Reference Costs, Unit Costs, costs provided by NHS Supply Chain or by experts (see Table 30 in the EAR).
- Some manufacturers have rebate arrangements with NHS Supply Chain.

Health state utilities

- The utility values for the high surgical risk group in the NG208 model were used in the base case analysis.
- The EAG applied utility values associated with a starting population, increments because of successful TAVI procedure at 1 year, and decrements associated with adverse events applied in the economic model (see Table 31 in the EAR).

Abbreviations: HES, Hospital Episode Statistics; NHS, National Health Service

Model parameters (2)

Predicted event proportions for base case (in hospital outcomes; % [95% CI])

Predicted outcome	Sapien 3 (male)	Sapien 3 (female)	Sapien 3 Ultra (male)	Sapien 3 Ultra (female)	ACURATE neo2 (male)	ACURATE neo2 (female)	Evolut R (male)	Evolut R (female)	Evolut Pro+ (male)	Evolut Pro+ (female)	Navitor (male)	Navitor (female)
In-hospital death	1.22 (0.14, 10)	1.74 (0.18, 15.01)	1.42 (0.22, 8.64)	2.03 (0.27, 13.57)	3.27 (0.35, 24.65)	4.63 (0.49, 32.51)	4.29 (0.45, 30.83)	6.04 (0.63, 39.52)	1.58 (0.18, 12.76)	2.25 (0.26, 17.13)	1.38 (0.09, 18.17)	1.97 (0.13, 23.92)
In-hospital stroke	0.85 (0.12, 5.78)	1.52 (0.2, 10.79)	0.26 (0.04, 1.65)	0.47 (0.07, 3.25)	0.25 (0.02, 3.65)	0.46 (0.03, 6.52)	1.4 (0.17, 10.9)	2.52 (0.3, 18.29)	1.35 (0.19, 8.86)	2.42 (0.35, 14.73)	1.35 (0.17, 10.03)	2.42 (0.3, 16.81)
In-hospital AR	5.09 (0.48, 37.5)	6.65 (0.6, 45.62)	3.29 (0.37, 23.81)	4.32 (0.44, 31.44)	16.02 (1.35, 72.62)	20.21 (1.79, 77.9)	22.46 (2.33, 77.86)	27.78 (3.06, 82.44)	24.98 (3.14, 77.39)	30.66 (4.27, 81.42)	45.54 (7.1, 90.15)	52.61 (9.13, 92.46)
In-hospital PPI	6.9 (2.7, 16.5)	5.99 (2.24, 15.03)	7.71 (3.46, 16.3)	6.7 (2.78, 15.26)	6.16 (1.91, 18.13)	5.34 (1.63, 16.11)	14.78 (5.6, 33.64)	12.97 (4.81, 30.53)	13.66 (5.63, 29.57)	11.97 (4.91, 26.35)	17.48 (6.7, 38.46)	15.4 (5.76, 35.15)
In-hospital major bleeding	0.61 (0.06, 5.73)	2.9 (0.29, 23.56)	0.63 (0.08, 4.66)	3 (0.38, 20.08)	1.11 (0.1, 11.03)	5.17 (0.52, 36.29)	0.48 (0.03, 6.49)	2.31 (0.19, 22.86)	0.26 (0.02, 2.81)	1.24 (0.13, 10.96)	0.67 (0.05, 8.35)	3.19 (0.26, 29.38)
In-hospital vascular comp	1.38 (0.13, 13.13)	3.4 (0.3, 29.05)	2.28 (0.29, 15.69)	5.54 (0.66, 33.95)	6.73 (0.65, 44.21)	15.37 (1.66, 66.16)	1.51 (0.1, 19.21)	3.71 (0.26, 36.18)	1.67 (0.15, 16.2)	4.1 (0.41, 31.04)	5.59 (0.51, 40.47)	12.97 (1.31, 62.66)

NICE

Abbreviations: AR, Aortic Regurgitation; CI, Confidence Interval; EAR, External Assessment Report; PPI, Permanent Pacemaker Implantation

Model parameters (3)

Predicted event proportions for base case (out of hospital outcomes; % [95% CI])

Predicted outcome	Sapien 3 (male)	Sapien 3 (female)	Sapien 3 Ultra (male)	Sapien 3 Ultra (female)	ACURATE neo2 (male)	ACURATE neo2 (female)	Evolut R (male)	Evolut R (female)	Evolut Pro+ (male)	Evolut Pro+ (female)	Navitor (male)	Navitor (female)
One-year death	11.24 (3.43, 18.41)	10.8 (2.94, 18.03)	13.73 (5.75, 21.03)	13.21 (4.88, 20.81)	15.46 (3.53, 25.92)	14.88 (3.33, 25.06)	11.41 (2.24, 19.71)	10.97 (2.07, 19.06)	11.34 (3.22, 18.78)	10.9 (3.15, 18.03)	21.94 (3.5, 36.86)	21.16 (3.36, 35.68)
One-year stroke	3.57 (0, 8.03)	2.79 (0, 6.49)	3.07 (0, 6.43)	2.39 (0, 5.27)	2.37 (0, 6.1)	1.84 (0, 4.82)	1.54 (0, 4.11)	1.2 (0, 3.25)	3.48 (0, 7.91)	2.71 (0, 6.22)	3.77 (0, 9.61)	2.94 (0, 7.58)
One-year PPI	4.22 (0, 9.54)	3.78 (0, 8.77)	3.06 (0, 6.45)	2.74 (0, 6.02)	5.55 (0, 13.2)	4.98 (0, 11.89)	5.19 (0, 12.39)	4.65 (0, 11.23)	3.76 (0, 8.68)	3.37 (0, 7.77)	3.18 (0, 8.69)	2.85 (0, 7.81)
One-year heart failure	1.9 (0.18, 3.59)	1.38 (0.06, 2.69)	1.47 (0.31, 2.62)	1.07 (0.14, 1.99)	2.03 (0, 4.1)	1.47 (0, 3.01)	2.57 (0, 5.15)	1.87 (0, 3.79)	2.34 (0.17, 4.47)	1.71 (0.13, 3.26)	2.16 (0, 4.67)	1.57 (0, 3.42)
Two-year death	23.15 (7.49, 36.16)	22.32 (6.46, 35.50)	27.83 (12.30, 40.62)	26.87 (10.52, 40.23)	31.00 (7.66, 48.44)	29.96 (7.27, 47.09)	23.47 (5.00, 38.36)	22.64 (4.64, 37.24)	23.34 (6.94, 36.86)	22.51 (6.82, 35.57)	42.15 (7.32, 63.89)	40.85 (7.05, 62.36)

Abbreviations: CI, Confidence Interval; PPI, Permanent Pacemaker Implantation

Model parameters (4)

- Some manufacturers have rebate arrangements with NHS Supply Chain.
- [redacted]
- [redacted]
- *Costs of the valves provided for reference even though the technologies have not been modelled.

Transacted and post-rebate prices of the devices in scope

Manufacturer	Valve	Transacted Price	[redacted]	[redacted]
Abbott	Navitor	[redacted]	[redacted]	[redacted]
Edwards	Sapien 3	[redacted]	[redacted]	[redacted]
Edwards	Sapien 3 Ultra	[redacted]	[redacted]	[redacted]
Medtronic	Evolut R	[redacted]	[redacted]	[redacted]
Medtronic	Evolut Pro+	[redacted]	[redacted]	[redacted]
Medtronic	Evolut FX	[redacted]	[redacted]	[redacted]
Boston Scientific	ACURATE neo2	[redacted]	[redacted]	[redacted]
Jenavalve	Trilogy*	[redacted]	[redacted]	[redacted]
Meril	Myval Octacor*	[redacted]	[redacted]	[redacted]
SMT	Hydra*	[redacted]	[redacted]	[redacted]
Biosensors	Allegra*	[redacted]	[redacted]	[redacted]

NICE

Abbreviations: AR, Aortic Regurgitation; EAR, External Assessment Report; PPI, Permanent Pacemaker Implantation

Deterministic scenario analyses

The EAG explored possible scenarios deterministically:

- Shorter time horizons (2, 5, 10 years).
- Shorter procedure duration (45 minutes).
- Reducing the proportion of procedures involving an anaesthetist (15%).
- Reducing ICU days for people who require an ICU stay (0 days).
- Cost of TAVI device
    a) transacted price (without 'added value')
    b) £17,500 based on NG208, where it was noted that 80% of hospitals purchased the TAVI at a discounted costs of £17,500
    c) £15,000 from threshold analysis in NG208.
- Cost of stroke (base case increased by 15%).
- Proportion requiring a conversion to SAVR (0.1%).
- Inclusion of additional cost of a cardiac balloon catheter for balloon dilatation to the TAVI procedure costs.

NICE

Abbreviations: EAG, External Assessment Group; ICU, Intensive Care Unit; NG, NICE Guideline; SAVR, Surgical Aortic Valve Replacement

Clinical scenario analyses

The EAG investigated additional clinical scenarios and comparisons guided by expert input:

- Coronary obstruction (anatomical coronary comorbidity left main stem disease or stenosis of at least 50% in one vessel).
- Younger age (preservation of coronary access; starting age 70 years).
- Small annular diameter size (<22mm).
- Large annular diameter size (>32mm).
- No severe symptoms.
- Left ventricular ejection fraction less than 30.
- Frail people (based on Katz/CSHA).
- Urgent procedures.
- Extensive calcification of ascending aorta.

All transition probabilities and rates for these scenarios were predicted from the linked UK TAVI Registry and HES real world datasets. See Table 32 in the EAR for further detail on the scenarios.

NICE

Abbreviations: CSHA, Canadian Study of Health and Aging; EAR, External Assessment Report; HES, Hospital Episode Statistics

Base case results (1)

Net Monetary Benefit (NMB)

- [redacted]
- [redacted]
- [redacted]

Probability of highest NMB

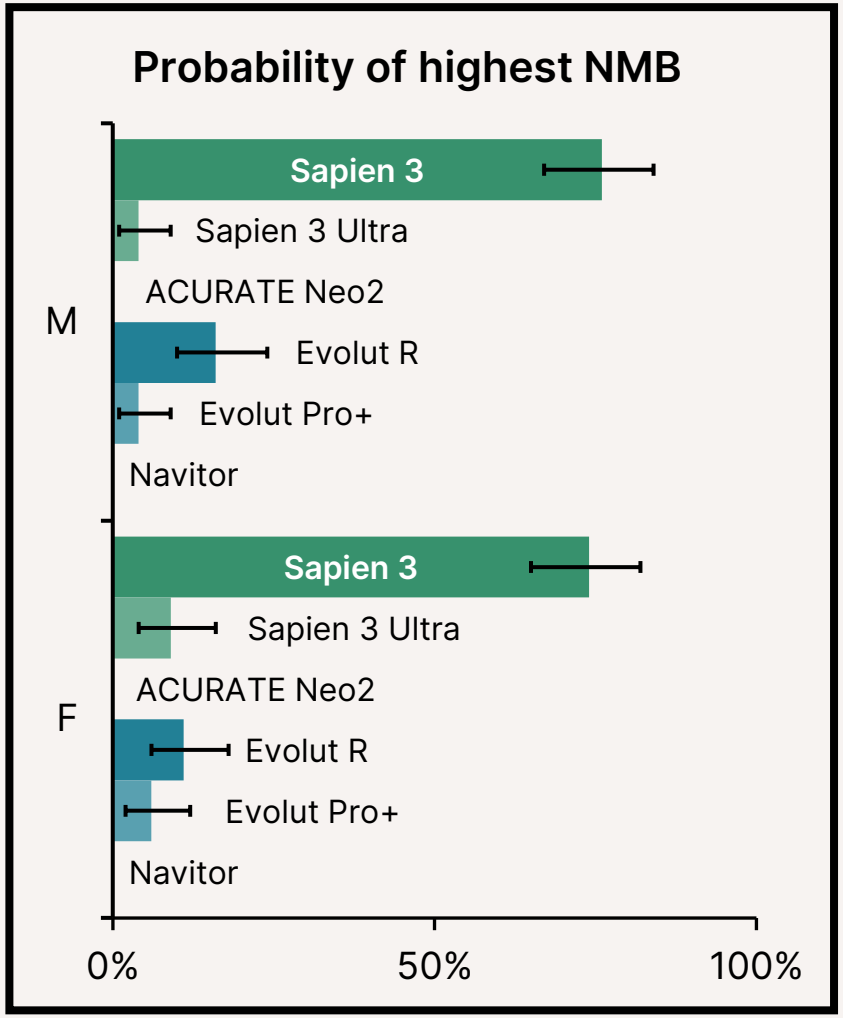
- Sapien 3 had the highest probability of greatest NMB in both males (76%) and females (74%). Across self-expanding TAVI devices, Evolut R had the highest probability of greatest NMB in both males and females (16% and 11%, respectively).
- ACURATE neo2 and Navitor had a 0% probability of having the highest NMB for both sexes.

NICE

Abbreviations: EAG, External Assessment Group; NMB, Net Monetary Benefit

Base case results (2)

[redacted]



NICE

Abbreviations: NMB, Net Monetary Benefit; QALY, Quality-adjusted Life Year; WTP, Willingness-to-pay

Deterministic scenario results (1)

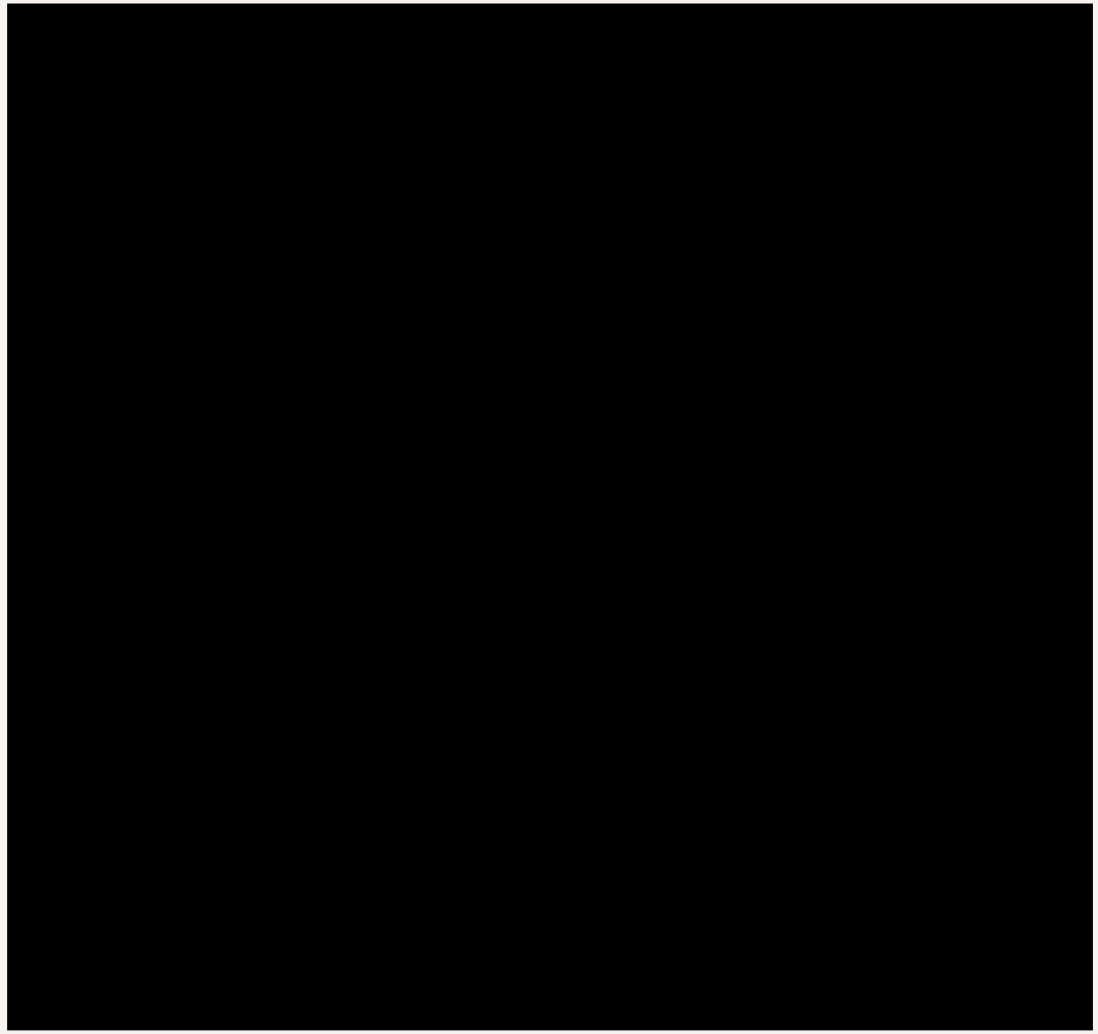
Most of the lifetime costs are incurred during the peri-procedural phase and in the early years post-procedure. So, as the time horizon was increased from 2 years to 10 years, the NMB of all valves increased the longer the time horizon. Regardless of the time horizon, Sapien 3 remained the device with the highest NMB.

Deterministic scenario results (2)

Variable costs

- Variations to the costs of conducting the procedure made little difference to the total cost incurred over the time horizon and did not change the profile of NMB. Neither did setting the price of all 6 valves to the same value or varying the percentage of surgeries converted to SAVR.
- Setting the valve price to the transacted price (that is, not accounting for rebates) led to Evolut R having the greatest probability of highest NMB in males (see right). In females, Sapien 3 still had the greatest probability of the highest NMB, but it was lower than in the base case.

See Tables 35 and 36 in the EAR for the full deterministic scenario results.



NICE

Clinical scenario results (1)

Coronary obstruction, younger age, no severe symptoms, LVEF<30, frail people, urgent procedures

- In these scenarios the relative differences between valves were very similar to the base case, but the total costs or QALYs were lower or higher. For example, in younger people, the accumulated QALYs were higher due to the difference in the standardized mortality rate of the starting population.

Extensive calcification in the ascending aorta

- The probability of having the highest NMB for Sapien was reduced from 76% in the base case to 61% in males, and from 74% to 57% in females.

  The EAG highlighted how this may reflect clinician choice in practice, in that Sapien 3 may not be used frequently in this scenario if annular rupture is judged to be a concern and reemphasized that the economic model results are a consequence of the prevalence of cases in the registry.

Small or large annular diameter size

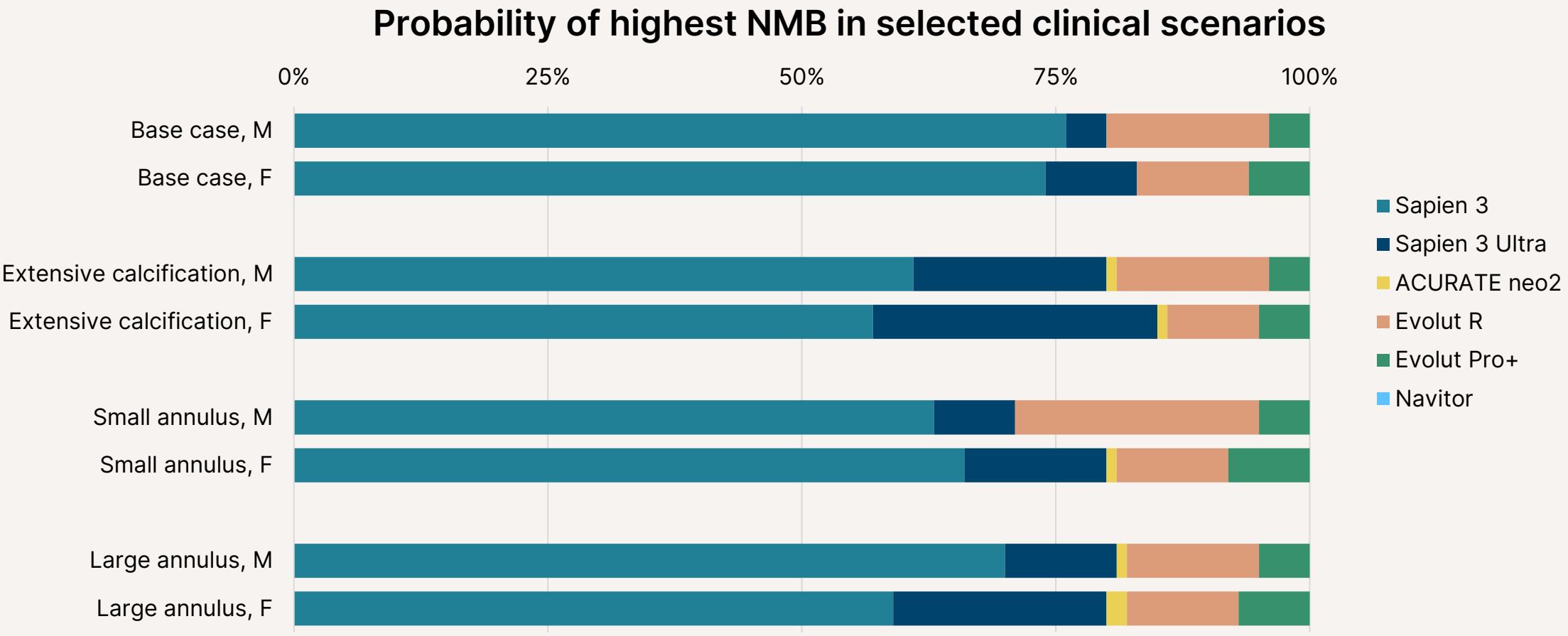
- These scenarios also presented notable departures from the base case. In the small annular diameter size scenario, the probability of highest NMB was notably lower for Sapien 3. This was offset by an increase of the probability of highest NMB for Evolut R in males and Sapien 3 Ultra in females. In the large annular diameter size scenario, the probability of highest NMB was lower for Sapien 3 in favour of Sapien 3 Ultra.

See next slide and Section 6.3.3 of the EAR for more details.

NICE

Abbreviations: EAG, External Assessment Group; LVEF, Left Ventricular Ejection Fraction; NMB, Net Monetary Benefit; QALY, Quality-Adjusted Life Year

Clinical scenario results (2)



NICE

Abbreviations: NMB, Net Monetary Benefit

Key limitations

1. Only TAVI devices for which there are data within the UK TAVI Registry were included in economic modelling.

   EAG comment: The EAG considered combining real-world and randomised trial data inappropriate, noting that it was unable to adjust for patient characteristics from the published literature to enable fair comparison.

2. The EAG did not consider the TAVI-in-TAVI or TAVI-in-SAVR cohorts in the economic evaluation.

   EAG comment: Valve-in-valve TAVIs represented a small proportion of the procedures in the linked dataset. In addition, there were differences in demographics and presentation (when compared with TAVI in native aortic valve) and not all TAVI devices are explicitly indicated for TAVI-in-TAVI or TAVI-in-SAVR.

3. The EAG was unable to model several scenarios, such as degenerative surgical bioprosthesis, bicuspid aortic valves, severe left ventricular outflow, annular calcification and coronary height.

   EAG comment: Data were not available in the UK TAVI Registry

4. The EAG noted concerns regarding the uncertainty of the results.

   EAG comment: The 95% confidence intervals did not fully capture the uncertainty because of the number of assumptions and missing data that led to their calculation. For some devices this may also be related to the infrequency of use in certain clinical scenarios.

Abbreviations: EAG, External Assessment Group; HES, Hospital Episode Statistics; PSA Probabilistic Sensitivity Analysis; SAVR, Surgical Aortic Valve Replacement

Summary of the economic evaluation (1)

The EAG adapted the NG208 economic model to enable comparisons of multiple TAVI devices and assessed the NMB and the probability of highest NMB for the 6 devices available in the UK TAVI Registry using real-world UK data.

For the base case and most scenario analyses, Sapien 3 was found to be most likely to provide the highest NMB at a willingness-to-pay threshold of £20,000/QALY. Evolut R was very often the second most likely to provide the highest NMB across most scenarios.

- The EAG noted that these results are partially due to Sapien 3 having the lowest mortality at 1 and 5 years in the economic model when compared with other devices. However, this is also likely a consequence of Sapien 3 being available in a 29 mm valve size and therefore being used in a higher proportion of males (who are typically are at lower risk of stroke and major bleeding than females).
- Neither Sapien 3 nor Evolut R are the latest generation devices by the respective manufacturer.

Abbreviations: EAG, External Assessment Group; NMB, Net Monetary Benefit; QALY, Quality-adjusted Life Year

Summary of the economic evaluation (2)

The EAG noted that Navitor and ACURATE neo2 had the lowest probability of having the highest NMB across virtually all scenarios.

- However, it advised caution in overinterpreting this finding, as it is likely a consequence of these devices having the least amount of data from the UK TAVI Registry and therefore having the largest uncertainty (which translates to having a low probability of highest NMB or a negative NMB in some cases).

As the economic evaluation relied on real-world data for clinical inputs, a significant proportion of the uncertainty in the results was related to the lack of adjustment for confounders that were not recorded in the UK TAVI Registry and the variable prevalence of use of each TAVI device in the NHS.

The EAG acknowledged that the results were subject to significant uncertainty but did not exclude the possibility that they reflect the true performance of the TAVI devices.

The EAG noted as a significant limitation the inability to assess the cost-effectiveness of the devices not captured in the UK TAVI Registry.

Abbreviations: EAG, External Assessment Group; NMB, Net Monetary Benefit

Summary of the combined evidence

Heat map presenting EAG's summary of all evidence for the devices in scope

Device	Summary of real-world evidence	Published evidence	Longest evidence	Evidence within TAVI-in-SAVR or TAVI-in-TAVI	Summary of economic evidence
Myval Octacor	No data in UK TAVI Registry	See slides 32, 35 and 36	30 days	Some published evidence	Not included in economic model
Sapien 3	Included in multivariate analysis	See slides 32, 35, 36, 37 and 38	1 year	24 TAVI-in-SAVR, 3 TAVI-in-TAVI cases in UK TAVI Registry	Greatest probability of highest NMB in most scenarios
Sapien 3 Ultra	Included in multivariate analysis	See slides 32, 35, 36, 37 and 38	1 year	101 TAVI-in-SAVR, 19 TAVI-in-TAVI cases in UK TAVI Registry	Single scenario where device has the highest NMB
ACURATE neo2	Included in multivariate analysis	See slides 32, 35, 38 and 39	1 year	Contraindicated	0% probability of highest NMB at £20,000 WTP across majority of analysis
Allegra	No data in UK TAVI Registry	No comparative evidence with population matching	3 years	Some published evidence	Not included in economic model
Evolut FX	Only 3 cases in UK TAVI Registry	See slides 32, 38 and 40	30 days	No evidence	Not included in economic model
Evolut Pro+	Included in multivariate analysis	See slides 32 and 35-40	3 years	51 TAVI-in-SAVR, 2 TAVI-in-TAVI cases in UK TAVI Registry	Greatest probability of highest NMB for self-expanding valves in some scenarios
Evolut R	Included in multivariate analysis	See slides 32 and 35-40	5 years	79 TAVI-in-SAVR, 3 TAVI-in-TAVI cases in UK TAVI Registry	Greatest probability of highest NMB in some scenarios and highest probability of highest NMB for among self-expanding valves
Hydra	No data in UK TAVI Registry	No comparative evidence against other manufacturers	1 year	Contraindicated	Not included in economic model
Navitor	Included in multivariate analysis	No comparative evidence against other manufacturers	1 year	Only 9 cases in cases in UK TAVI Registry	0% probability of highest NMB at £20,000 WTP
Trilogy	No data in UK TAVI Registry	No comparative evidence with population matching	30 days	No evidence	Not included in economic model

Abbreviations: NMB, Net Monetary Benefit; WTP, Willingness-to-pay

User preferences

NICE National Institute for Health and Care Excellence

User preferences (1)

Aims

- The purpose of this exercise was to capture the opinion of users to identify which features of a TAVI device influences their decision on which technology to choose.

Methods

- The exercise utilised the principles of multi-criteria decision analysis (MCDA) to establish:
  - the criteria that are important to users when choosing a TAVI valve
  - the relative importance of the criteria
  - and how the criteria can be measured.
- NICE identified interventional cardiologists as the relevant users. Nine consultant interventional cardiologists were recruited and took part in the user preference exercise (see the Methods section in the User Preferences report for further information, including on conflicts of interest).
- The process followed 4 stages:
  - Stage 1: identifying and defining criteria
  - Stage 2: ranking criteria in order of importance
  - Stage 3: weighting of criteria
  - Stage 4: development of performance rules.

NICE

Abbreviations: MCDA, Multi-criteria Decision Analysis

User preferences (2)

Results

- In combination with the outcomes presented in the EAG's report, a total of 23 criteria were set and agreed (see Table 1 in the User Preferences report).
- The list was truncated to the top 10 criteria and again to the criteria whose relative weight was above 5%, resulting in the final list of criteria (see below).

Order of importance	Weight (%)	Criteria	Performance rule
1	27	long-term mortality	Criterion is captured in model
2	24	procedural stroke	Criterion is captured in model
3	15	severe paravalvular leak	Device has moderate to severe paravalvular leak rate of less than 5%, 3%, 1% (note: rate of aortic regurgitation, which includes paravalvular leak, is captured in the economic model)
4	12	safety and effectiveness in annulus/left ventricular outflow tract calcium	Lack of consensus on performance rule
5	9	vascular complications	Criterion is captured in model
6	7	predicted post-procedural haemodynamics/ risk of patient prothesis mismatch	Lack of consensus on performance rule
7	6	minimum vessel size for access	Having a minimal vessel size access for smallest device 5 mm, largest device 5.5 mm

NICE

Abbreviations: EAG, External Assessment Group

User preferences (3)

Results (cont.)

- There was no consensus on the performance rules for 2 criteria - safety and effectiveness in annulus/left ventricular outflow tract calcium and predicted post-procedural haemodynamics/risk of patient prothesis mismatch (see Appendix A in the User Preferences report).

- From the extended list, 3 criteria were judged to be sub-population criteria, i.e. only relevant to a sub-population of people treated with TAVI - Safety and effectiveness in bicuspid anatomy, use for TAVI-in-SAVR and use for TAVI-in-TAVI (see Table 3 in the User Preference report). No consensus was achieved on the performance rules for these criteria either.

- Of the seven most important criteria, five (including the top three) were captured in the EAG's assessment.
    - Long-term mortality, procedural stroke, severe paravalvular leak (using the broader outcome AR) and vascular complications were directly covered in the EAG's health economic model. The EAG used real world data (see slides 55 to 57) to inform the model where information was available and summarised the available published evidence where not (see slide 49). The EAG was only able to investigate the effect of annulus/left ventricular outflow tract calcification in a scenario analysis (see slide 65).

NICE

Abbreviations: AR, Aortic Regurgitation; EAG, External Assessment Group; SAVR, Surgical Valve Replacement

User preferences (4)

Results (cont.)

- The only criterion which was not captured in the economic model and had consensus on the performance rule was minimum vessel size for access, which accounted for 6% of the user preference (see Table 12 in the User Preferences report).
    - The Navitor device was the only one to achieve the minimum vessel size for access for the smallest and largest available valves as per the performance rule. In total, 5 devices achieved the rule for smallest valve and 4 for largest valve.

- The EAG's model captured 87% of the weight of users' decision making either directly or indirectly.

NICE

Abbreviations: EAG, External Assessment Group

User preferences (5)

Strengths and limitations

- There were 4 main sources of uncertainty in the user preference assessment: engagement levels, interests of users, levels of agreement between users and lack of consensus when developing performance rules.
  - The level of agreement was generally consistent among the group for both the ranking and weighting exercises.
  - The levels of engagement varied and were lower through the stages of ranking, weighting, and performance rule setting (6 in stage 2, 5 in stage 3, and 7 in stage 4).
  - See Appendix A in the User Preferences report for details on the levels of consensus achieved.
- Although consensus was not achieved for all criteria, most were covered within the EAG's economic assessment.
- Even within the final list of most important criteria, their relative weight varied significantly.
  The top 3 criteria carried 66% of the total weight.
- Seven out of the 9 users had direct financial interests, often with multiple relevant companies.

Abbreviations: EAG, External Assessment Group

Equality considerations

- Some people may not accept or may have preferences for specific TAVI devices on religious or cultural beliefs because of the use of bovine or porcine leaflets. People would usually have choice, but long-term durability may differ between the two materials.
- One clinical expert noted that several datasets show disproportionately lower implant rates in females and speculated that this may related to referral patterns and diagnostic tests. Another clinical expert advised that this could be due to smaller femoral vessels for access and smaller aortic annuli, leading to TAVI being more challenging or technically not feasible. There may also be sex-related differences in the prevalence, pathophysiology and natural history of aortic stenosis.
- There are geographical inequalities with regards to access to heart valve clinics.
- The EAG noted that all devices included in this assessment contain nickel and are contraindicated in people with nickel allergy; the prevalence of an allergy or hypersensitivity to nickel is between 8%-19% and disproportionately affects females. However, four clinical experts noted that screening for nickel allergy is not routinely done, nor does it influence the choice between TAVI devices or TAVI compared with SAVR.
- The prevalence of aortic stenosis rises with age. The associated mortality is also higher in older age groups.

See Section 3.1 of the EAR and NICE's scoping equality impact assessment.

Abbreviations: EAG, External Assessment Group; EAR, External Assessment Report; SAVR, Surgical Valve Replacement

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Late-stage assessment guidance GID-HTE10027 Transcatheter heart valves for transcatheter aortic valve implantation (TAVI) in people with aortic stenosis

Late-stage assessment report

Produced by: Newcastle EAG

Authors: **Kim Keltie**, Lead Evaluation Healthcare Scientist, The Newcastle upon Tyne Hospitals NHS Foundation Trust (NuTH);

Rosalyn Parker, Evaluation Healthcare Scientist, NuTH;

Rachel O'Leary, Clinical Scientist, NuTH;

Edward O'Toole, Clinical Scientist, NuTH;

Paula Leslie, Pre-registrant Clinical Scientist, NuTH;

David Muir, Clinical Scientist, NuTH;

Elliot Blacklock, EAG Administrator, NuTH;

Emma Belilios, Project Co-ordinator, NuTH;

Oleta Williams, Research Assistant (Information Specialist), Newcastle University;

Sheila Wallace, Research Fellow (Information Specialist), Newcastle University;

Ryan Kenny, Research Associate, Newcastle University;

Nick Meader, Principal Research Associate, Newcastle University;

Nawaraj Bhattarai, Senior Research Associate (Health Economics), Newcastle University;

Sedighe Hosseini-Jebeli, Research Associate (Health Economics), Newcastle University;

Gurdeep S Sagoo, Senior Lecturer (Health Economics), Newcastle University;

Luke Vale, Professor of Health Economics, London School of Hygiene and Tropical Medicine; NuTH;

Andrew Sims, EAG Director, NuTH

Correspondence to: Andrew Sims
Northern Medical Physics and Clinical Engineering,
NMPCE (Medical Physics, NCCC Level 2)
Freeman Hospital
Freeman Road,
High Heaton,
Newcastle upon Tyne
NE7 7DN
nuth.nmpce.hta@nhs.net

Date completed: 16 July 2024

Contains confidential information: Yes

Number of attached appendices: 7

Purpose of the late-stage assessment report

Late-stage assessment forms part of NICE's new lifecycle approach to technology evaluation, that ensures NICE can look at any technology at any stage across the product lifecycle. This external assessment report is part of the late-stage guidance process described in the Late-Stage Interim Methods and Process Statement (2024). NICE has commissioned this work and provided the template for the report. The report forms part of the papers considered by the Committee when it is making decisions about the late-stage assessment.

Declared interests of the authors

Description of any declared interests with related companies, and the matter under consideration. See NICE's Policy on managing interests for board members and employees.

None.

Acknowledgements

Data from the UK TAVI Registry have been provided by the National Institute for Cardiovascular Outcomes Research with approval from NHS England and GIG Cymru/NHS Wales. With clinical oversight provided by Rajesh Kharbanda, Registry Clinical Lead. The views presented in this publication are not endorsed by NHS England or NICOR.

Data from Hospital Episode Statistics and Civil Registration of Deaths have been provided by NHS England. This work uses data provided by patients and collected by the NHS as part of their care and support.

Muhammad Aetesam-ur-Rahman, Consultant Interventional Cardiologist, Sheffield Teaching Hospital;

Jon Anderson, Consultant Cardiac Surgeon, Imperial College Healthcare NHS Trust;

Clare Appleby, Consultant Interventional Cardiologist, Liverpool Heart and Chest Hospital NHS Foundation Trust;

Dan Blackman, Consultant Cardiologist, Leeds Teaching Hospitals NHS Trust;

Norman Briffa, Consultant Cardiac Surgeon, Sheffield Teaching Hospitals NHS Trust;

Betsy Evans, Consultant Cardiac Surgeon, Leeds Teaching Hospitals NHS Foundation Trust, Senior Lecturer, University of Leeds;

Sam Firoozi, Consultant Cardiologist and Lead for Structural Heart Intervention, St George's Hospital;

David Hildick-Smith, Consultant Cardiologist, University Hospitals Sussex NHS Foundation Trust; President of British Cardiovascular Intervention Society (BCIS);

Richard Jabbour, Consultant Interventional Cardiologist, University Hospital Southampton NHS Foundation Trust;

Marjan Jahangiri, Professor of Cardiac Surgery, St George's University Hospitals NHS Foundation Trust;

Rajesh Kharbanda, Consultant Cardiologist, Oxford University Hospitals;

Dawn Lee, Associate Professor of Health Economics and Health Policy, Peninsula Technology Assessment Group (PenTAG), Interventional Procedures Advisory Committee Member;

Mahmoud Loubani, Consultant Cardiothoracic Surgeon, Hull University Teaching Hospitals NHS Trust;

Philip MacCarthy, Consultant Cardiologist, King's College London and King's College Hospital;

Ranjit More, Coronary Interventionalist, Blackpool Teaching Hospital NHS Foundation Trust;

Douglas Muir, Consultant Cardiologist with Special Interest in Intervention, South Tees NHS Foundation Trust;

Hayley Richardson, Clinical Coding Trainer, The Newcastle upon Tyne Hospitals NHS Foundation Trust;

Jaydeep Sharma, Consultant Interventional Cardiologist, Manchester University Hospitals NHS Foundation Trust;

Azfar Zaman, Consultant Cardiologist, NuTH;

Responsibility for report

The views expressed in this report are those of the authors and not those of NICE. Any errors are the responsibility of the authors.

Contents

Tables

Figures

Abbreviations

Term	Definition
A&E	Accident and Emergency
ACC	American College of Cardiology
AF	Atrial fibrillation
AHA	American Heart Association
AIC	Akaike information criterion
AKI	Acute Kidney Injury
APC	Admitted patient care
AR	Aortic regurgitation
AVR	Aortic valve replacement
AUC	Area under the curve
BCIS	British Cardiovascular Intervention Society
BE	Balloon Expanding
BLR	Binary Logistic Regression
CABG	Coronary artery bypass grafting
CADTH	Canadian Agency for Drugs and Technologies in Health
CC	Complication and comorbidity
CCS	Canadian Cardiovascular Society
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CNS	Central nervous system
CI	Confidence interval
CPH	Cox Proportional Hazards
CPRD	Clinical Practice Research Datalink
CSHA	Canadian Study of Health and Aging
CVA	Cerebrovascular accident
DataSAT	Data Suitability Assessment Tool
EAG	External Assessment Group
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EuroSCORE	European System for Cardiac Operative Risk Evaluation Score
GA	General anaesthesia
GIRFT	Getting It Right First Time
HES	Hospital Episode Statistics
HIQA	Health Information and Quality Authority
HR	Hazard ratio
HRG	Healthcare resource group
HTA	Health technology assessment
ICE	Intracardiac echocardiography
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IPG	Interventional Procedures Guidance
iEOA	indexed effective orifice area
KCCQ	Kansas City Cardiomyopathy Questionnaire
LASSO	Least Absolute Shrinkage and Selection Operator
LBBB	Left bundle branch block

Term	Definition
LMS	Left main stem disease
LV	Left ventricular
LVEF	Left ventricular ejection fraction
MCDA	Multicriteria decision analysis
MDM	Multidisciplinary meeting
MDT	Multidisciplinary team
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Myocardial infarction
MLHFQ	Minnesota Living with Heart Failure Questionnaire
N/A	Not applicable
NACSA	National Adult Cardiac Surgery Audit
NEC	Not elsewhere classified
NHSCII	NHS Cost Inflation Index
NHSE	National Health Service England
NICE	National Institute for Health and Care Excellence
NICOR	National Institute for Cardiovascular Outcomes Research
NIPH	Norwegian Institute of Public Health
NMB	Net monetary benefit
NOAC	Non-vitamin-K oral anticoagulant
NR	Not reported
NYHA	New York Heart Association
ODP	Operating Department Practitioner
ONS	Office for National Statistics
PA	Pulmonary artery
PCI	Percutaneous coronary intervention
PPI	Permanent pacemaker implantation;
PSA	Probabilistic sensitivity analysis
PVL	Paravalvular leak
PVR	Paravalvular regurgitation
Q1	Quartile 1
Q3	Quartile 3
QALY	Quality-adjusted life year
RBBB	Right bundle branch block
RCP	Royal College of Physicians
RCT	Randomised controlled trial
RFI	Request for information
RIND	Reversible ischemic neurologic deficit
RR	Risk ratio
RRT	Renal replacement therapy
SAVR	Surgical aortic valve replacement
SD	Standard deviation
SE	Self expanding
SOC	Standard of Care
SSDP	Specialised Service Devices Programme
STS	The Society of Thoracic Surgeons

Term	Definition
SUCRA	Surface under the cumulative ranking curve
TAVI	Transcatheter aortic valve implantation
TEE	Transoesophageal echocardiogram
TIA	Transient ischaemic attack
TOE	Transoesophageal echocardiogram
TTE	Transthoracic echocardiogram
VARC-2	Valve Academic Research Consortium-2
VARC-3	Valve Academic Research Consortium-3
VMD	Valve micro-dislodgement
VSD	Ventricular septal defect
WTP	Willingness to pay

Executive summary

Background: Transcatheter aortic valve implantation (TAVI) is a procedure used to replace a narrowed aortic valve through a blood vessel in the leg (transfemoral) or chest. TAVI is now considered standard of care in patients where open surgery is considered high risk. A total of 11 TAVI devices were included in the Final Scope by NICE for this late-stage assessment (3 balloon-expanding: Myval Octacor, Sapien 3, Sapien 3 Ultra; 8 self-expanding: ACURATE neo2, Allegra. Evolut R, Evolut Pro+, Evolut FX, Hydra, Navitor, Trilogy), which represented the TAVI devices available on NHS Supply Chain as of 21 February 2024. The aim of this late-stage assessment is to evaluate the evidence available for these devices to support procurement and commissioning decisions.

Clinical and technological evidence: The EAG identified 4 network meta-analyses comparing multiple TAVI devices. This evidence was limited as it included devices and generation of devices not listed in Scope, and suffered from lack of transitivity (that is selection of TAVI devices is driven by patient and clinical characteristics therefore combining studies does not enable indirect comparison). The EAG then summarised results from 4 key studies which both compared more than 2 TAVI devices and adjusted for multiple confounders (through study methodology or subsequent statistical analysis), and 3 additional studies which did not adequately adjust for confounders. None were conducted in a UK setting, outcomes were reported up to 1 year; therefore, results may not be generalisable to NHS practice or predict longer term outcomes. Overall, there was a lack of robust published evidence for the comparative effectiveness between the valves in scope, for all clinical outcomes simultaneously, to inform the economic model.

Additional evidence was considered by the EAG looking at differences in outcomes between devices by the same manufacturer and longest available follow-up. The EAG considered that there was a high risk of bias across the published evidence, which casts further uncertainty on the robustness of the conclusions that can be drawn from them. Published comparative evidence was scarce for Trilogy (JenaValve) and Hydra (SMT), meaning that their

clinical performance when compared with the other TAVI devices available on NHS Supply Chain remains uncertain. Clinical Experts have advised that Trilogy is used primarily in aortic regurgitation.

The UK TAVI Registry is a collection of data from all NHS TAVI procedures. Data were made available for procedures that took place between 01 April 2021 and 31 March 2023. The Registry contained in-hospital data for 11,076 transfemoral TAVI procedures. After excluding procedures inserting a TAVI in a native aortic valve with only aortic regurgitation (that is, not stenosis or narrowing), and excluding older generation TAVI devices or TAVI devices that could not be identified or verified, this included data from 7,119 procedures where a TAVI device was placed into a native aortic valve, 263 procedures where the TAVI device was placed into a valve previously inserted surgically (TAVI-in-SAVR) and 27 procedures where the TAVI device was placed into a previous TAVI (TAVI-in-TAVI). Data were analysable for the following 6 TAVI devices in scope for this assessment: ACURATE neo2, Evolut R, Evolut Pro+, Navitor, Sapien 3, Sapien 3 Ultra (Evolut FX was not included in analysis comparing different TAVI devices, because it was used in fewer than 5 procedures). Four TAVI devices were added to the NHS Supply Chain after the collection period and so there was no information on them in the Registry (Allegra, Hydra, Myval Octacor, Trilogy).

Clinical and in-hospital outcomes from the UK TAVI Registry were linked to Hospital Episode Statistics (HES) and Civil Registration of Mortality as provided by the Office of National Statistics (ONS), using hospital, date of procedure, sex, age, and other patient and procedural characteristics and comorbidities to enable tracking of longer-term outcomes by device. Multivariate analysis (accounting for differences in population) of UK TAVI Registry data linked to HES data for all 6 TAVI provided evidence of differences in in-hospital outcomes (stroke, pacemaker implantation and aortic regurgitation, possibly driven by device selection in patients with certain characteristics), but no evidence of a difference in outcomes after discharge. The analysis may be influenced by unmeasured confounders that cannot be adjusted for. Comparing only the 4 self-expanding TAVI devices

demonstrated a difference in 1 in-hospital complication (major vascular complication). The clinical significance of these differences is uncertain. Some patient characteristics (such as surgical risk group, calcium burden and distribution, aortic valve and left ventricular outflow tract) that influence device selection could not be adjusted for because they are not currently recorded in the Registry. Only 6,508 of the 7,028 procedures in England, recorded in the UK TAVI Registry, were successfully linked to a HES record, and of these, 6,270 were undergoing TAVI in a native aortic valve. Only 3,917 (62% of the 6,270) had complete data available and could contribute to the multivariate analysis.

Economic evidence: The EAG used for its reference an existing economic model which compared TAVI with open surgery, which informed NICE NG208 (2021). Its design was adapted to address the decision problem of a late-stage assessment, including comparison of multiple TAVI devices at the same time. Non-device costs were sourced from, and if appropriate, adjusted using, publicly available sources, and device costs were provided by NHS Supply Chain and the Companies. The model parameters were informed by multivariate analysis of the UK TAVI Registry as described in the previous sub-section. The model was used to compute the net monetary benefit of each device for a range of scenarios and sensitivity settings. Probabilistic sensitivity analysis was used to measure the proportion of times that a particular device achieved the greatest net monetary benefit in each model run.

In the base case (82 years at implant, median annular diameter 26 mm for male, 23 mm for female, severe symptoms of aortic stenosis, no other complicating factors), and in most scenarios, the Sapien 3 had the highest proportion with the greatest net monetary benefit among the balloon-expanding devices for males and females. For self-expanding devices, the Evolut R had the highest proportion with the greatest net monetary benefit for both males and females. The EAG note that the results of the economic modelling were impacted by less frequent use of some devices in the NHS at the time of the data extract, and that only data from 2 balloon expanding

devices (Sapien 3 and Sapien 3 Ultra) were available during the time period analysed. This reflects UK practice, where valves more commonly chosen in clinical situations matching these scenarios are more prevalent in the data, leading to narrower confidence intervals for the inputs to the economic model.

Increasing the time horizon had little effect on the relative probabilities of net monetary benefit because most costs are incurred at the time of the procedure and in the early years, and the mortality in the population is high. The probability of having the greatest net monetary benefit was highly sensitive to changes in the price of the TAVI devices, leading to changes in the device with the highest proportion of highest NMB in some scenarios.

Key points for decision makers: The majority of costs in the economic modelling arise from the procedure costs and in-hospital events associated with the initial surgical procedure. The published evidence comparing TAVI devices is subject to bias and limited by short term follow up, whereas the analysis of real-world linked data from the UK NHS is limited by data availability and completeness and subject to different biases, but is still the best available data for the decision problem. Economic modelling using the multivariate analysis from the real-world data is therefore subject to the same limitations. Choice of TAVI valve is dependent upon clinical characteristics; however, the use of net monetary benefit enables appropriate TAVI devices to be compared in any given clinical scenario (to the extent to which data are available). Because of a lack of patient-level data enabling adjustment for population differences, multivariate analysis and subsequent economic modelling were not possible for TAVI devices with no data, or minimal data, in the Registry. This limitation affected those TAVI devices recently added to the NHS Supply Chain (Allegra, Hydra, Myval Octacor, Trilogy), or used in only a few cases (Evolut FX); therefore, their incremental value remains uncertain. The EAG would advise caution in interpreting the economic analyses in isolation. Although Clinical Experts have suggested that centres may have one preferred TAVI device they use wherever possible, the UK TAVI Registry has shown that patient characteristics are significantly different (statistically and clinically) between devices, meaning that clinical features are contributing

to device choice. As the Registry does not capture sufficient detail of the clinical characteristics that contribute to device choice, the EAG analysis needs to be interpreted carefully and draw upon other evidence such as that generated by a multi-criteria decision analysis exercise to determine whether pricing variations between devices is justified.

Overview of EAG Key Issues

Key issue #	Summary of issue	Report sections
1.	Different TAVI devices are indicated and used in different patient groups (for example TAVI placed within a prior failed bioprosthesis) or subgroups (for example, different surgical risk groups which are defined using several different methods, different aortic valve morphologies).	2; 3.1; Table 2
2.	Some manufacturers have multiple valve models that supersede previous models; with technological differences aimed at improving performance. Longitudinal evidence is only available on earlier generation devices where poorer outcomes are expected. Newer device models typically phase out earlier models, however device sizes may vary between models and therefore the populations in which different generations of valves are used cannot be assumed to be exactly equivalent.	Table 2; Table 3; 5.2
3.	The quality of published literature comparing multiple TAVI devices from a single source was generally poor. Few studies attempted to control for different population characteristics between devices, few studies were conducted in a UK setting (therefore likely different baseline characteristics, care pathways, procedures, and aftercare), and the majority only reported short-term (in-hospital or 30 day) outcomes.	5.1; 5.2
4.	Data entry to the UK TAVI Registry is mandatory for all TAVI procedures conducted in England, Wales and Northern Ireland but it does not collect all clinical information that may inform decision to proceed to TAVI, or choice of TAVI device (for example surgical risk, anatomy, valve morphology). This means that use of real-world evidence incorporates confounding by indication which cannot be adjusted for in either the clinical effectiveness or health economic analysis (see also Key Issue 8).	Table 1; 5.3
5.	Data entered into the UK TAVI Registry is self-reported and unvalidated. The data quality of TAVI device model recording was poor within the registry. This required each manufacturer to verify serial numbers to confirm which device model was used. Outcomes captured in the registry post-discharge are restricted to quality of life measures which were almost entirely incomplete in the registry data received by the EAG. Despite this, data from the Registry represents the largest in a UK setting, enabling comparison of TAVI devices.	5.3.1; Appendix C5
6.	The data cut from the UK TAVI Registry (31 March 2023) was before 5 devices were added to NHS Supply Chain. Therefore, the incremental clinical and economic value of these devices in an NHS setting remain uncertain.	Table 2; 5.3
7.	The EAG linked UK TAVI Registry data with Hospital Episode Statistics (HES) with ONS mortality data to obtain longitudinal outcomes (reintervention, stroke, death). However multivariate analysis was only conducted in 3,917 patients (62% of those recorded as having TAVI in the native valve) due to the need for complete cases, which may introduce bias and imprecision.	5.4; 5.5.2
8.	The EAG adapted the economic model from NG208 to permit multi-way comparisons between TAVI devices, however requires extrapolation of short-term data and the parameter values in the economic model do not account for all potential differences in clinical effectiveness (for example, quality of life)	6.2; 6.4

Abbreviations: EAG, External Assessment Group; ONS, Office for National Statistics; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation

1 Decision problem

The decision problem for the late-stage assessment on transcatheter aortic valve implantation (TAVI) was described in the Final Scope, published 11 December 2023. The External Assessment Group (EAG) reviewed and provided comment on the decision problem are as described in the EAG protocol.

2 Technologies

Transcatheter aortic valve implantation (TAVI) is a procedure that involves replacing a heart valve using a narrow flexible tube (catheter) inserted through a blood vessel in the leg or chest. The procedure is carried out under general anaesthesia or under local anaesthesia with or without sedation, and is predominantly undertaken electively with some centres conducting TAVI as a day-case procedure. TAVI is used to treat people with impaired outflow of blood from the heart (aortic stenosis), which is a condition that can lead to heart failure and death. UK prevalence of severe aortic stenosis in people aged 55 years and older in 2019 was estimated to be 1.48% (Strange et al. 2022). Severe aortic stenosis can be treated with surgical aortic valve replacement (SAVR), which requires a sternotomy and cardiopulmonary bypass. TAVI provides a less invasive treatment and is the recommended option for people considered at high surgical risk or for whom SAVR is otherwise unsuitable (NG208).

The TAVI valve comprises an expandable metal alloy stent frame, predominantly either cobalt-chromium, cobalt-nickel, or nickel-titanium (nitinol); however, all contain nickel. This frame suspends either bovine or porcine pericardium tissue leaflets (Santangelo et al. 2022) in either a supra- or intra-annular design (Ali and Blackman, 2019). All currently available TAVI devices have an outer skirt or pericardial wrap that increases surface area contact between the device and the valve which reduces leakage around the valve, also known as paravalvular leak (Chiarito et al. 2022). Aortic regurgitation includes leakage through the valve (transvalvular) and around the valve (paravalvular). When positioned in place, some valves are designed

to expand autonomously (self-expanding), others are expanded by inflating a balloon in the catheter tip (balloon-expanding). A range of valve sizes are available to meet individual anatomical valve size requirements, currently ranging from 20 mm to 34 mm (Table 2), with a 35 mm Navitor (Abbott Medical) valve due for release to the NHS in 2024 (Table 3). The procedure needs a manufacturer-specific loading system (which compresses the bioprosthesis into the catheter) and a delivery system (which enables the user to control deployment) for implantation of the valve, consequently the External Assessment Group (EAG) used the term 'TAVI devices' to encompass the valve and implantation systems and 'TAVI' when referring to the procedure. Features of the delivery and loading systems include deployment mechanisms and profile, which can impact the manoeuvrability and ease of use during TAVI. Features of the TAVI valve also include ability for recapture and reposition (such as, where the valve has been deployed in a suboptimal position), anchors which fix onto native valve leaflets to support valve stability, or locators to support better alignment in the native aortic valve prior to deployment.

The choice of intervention as well as specific valve is determined by the multidisciplinary heart team, which includes cardiologists, cardiac and vascular surgeons, anaesthetists, electrophysiologists, and radiologists (Archbold et al. 2022). The choice of TAVI device may be driven by clinical considerations or technical challenges. For example, use of a valve with supra-annular leaflets may be favourable where there is an existing surgical bioprosthetic aortic valve in situ, self-expanding valves may reduce risk of annular rupture in cases with severe left ventricular outflow tract and annular calcification, or a shorter frame where preservation of coronary access is important (Ali and Blackman, 2019), Table 1

Table 1: Summary of technical challenges, theoretical considerations for valve design (extracted and adapted from Ali and Blackman, 2019)

Patient or anatomic subgroup	Technical challenges	Theoretical consideration for valve design
Degenerative surgical bioprothesis: "valve-in-valve"	Interaction between transcatheter and bioprosthetic valves causes elevated pressure gradients after TAVI. Risk of coronary obstruction.	Supra-annular valves allow a larger effective orifice, resulting in a better haemodynamics (for example, lower post-TAVI gradient).
Bicuspid aortic valves	Increased risk of PVL because of eccentricity, calcification and large annulus. Increased risk of malposition or embolisation because of distorted root anatomy. Increased risk of annular rupture.	Devices with minimal PVL are preferable. Self-expanding valves better able to conform to asymmetric valve orifice and less likely to cause annular rupture. Valves with the ability to be retrieved and repositioned to reduce risk of migration/embolisation.
Severe left ventricular outflow tract and annular calcification	Increased risk of annular rupture. Increased risk of PVL.	Self-expanding valves that reduce risk of annular rupture. Effective mitigation of PVL both to minimise PVL and to obviate the need for post-dilatation which may risk annular rupture.
Pure aortic regurgitation	Absence of calcification renders difficulty in anchoring the device and increases risk of malposition, migration or embolisation.	Devices with an anchoring mechanism independent of calcium. Self-expanding valves less reliant on calcification. Valves with the ability to be retrieved and repositioned, which reduces risk of migration/embolisation.
Mitigating coronary obstruction	Displacement of valve leaflets can obstruct coronary ostia.	Patient anatomy is the dominant consideration, rather than valve design. Valve design that actively controls the deflection of the native leaflets can mitigate risk of obstruction. Valves with the ability to be repositioned in the event of occlusion are preferred.
Preservation of coronary access	Accessing coronary arteries can be challenging after TAVI. Should be a specific consideration in patients with existing coronary artery disease and younger	Low frame height to sit below the coronary ostia. Low-density mesh with large cells enables easier access. Orientation of commissures can impede coronary access.

Patient or anatomic subgroup	Technical challenges	Theoretical consideration for valve design
	patients. Coronary access should be straight forward even in non-TAVI centres and emergency settings (for example primary percutaneous coronary intervention).	
Young patients	Long-term valve durability is essential. May require subsequent TAVI-in-TAVI. More likely to require subsequent coronary access. Greater potential long-term consequences of PVL and conduction abnormalities.	Evidence of long-term durability. Shorter frame and intra-annular leaflets to facilitate TAVI-in-TAVI without risk of coronary obstruction; low frame height and low-density mesh allowing for easier coronary access. Low incidence of PVL/conduction abnormalities.

Abbreviations: PVL; paravalvular Leak, TAVI; transcatheter aortic valve implantation

The 2020 American College of Cardiology and American Heart Association Guideline for the management of patients with valvular heart disease (Otto et al. 2021) states that "the specific choice of a balloon-expanding valve or self-expanding valve depends on patient anatomy and other considerations". The Clinical Experts have advised that the factors that influence decision-making for specific TAVI devices are led by anatomical features, such as calcification, vascular access, surgical risk, and risk of pacemaker implantation, coronary occlusion or disturbance, future, paravalvular leak (PVL) or valve replacement (previous or future) (Appendix G). Four Clinical Experts reported that NHS hospitals routinely have access to at least 1 balloon-expanding and 1 self-expanding TAVI device. There may also be patient preferences for specific devices, see Section 3.1.

This late-stage assessment includes 11 TAVI devices from 8 manufacturers that cover the different expansion methods, different valve materials, and different indications Table 2.

All 11 TAVI devices had valid CE certification for their Class III implantable valve:

- 4 were certified to the Medical Device Directive (MDD) [redacted]. All companies confirmed that they are seeking extension to 31 December 2027 as outlined by MHRA under the revised EU Medical Device Regulation (MDR) transitional arrangements for Class III devices (with the exception of Evolut R where sales are expected to stop at the end of 2024);
- 7 were certified to the MDR [redacted]

The EAG note that the shelf life of the TAVI valves varied:

- 1 year (Myval Octacor), minimum 1 year (Sapien 3, Sapien 3 Ultra, Hydra),
- 18 months (Trilogy),
- 2 years (ACURATE neo2, Evolut R, Evolut Pro+, Evolut FX),
- 3 years (Allegra, Navitor).

Key features of each TAVI device and differences between TAVI devices listed in the Scope and their predecessors were directly obtained from the Company responses to NICE's standard request for information and manufacturer websites and summarised in Table 3. The EAG has made no attempt to verify each manufacturer claim.

Table 2: TAVI devices included within this late-stage assessment

Manufacturer	TAVI valve	Expansion type	Pericardial tissue material	Predominant frame alloy material	Supra- or Intra-annular	Valve sizes (mm)	Delivery system diameter (Fr)	Minimum vessel size for access (mm)	Treatable annulus diameter range (mm, across all valves)	Indicated for high Surgical Risk Group (definition of risk group where reported)	Indicated for intermediate Surgical Risk Group (definition of risk group where reported)	Indicated for low Surgical Risk Group (definition of risk group where reported)	Indicated for TAVI in SAVR	Indicated for TAVI in TAVI	New to NHS Supply Chain Sept 2023 [date added]
Meril UK	Myval Octacor	Balloon	Bovine	Cobalt-nickel-chromium	Intra	20, 21.5, 23, 24.5, 26, 27.5, 29, 30.5, 32	14	5.5	18.5 to 32.7	Yes (STS score ≥4% or clinically defined)‡	Yes (STS score ≥4% or clinically defined)‡	Not explicitly contraindicated	Not explicitly contraindicated (limited experience)	Not explicitly contraindicated	Yes [Sept 2023]
Edwards Lifesciences	Sapien 3	Balloon	Bovine	Cobalt-chromium	Intra	20, 23, 26, {29}	16	5.5, {6.0}	16 to 28	Yes (STS ≥8% or clinically defined)	Yes*	Yes*	Yes	Yes	No [Dec 2017]
Edwards Lifesciences	Sapien 3 Ultra	Balloon	Bovine	Cobalt-chromium	Intra	20, 23, 26	14	5.5	16 to 25	Yes (STS ≥8% or clinically defined)	Yes*	Yes*	Yes	Yes	No [Sept 2019]
Boston Scientific	ACURATE neo2	Self	Porcine	Nickel-titanium (Nitinol)	Supra	23, 25, 27	14	5.5	20.5 to 27.0	Yes (clinical decision deemed suitable for TAVI)	Yes (clinical decision deemed suitable for TAVI)	Yes (clinical decision deemed suitable for TAVI)	No (contraindicated)	No (contraindicated)	No [June 2023]
Biosensors International	Allegra	Self	Bovine	Nickel-titanium (Nitinol)	Supra	23, 27, 31	18	6.0	19 to 28 (16.5 to 28.0 TAVI-in-SAVR)	Yes (STS or EuroSCORE II >8% or clinically defined)	Not explicitly contraindicated	Not explicitly contraindicated	Yes	Not explicitly contraindicated	Yes [Sept 2023]
Medtronic	Evolut R	Self	Porcine	Nickel-titanium (Nitinol)	Supra	23, 26, 29, {34}	14, {16}	5.0, {6.0}	18 to 26, {26 to 30}	Yes (STS score ≥4% or clinically defined)‡	Yes (STS score ≥4% or clinically defined)‡	Yes (STS score <4%, ≥70 years, LVEF >30%)	Yes	Not explicitly contraindicated	No [Jun 2020]
Medtronic	Evolut Pro+	Self	Porcine	Nickel-titanium (Nitinol)	Supra	23, 26, 29, {34}	14, {16}	5.0, {6.0}	18 to 26, {26 to 30}	Yes (STS score ≥4% or clinically defined)‡	Yes (STS score ≥4% or clinically defined)‡	Yes (STS score <4%, ≥70 years, LVEF >30%)	Yes	Not explicitly contraindicated	No [Aug 2021]
Medtronic	Evolut FX	Self	Porcine	Nickel-titanium (Nitinol)	Supra	23, 26, 29, {34}	14, {16}	5.0, {6.0}	18 to 26, {26 to 30}	Yes (STS score ≥4% or clinically defined)‡	Yes (STS score ≥4% or clinically defined)‡	Yes (STS score <4%, ≥70 years, LVEF >30%)	Yes	Not explicitly contraindicated	Yes [Dec 2023]
SMT	Hydra	Self	Bovine	Nickel-titanium (Nitinol)	Supra	22, 26, {30}	18	5.0, {5.5}	18 to 27	Yes	Not explicitly contraindicated	Not explicitly contraindicated	No (contraindicated)	No (contraindicated)	Yes [Sept 2023]

Manufacturer	TAVI valve	Expansion type	Pericardial tissue material	Predominant frame alloy material	Supra- or Intra-annular	Valve sizes (mm)	Delivery system diameter (Fr)	Minimum vessel size for access (mm)	Treatable annulus diameter range (mm, across all valves)	Indicated for high Surgical Risk Group (definition of risk group where reported)	Indicated for intermediate Surgical Risk Group (definition of risk group where reported)	Indicated for low Surgical Risk Group (definition of risk group where reported)	Indicated for TAVI in SAVR	Indicated for TAVI in TAVI	New to NHS Supply Chain Sept 2023 [date added]
Abbott Medical UK	Navitor	Self	Bovine	Nickel-titanium (Nitinol)	Intra	23, 25, {27, 29}	14, {15}	5.0, {5.5}	19 to 27	Yes (STS score >7% or clinically defined)	Not explicitly contraindicated	Not explicitly contraindicated	Not explicitly contraindicated (not evaluated)	Not explicitly contraindicated (not evaluated)	No [Oct 2021]
JenaValve	Trilogy	Self	Porcine	Nickel-titanium (Nitinol)	Supra	23, 25, 27	20	7.0	21 to 27	Yes (STS ≥8% or clinically defined)	Not explicitly contraindicated	Not explicitly contraindicated	Not explicitly contraindicated (not evaluated)	Not explicitly contraindicated (not evaluated)	Yes [Sept 2023]

Key: *Valve only indicated for this surgical risk groups when used with the Commander delivery system and transfemoral, transseptal, subclavian, axillary access route only; ‡High and Intermediate risk groups not defined separately; †assumed indicated as available on NHS Supply Chain; ¶calculated by the EAG based on Company-provided information (18 Fr); {denotes the minimum vessel size associated with specific valve size}; Abbreviations: LVEF, left ventricular ejection fraction; SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgeons operative risk score; TAVI, transcatheter aortic valve implantation

Table 3: Valve characteristics based on Company data

Manufacturer (device)	Company description of unique technology elements from their Request for Information (RFI) and company website.	Technological differences between generations (within same manufacturer)	Newer generations expected within next 6 to 12 months
Meril (Myval Octacor)	From RFI documentation: No difference with other technologies stated. From stakeholder consultation: Device size matrix includes conventional (20, 23, 26 and 29 mm), intermediate (21.5, 24.5 and 27.5 mm) and extra-large (30.5 and 32 mm) diameters. All sizes of Myval Octacor THV are compatible with 14F Python introducer sheath and that all diameters of undeployed devices can be fully retrieved using the 14F Python Myval Octacor THV is a tri-leaflet valve manufactured using bovine pericardium tissue that is decellularized using Meril's proprietary AntiCa treatment.	Earlier generations: Myval From Elkoumy et al. 2023: • 2 rows of identical octagonal cells. same conventional sizes as predecessor (20, 23, 26, 29 mm) and additional intermediate sizes (21.5, 24.5, 27.5 mm) and XL sizes (30.5 and 32 mm). From stakeholder consultation: • The Myval Octacor THV retains the similar short, expanded frame height as that of its predecessor technology (17-21mm) • Myval Octacor THV is manufactured from the same cobalt alloy (MP35N) as before for optimal radial strength and radiopacity.	No updated versions expected within 6 to 12 month timeframe.
Edwards Lifesciences (Sapien 3, Sapien 3 Ultra)	The only FDA and CE marked balloon-expandable valve for the treatment of symptomatic severe aortic stenosis of all surgical risk levels (inoperable, high, intermediate, low risk). The only valve to have specific approval for TAVI-in-TAVI and TAVI-in-mitral valve indications. Delivery system allows for greater steerability to assist implantation in patients with challenging vascular anatomy. The delivery system and accessories are intended to facilitate the placement of the bioprosthesis via the transapical and transaortic access approaches	Earlier generations: Sapien and Sapien XT. From RFI: • First generation Sapien (CE marked in 2007, sold in the UK until 2016), was available in 2 sizes (23 and 26 mm) with 2 different delivery systems (transfemoral and transapical) with 22-24 Fr diameter. • Second generation Sapien XT (CE marked in 2010, sold in the UK until 2020), available in 3 sizes (23, 26, 29 mm), delivery system diameter reduced to 16-20 Fr diameter. • Third generation Sapien 3 (CE marked in 2014), available in 4 sizes (20, 23, 26, 29 mm), additional smaller diameter system (14-16 Fr diameter), an outer skirt added. Fourth generation Sapien 3 Ultra (CE marked in 2018), available in 3 sizes (20, 23, 26 mm), augmented outer skirt.	Sapien 3 Ultra RESILIA (3SUR); CE marked and available via NHS Supply Chain. This includes advanced anti-calcification technology on the bovine pericardial tissue.
Boston Scientific (ACURATE neo2)	Open upper frame with no aortic flare, which allows for implantation of another intra-annular valve without concerns around future coronary access. Supra-annular leaflets and sealing skirt, resulting in lower mean gradients. Top-down deployment with upper and lower crown anchoring to minimise left ventricular outflow tract protrusion, conduction disturbance and rate of permanent pacemaker implantation when compared with other self-expanding valves.	Earlier generations: ACURATE neo (no longer available in the UK market), the Company reported a transition to ACURATE neo2 in 2021. From https://pubmed.ncbi.nlm.nih.gov/36277320/Reardon et al. (2021): *"… both the neo and neo2 valves have a pericardial sealing skirt to reduce paravalvular leak (PVL), the skirt on the ACURATE neo2 is 60% larger, reaching to the waist of the stent. Additionally, the flexible ACURATE neo delivery catheter has been upgraded with a new atraumatic tip design, and when coupled with the low-profile expandable introducer, is able to accommodate a wide range of complex patient anatomies. The ACURATE neo2 also features a new radiopaque positioning marker to enhance visualization and accuracy. Valve sizing remains the same, with the largest valve treating up to a 27 mm annulus, and the addition of a larger valve planned. Valve crimping and loading remains essentially unchanged in the new system.*" "*the enhanced and extended pericardial sealing skirt features a supra-annular flap that actively seals during each cardiac cycle."* From RFI: • Longer positioning tube to improve accuracy during delivery (of benefit in smaller patients) • Shorter insertion aid to make it compatible with the increased height in the valve outer skirt. • Modified shape of distal tip (nosecone) to optimise the stiffness gradient and transition to the guidewire.	[redacted]this will include additional valve size to treat patients with 29 mm annulus diameter, and new loading system to facilitate short loading times.
Biosensors (Allegra)	Uses bovine pericardium for all valve tissues parts (leaflets and skirts), to support long-term durability. The bovine pericardium is treated to reduce calcification potential. Supra-annular valve, which contributes to large effective orifice area and low mean pressure gradient. Low frame height supports use in valve-in-valve procedures. Can be used in annular diameters as low as 19 mm in native valves and 16.5 mm in surgical valves.	No previous versions.	[redacted]

Manufacturer (device)	Company description of unique technology elements from their Request for Information (RFI) and company website.	Technological differences between generations (within same manufacturer)	Newer generations expected within next 6 to 12 months
	Occlusion free deployment technique and permits repositioning and retrieval before complete deployment.		
Medtronic (Evolut R, Evolut Pro+, Evolut FX)	Valves indicated for all surgical risk groups, for TAVI-in-SAVR and for use in bicuspid valves. Supra-annular design optimises blood through the valve. Hour-glass design to reduce thrombosis and stroke rates. Porcine pericardial tissue is half the thickness of bovine pericardium enabling a low delivery profile. Anti-calcification treatment to mitigate calcification in the wall and leaflets of the valves. Can be recaptured up to 3 times up to 80% deployment. Treats the widest range of annular sizes (18-30 mm) of any commercially available TAVI. Patient selection and treatment sections of supplied IFUs refers to transfemoral access, subclavian access and direct aortic access.	Earlier generations: CoreValve, Evolut Pro <u>From RFI:</u> • First generation CoreValve (CE marked in 2007, sold in the UK until 2014), available in 4 sizes (23, 26, 29, 31 mm), anti-calcification treated leaflets, was not recapturable. • Second generation Evolut R (CE marked in 2014), available in 4 sizes (23, 26, 29, 34 mm), recapturable. • Third generation Evolut Pro (CE marked in 2017, sold in the UK until 2023, replaced by Pro+), available in 3 sizes (23, 26, 29 mm), external pericardial wrap. • Fourth generation Evolut Pro+ (CE marked in 2021), updated Pro+ delivery system reduced profile for 23,26,29 mm and increased profile for 34 mm. • Fifth generation Evolut FX (CE marked in 2023) with gold markers for visualisation of implant depth and coronary alignment, Evolut FX delivery system with improved flexibility.	[redacted] Estimated stop of sales of Evolut R end of 2024.
SMT (Hydra)	Flexible tentacles for easy navigation through the aortic arch. Large cell frame size (15 Fr) for easier coronary access. Non-flared inflow part to reduce conduction abnormalities. Extended skirt for reduced paravalvular leak. Recapturable, repositionable, and uses 14 Fr inline sheath.	No previous versions.	No updated versions expected within 6 to 12 month timeframe.
Abbott Medical (Navitor)	Cuff expands to fill calcification-related gaps between the annulus and valve. The only self-expanding valve with intra-annular leaflets. Large cell geometry (valve sizes 23, 25, 27, 29 mm) and intra-annular valve design preserve coronary access for future intervention. Anti-calcification technology resists calcification to improve long-term valve performance. Highly flexible delivery system supporting patients with small vessel access and tortuous anatomies. Less than 80% deployment can be re-sheathed up to a maximum of 2 times and redeployed to allow for optimal placement. The FlexNav delivery system facilitates Navitor valve implantation using transfemoral, subclavian, and axillary access methods.	Earlier generations: Portico (originally CE marked in 2012, sold in the UK until 2022). <u>From Eckel et al. (2023):</u> "*a new and especially active PVL sealing cuff (NaviSeal) that fills and expands during diastole like a parachute.*" <u>From RFI:</u> Technical features that differ to Portico: • Introduction of NaviSeal cuff. • Proprietary fabric maintains lowest delivery profile indicated for 5 mm and 5.5 mm arteries with small and large FlexNav delivery system respectively. • Curved aortic cells to reduce risk of injury to native aortic structures. • Large cell design to minimise coronary obstruction. • Optimised radial-force providing consistent and predictable anchoring and sealing across valve sizes. No changes to the valve leaflets or haemodynamics between Portico and Navitor.	New generation Navitor including radiopaque markers and additional valve size (35 mm) is expected in UK in 2024. This will be introduced through phased transition with both technologies available for a period. At stakeholder consultation, Abbott confirmed that Navitor is now available in size 35, with a treatable annulus diameter range up to 30 mm.
JenaValve (Trilogy)	Optionally, a transoesophageal echocardiogram can be applied during the procedure to check the exact position of the fixation mechanism of the valve. Only medical device approved for treatment of both aortic stenosis and aortic regurgitation. From JenaValve Trilogy brochure: • Indicated for use in patients with native symptomatic, severe aortic regurgitation (AR) or symptomatic, severe aortic stenosis (AS), • "*Alignment – locator technology ensures proper alignment with native anatomy before the valve is deployed.* • *Anchoring – locators anchor the valve by attaching to native leaflets for secure placement and sealing.* • *Deployment – commissure-to-commissure alignment upon deployment is achieved*."	Earlier iteration: JenaValve (CE marked in 2011, Treede et al. 2012). At stakeholder consultation the Company confirmed that the first iteration was the porcine root valve and transapical delivery system which was available from 2009 to 2013, and the second iteration was the Trilogy porcine pericardial valve with transfemoral delivery system available from 2014 to present. <u>From Zaid et al. (2023):</u> • Three locators. • Sealing ring comprises 24 diamond-shaped cells.	Not reported.

Abbreviations: FDA, Food and Drug Administration; PVL, paravalvular leak; RFI, request for information; TAVI, transcatheter aortic valve implantation

Usage in the NHS

In terms of TAVI device availability, the NHS Supply Chain Framework was updated on 18 September 2023, when 4 of 8 manufacturers (Biosensors, Meril, SMT, JenaValve) were added for the first time. The EAG note that an additional TAVI device was subsequently added to NHS Supply Chain in December 2023; Evolut FX (Medtronic), Table 2.

The British Cardiovascular Intervention Society (BCIS) annual audit report for data from 2021 to 2022, reported that devices from some TAVI manufacturers are used more widely within the NHS, with over 60% of TAVI procedures using Edwards Lifesciences devices and 25% using Medtronic devices (BCIS, 2023). Based on NHS reference costs, a total of 5,339 TAVI procedures (representing a combination of TAVI in native aortic valve, and failure of prior bioprosthesis), including 4,577 using a transfemoral approach, were undertaken in the NHS in England between 2021 and 2022. This represented a procedure cost (excluding the cost of the TAVI valve) of £44,115,770 to the NHS (NHS England, 2023; Hospital Resource Group [HRG] codes EY20A-B, EY21A-B). The TAVI valve cost is reimbursed separately under the NHSE High-Cost Tariff Excluded Devices Programme, now known as the Specialised Services Devices Programme (SSDP). In NG208 the average price across TAVI valves was £17,500 (NG208, 2021). As of November 2023, the EAG calculated the weighted average TAVI valve cost (post Specialised Services Devices Programme [SSDP] with rebate using market share) is [redacted].

TAVI-in-SAVR indications

Between 2022 and 2023, 3,623 isolated SAVR procedures were done (National Adult Cardiac Surgery Audit [NACSA], 2024) using biological heart valves. Bioprostheses have limited durability and are expected to degenerate and potentially fail within 10 to 20 years (Dvir et al. 2012); with authors reporting stenosis (42%), regurgitation (34%) or combined stenosis and regurgitation (24%) as indications for further valve replacement. Beaver et al. (2023) reported 99.3% freedom from structural valve deterioration at 7 years

with a Resilia tissue bioprosthesis (Edwards Lifesciences) from the COMMENCE trial (NCT01757665).

Currently, 6 of 11 TAVI devices included in this late-stage assessment are indicated for TAVI-in-SAVR; Sapien 3, Sapien 3 Ultra, Allegra, Evolut R, Evolut Pro+, Evolut FX, Table 2. The Clinical Experts advised that annulus size, coronary access or protection, and haemodynamic performance are key considerations informing the choice of TAVI valve where TAVI-in-SAVR is indicated, Appendix G.

TAVI-in-TAVI indications

A TAVI valve can also be inserted into another TAVI valve, and this can occur at different timepoints. For example, TAVI-in-TAVI can be undertaken during the initial TAVI procedure to resolve acute severe aortic regurgitation or an unretrievable failed device (Giordano et al. 2024a), known as bailout TAVI-in-TAVI, but can also be needed longitudinally (after 1 year since discharge from the initial TAVI) because of valve degradation or deterioration (Capodanno et al. 2017).

TAVI-in-TAVI procedures represent a small proportion of patients undergoing TAVI in the UK, with 0.5% between 2022 and 2023 (NICOR, 2024). As growing numbers of patients undergo TAVI (including patients with lower surgical risk) longer life expectancy, long-term durability, and ability to receive secondary TAVI may become increasingly clinically important (Ali and Blackman, 2019). Landes et al. (2020) reported 212 TAVI-in-TAVI procedures in 63,876 patients (0.33%) receiving TAVI across registries covering 37 centres in Europe, North America, and the Middle East (including 2 UK centres) although the time period was not reported. Overall indications for TAVI-in-TAVI were stenosis (37%), stenosis-regurgitation (33%), and regurgitation (30%). Reasons for intervention were different depending on when the procedures were done (35% within 1 year, compared with 65% beyond 1 year) with higher proportions of stenosis in the latter group (37% compared with 16%, p=0.028). Currently, Sapien 3 and Sapien 3 Ultra are the only devices explicitly indicated for TAVI-in-TAVI. When considering the

separate TAVI-in-TAVI cohort, the EAG will only include devices where this is not explicitly contraindicated (as stated in the device Instructions for Use). Recommendation 6.2.4 of the NICE Health Technology Evaluations Manual (PMG36) enables consideration of evidence for comparator technologies outside regulatory approval, the EAG note this is only where use is considered as part of established clinical practice. The extent and quality of evidence, particularly for safety and efficacy, in this specific emerging subgroup is lacking. The EAG have, however, considered that use of a technology may occur outside of CE-mark indications in other areas of TAVI, such as in a native aortic valve within different surgical risk groups, which would be consistent with established clinical practice.

Four Clinical Experts advised that the proportion of patients receiving SAVR after TAVI would be low (1% to 5%) compared with secondary TAVI (95% to 99%), Appendix G, and SAVR following TAVI has been shown to be independently associated with an increased risk of mortality (Bowdish et al. 2024; Hawkins et al. 2023).

Additional indications

Aortic heart valves typically have 3 leaflets, known as a tricuspid aortic valve, with all TAVI devices included in this late-stage assessment indicated in this population. Non-tricuspid leaflet configurations have been considered within the EAG Protocol (2024). The EAG note that none of the included technologies are indicated for people with a unicuspid aortic valve morphology. Biscuspid aortic morphology is explicitly contraindicated for 2 devices (ACURATE neo2, Allegra), and any leaflet configuration other than tricuspid is explicitly contraindicated for 1 device (Navitor). For the 3 devices manufactured by Medtronic (Evolut R, Evolut Pro+, Evolut FX) their instructions for use state that the use in bicuspid aortic valves is explicitly indicated when the patient is at intermediate or high surgical risk. For the remaining 5 devices, no explicit indication or contraindication of aortic valve morphology is listed in the device instructions for use. The systematic review and meta-analysis by Ueshima et al. (2020) of 11,738 patients reported outcomes from TAVI in 7,291 patients with tricuspid aortic valves compared

with 3,741 patients with bicuspid valves. Additionally, authors compared TAVI outcomes for patients with bicuspid anatomy treated with balloon-expanding (n=367) or self-expanding (n=339) TAVI devices. Mortality at 30 days and 1 year was not statistically different in either comparison, however patients with bicuspid anatomy were at a higher risk of adverse events (conversion to SAVR, bailout TAVI, moderate or severe paravalvular leak, device failure) than those with a tricuspid anatomy. Balloon-expanding devices were associated with lower rates of bailout TAVI and new pacemaker implantation but carried a higher risk of annular rupture. The EAG note that the aortic valve leaflet configuration is not captured within the UK TAVI Registry therefore are not able to identify a bicuspid subgroup within the Registry, nor assess whether devices are used within their indications for this population. However, the EAG note that this represents a small proportion of patients in the general population (Hoffman and Kaplan, 2002).

The EAG note that 3 of the 11 TAVI devices included in the late-stage assessment (Sapien 3, Sapien 3 Ultra, Allegra) are indicated where mitral valves have also been replaced. The EAG identified two papers which reported TAVI in patients with prior mitral valve replacement (Rogers and Thourani 2018; Salaun and Pibarot 2019). While non-aortic valve replacements are out of Scope of this late-stage assessment (and therefore have not been explored further by the EAG), the EAG acknowledge that this may influence TAVI device choice, as an incremental benefit of a technology and may impact costs.

Five devices were not indicated for use in a low surgical risk group, four were not indicated for use in an intermediate surgical risk group; however, the EAG note that the definition of surgical risk varies across devices. Where contraindications were not explicitly identified within the instructions for use or from the Company responses, the EAG have assumed that the devices are indicated.

Three of four Clinical Experts noted that the late-stage assessment should include all patients with aortic stenosis regardless of the cause, for example

including patients with rheumatic or congenital aortic stenosis, although one Expert noted that evidence is likely to be lacking and the numbers of patients may be too small to draw conclusions (Appendix G).

One Expert reported that the Trilogy (JenaValve) would be used where there is no calcium present on the valve (Appendix G); the EAG note that the device brochure indicates that Trilogy can be used in the absence of calcium in patients with aortic regurgitation, however according to the device instructions for use, received by the EAG on 06 March 2024, patient selection should include "acceptable calcification as identified per appropriate imaging modality". The EAG note from the Trilogy instructions for use that this is the only TAVI device explicitly indicated for patients with native severe aortic regurgitation in the absence of aortic stenosis.

3 Clinical context

NICE produced its original Interventional Procedures Guidance (IPG) on transcatheter aortic valve implantation (TAVI, IPG421) in 2012. TAVI is currently recommended for people who are at high surgical risk or where surgical aortic valve replacement (SAVR) is considered unsuitable (NG208, IPG586). The decision to proceed with intervention, such as the choice between TAVI and SAVR, is made by a multidisciplinary (MDT) heart team (Archbold et al. 2022), which includes interventional cardiologists, cardiac surgeons, imaging healthcare professionals, and electrophysiologists. Recommendation 1.2 of IPG586 and IPG653 note that details of all TAVI procedures should be entered into the UK TAVI Registry and that data entry is mandated (Ali et al. 2023).

While TAVI was determined to be clinically effective in all surgical risk groups, section 1.5.3 of the NICE Guideline NG208 concluded that "TAVI is not cost-effective for people at low or intermediate surgical risk at the current list price". However, in January 2023 (updated May 2023), NHS England (NHSE) published a commissioning policy position statement broadening access to TAVI for eligible patients with intermediate or low SAVR risk to alleviate pressures on local systems in supporting elective performance. In response to

this policy change the Society for Cardiothoracic Surgery in Great Britain & Ireland, The Royal College of Surgeons, submitted a response to the National Clinical Director for Heart Disease at NHS England, on 28 February 2023. This response acknowledged the concern for long waiting times following the pandemic and ongoing staffing shortages but stated the policy change was contrary to NICE guidance, not clinically appropriate and may increase patient risks if subsequent surgery was required. Three issues raised by the Society for Cardiothoracic Surgery in Great Britain and Ireland were summarised in a Bulletin (August, 2023):

- *"A robust, quorate, aortic valve multidisciplinary meeting (MDM), with all appropriate specialists present, should be employed for patients at clinical equipoise between TAVI and surgical aortic valve replacement (SAVR) following the Joint Societies MDM guidance (Attachment 1 – Getting the best from the Heart Team).*

- *Clinical decisions made in a patient's best interest in line with national guidelines should not be altered solely based on waiting times, given that in many hospitals waiting times for TAVI are longer than for SAVR.*

- *The NHSE interim position statement should not be used to inappropriately redirect patients towards TAVI who would otherwise have undergone SAVR."*

Four Clinical Experts estimated that most TAVI procedures are in high risk patients (between 40% to 80%) although 1 Expert noted that equal proportions of patients would be of intermediate and high surgical risk. The Clinical Experts estimated that between 0% and 20% of patients classed as low surgical risk received TAVI in the 12 months prior to the NHSE position statement, with an increase of between 5% and 20% in the 12 months following, Appendix G. The Clinical Experts report that the TAVI population has remained the same in terms of high or intermediate surgical risk patients taking priority over low risk patients on the TAVI waiting lists, thus low risk patients may face longer waits for TAVI than for SAVR, some patients may

opt for reinstatement to surgical lists because of deteriorating symptoms unless there is very strong patient preference Appendix G.

The Clinical Experts have advised that use of TAVI is also emerging in people with severe aortic stenosis who present as asymptomatic (Table 1). TAVI is also recommended with standard arrangements as a less invasive treatment option to SAVR where a previous bioprosthetic aortic valve has failed (IPG653), known as valve-in-valve TAVI (for device indications for in-valve TAVI, see Table 2). Decision-making about the most appropriate intervention happens at an MDT meeting (NICE Final Scope, 2023). The proportion of patients undergoing a secondary aortic valve intervention using a TAVI device is small (between 3% and 5% annually between 2013 to 2022 requiring TAVI for aortic bioprosthetic valve failure, British Cardiovascular Intervention Society [BCIS], 2023), the expansion of TAVI use in low and intermediate surgical risk groups will likely result in an increase in this proportion going forward.

The Clinical Experts have advised that there may be occasions where only 1 TAVI device is suitable, Appendix G. The Clinical Experts also advised that while many patients can be treated with any TAVI device, there are some subgroups, such as those with a small annulus, who may be better suited to a particular device for its specific features, such as expansion type or intra- or supra-annular leaflets (Appendix G; Herrmann et al. 2024).

The 2021 Getting It Right First Time (GIRFT) Report for Cardiology acknowledged high levels of price variation across the specialty. GIRFT considered efficiency benefits, relating to financial, administrative and inventory management, of more than £35m to £40m per year could be achieved by ensuring procurement and NHS Supply Chain activities are clinically led and product choices are evidence-based with safety and outcomes unaffected by product change. GIRFT explicitly stated that TAVI should be done under conscious sedation via a transfemoral route as the default, enabling 4 straight-forward cases on a full day list.

3.1 *Equality issues*

Equality considerations for TAVI were described in IPG586 and NG208, within the supporting equality impact assessment scoping document (NICE, 2023) and within the EAG Protocol (2024) for this late-stage assessment. Multivariable logistic regression adjusted for age, region and comorbidity applied to HES data linked to primary care data revealed significant differences in timely AVR based on sex, black or South Asian ethnicity, and levels of social deprivation (Rice et al. 2023).

The EAG identified evidence of adverse events (in-stent restenosis, device syndromes, flow diverter valve deformity also referred to as 'fish-mouthing') from nickel hypersensitivity associated with endovascular coronary and structural heart procedures, although not specific to TAVI (Guéroult et al. 2022). The EAG note that all TAVI devices included within this assessment contain nickel and are contraindicated in patients with nickel allergy; the prevalence of an allergy or hypersensitivity to nickel was estimated to be between 8% and 19% in 2010 and disproportionately affects females (Ahlström et al. 2019; Schuttelaar et al. 2018). Four Clinical Experts noted that screening for nickel allergy is not routinely done, nor does it influence the choice between TAVI devices or TAVI compared with SAVR as an intervention, Appendix G. The EAG contacted all 8 manufacturers to determine the proportion of nickel allergy adverse events reported for their TAVI device, 7 of which responded by 10 May 2024. Biosensors confirmed that they had no record of nickel allergy adverse events related to their Allegra TAVI device. Meril reported [redacted]. Abbott and SMT were not aware of any available data for the Navitor or Hydra TAVI devices. Edwards Lifesciences confirmed that no adverse events related to nickel allergy have been reported to the US Food and Drug Administration Manufacturer and User Facility Device Experience database between March 2019 and February 2024 related to their Sapien 3 or Sapien 3 Ultra devices. The Company also noted the poster presentation of a case report by Anderson et al. (2023), which reported successful implantation of the Edwards Lifesciences Sapien 3 valve without any notable adverse reactions in a patient with documented

nickel allergy and positive patch test to nickel and cobalt. This study reported that “according to the Agency for Toxic Substance and Disease Registry, the daily nickel dose rate from food intake is 170 micrograms per day, which is at least 10,000 times higher than what was demonstrated to be released from the CoreValve bioprosthesis during phase II in-vitro testing”. Medtronic searched in their complaints database across all Evolut TAVI devices since 2018 [redacted] Similarly, Boston Scientific reviewed their complaints database for the ACURATE neo2 TAVI device [redacted] Therefore, the EAG did not consider nickel allergy of TAVI devices as a significant outcome that would contribute to the economic evaluation within the context of this late-stage assessment.

The EAG consulted with the Clinical Experts who did not report any other equality considerations for this late-stage assessment. One Clinical Expert noted that several datasets show disproportionately lower implant rates in females and speculated that this is likely related to referral patterns and diagnostic tests (Appendix G). Another Clinical Expert advised that this could be related to anatomical factors such as small femoral vessels for access and small aortic annuli where TAVI may be challenging or technically not feasible. Religion or belief, and sex are protected characteristics under the Equality Act (2010).

4 Methods

4.1 Clinical and technological evidence

The objective of identifying and selecting the clinical evidence is twofold:

- To provide inputs for the economic model as part of this evaluation.
- To provide evidence for the comparative clinical effectiveness of transcatheter aortic valve implantation (TAVI) devices in Scope of this late-stage assessment.

To search for published and real-world evidence relevant to the decision problem, the EAG followed the Evidence Synthesis section (section 3) of the published protocol (EAG Protocol, 2024) for this late stage assessment.

Following the hierarchical approach described in the protocol, the EAG considered sources of UK real-world data and requested patient-level data from the national UK TAVI Registry, a mandatory registry which collected information from all TAVI procedures conducted across England, Wales and Northern Ireland. These data were linked to longitudinal outcomes from the Hospital Episodes Statistics (HES) database. Details of the methods are described in sections 4.1.2, 4.1.3 and 4.1.4.

Following the protocol, the EAG also searched the literature for network meta-analyses which informed the relative effectiveness of devices and made targeted searches for studies involving devices where UK real-world data were lacking. These methods are described in section 4.1.1.

The EAG sent 2 sets of questions to 8 Clinical Experts (Appendix G), and 2 versions of the EAG report were spent to Specialise Committee Members for comment. Feedback have been summarised in a narrative form within this report, however no formal elicitation techniques were included in the development of this EAG assessment report.

4.1.1 Published evidence

The EAG searched for systematic reviews with network meta-analyses where multiple TAVI devices were compared. Network meta-analysis were critically appraised using ISPOR guidelines (Appendix B2), and provided a narrative summary of the key results and limitations.

The EAG noted that 4 of the 8 manufacturers were added to NHS Supply Chain after June 2023 (Table 2), and therefore did not have data included within the UK TAVI Registry that could be used to inform economic modelling. The EAG made targeted searches for other national (non-UK) TAVI registries and for peer-reviewed published evidence for those devices. These searches were supplemented by requesting published longest-term evidence and

comparative evidence against other similar TAVI devices directly from the Companies. The EAG considered the relevance of the published evidence against current NHS clinical practice and the appropriateness for use within the economic evaluation. An acknowledged limitation is that this evidence was not identified from systematic searching across all manufacturers (and is therefore subject to bias).

The EAG also conducted pragmatic and targeted literature searches (based on device name) to identify published peer-reviewed comparative evidence to inform potential uncertainties in clinical performance. The EAG considered published evidence sources provided by the Companies as part of the standard NICE request for information and through direct correspondence. All Companies were requested to provide peer-reviewed published evidence supporting their longest-term follow-up, comparative evidence against other TAVI devices in Scope of this assessment and any non-UK registries capturing evidence on their device. The EAG acknowledge that this approach was not equivalent to a systematic search for each device, however a pragmatic approach was taken because of the broad volume of evidence in TAVI and timescales of this late-stage assessment.

As data on newer generation devices were lacking, the EAG also considered comparative and long-term evidence from older generations to support decision-making. This approach is limited as the Companies had stated technological differences between generations (described in Table 3) and there is existing evidence suggesting differences in clinical outcomes between TAVI device generations (EAG Protocol, 2024; section 5.2.6). It was not feasible for the EAG to systematically search and sift evidence related to all older generations of TAVI devices for each manufacturer listed in the Final Scope. Instead, the EAG took a pragmatic approach, reviewing the published evidence provided by the Companies where more than 2 devices were compared. This was supplemented by additional focused searches of national registries identified from scoping (including the Austrian, Belgian, Brazilian, French, German, Israeli, Italian, the Netherlands, Swiss, US registries), and selected publications with the greatest number of TAVI devices compared,

largest sample size or longest follow-up. Evidence comparing different generations of devices by the same manufacturer listed in the Final Scope were also considered to determine the generalisability of long-term evidence of older generations.

The EAG excluded publications that reported in-vitro or lab-based studies, or where all outcomes were not reported exclusively for interventions in Scope (unless reporting adverse events that could be applicable to TAVI procedures in general). Where multiple publications were available for a technology, the EAG prioritised studies within a UK setting, comparative evidence against the greatest number of TAVI devices in Scope, longest follow-up data, largest sample size, or reporting adverse events. Because of the time restrictions for the late-stage assessment the EAG did not approach corresponding authors for clarification where the EAG had identified potential cases of overlap of patient groups between published papers or where information was not explicitly reported (such as inclusion criteria, proportion of use in specific subgroups). Where no comparative evidence was available for a TAVI device in Scope, including for predecessor devices, non-comparative evidence was also considered and summarised using the same prioritisation methods applied to the comparative evidence.

Due to time constraints and large volume of evidence for TAVI, the EAG focused on tabulation of evidence relating to TAVI implantation into the native aortic valve, which represents the majority of procedures in the UK TAVI Registry (96%, NICOR, 2024).

The EAG applied the hierarchy of published evidence, prioritising data source where more than 2 TAVI devices were compared and where confounders could be adjusted for. As patient characteristics inform the most appropriate TAVI device to use during the procedure (see Table 1), the EAG only considered critical appraisal for studies comparing TAVI devices by different manufacturers where the study design incorporated adjustment for baseline differences in and in studies comparing devices from the same manufacturer with the largest sample size. Critical appraisal of the selected studies was

conducted by the EAG using ISPOR good research practices for network meta-analysis (Jansen et al. 2011), the Cochrane Collaboration's tool for assessing risk of bias in randomised trials (Higgins et al. 2011), and the Joanna Briggs Institute (JBI): Critical Appraisal Checklist for Cohort Studies (Joanna Briggs Institute, 2017), (Appendix B2). Additional published evidence identified and considered in Scope but not selected as key evidence is summarised in Appendix B3. Evidence identified and excluded as out of Scope of this late-stage assessment has been tabulated in Appendix B4.

The EAG also summarised adverse events, device usability, and additional subgroup outcomes that were incidentally identified from published evidence (Sections 5.2.3, 5.2.4, 5.2.5); however, an acknowledged limitation is that these were not identified from systematic searching across all manufacturers (and therefore subject to bias).

Where comparative evidence was lacking for a device, the EAG summarised ongoing studies from the Company completed requests for information. The EAG did not conduct a comprehensive search of ongoing studies related to each TAVI device in Scope as this would not have been feasible within the timescales of this late-stage assessment.

4.1.2 UK TAVI Registry

A request for patient-level and aggregate data from 01 April 2021 onwards was submitted to NICOR (22 December 2023). The EAG received patient-level data from the UK TAVI Registry managed by NICOR, on 05 March 2024 for all TAVI procedures undertaken in England, Wales, and Northern Ireland between 01 April 2021 and 31 March 2023, which represents the latest validated data in the registry.

Data entry into the UK TAVI Registry is mandated (Ali et al. 2023), but the BCIS latest audit report for 2021-2022 reported that as of 27 September 2022, coverage by centre was 88.1% (37 of 42 centres), and coverage by procedure was 85.8% (6,520 TAVI procedures entered in the registry compared with the 7,601 procedures declared by centres in response to a survey). The data

entered by sites is self-reported and no external data validation takes place. Mean data completeness in the latest annual UK TAVI Registry audit for 2022 to 2023 across all data fields is 88.0%, ranging from 65.1% for post-procedure valve indices (prior to discharge) to 100.0% for date and time of operation (NICOR, 2024).

Ethics

Data were collected as part of a mandatory UK TAVI audit, and all patient-identifiable fields were removed by NICOR, with only pseudonymised data sent to the EAG. As analysis within the context of this late-stage assessment was considered a national service evaluation, formal ethical approval was not needed, and national data opt outs were not applied.

Cohort identification

Inclusion:

- All procedures within the UK TAVI Registry with a procedure date between 01 April 2021 and 31 March 2023.
- On inspection of the data, the EAG found that the TAVI device used was poorly completed and of low quality: 1,056 (7.3%) procedures reported using TAVI devices that were not available for sale in the UK during the audit period, 949 (6.7%) procedures were missing device manufacturer and model, and 71 (0.5%) had invalid combinations of device manufacturer and model. For context, the Clinical Lead advised that poor reporting of device model in the registry was likely a consequence of local reporting systems not updating device model options when uploading to the national system (as such, earlier generation devices may be selected even when a later generation device was used). To address this the EAG extracted the serial numbers reported in the Registry for each manufacturer (including those with similar pattern) and asked each manufacturer to verify the device model used in each case. Serial numbers where the manufacturer was unknown or missing were sent to each manufacturer. It is important to note that only devices from Abbott,

Boston Scientific, Edwards Lifesciences and Medtronic were in the Registry after data cleaning, and that each of these 4 Companies verified device models by serial number and returned this information to the EAG (Abbott and Boston Scientific: 23 May, Edwards Lifesciences: 24 May, Medtronic 05 June). Abbott and Boston Scientific also returned generic rules that could be applied to their serial numbers such that they could be cleaned at data entry to the UK TAVI Registry (which the EAG shared with NICOR to support improvements in data quality). The EAG restricted detailed analysis to the named devices listed in the Final Scope representing the latest versions available in the NHS. The EAG ultimately analysed data from each device separately, rather than combining by manufacturer, to avoid older devices (likely to have been used more frequently in the UK TAVI Registry, and likely to have poorer outcomes) adding extra weight to the analysis. Clinical Experts advised that they typically choose the newest version of a device, unless the size needed is not available (for example, Edwards Sapien 3 Ultra is not available in a 29 mm size). The EAG did not compare balloon- and self-expanding TAVI devices because the Sapien 3 and Sapien 3 Ultra are the only balloon-expanding TAVI devices available in the Registry, and the 2 expansion types are used in patients with different characteristics. If the analysis were to be repeated in the future, when a greater number of TAVI devices may have data available in the UK TAVI Registry, it is important to note that Clinical Experts have advised that Trilogy is primarily used in cases of aortic regurgitation, rather than aortic stenosis.

Exclusion:

- Procedures for which the device manufacturer was in Scope, but model was unknown or not verified by serial number.
- Procedures with unknown manufacturer where the model was not verified by serial number.
- Procedures which used a non-transfemoral percutaneous access route which represented a minority of TAVI procedures (less than 8% between

2021 and 2022 [BCIS 2021-22 report], and less than 5% between 2022 and 2023 [NICOR, 2024]) with known differences in patient outcomes (univariate analysis in Heathcote et al. 2023). The EAG note that Getting it Right First Time (GIRFT) recommend that patients being treated under conscious sedation via the transfemoral route should be the default, allowing for 4 straightforward cases on a full day list (GIRFT, 2021).

- Procedures missing aortic valve pathology, valve mean pressure gradient (mean difference in pressure between sides of the valve), and aortic valve area. This would prevent the EAG being able to restrict to a population of aortic stenosis (when TAVI was implanted in the native aortic valve) using the definition from the American College of Cardiology/American Heart Association ACC/AHA 2006.

- Procedures with no confirmation of successful or unsuccessful deployment of valve.

- Procedures carried out in a private hospital; not representative of NHS practice.

- Procedures carried out as a proctored case. These supervised cases could either represent new operators on the initial learning curve receiving training to achieve competency, or complex cases or anatomy that needs extensive expertise to ensure positive clinical outcome; not considered representative of NHS practice.

- The EAG restricted to the index procedure (earliest within the study period) for each patient. Duplicated procedures in the dataset (NICOR advised that some procedures were included with a procedure start time of 00:00 and included a second entry with the correct start time, and all other data identical).

- The EAG also excluded procedures that used a device which was explicitly contraindicated for that use (for example ACURATE neo2 used for TAVI-in-TAVI or TAVI-in-SAVR, see Table 2).

Details on cohort identification are provided in Appendix C1.

Three Clinical Experts confirmed that the population of patients undergoing TAVI has remained broadly the same before and after the NHSE position statement released in January 2023 (Appendix G). This is supported by other published UK data. A total of 1,063 patients with severe aortic stenosis were entered into the Mater TAVI database in Ireland (including one private and one university hospital) which reported no statistical difference in age or surgical risk (as determined by Society of Thoracic Surgeons (STS) scores less than 4%, between 4% and 8% and greater than 8%, and EuroSCORE II) across 5-year tertiles, incorporating TAVI procedural data from 2008 to 2022 (Tanner et al. 2024). As the NHSE position statement was released near the end of the data extract received by the UK TAVI Registry (data included up to 31 March 2023), the EAG determined changes in patient case-mix by comparing patient demographics that contribute to the EuroSCORE II surgical risk score between financial years (01 April 2021 to 31 March 2022, and 01 April 2022 to 31 March 2023; Appendix C3). The EAG note that pulmonary hypertension and active endocarditis are two components which contribute to the EuroSCORE II which are not recorded in the current UK TAVI Registry dataset, and that data completeness of each component is variable, thus preventing robust calculation of the EuroSCORE II retrospectively. After accounting for multiple hypothesis testing, there were statistically significant differences for patient populations between 2021 to 2022 and 2022 to 2023 financial years for 4 components: poor mobility (94.2% compared with 86.9%; data completeness: 20% so interpreted with caution), previous cardiac surgery (14.4% compared with 11.6%), poor LVEF (71.8% compared with 75.2%), NYHA class III or IV (75.6% compared with 72.6%).

The data were split into 3 separate cohorts, with additional criteria that procedures placing TAVI in a native aortic valve must be in patients with aortic valve stenosis, identified either by completion of the aortic valve pathology field (noting that this is multiple choice, and may include regurgitation), or aortic valve mean gradient greater than 40 mmHg, or valve area less than 1 cm2. For TAVI procedures after previous TAVI or SAVR (that is TAVI-in-TAVI,

or TAVI-in-SAVR), no such restriction was applied, such that aortic regurgitation without indication of stenosis was a valid valve pathology. For a procedure to be considered TAVI-in-SAVR, data must have been entered that the patient had no previous TAVI and that their valve aetiology was bioprosthetic. Procedures placed into the TAVI-in-TAVI cohort were in patients either recorded as having had previous TAVI in the relevant field, or with a date given for previous TAVI. Where a single TAVI device fails and cannot be retrieved during surgery, or when there are sub-optimal results (for example acute aortic regurgitation), an additional TAVI device can be inserted within the same procedural admission (Giordano et al. 2024a). Where a date of previous TAVI was recorded and this was the same as the date of the procedure, this was assumed to relate to a bailout procedure and therefore reassigned as being a TAVI in a native aortic valve, with the bailout procedure treated as an outcome.

Cleaning

Data fields were formatted against the data fields specification (v4.09) available on the NICOR website, with data reclassified as missing if they were outside of the allowed upper and lower limits, Appendix C2. Because some covariates were potentially associated with one another (for example: sex, height, valve diameter, valve area, valve size), and the plausibility that data were missing at random was uncertain (Sterne et al. 2009) multiple imputation was not used to correct for missing data for each variable in isolation.

The EAG also reviewed the UK TAVI Registry data fields against standardised endpoint definitions for aortic valve clinical research as defined by the Valve Academic Research Consortium (VARC-3, 2021), Appendix C4. The EAG noted that a number of outcomes were missing (for example heart failure related hospitalisation subsequent to TAVI) or were partially captured (for example neurological events captured up to discharge did not include TIA) in the Registry. The extract of data from the UK TAVI Registry also included a Logistic EuroSCORE data field, which was calculated by NICOR based on availability of data from other recorded data fields. This data field

was considered by NICOR as poor quality and therefore not included in analysis by the EAG because not all parameters that contribute to Logistic EuroSCORE are available in the Registry (for example endocarditis, pulmonary hypertension), preventing robust calculation, and there was a large amount of missing data (64%). As it was unclear whether the data were missing at random, including this variable in analysis would have introduced potential bias. Clinical Experts also advised that EuroSCORE is not routinely captured in clinical practice, and that the EuroSCORE may not directly translate to TAVI risk because of clinical factors not included in the tool such as frailty, porcelain aorta, and previous chest radiation, with further specific issues in elderly patients (SEC Working Group for the 2017 ESC/EACTS Guidelines for the Management of Valvular Heart Disease, 2018).

In cases where data were available and valid, the EAG calculated body mass index (BMI, from height and weight data fields), creatinine clearance (from creatinine, weight, age, and sex), and length of hospital stay (from admission and discharge dates).

Analysis

Because the patient and procedural characteristics differ between TAVI in native aortic valve, TAVI-in-TAVI and TAVI-in-SAVR, these were treated as separate cohorts in the analysis. Data were treated in the aggregated form (TAVI in native aortic valve, TAVI-in-TAVI and TAVI-in-SAVR combined) to enable comparison with the NICOR annual report as part of data validation. Data from the Registry were expressed as mean (95% CI), mean (SD), median (first quartile, third quartile), median (range), percentage or distributions (ordinal or categorical factors), where appropriate. The cleaned data fields described previously were used to tabulate the patient characteristics, procedural characteristics, and in-hospital outcomes of interest (noting that post-discharge outcomes are sparse in the Registry). The EAG reported the aggregate total number of hospitals using each TAVI device and reported the mean TAVI centre volume, however the EAG did not name specific hospitals to protect this commercially sensitive information.

Differences between cohorts (native aortic valve, TAVI-in-TAVI, TAVI-in-SAVR) were tested using chi-square test, Fishers exact test (using a simulated p-value from Monte Carlo simulation) or Kruskal-Wallis where appropriate. Holm-Bonferroni correction was applied to adjust the significance level (p=0.05) to account for multiple hypothesis testing in univariate analysis. Scripts for applying eligibility criteria, data cleaning, processing and statistical analysis were written using statistical programming language R.

4.1.3 Hospital Episode Statistics (HES)

The EAG noted that long-term evidence for TAVI was lacking within NG208 and that the UK TAVI Registry data focuses on in-hospital outcomes only. Because of this the EAG identified a cohort of TAVI patients in England from the Hospital Episode Statistics (HES) database using clinical codes. Linkage of HES and UK TAVI Registry data was completed to identify longer-term outcomes beyond discharge to inform the economic modelling.

An aggregated TAVI cohort (across all TAVI devices) of procedures undertaken in NHS hospitals across England were identified and followed in the Hospital Episode Statistics (HES) Admitted Patient Care dataset, linked to the Civil Registrations of Deaths as provided by the Office of National Statistics). The aim of this analysis was to provide an average that represented current TAVI care in the NHS, which could be used to determine the coverage and representativeness of the UK TAVI Registry and determine longer-term outcomes that were not captured in the Registry that could be extrapolated for subsequent use in an economic evaluation. For a high-level summary of the 2 real-world evidence sources, see Table 4.

Ethics

Data were available as pseudonymised data extracts supplied under the Data Access Request Service agreement (DARS-NIC-170211-Z1B4J) to the Newcastle EAG; therefore, formal ethical opinion was not sought.

Cohort identification

The initial cohort was identified from the HES Admitted Patient Care (APC) dataset with admission dates between 01 April 2021 and 31 October 2023 (latest data available) using procedure and diagnosis codes (see Appendix D1). Episodes of care including TAVI were aggregated into spells (or admissions) and each patient longitudinally followed in APC, Critical Care, and Civil Registration of Mortality (formerly Office for National Statistics, ONS) until 31 October 2023. Each patient was also retrospectively followed in APC as far back as 01 April 2007 to identify prior cardiac surgery and prior diagnoses.

Cleaning

Data fields were formatted against the NHS Data Dictionary available on the NHS Digital website. Additional cleaning rules were applied (see Appendix D1). The EAG also reviewed the data fields from HES APC against standardised endpoints defined by VARC-3 (2021), Appendix D2.

Analysis

Patient demographics (age, sex, presence of diabetes, prior diagnoses of myocardial infarction [MI], stroke or transient ischaemic attack [TIA] and conduction abnormalities or arrhythmia, prior coronary artery bypass grafting [CABG], prior percutaneous coronary intervention [PCI] or prior dialysis), in-hospital outcomes (length of hospital stay, length of intensive care unit [ICU] stay, pacemaker implantation, vascular complications, bleeding, stroke, death) and longitudinal outcomes occurring within 30 days, 1 year and 2 years of discharge (subsequent aortic valve intervention, pacemaker implantation, stroke, death) were reported for the extracted cohort (see Appendix D3). When reporting demographics and outcomes in tables, it was assumed that full details of diagnoses and procedures were available. For other data items, the number of patients for which data was available (that is, not missing) is reported. Data items captured by the 2 real-world evidence sources were summarised, and patient demographics, administrative data (admission date, length of stay, admission method) and in-hospital outcomes were compared descriptively, for the same period, as part of data validation checks.

Analysis was undertaken in line with that reported for the UK TAVI Registry (see Section 4.1.2) except for between-TAVI device comparisons because this information is not captured in HES, and separate cohorts because historic procedures before 2007 would not be captured.

Kaplan-Meier analysis was also undertaken to report longer-term outcomes at 30 days, 1 year and 2 years, accounting for variable patient follow-up (including number of events and number at risk at these timepoints), which could be extrapolated for use in long term economic modelling. Patients were followed from the date of discharge after their TAVI procedure until the date of the event of interest or death (whichever was earlier). All-cause mortality was reported for deaths during the TAVI procedural admission or within 30 days of discharge. In line with standardised VARC-3 endpoints, the main cause of death reported in the Civil Registration of Mortality was dichotomised into major cardiovascular causes and other causes, including non-major cardiovascular causes (using ICD10 codes reported by Joshy et al. 2015). The type of cerebrovascular event was categorised (haemorrhagic, ischaemic, TIA) by diagnosis code (Appendix D1).

Table 4: Real-world evidence sources of clinical and technological evidence used to inform the economic modelling

Study name, design and location	Intervention(s) and comparator	Participants and setting length of follow-up	Relevant outcomes	Limitations
UK TAVI Registry (patient-level data; received 05 March 2024). NHS hospitals in England, Wales and Northern Ireland.	Manufacturers listed in NICE Final Scope included, however quality and completeness of device model was poorly reported therefore serial numbers sent to Companies to verify device model used: • Edwards Lifesciences (Sapien 3, Sapien 3 Ultra), in Scope for all cohorts • Abbott Medical (Navitor), in Scope for all cohorts • Boston Scientific (ACURATE neo2), in Scope for TAVI in native aortic valve only • Medtronic (Evolut R, Evolut Pro+), in Scope for all cohorts	Cohort identification 01 April 2021 to 31 March 2023 (latest validated data). Three cohorts identified: • TAVI in native aortic valve • TAVI-in-SAVR • TAVI-in-TAVI	In-hospital outcomes: Total length of hospital stay, pacemaker implantation, vascular complications, bleeding, stroke, new renal replacement therapy, reintervention, death. Out-of-hospital outcomes: New York Heart Association (NYHA) dyspnoea and Canadian Cardiovascular Society (CCS) angina status at 1 and 3 years recorded in the Registry but poorly reported.	UK TAVI Registry captured in-hospital outcomes only. Surgical risk not recorded in the Registry (unable to conduct subgroup analysis). Aortic valve jet velocity not recorded in the registry (definition of aortic stenosis based on recorded pathology, mean gradient >40 mmHg, or aortic valve area <1 cm2). Data poorly reported for some fields, invalid data included outside of allowed limits, and invalid combinations of TAVI device manufacturer and device model included. Issue known to NICOR where some procedures have 2 records, 1 with a procedure time of 00:00 and another with the correct time, some records from different patients have the same pseudonymised NHS number, and in cases where this is missing, all procedures from the same hospital have the same ID.

Study name, design and location	Intervention(s) and comparator	Participants and setting length of follow-up	Relevant outcomes	Limitations
Hospital Episode Statistics (HES): Admitted Patient Care linked to Critical Care and Civil Registration of Mortality formerly obtained from Office of National Statistics); patient level data; extracted 13 February 2024. NHS hospitals in England only.	All TAVI devices used in NHS hospitals included (unable to differentiate in HES data, devices not captured)	Cohort identification 01 April 2021 to 31 October 2023 (latest data available). History of patients dating back to 01 April 2007.	In-hospital outcomes: Total length of hospital stay, length of intensive care unit (ICU) stay, pacemaker implantation, vascular complications, bleeding, stroke, death. Out-of-hospital outcomes: aortic reintervention, pacemaker implantation, stroke, readmission with primary reason of heart failure, death.	Cannot differentiate TAVI device make and model from HES data. No clinical detail to quantify severity of disease, medications, or quality of life. Data from 2023 to 2024 financial year represents a partial year (01 April 2023 to 31 October 2023); which is the latest data available.

Abbreviations: CCS, Canadian Cardiovascular Society; HES, Hospital Episode Statistics; ICU, Intensive care unit; NICE, National Institute for Health and Care Excellence; NICOR, National Institute for Cardiovascular Outcomes Research; NYHA, New York Heart Association; SAVR, Surgical aortic valve replacement; TAVI, Transcatheter aortic valve implantation

4.1.4 Linkage of UK TAVI Registry and HES

To combine the clinically rich data from the UK TAVI Registry with the comprehensive coverage and longitudinal outcomes of HES, the EAG carried out anonymous linkage of the two datasets (restricted to procedures conducted in NHS hospitals in England) using programming language R (Keltie et al. 2021). Procedures in each dataset were allocated a unique ID to facilitate identification of unique matches. Firstly, the EAG replaced the hospital codes in the UK TAVI Registry with the NHS Trust code used in the HES dataset (NHS Digital Organisation Data Service Portal). The two cleaned datasets were merged using this code, and patient sex, therefore creating a linked dataset where each row corresponded to a unique match on both fields. At each subsequent step, rules were applied to pull out rows containing potential matches, to be assessed further. For example, the first main matching step required age, plus admission, procedure, and discharge dates to be exact matches between the Registry and HES datasets. For the extracted records meeting these criteria, any unique matches (that is, where the Registry ID and matched HES ID each appear only once in the extracted data) are considered true matches, added to a list of matched IDs, and removed from the linked dataset for subsequent steps. Some potential matches were identified as not being unique, that is, 1 Registry ID had multiple potential HES matches, or 1 HES ID had multiple potential Registry matches. In these cases, every unique combination of patient characteristics available in both datasets (diabetes, whether the procedure was non-elective, previous MI, previous stroke) were added in a stepwise fashion to make further unique matches. As before, once a match was established, these were added to a list of matched IDs, and removed from the linked dataset for further matching. These steps were followed for further matches, using the criteria described in Appendix E1, which become less strict as fewer records remain available for matching. This allows age to differ, for example, where it may have been calculated differently between the two datasets and a birthday occurred around the time of the procedure. Dates may differ, for example, where a patient was transferred from another Trust for their procedure, or transferred to another Trust after their procedure, and this information was

missed when inputting data to the Registry. Because data is entered manually, and not verified, small discrepancies such as these are likely.

Where sex was missing from either dataset and records could not be matched as described above, a separate linked dataset was created using only NHS Trust code, and records were matched only on exact age and procedure date, with further characteristics added, as needed, to maximise unique 1:1 matching.

After all possible matches had been identified, the data were split into the cohorts (TAVI in native aortic valve, TAVI-in-TAVI, TAVI-in-SAVR) assigned using the aortic valve aetiology and previous TAVI or valve surgery as recorded for each patient in the UK TAVI Registry. To check the generalisability of results from the matched cohort, the patient and procedural characteristics (UK TAVI Registry clinical data) of the matched cases were compared with the unmatched cases. As a validation step for the matched procedures, frequencies of in-hospital deaths and strokes, non-elective procedures, and lengths of stay were compared between the Registry and HES datasets. Within the linked dataset, admission type (elective or non-elective) was taken from the UK TAVI Registry, as were all in-hospital outcomes, except death, for which the HES ONS record was considered to be most accurate.

The EAG undertook multivariable analyses only for the TAVI in native aortic valve cohort due to the limited data for other cohorts, which represented most of the cases (96%), as also reported in a recent report by NICOR, 2024. Univariable tests were used to explore the relationship between covariates and TAVI device manufacturer in the Registry; with cases with missing data omitted, creating a complete case analysis. Quantile-quantile (Q-Q) plots were inspected to check for normality. These offer advantages over formal statistical tests (for example Kolmogorov-Smirnov) as they are insensitive to sample size. For large sample sizes (such as those in the UK TAVI registry, with populations of almost 4,000) small deviations from the expected normal can lead to rejection of the null hypothesis (of normality), whereas Q-Q plots are less sensitive to outliers. After inspection, log transformations were

applied to those variables that were found to be from a non-Gaussian distribution (valve area, annular diameter, creatinine clearance). Analysis of variance (ANOVA) testing was used for patient age, height, weight, pulmonary artery systolic pressure, aortic valve mean gradient, aortic valve peak gradient, and log transformed valve area, annular diameter, and creatinine clearance. All other variables were categorical, therefore chi-squared tests were used. For the main cohort (TAVI in native aortic valve; where data from 4 TAVI valve manufacturers were included), and the TAVI-in-SAVR cohort (where data from 2 TAVI valve manufacturers were included), Student's t-test was used for continuous variables. For all other characteristics, chi-squared tests were used. Holm-Bonferroni correction was applied to adjust the significance level (p=0.05) to account for multiple hypothesis testing.

For multivariable analysis, the EAG first considered a Poisson regression model of the number of observed counts of patients for each combination of factor levels. This approach requires categorisation/dichotomisation of continuous variables, for example, above or below median, which carries risks, reduced precision and power, assumes linear relationships between predictor and response, and potential influence of the choice of cut-off points; Bennette et al. 2012; Royton et al. 2006). Further, due to the number of outcomes of interest (10) and other covariates (at least 8), the resulting contingency table would have at least two to the power of 18 cells, many of which would be empty because there are approximately 5000 patients with incomplete data. This is impractical and the model is unlikely to converge, therefore the EAG decided to create a Binary Logistic Regression (BLR) model for each outcome. It was decided that each model should be trained on the same patients because of the simultaneous use of the regression model predictions in the economic model (that is, only complete datasets with all covariates and outcomes). The EAG chose to adjust for covariates rather than using propensity score techniques as it has been shown to perform as well as, or better than, propensity score methods in observational studies (Elze et al. 2017). Additionally, adjusting for covariates preserves the ability to identify which covariates are driving the model, which is lost in propensity score techniques. Moreover, it has been demonstrated that propensity score

methods risk the introduction of bias and diminished statistical power in studies with rare outcomes (Wilkinson et al. 2022).

The following assumptions apply to each model:

1. Observations are independent.
2. No multicollinearity (that is, independent variables are not correlated with one another).
3. Independent variables are linearly related to the log-odds of the event.

Each model was trained on a subset of clinically relevant covariates from the UK TAVI registry. The subset of covariates was informed by discussion with the UK TAVI Registry Clinical Lead. Covariates included single patient characteristics (for example, age), and composition of multiple characteristics (see Appendix C2). To aid the interpretation of each model the EAG looked at main effects only (no interactions between covariates), TAVI device name was incorporated as a factor to determine whether valve model was a significant contributor to outcomes when accounting for other variables, using the most used device as the model reference for contrasts. The same covariates were included in each model (that is all models were trained on the same data). Stepwise methods for variable selection were avoided as this would likely select different covariates for each model, which would yield different datasets. Additionally, stepwise methods are known to under-estimate standard errors of regression coefficients, produce p-values that are too small, and are susceptible to residual confounding. Continuous variables were median adjusted (centred around the median), and height (collected in metres) was adjusted to units of 10 cm, to allow a more meaningful interpretation of odds ratio (which represent a difference in odds per unit). Setting all continuous variables to the median at the intercept provides an interpretable reference point (within the ranges of the observed data) making it easier to understand the impact of other variables in the logistic model (Appendix C2).

A BLR model will estimate the probability of an outcome occurring, that is, it will produce a real number between zero and one. The receiver operating characteristic (ROC) curve describes a model's ability to discriminate between individuals who experience an outcome and those who don't. The ROC curve plots the probability of detecting a true and false signal for various cut-off points for the probability estimated by the model (below the cut-off point model predicts no event, above the cut-off point model predicts occurrence of event). The area under the ROC curve (AUC) ranges from 0.5 to 1.0 and quantifies the predictive ability of the model. There is no universally agreed upon threshold for AUC estimate; only guidelines which the EAG used in their interpretation of each model (Hosmer, 2013):

- AUC equal to 0.5: No better at discriminating than a coin toss.
- AUC greater than 0.5 and less than 0.7: Poor, not much better than a coin toss.
- AUC greater than or equal to 0.7 but less than 0.8: Acceptable fit, able to discriminate between an event and non-event well.
- AUC greater than or equal to 0.8: Excellent discrimination.

The odds ratio for each covariate represents the risk of the outcome for that covariate *relative to the reference case* (odds greater than 1.0 indicated increased risk, lower than 1.0 indicated decreased risk), the null and residual deviance, AUC, and Akaike information criterion (AIC) are reported for each BLR model. The log-odds were plotted against the continuous variables to check for the assumption that log-odds were linearly related to predictors using a locally weighted scatterplot smoothing function; an approximate monotonic line should be observed. Covariance amongst covariates was inspected to verify independence.

All patients were followed in HES until 31 October 2023, and a Cox proportional hazard (CPH) model was completed for each long-term outcome (death, stroke, permanent pacemaker implantation [PPI], aortic valve

reintervention, admission for heart failure). Patients were censored in each model as follows:

- Death model: censored if alive at the end of follow-up OR if they had a reintervention (censored at date of reintervention)
- Stroke model: censored if no stroke at the end of follow-up OR if they died in follow-up (including in-hospital death censored at date of death) OR if they had a reintervention (censored at date of reintervention)
- PPI model: censored if no PPI at end of follow-up OR if they died in follow-up (including in-hospital death censored at date of death) OR if they had a reintervention (censored at date of reintervention)
- Reintervention model: censored if no reintervention at end of follow-up OR if they died in follow-up (including in-hospital death censored at date of death).
- Heart failure model: censored if no readmission for heart failure at the end of follow-up OR died in follow-up (including in-hospital death censored at death date).

In addition to the key covariates included in all BLR models, the EAG explored the effects of certain in-hospital outcomes on long-term outcomes (also reflected in the economic modelling). Both the long-term death and stroke CPH models included in-hospital stroke during TAVI admission and the heart-failure model included in-hospital aortic regurgitation during TAVI admission. The EAG note that the PPI model included in-hospital PPI during TAVI admission, and results of this analysis reflected the need for ongoing maintenance and follow up related to the pacemaker which are not directly relevant to the decision problem. Other clinically relevant short-term outcomes captured in the registry could be incorporated in the future analysis of specific long-term outcomes. For each CPH model, the number of events, model concordance and 1 year estimated event rate are reported.

4.2 *Economic evidence*

4.2.1 Published evidence

To assess the suitability of the economic model from NG208 for use in this assessment, the EAG undertook early scoping literature searches (EAG Protocol 2024) to identify current evidence reporting economic evaluations of TAVI. This included a search within MEDLINE ALL for systematic reviews of economic evaluations or models published from 01 January 2020 to 28 November 2023 on 29 November 2023 (2 search filters, developed by the Canadian Agency for Drugs and Technologies in Health (CADTH), were applied to: 1) identify systematic reviews, meta-analyses, health technology assessments and indirect treatment comparisons (CADTH, 2021); and 2) identify economic evaluations and models (CADTH, 2016). This work confirmed that the economic modelling developed for NG208 remains consistent with other economic evaluations for TAVI (including structure and cost-drivers) published post-guidance, therefore the EAG did not conduct any further systematic searches for economic evidence relating to TAVI.

4.2.2 Included and excluded studies

From early scoping searches (EAG Protocol 2024), the EAG identified 6 systematic reviews (Chotnoppharatphatthara et al. 2023; Heathcote et al. 2023; Ruggeri et al. 2022; Edlinger et al. 2021; Tam et al. 2021b; Azraai et al. 2020) focusing on economic evaluations or cost-effectiveness of TAVI, which included a total of 55 publications, of which 49 were relevant to the decision problem (Appendix B5). The EAG identified 11 studies (Gilard et al. 2021; Haute Autorite de Sante (HAS) 2021a; Haute Autorite de Sante (HAS) 2021b; Himmels et al. 2021; Lorenzoni et al. 2021; Pinar et al. 2021; Tam et al. 2021a; Zhou et al. 2021; Health Technology Wales, 2020; Inoue et al. 2020; Kuntjoro et al. 2020) with associated economic models published after 2020 included within the 6 systematic reviews.

5 Results

5.1 *Network meta-analyses*

The EAG identified a total of 4 published network meta-analyses (NMA) which compared TAVI devices, Table 5 (critical appraisal summary in Appendix B2). Of these 3 included devices which have been withdrawn from market (Lotus and Direct Flow Medical TAVI devices).

- Yang et al. (2023) was the largest systematic review with network meta-analysis, which included 79 studies (including 5 RCTs and 74 observational studies of which 19 were propensity matched observational studies) and compared Sapien 3 (n=54,691 patients), Evolut (n=35,339 including Evolut R and Evolut Pro), ACURATE (n=4,634 including ACURATE and ACURATE neo), Portico (n=2,001), DFM (n=450) and Lotus (n=2,610) TAVI devices. It is unclear whether any corrections have been applied to account for RCTs and observational studies being included. The best performing valve varied by the outcome of interest: procedural mortality (Portico), short-term mortality and no correct position (Sapien 3), stroke (DFM), PPI (ACURATE), moderate to severe PVL (Lotus), prothesis patient mismatch and mean aortic valve gradient (Evolut). The authors acknowledged that the analysis was restricted to short-term outcomes only, and that differences in aortic valve area, annulus diameter, annulus perimeter, annulus area, aortic angle and extent of aortic valve calcification between arms may have contributed to heterogeneity. Lack of data limited subgroup analysis on these factors, which limits generalisability of findings.

- Dogosh et al. 2022 included 12 RCT and 13 propensity matched studies in Bayesian network meta-analysis comparing TAVI with SAVR, comprising a total of 42,105 patients and mean follow-up of 2 years. It is unclear how RCT and observational studies were combined. This included 27,134 patient who had undergone TAVI with Sapien or Sapien XT, Sapien 3, CoreValve, Evolut R or Evolut Pro, ACURATE neo or Portico devices. The study reported that newer generation devices (Sapien 3, Evolut R, Evolut Pro) were associated with improved outcomes when compared to SAVR and older generation TAVI

devices. This study reported that when limiting analysis to RCTs that no statistical difference was observed in all-cause mortality, stroke or aortic regurgitation between TAVI devices and SAVR. The authors acknowledged that there could be additional confounders that may impact results that were not reported, and state that different criteria and inconsistent reporting prevented additional subgroup and outcome analysis (such as valve thrombosis, valve gradient, valve area, patient-prosthesis mismatch, paravalvular regurgitation).

- Takagi et al. (2019) combined 29 studies (including 1 RCT; minimal information reported on statistical analysis process) which compared 4 new generation TAVI valves (ACURATE, Evolut R, Lotus, and Sapien 3) and an earlier generation reference (CoreValve), comprising a total of 17,817 patients. The best performing TAVI device varied by outcome. Sapien 3 had the lowest mortality, Lotus had the lowest proportion with moderate or severe aortic regurgitation but the highest for pacemaker implantation. ACURATE had the lowest pacemaker implantation. The authors acknowledged that the indirect comparisons may incur bias due to confounding.

- The pre-print by Hiltner et al. (2022) was the only study which included RCTs exclusively (12 RCTs, including a total of 10,307 patients) comparing balloon-expanding devices by Edwards Lifesciences (Sapien, Sapien XT, Sapien 3), self-expanding devices by Medtronic (CoreValve, Evolut R, Evolut Pro), self-expanding devices by Boston Scientific (ACURATE neo) and mechanically expanding valve by Boston Scientific (Lotus). ACURATE neo was associated with higher odds of mortality and moderate or severe aortic regurgitation at 30 days when compared to balloon-expanding devices by Edwards Lifesciences, but no difference in either outcome was observed at 1 year. Self-expanding valves by Medtronic were at higher odds of pacemaker implantation at 30 days and 1 year, and higher odds of implantation of multiples valves when compared to balloon expanding devices by Edwards Lifesciences. No difference across valves was observed for Stroke at 30 days and 1 year.

Only two of the NMA published results from the individual contributing studies (Takagi et al. 2019; Yang et al. 2023), which demonstrated large variation in patient

characteristics between studies. For example, across the 79 studies included in the NMA by Yang et al. 2023, where each clinical characteristic was recorded:

- The median/mean ages ranged between 78 and 87 years.
- The proportion male sex was between 0% and 94.5%.
- Left ventricular ejection fraction less than 30% up to 69%.
- A transfemoral delivery approach was used between 44% and 100%.
- General anaesthesia used between 0% and 100%.

Additionally, there were a number of missing values across the outcomes. These large differences in clinical characteristics across included studies demonstrate a potential lack of transitivity between studies (transitivity is the requirement that all participants could have been randomized to any arm of any study), meaning that the results from indirect comparisons of TAVI devices being compared may not be related solely to the treatment effects, but could be related to other factors. However, the authors do provide a quantitative assessment of transitivity, which showed significant differences between direct and indirect comparison. This is a threat to the internal validity of the analysis. The authors do not appear to have explored this further or attempted to correct for this. Only reported, qualitatively, that the distribution of potential effect modifiers were balanced across most of the treatment comparisons.

Three of the four NMAs combine evidence from RCT and observational studies in the same analysis. Evidence from observational studies are more likely to be biased if confounding has not been adequately addressed (Efthimiou et al. 2017), which can lead to disagreements between the randomised and non-randomised evidence. None of the reviews appear to have addressed this directly, however, one review did conduct a sensitivity analysis to show that the RCT evidence alone presented the same direction of effect (Dogosh et al. 2022); although the effect did become non-statistically significant and potentially suggests differences in the randomised and non-randomised evidence. This could be due to imprecision, however, it could also be due to other unknown factors (for example less studies in analysis). The other two

studies included minimal RCT evidence compared to observational evidence. Finally, an additional general limitation of NMA is that it can highly rank interventions supported by small, low-quality trials that report large effects (Phillips et al. 2022).

Table 5: Summary of 4 network meta-analyses comparing TAVI devices

Study (year)	Total studies (n=number of patients)	Population	Interventions included [Comparator]	Key findings	Limitations
Dogosh et al. (2022)	12 RCT, 13 Propensity matched (n=42,105)	Severe aortic stenosis	[SAVR (n=14,971)] Sapien and Sapien XT (n=15,345) Sapien 3 (n=2,987) CoreValve (n=5,898) Evolut and Evolut Pro (n=1,447) ACURATE neo (n=1,076) Portico (n=381)	Sapien 3 was ranked as having the best probability for being the most effective valve in reduction of all-cause mortality, cardiovascular mortality, stroke, bleeding. Evolut R/Pro was ranked together with Sapien 3 with regards to AF, rehospitalisation and AKI. SAVR and Sapien 3 were ranked highest for decreased incidence of pacemaker implantation, and decreased risk of AR. Limiting to RCTs demonstrated no statistically significant difference in all-cause mortality, stroke, AR between devices and SAVR.	Authors acknowledge changes in valve design over time may influence results, and follow-up was up to 2 years. Differences in outcomes definition precluded additional subgroups (valve thrombosis, valve gradient, valve area, patient-prothesis mismatch, paravalvular regurgitation).
Hiltner et al. (2022) *[pre-print]*	12 RCT (n=10,307)	Patients with aortic stenosis	[SAVR] Sapien/Sapien XT/Sapien 3 CoreValve/Evolut R/Evolut Pro ACURATE neo LOTUS	CoreValve was associated with higher risk of pacemaker implantation and use of more than 1 valve. ACURATE was associated with high risk of moderate/severe AR and death. Lotus was associated with lower risk of moderate/severe AR but higher risk of pacemaker at 30 days. CoreValve and Lotus were associated with higher pacemaker rates compared with balloon at 1 year. No difference across valves in stroke at 30 days or 1 year.	Excluded transapical to try and preserve transitivity. Limited number of studies, more than one iteration of valves unable to conduct all comparisons.
Takagi et al. (2019)	29 studies (n=17,817)	Not reported	[CoreValve (n=8,272)] Evolut R (n=5,032) Sapien 3 (n=2,776) Lotus (n=1,285) ACURATE (n=452)	SAPIEN 3 patients had the lowest risk of early postprocedural all-cause death and the second lowest risk of ≥moderate AR and PMI. Lotus patients had the lowest risk of ≥moderate AR, but the highest risk of PMI and second highest risk of all cause death. ACURATE patients are at the lowest risk of pacemaker implantation I and second lowest risk of all cause death.	Only RCT and a few matched observational studies were included and there were non-negligible dissimilarities between patient baseline characteristics.
Yang et al. (2023)	5 RCT and 74 observational studies; which included 19 propensity matched studies	Patients undergoing TAVI for aortic stenosis	Sapien 3 (n=54,691) Evolut/Evolut R/Pro (n=35,339) ACURATE neo/neo2 (n=4,634) Portico (n=2,001) Lotus DFM	Sapien 3 had the lowest short-term mortality and stroke rates (after excluding DFM). Lotus had the lowest paravalvular leak. Evolut had the lowest major and life-threatening bleed and mean aortic valve gradients. ACURATE neo/neo2 had the lowest permanent pacemaker implantation. Portico had the lowest AKI.	Acknowledged that differences of aortic valve area, annulus diameter, annulus perimeter, annulus area, aortic angle and the extent of aortic valve calcification among individual patients and surgeon experience might explain the moderate amounts of heterogeneity in some analyses such as permanent pacemaker implantation, major vascular complications, major or life-threatening bleeding, and patient-prosthesis mismatch. Only investigated the device related factors contributing to the different findings; however, patient-related factors and operators learning curve are also potential contributors for the results. Study only investigated the short-term clinical outcomes of the new-generation devices.

5.2 *Key primary evidence*

Due to lack of transitivity between studies, as identified in the network meta-analysis described in section 5.1, the EAG prioritised clinical evidence that compared multiple TAVI devices (thus enabling direct comparison of TAVI devices from a single source). There were 4 studies (Baumbach et al. 2024; Costa et al. 2022; Rudolph et al. 2024; Voigtländer et al. 2021) which compared multiple TAVI devices which adjusted for confounders, Table 6 (critical appraisal in Appendix B2). Of these:

- 3 were conducted exclusively in patients undergoing TAVI in native aortic valve (1 did not report aortic valve aetiology),
- 2 were conducted exclusively in symptomatic patients and 1 reported the proportion of patients with NYHA status greater than class II (slight limitation of ordinary physical activity) which was between 69.5% and 76.3% across the different devices, 1 did not report symptom status,
- the majority of patients underwent transfemoral TAVI procedures in all 3 studies (ranged between 91.4% and 100%),
- surgical risk was reported using the Society of Thoracic Surgeons (STS) score (N=3), and EuroSCORE II (N=1). For context, the Clinical Experts have advised that most of the TAVI procedures in the NHS continue to be conducted in high-risk patient group (Appendix G).

The international (N=16 countries) non-inferiority RCT by Baumbach et al. (2024) compared Myval (n=384 randomised, 381 ITT at 30 days; combination of Myval and Myval Octacor, including 15 crossover and Portico=1) with a contemporary TAVI group (n= 384, 381 ITT at 30 days; including combination of Sapien 3, Sapien 3 Ultra, Evolut R, Evolut Pro, Evolut Pro+, Evolut FX, and 5 patients having Myval implanted). This study demonstrated no statistical difference in the primary endpoint at 30 days or its components. No statistical difference was observed in technical success, 30-day device success or early safety between arms. However, the EAG note that the intervention arm included different generations of devices (both Myval Octacor and Myval). The comparator group included an aggregation of different manufacturer devices and their generations. Both arms included crossover of

intervention and comparator valves in analysis groups, and combined balloon- and self-expanding TAVI valves. Patients with aortic annulus mean diameters greater than 29 mm were excluded from the trial (included in a nested registry). Therefore, it is difficult to determine the generalisability of results from this study.

The prospective non-randomised study by Costa et al. 2022 conducted in Italy (28 centres) incorporated inverse probability treatment weighting-based multiple adjustment to produce 5 treatment groups with homogeneous baseline characteristics across separate Evolut R, Evolut Pro, Sapien 3, ACURATE neo and Portico groups. This study reported statistical differences in in-hospital outcomes (pacemaker implantation, moderate to severe paravalvular regurgitation, residual transvalvular gradients, length of ICU and hospital stay) and 1 year pacemaker outcome. No statistical differences were observed for all-cause mortality (at 30 days, 1 year), stroke (in-hospital, 1 year), heart failure rehospitalisation (1 year), bleeding (in-hospital), vascular complication (in-hospital), AKI (in-hospital), or MI (1 year).

The multicentre retrospective non-randomised study by Rudolph et al. (2024) conducted in Germany included propensity adjusted logistic regression analysis on age, sex, STS score and left ventricular function to compare Sapien 3, Evolut R, ACURATE neo, Portico (using ACURATE neo as the reference). This study reported statistical differences in in-hospital outcomes (death, vascular complications, paravalvular leak, transvalvular gradient at discharge) and new pacemaker or implantable cardiovertor defibrillators at 1 year.

The multicentre retrospective non-randomised study by Voigtländer et al. (2021) conducted in Germany included multivariable logistic regression analysis for patient-prosthesis mismatch outcome which compared Sapien 3 (n=288), Evolut or Evolut R or Evolut Pro (n=179), ACURATE neo (n=428), Portico (n=110) and Lotus (n=64) in patients with a small aortic annulus (defined as annulus area less than 400 mm2 on MDCT). This study reported that higher age, self-expanding valves (Evolut, ACURATE neo and Portico), post-dilatation were associated with fewer instances of moderate or severe patient-prosthesis mismatch.

An additional 3 studies compared multiple TAVI devices, but with additional limitations:

- Santos-Martinez et al. (2022); the European multicentre retrospective non-randomised study which compared Evolut R or Pro (n=298), Sapien 3 (n=290), ACURATE neo (n=180), Portico (n=125), Allegra (n=103) all to Myval (n=135) as the reference. However, this study only reported in-hospital outcomes and did not adjust for differences in baseline characteristics between devices.

- Brown et al. 2023; single centre retrospective non-randomised study conducted in the US compared Evolut Pro+ (n=278), Sapien 3 Ultra (n=176) and Portico (n=106). This study conducted multivariable mixed effects modelling for one outcome (mean transvalvular pressure gradient measured at days 0,1, and 30 post-TAVI) treating TAVI device as a fixed effect (Evolut Pro+ as the reference) including timepoint (random effect) but adjusted only for aortic annular. The clinical impact of the haemodynamic findings was unknown.

- Seiffert et al. (2015); single centre retrospective non-randomised study conducted in Germany reported 1-year outcomes of transapical TAVI in patients with aortic stenosis using JenaValve (n=88), ACURATE (Symetis, n=62, which the EAG assumes is a predecessor to the ACURATE neo devices) and Engager (Medtronic, n=50, which the EAG assumes is a predecessor to the Evolut series). Fluoroscopy and procedure time and use of contrast agent were highest in those receiving JenaValve; ($p<0.001$, $p=0.004$, $p<0.001$ respectively). All-cause mortality at 1 year was also highest for those receiving JenaValve (32.1%, compared with 29.8% Engager and 12.4% ACURATE; $p=0.047$).

Table 6: Key comparative evidence compared with other devices in Scope

Author (year); design, location	Intervention arms (number of patients); demographic descriptors	Individual outcomes with statistically significant differences reported between comparator(s); ordered best to worst performance (at specified timepoint)	Outcomes where **no statistically significant differences** were found between comparator(s) (at specified timepoint)
Baumbach et al. (2024) RCT non-inferiority International (N=16 countries)	- Myval or Myval Octacor (n=384) age: 80.0 years male: 50% STS: 2.6% (76% low risk, 20% intermediate, 4% high) - Contemporary group; Evolut or Sapien series (n=384) age: 80.4 years male: 54% STS: 2.6% (75% low risk, 20% intermediate, 4% high)	None	All-cause mortality, all stroke, bleeding types 2 to 4, AKI stages 3 or 4, major vascular complications, moderate or severe valve regurgitation, and conduction system disturbances resulting in permanent pacemaker implantation, technical success, devices success (30-days)
Costa et al. 2022; Prospective non-randomised (with propensity matching) Italy (N=28)	- Evolut R (n=1,125) age, year: 83.0 male: 47.4% EuroSCORE II: 5.0 - Evolut Pro (n=337) age, year: 83.1 male: 41.9% EuroSCORE II: 5.2 - Sapien 3 (n=768) age, year: 83.0 male: 48.0% EuroSCORE II: 4.8 - ACURATE neo (n=290) age, year: 83.0 male: 42.9% EuroSCORE II: 5.1 - Portico (n=208) age, year: 83.0 male: 40.9% EuroSCORE II: 5.1	PPI (in-hospital, p=0.002) - Sapien 3: 9.6% - ACURATE neo: 9.6% - Evolut R: 16.0% - Evolut Pro: 17.4% - Portico: 18.2% Moderate to severe paravalvular regurgitation (in-hospital, p<0.01) - Sapien 3: 2.1% - Evolut Pro: 4.9% - Evolut R: 10.0% - Portico: 10.7% - ACURATE neo: 11.4% Residual transvalvular gradients (in-hospital, p<0.01) - Evolut Pro: 6 mmHg - Evolut R: 7 mmHg - ACURATE neo: 7 mmHg - Portico: 8 mmHg - Sapien 3: 10 mmHg ICU length of stay (discharge, p<0.001) - Portico: 0 days - Evolut R: 1 day - Evolut Pro: 1 day - ACURATE neo: 1 day - Sapien 3: 1 day Post-procedural hospital length of stay (discharge, p<0.001) - Sapien 3: 5 days - ACURATE neo: 5 days - Evolut R: 6 days - Evolut Pro: 6 days - Portico: 6 days PPI (1 year, p<0.01) - Sapien 3: 12.5% from KM analysis - ACURATE neo: 14.7% - Evolut Pro: 19.3% - Evolut R: 19.9% - Portico: 22.1% HR (Evolut R compared with Sapien 3): 1.67 [1.44 to 1.94] HR (Evolut R compared with ACURATE neo): 1.42 [1.23 to 1.64] HR (Evolut Pro compared with Sapien 3): 1.61 [1.38 to 1.88] HR (Evolut Pro compared with ACURATE neo): 1.37 [1.18 to 1.59] HR (Evolut Pro compared with Portico): 0.86 [0.75 to 0.98]	Neurological events, bleeding, AKI, vascular complication (in-hospital) All-cause mortality (30 days) All-cause death, stroke, heart failure rehospitalisation, MI, composite outcome (all-cause death, stroke and heart failure rehospitalisation) (1 year)

Author (year); design, location	Intervention arms (number of patients); demographic descriptors	Individual outcomes with statistically significant differences reported between comparator(s); ordered best to worst performance (at specified timepoint)	Outcomes where **no statistically significant differences** were found between comparator(s) (at specified timepoint)
Rudolph et al. (2024) Retrospective non-randomised (propensity matched adjusted logistic regression analysis based on: age, sex, STS score and LV function; ACURATE neo used as reference) Germany	- Sapien 3 (n=13,296) age: 80.4 years male: 37.2% STS: 5.19 - Evolut R (n=7,028) age: 80.3 years male: 37.0% STS: 5.22 - ACURATE neo (n=2,922) age: 80.3 years male: 37.1% STS: 5.23 - Portico (n=878) age: 80.4 years male: 36.9% STS: 5.20	Death (procedural, p=0.03) - ACURATE neo: 0.1% - Evolut R: 0.2% - Sapien 3: 0.2% - Portico: 0.4% Vascular complications (procedural, p<0.0001) - Sapien 3: 2.0% - ACURATE neo: 3.7% - Evolut R: 3.9% - Portico: 4.6% Dilatation (post-procedure, p<0.0001) - Sapien 3: 13.7% - Evolut R: 27.7% - ACURATE neo: 36.8% - Portico: 38.0% Paravalvular leak – grade II or higher (discharge, p<0.0001) - Sapien 3: 1.2% - Evolut R: 2.0% - ACURATE neo: 2.1% - Portico: 3.1% Transvalvular gradient, mean (SD) (discharge, p<0.0001) - ACURATE neo: 8.60 (0.09) mmHg - Evolut R 8.80: (0.09) mmHg - Portico: 9.27 (0.09) mmHg - Sapien 3: 12.11 (0.09) mmHg New pacemaker / implantable cardioverter defibrillators (1 year, p<0.0001) - ACURATE neo: 13.0% - Sapien 3: 16.5% - Portico: 21.6% - Evolut R: 21.9%	Conversion to surgery, coronary obstruction, bailout valve-in-valve, stroke, MI, procedural success (procedural). Paravalvular leak – grade III (discharge). Overall survival (at 30 day and 1 year). NYHA, MI, Stroke, TIA, PCI, further hospitalisation, further hospitalisation due to complication related to the aortic valve intervention, reintervention (1 year).
Voigtländer et al. (2021) Retrospective non-randomised (with multivariable analysis) Germany (N=4)	- Sapien 3 (n=288) age: 82.8 years male: 8.3% STS: 4.5% - Evolut/Evolut R/Evolut Pro (n=179) age: 83.0 years male: 6.1% STS: 4.7% - ACURATE neo (n=428) age: 82.4 years male: 7.0% STS: 4.4% - Portico (n=110) age: 83.3 years male: 3.6% STS: 4.9% - Lotus (n=64) age: 83.0 years male: 9.4% STS: 4.0%	Patient-prosthesis mismatch (post-procedural; compared to Sapien 3 as the reference) OR (95% CI) - Evolut/Evolut R/Evolut Pro: 0.341 (0.193, 0.591); p<0.001 - ACURATE neo: 0.436 (0.301, 0.629); p<0.001 - Portico: 0.291 (0.164, 0.502); p<0.001 - Lotus: 0.527 (0.26, 1.046); p=0.070 - Age: 0.968 (0.943, 0.992); p=0.011 - Post-dilatation of TAVI: 0.648 (0.449, 0.928); p=0.019	-

Abbreviations: AF, Atrial fibrillation; AKI, Acute kidney injury; LVEF, Left ventricular ejection fraction; MI, Myocardial infarct; NYHA, New York Heart Association; PPI, Permanent pacemaker implantation, RBBB, Right bundle branch block; RCT, Randomised controlled trial; TIA, Transient ischaemic attack; STS, The Society of Thoracic Surgeons

5.2.1 Balloon-expanding

Myval Octacor (Meril)
The EAG note that the Myval Octacor is the newer generation of the Myval TAVI device. Published evidence for Myval Octacor is limited at present therefore studies of the previous generation (Myval) have been included.

Single arm studies were identified which reported the use of Myval Octacor (study characteristics described in Table 7). These included studies in multiple centres in India (Jose et al. 2024, Elkoumy et al. 2023) with overlap in centres and recruitment periods, 1 retrospective cohort of 68 patients with bicuspid aortic stenosis (Elkoumy et al. 2022) and 1 Italian case study (Ielasi et al. 2024) which reported in-hospital or 30-day outcomes (including commissural alignment, pacemaker implantation, AKI, mortality, paravalvular leak, haemodynamic performance and complication).

The longest follow-up for Myval (earlier generation) was 2 years reported by Moscarella et al. (2024) that retrospectively compared 108 patients treated with Evolut R with 58 patients treated with Myval. However, the EAG note that reporting of baseline demographics between arms were lacking, and no adjustment were made to results to account for any difference in populations. The longest follow-up specific to the Myval Octacor valve was 30 days reported by the single arm cohort by Jose et al. (2024) that included 123 patients with severe aortic stenosis recruited from 16 centres in India.

The Company reported that there are two ongoing studies. One directly compares Myval (including Octacor) to the Sapien series in Denmark (NCT04443023) with an estimated recruitment of 1,062 patients. The EAG note that recruitment was completed (November 2023), however the Company advised that the trial would compare outcomes at 30 days, 1, 5, and 10 years follow up. The other is a retrospective multicentre (N=8; Estonia, Italy, the Netherlands, Poland, Slovenia, Spain, Turkey) observational single-arm study with an estimated enrolment of 200 consecutive participants with native severe aortic valve stenosis (Myval-3; NCT04703699). The primary completion date was 30 May 2024, with a primary combined safety and efficacy endpoint at 30 days; full study completion is due in 2028 (for long-term outcomes).

Table 7: Key studies for Myval Octacor (N=6 studies)

Author (year)	Country (N centres)	Study design	Duration of follow-up	**Total no. of patients**	Myval Octacor (Meril)	Sapien 3 (Edwards Lifesciences)	Sapien 3 Ultra (Edwards Lifesciences)	Navitor (Abbott Medical)	Allegra (Biosensors Int)	ACURATE neo2 (Boston Scientific)	Trilogy (JenaValve)	Evolut R (Medtronic)	Evolut Pro+ (Medtronic)	Evolut FX (Medtronic)	Hydra (SMT)
Baumbach et al. (2024)	International (N=16 countries)	RCT (non-inferiority)	30 days	**762 [ITT]**	**381** {included Myval n=336, Octacor n=32}	**108** [combined comparator group]	**87** [combined comparator group]	-	-	-	-	**71** [combined comparator group]	**116** [combined comparator group] {included Evolut Pro n=106}	**5** [combined comparator group]	-
Santos-Martinez et al. (2022)†	Europe (N=9)	Retrospective non-randomised	Hospital discharge	**1131**	**135** {Myval}	**290**	-	**125** {Portico}	**103**	**180** {ACURATE neo}	-	-	**298** {combined comparator group, Evolut R/Pro}	-	-
Jose et al. (2024)	India (N=16)	Retrospective single arm	30 days	**123**	**123**	-	-	-	-	-	-	-	-	-	-
Elkoumy et al. (2023)	India (N=18)	Retrospective single arm	Post-procedure	**103**	**103**	-	-	-	-	-	-	-	-	-	-
Elkoumy et al. (2022)	India, Denmark, Italy, Croatia	Retrospective single arm	30 days	**68**	**68** {Myval}	-	-	-	-	-	-	-	-	-	-
Ielasi et al. (2024)	Italy (N=1)	Case report	Peri-procedure	**1**	**1**	-	-	-	-	-	-	-	-	-	-

Abbreviations: ITT, intention to treat; PM, propensity matched; RCT, randomised controlled trial

Sapien 3, Sapien 3 Ultra (Edwards Lifesciences)

The Sapien 3 and Sapien 3 Ultra devices are the third and fourth generations of TAVI devices from Edwards Lifesciences; earlier generations include Sapien and Sapien XT. Increasing evidence for these valves is available, but interpretation needs caution because of the variation in comparators for each study. Specific outcome ranking is different for each valve type with no single device showing complete superiority. Evidence that compared generations of Sapien devices was also identified Table 8, Table 9), including:

- Nazif et al. (2021); non-randomised propensity matched analysis comparing Sapien 3 Ultra (n=1,287) with Sapien 3 (n=1,287) with 30 days follow-up.
- Cannata et al. (2023); non-randomised propensity matched analysis comparing Sapien 3 Ultra (n=496) with Sapien 3 (n=496) at 1 year follow-up.
- Abdelfattah et al. (2022); meta-analysis (N=7 observational studies) comparing Sapien 3 Ultra (n=1,996 patients) with Sapien 3 (n=2,111).
- Russo et al. (2019); retrospective non-randomised analysis of learning curve and volume outcome relationship data from the STS/ACC TVT Registry which compared Sapien 3 (n=28,229) with Sapien (n=18,195) and Sapien XT (n=15,532).

The longest follow-up identified for the Sapien series was 12 years (median [Q1,Q3] 7.0 [5.5,8.7] years) as reported by Ali et al. (2023) which summarised outcomes from the UK TAVI Registry and included 40 Sapien and 27 Sapien XT devices compared with 143 CoreValve (Evolut R predecessor, Medtronic) TAVI devices. Severe structural valve deterioration was seen more frequently with Sapien devices (11.9% compared with 3.5% CoreValve, p=0.02), however it was noted that more patients were treated with small valves in the Sapien arm (28.6% compared with 3.0%, p<0.01) which may confound results.

Table 8: Key studies for Sapien 3 and Sapien 3 Ultra (N=9)

Author (year)	Country (N centres)	Study design	Duration of follow-up	**Total no. of patients [n. after matching]**	Myval Octacor (Meril)	Sapien 3 (Edwards Lifesciences)	Sapien 3 Ultra (Edwards Lifesciences)	Navitor (Abbott Medical)	Allegra (Biosensors Int)	ACURATE neo2 (Boston Scientific)	Trilogy (JenaValve)	Evolut R (Medtronic)	Evolut Pro+ (Medtronic)	Evolut FX (Medtronic)	Hydra (SMT)	Other valves (out of scope)
Yang et al. (2023)	International	Systematic review with network meta-analysis (N=79 studies, including 5 RCTs, 19 propensity matched)	Short term (timepoint NR)	**99,725**	-	**54,691**	-	**2,001** {Portico}	-	**4,634** {included ACURATE and ACURATE neo}	-	-	**35,339** {included Evolut, Evolut R, Evolut Pro}	-	-	DFM Lotus
Rudolph et al. (2024)	Germany (N=NR, multicentre)	Retrospective non-randomised (propensity-score weighted analysis)	1 year	**24,124**	-	**13,296**	-	**878** {Portico}	-	**2,922** {ACURATE neo}	-	**7,028**	-	-	-	-
Costa et al. (2022)	Italy (N=28 centres)	Prospective non-randomised study (inverse propensity of treatment weighting)	1 year	**2,728**	-	**768**	-	**208** {Portico}	-	**290** {ACURATE neo}	-	**1,125**	**337** {Evolut Pro}	-	-	-
Santos-Martinez et al. (2022)†	Europe (N=9)	Retrospective non-randomised	Hospital discharge	**1,131**	**135** {Myval}	**290**	-	**125** {Portico}	**103**	**180** {ACURATE neo}	-	-	**298** {combined comparator group, Evolut R/Pro}	-	-	-
Brown et al. (2023)	US (N=1)	Retrospective non-randomised	30 days	**560**	-	-	**176**	**106** {Portico}	-	-	-	-	**278**	-	-	-
Ali et al. (2023)	UK (N=11)	Retrospective non-randomised	Median: 7 years (up to 12 years)	**214**	-	**67** {included Sapien n=40, Sapien XT n=27}	-	**4** {Portico}	-	-	-	**143** {Corevalve}	-	-	-	-
Nazif et al. (2021)	US (N=NR, multicentre)	Retrospective non-randomised (propensity score matched)	30 days	**34,306 [2,648 PM]**	-	**32,982**	**1,324**	-	-	-	-	-	-	-	-	-
Cannata et al. (2023)	Italy, the Netherlands, Portugal, Span (N=12)	Retrospective non-randomised (propensity score matched)	1 year	**1,692 [992 PM]**	-	**1,173**	**519**	-	-	-	-	-	-	-	-	-
Abdelfattah et al. (2022);	NR	Systematic review and meta-analysis (N=7 observational)	NR	**4,107**	-	**2,111**	**1,996**	-	-	-	-	-	-	-	-	-
Russo et al. (2019)	US (N=450)	Retrospective non-randomised	30 days	**61,949**	-	**28,227 {Compared with Sapien XT n=15,530 and Sapien n=18,192}**	-	-	-	-	-	-	-	-	-	-

Abbreviations: NR, Not reported; PM, propensity matched; RCT, randomised controlled trial

Table 9: Key clinical evidence for Sapien 3 and Sapien 3 Ultra (Edwards Lifesciences) compared with other devices in Scope

Author (year); design, location	Intervention arms (number of patients); demographic descriptors	Individual outcomes with **statistically significant differences** reported between comparator(s); ordered best to worst performance (at specified timepoint)	Outcomes where **no statistically significant differences** were found between comparator(s) (at specified timepoint)
Nazif et al. (2021) Retrospective non-randomised cohort from STS/ACC TVT Registry (propensity matched on 27 covariates) US	- **Sapien 3 Ultra (n=1,324)** **age, mean: 79.5 years** **male: 44.2%** **STS, mean: 4.3%** - Sapien 3 (n=1,324) age, mean: 79.9 years male: 44.0% STS, mean: 4.4%	Aortic valve area, mean (discharge, p<0.01) - **Sapien 3 Ultra: 1.90 cm2** - Sapien 3: 1.79 cm2 Paravalvular regurgitation (discharge, p<0.01) - **Sapien 3 Ultra: None (90.9%), mild (9.0%), moderate or severe: 0.1%** - Sapien 3: None (85.7%), mild (13.9%), moderate or severe: 0.4% (30 days, p=0.02) - **Sapien 3 Ultra: None (85.7%), mild (13.8%), moderate or severe: 0.6%** - Sapien 3: None (77.0%), mild (21.6%), moderate or severe: 1.4%	Device success, conversion to open-heart surgery, annulus rupture, annular dissection, aortic dissection, coronary compression or obstruction, device embolization aorta, device embolization left ventricle, perforation with or without tamponade (procedural) ICU stay in hours, proportion with no ICU stay, hospital stay in days, discharge location, all-cause mortality, cardiac death, stroke, aortic valve reintervention, life-threatening bleed, major vascular complications, new need for dialysis, new pacemaker, mean aortic gradient (discharge) All-cause mortality, cardiac death, stroke, aortic valve reintervention, life-threatening bleed, major vascular complications, new need for dialysis, new pacemaker, any readmission, NYHA class III or IV, KCCQ, mean aortic gradient, LVEF (30 days)
Abdelfattah et al. (2022) Meta-analysis observational studies (N=7)	- **Sapien 3 Ultra (n=1,996)** **age, mean: 79.8 years** **males: 47.2%** **STS, mean: 4.2%** - Sapien 3 (n=2,111) age, mean: 80.1 years male: 48.7% STS, mean: 4.5%	Moderate or severe paravalvular leak (timepoint NR) - **Sapien 3 Ultra: 0.71%** - Sapien 3: 1.71% - OR: 0.42 [0.21 to 0.85] Mild paravalvular leak (timepoint NR) - **Sapien 3 Ultra: 13.4%** - Sapien 3: 28.4% - OR: 0.29 [0.19 to 0.45]	All-cause mortality, stroke, major bleeding, permanent pacemaker (timepoint NR)

Abbreviations: AF, Arterial fibrillation; AKI, Acute kidney injury; HR, Hazard ratio; ICU, Intensive care unit; iEOA, indexed effective orifice area; KCCQ, Kansas City Cardiomyopathy Questionnaire; LBBB, Left bundle branch block; LVEF, Left ventricular ejection fraction; MI, Myocardial infarction; NR, Not reported; NYHA, New York heart Association; PCI, Percutaneous coronary intervention; PPI, Permanent pacemaker implantation; PVL, Paravalvular leak; STS, Society of Thoracic Surgeons; SUCRA, Surface under the cumulative ranking curve, TAVI, transcatheter aortic valve implantation; TIA, Transient ischaemic attack; VARC-3, Valve Academic Research Consortium-3

5.2.2 Self-expanding

ACURATE neo2 (Boston Scientific)

The ACURATE neo2 is a subsequent generation of the ACURATE neo TAVI device.

Evidence was also identified that compared generation of devices (Table 10, Table 11):

- Buono et al. 2022; retrospective non-randomised with propensity matching comparing ACURATE neo2 (n=205) with ACURATE neo (n=205)
- Kim et al. 2022c; retrospective non-randomised comparing ACURATE neo2 (n=810) with ACURATE neo (n=2,055)
- Scotti et al. 2022; retrospective non-randomised (overlap with Baggio et al. 2023) comparing ACURATE neo2 (n=763) with ACURATE neo (n=1,263). This study reported fewer and less severe paravalvular regurgitation, vascular complications, and bleeding complications at discharge with ACURATE neo2 than its predecessor. ACURATE neo2 was associated with a statistically worse mean aortic gradient at 30 days, however the clinical significance of the difference is unclear.

A median follow-up of 3 years (maximum of 7 years) was reported in a non-comparative cohort of 104 patients treated with ACURATE neo (Siqueira et al. 2021). The longest follow-up specific to ACURATE neo2 was 1 year, reported in the post-market surveillance non-comparative study of 250 patients by Kim et al. (2024).

Table 10: Key studies for ACURATE neo2 (N=9)

Author (year)	Country (N centres)	Study design	Duration of follow-up	**Total no. of patients [n. after matching]**	Myval Octacor (Meril)	Sapien 3 (Edwards Lifesciences)	Sapien 3 Ultra (Edwards Lifesciences)	Navitor (Abbott Medical)	Allegra (Biosensors Int)	ACURATE neo2 (Boston Scientific)	Trilogy (JenaValve)	Evolut R (Medtronic)	Evolut Pro+ (Medtronic)	Evolut FX (Medtronic)	Hydra (SMT)	Earlier generation valves in study
Yang et al. (2023)	International	Systematic review with network meta-analysis (N=79 studies, including 5 RCTs, 19 propensity matched)	Short term (timepoint NR)	**99,725**	-	**54,691**	-	**2,001** {Portico}	-	**4,634** {included ACURATE and ACURATE neo}	-	-	**35,339** {included Evolut, Evolut R, Evolut Pro}	-	-	DFM Lotus
Costa et al. (2022)	Italy (N=28 centres)	Prospective non-randomised study (inverse propensity of treatment weighting)	1 year	**2,728**	-	**768**	-	**208** {Portico}	-	**290** {ACURATE neo}	-	**1,125**	**337** {Evolut Pro}	-	-	-
Rudolph et al. (2024)	Germany (N=NR, multicentre)	Retrospective non-randomised (propensity-score weighted analysis)	1 year	**24,124**	-	**13,296**	-	**878** {Portico}	-	**2,922** {ACURATE neo}	-	**7,028**	-	-	-	-
Santos-Martinez et al. (2022)†	Europe (N=9)	Retrospective non-randomised	Hospital discharge	**1,131**	**135** {Myval}	**290**	-	**125** {Portico}	**103**	**180** {ACURATE neo}	-	-	**298** {combined comparator group, Evolut R/Pro}	-	-	-
Seiffert et al. (2015)	Germany (N=1)	Retrospective non-randomised	1 year	**200**	-	-	-	-	-	**62** {ACURATE}	**88** {JenaValve}	-	-	-	-	Engager
Kim et al. (2022c)	Germany (N=2)	Retrospective non-randomised	Procedural (30 day mortality)	**2,865**	-	-	-	-	-	**810** [compared with ACURATE neo n=2,055]	-	-	-	-	-	-
Scotti et al. (2022)	International (N=29 centres)	Retrospective non-randomised	30 days	**2,026**	**-**	**-**	-	**-**	**-**	**763** [compared with ACURATE neo n=1,263]	-	-	**-**	-	-	-
Kim et al. (2024)†	International (N=NR, multicentre)	Prospective post-market surveillance single arm	1 year	**250**	-	-	-	-	-	**250**	-	-	-	-	-	-
Siqueira et al. (2021)	Brazil (N=1)	Prospective single arm	Median 3 years	**104**	-	-	-	-	-	**104** {ACURATE neo}	-	-	-	-	-	

Abbreviations: NR, Not reported; PM, propensity matched

Table 11: Key clinical evidence for ACURATE neo2 and ACURATE neo (Boston Scientific) compared with other devices in Scope

Author (year); design, location	Intervention arms (number of patients); demographic descriptors	Individual outcomes with **statistically significant differences** reported between comparator(s); ordered best to worst performance (at specified timepoint)	Outcomes where **no statistically significant differences** were found between comparator(s) (at specified timepoint)
Buono et al. (2022a) Retrospective non-randomised (with propensity matching) Italy (N=13)	- **ACURATE neo2 (n=205)** **age, median: 83 years** **male 32.2%** **EuroSCORE II, median: 3.01%** **STS, median: 3.40%** - ACURATE neo (n=205) age, median: 84 years male: 33.2% EuroSCORE II, median: 3.07% STS, median: 3.33%	ICU stay, median (in-hospital, p=0.003) - **ACURATE neo2: 1.00 days** - ACURATE neo: 1.50 days Moderate or severe paravalvular aortic regurgitation (discharge, p<0.001) - **ACURATE neo2: 3.5%** - ACURATE neo: 11.2%	All-cause mortality, cardiovascular death, procedural death, PPI, cerebral ischaemic event, bleeding, vascular complication, coronary occlusion, cardiac tamponade, AKI, technical success (VARC-3), hospital length of stay (in-hospital) LVEF, mean transvalvular gradient, peak transvalvular gradient, aortic valve area, prosthesis-patient mismatch (discharge)
Kim et al. (2022c) Retrospective non-randomised Germany (N=2)	- **ACURATE neo2 (n=810)** **age, median: 82.0 years** **male 37.4%** **EuroSCORE II, median: 3.3%** - ACURATE neo (n=2,055) age, median: 82.0 years male: 37.5% EuroSCORE II, median: 3.4%	Paravalvular regurgitation (procedural; p=0.03) - **ACURATE neo2: 2.7%** - ACURATE neo: 4.5% Bleeding, type 2 to 4 (procedural; p<0.01) - **ACURATE neo2: 14.8%** - ACURATE neo: 19.8%	Paravalvular leak – moderate or greater, annular rupture, conversion to sternotomy, multiple valve implantation, device embolization, major vascular complication, any stroke, AKI – stage 2 to 4, pacemaker implantation (procedural) All-cause mortality (30 days)
Scotti et al. (2022) Retrospective non-randomised *[Overlap with Baggio et al. 2023]* International (N=29 centres)	- **ACURATE neo2 (n=763)** **age, mean: 82 years** **male: 33%** **EuroSCORE II, median: 3.1%** **STS, median: 3.5%** - ACURATE neo (n=1,263) age, mean: 82 years male: 35% EuroSCORE II, median: 4.4% STS, median: 4.1%	Paravalvular aortic regurgitation (discharge, p<0.01) - **ACURATE neo2: none: 59%, mild: 39%, moderate: 2%, severe: 0%** - ACURATE neo: none: 38%, mild: 57%, moderate: 5%, severe: 0.1% Vascular complications (30 days, p<0.001) - **ACURATE neo2: none: 94%, minor: 2%, major: 3%** - ACURATE neo: none: 83%, minor: 11%, major: 6% Bleeding complications (30 days, p=0.02) - **ACURATE neo2: none: 88%, type 1: 6%, type 2: 3%, type 3: 2%, type 4: 0.3%** - ACURATE neo: none: 85%, type 1: 6%, type 2: 5%, type 3: 5%, type 4: 0% Mean aortic gradient, (30 days, p<0.001) - ACURATE neo: 8.0 mmHg - **ACURATE neo2: 8.9 mmHg** Moderate or severe paravalvular aortic regurgitation (30 days, p<0.001) - **ACURATE neo2: 2%** - ACURATE neo: 5%	Mortality, valve embolization, second valve implanted, annular rupture, pericardial tamponade, aortic dissection, coronary occlusion, conversion to open heart surgery (procedural) All-cause mortality, technical success (VARC-3), device success (VARC-3), pacemaker implantation, AKI (stage 2 or 3), aortic valve area, indexed aortic valve area (30 days) All-cause mortality (1 year)

Abbreviations: AKI, Acute kidney injury; ICU, Intensive care unit; iEOA, indexed effective orifice area; LVEF, Left ventricular ejection fraction; MI, Myocardial infarct; NYHA, New York Heart Association; THV, transcatheter heart valve; TIA, Transient ischaemic attack; STS, Society of Thoracic Surgeons; VARC-3, Valve Academic Research Consortium-3

Allegra (Biosensors)
The Company confirmed that there are no previous versions of the technology.

The longest available evidence for the Allegra device was reported in the single arm study reporting outcomes for 103 patients extracted from the Swiss TAVI Registry from a single centre (Wolfrum et al. 2023). All-cause mortality and cardiovascular mortality from Kaplan-Meier analysis of 31.4% and 18.8% respectively (no confidence intervals were reported) to 3 years, with other clinical outcomes reported to 1 year.

The Company advised that there are 2 ongoing RCTs involving the Allegra TAVI device. One RCT (NCT05989074) aims to recruit 130 women only, randomised to Allegra or any balloon-expanding TAVI device, for severe native aortic stenosis. The study has an estimated start date of February 2024 (recruitment status at 11 June 2024: not yet recruiting) and end date of August 2025. The VIVALL 2 study (NCT06049654) is a single site (Spain) RCT comparing supra-annular self-expanding Allegra device with intra-annular balloon-expanding Edwards Sapien 3 or Sapien 3 Ultra valves specifically for valve-in-valve indication. The study aims to recruit 104 patients, with study start date of February 2024 (currently recruiting) and end date of November 2025. The primary outcome measure of both trials is transaortic mean gradient after the procedure as measured by echocardiography at 30 days.

Evolut R, Evolut Pro+, Evolut FX (Medtronic)

Evolut R, (Evolut Pro out of Scope), Evolut Pro+, and Evolut FX are later generations of the CoreValve TAVI device, with Evolut FX being added to NHS Supply Chain procurement framework from December 2023.

Comparative between-generation evidence was available for all 3 Medtronic devices in Scope (Table 12, Table 13):

- Merdler et al. (2023) comparing Evolut FX (n=100) with Evolut Pro+ (n=100).
- Zaid et al. 2023b comparing Evolut FX (n=226) and Evolut Pro+ (n=378) but reported on fewer outcomes.
- Tang et al. (2021): data from the STS/ACC TVT Registry but only comparing prosthesis-patient mismatch outcome at 1 year between Evolut Pro and Pro+ combined (n=18,141 patients; none: 83.1%, moderate: 12.5%, severe: 4.4%) and Evolut R (n=14,401 patients; none: 79.4%, moderate: 14.4%, severe: 6.3%), p<0.001.
- Gozdek et al. (2023): systematic review and meta-analysis of 11 observational studies comparing Evolut Pro (n=3,439) with Evolut R (n=8,924). However, the authors acknowledged statistically different age, sex, STS risk score and prothesis valve size (likely linked with Evolut R being available in 34 mm valve size and the largest Evolut Pro available being 29mm).
- Forrest et al. (2020): comparing 3 generations of Medtronic TAVI valves (CoreValve n=5,514 patients, Evolut R n=11,295, Evolut Pro n=2,065) using the STS/ACC TVT Registry data, including 30-day outcomes from 1,500 propensity matched patients from each using Evolut Pro as a common reference point.

Longest available data identified for Evolut R was 5 years (Tamm et al. 2021), Evolut Pro or Pro+ was 3 years (Wyler von Ballmoos et al. 2021) and Evolut FX was 30 days (Merdler et al. 2023; Zaid et al. 2023b).

Ali et al. (2023) reported outcomes from the UK TAVI Registry up to 12 years which included 143 patients (67%) receiving CoreValve, reported previously.

Table 12: Key studies for Evolut R, Evolut Pro+ and Evolut FX (N=13)

Author (year)	Country (N centres)	Study design	Duration of follow-up	**Total no. of patients [n. after matching]**	Myval Octacor (Meril)	Sapien 3 (Edwards Lifesciences)	Sapien 3 Ultra (Edwards Lifesciences)	Navitor (Abbott Medical)	Allegra (Biosensors Int)	ACURATE neo2 (Boston Scientific)	Trilogy (JenaValve)	Evolut R (Medtronic)	Evolut Pro+ (Medtronic)	Evolut FX (Medtronic)	Hydra (SMT)	Other valves (out of scope)
Yang et al. (2023)	International	Systematic review with network meta-analysis (N=79 studies, including 5 RCTs, 19 propensity matched)	Short term (timepoint NR)	**99,725**	-	**54,691**	-	**2,001** {Portico}	-	**4,634** {included ACURATE, ACURATE neo}	-	-	**35,339** {included Evolut, Evolut R, Evolut Pro}	-	-	DFM Lotus
Costa et al. (2022)	Italy (N=28 centres)	Prospective non-randomised study (inverse propensity of treatment weighting)	1 year	**2,728**	-	**768**	-	**208** {Portico}	-	**290** {ACURATE neo}	-	**1,125**	**337** {Evolut Pro}	-	-	-
Rudolph et al. (2024)	Germany (N=NR, multicentre)	Retrospective non-randomised (propensity-score weighted analysis)	1 year	**24,124**	-	**13,296**	-	**878** {Portico}	-	**2,922** {ACURATE neo}	-	**7,028**	-	-	-	-
Santos-Martinez et al. (2022)†	Europe (N=9)	Retrospective non-randomised	Hospital discharge	**1,131**	**135** {Myval}	**290**	-	**125** {Portico}	**103**	**180** {ACURATE neo}	-	-	**298** {combined comparator group, Evolut R, Evolut Pro}	-	-	-
Brown et al. (2023)	US (N=1)	Retrospective non-randomised	30 days	**560**	-	-	**176**	**106** {Portico}	-	-	-	-	**278**	-	-	-
Gozdek et al. (2023)	NR	Systematic review and meta-analysis (N=11 observational studies)	Procedural, other short term (timepoint NR), 30 day mortality	**12,363**	-	**-**	-	**-**	-	**-**	-	**8,924**	**3,429** {Evolut Pro}	-	-	-
Forrest et al. (2020)	US (N=381)	Retrospective non-randomised (propensity score matched)	30 days	**18,874 [4,500]**	-	-	-	-	-	-	-	**11,295, 5,514 {Evolut R, {CoreValve}**	**2,065** {Evolut Pro}	-	-	-
Tang et al. (2021)	US (N=NR, multicentre)	Retrospective non-randomised	1 year	**32,542**	-	-	-	-	-	-	-	**14,401**	**18,141** {Evolut Pro}	-	-	-
Tamm et al. (2021)	Germany (N=1)	Retrospective non-randomised	3 years	**359**	-	**215**	-	-	-	-	-	**144**	-	-	-	-
Ali et al. (2023)	UK (N=11)	Retrospective non-randomised	Median: 7 years (up to 12 years)	**214**	-	**67** {included Sapien n=40, Sapien XT n=27}	-	**4** {Portico}	-	-	-	**143** {Corevalve}	-	-	-	-
Zaid et al. (2023b)	US (N=9 Evolut FX, N=1 Evolut Pro+)	Retrospective non-randomised	30 days	**604**	-	-	-	-	-	-	-	-	**378**	**226**	-	-
Merdler et al. (2023)	US (N=1)	Retrospective non-randomised	30 days	**200**	-	-	-	-	-	-	-	-	**100**	**100**	-	-
Wyler von Ballmoos et al. (2021)	US (N=8)	Prospective single arm	3 years	**60**	-	-	-	-	-	-	-	-	**60** {Evolut Pro}	-	-	-

Abbreviations: NR, Not reported;

Table 13: Comparative clinical evidence for Evolut R, Evolut Pro+, Evolut FX (Medtronic) compared with other devices in Scope; latest version in bold)

Author (year); design, location	Intervention arms (number of patients); demographic descriptors	Individual outcomes with **statistically significant differences** reported between comparator(s); ordered best to worst performance (at specified timepoint)	Outcomes where **no statistically significant differences** were found between comparator(s) (at specified timepoint)
Merdler et al. (2023) Retrospective non-randomised cohort US	- **Evolut FX (n=100)** **age, mean: 79.6 years** **male: 52.0%** **STS, mean: 3.4%** - Evolut Pro+ (n=100) age, mean: 78.7 years male: 51.0% STS, mean: 3.4%	Aortic mean gradient (discharge, p=0.006) - Evolut Pro+: 6.5 mmHg - **Evolut FX: 8.1 mmHg** Aortic peak velocity (discharge, p=0.002) - Evolut Pro+: 1.7 m/s - **Evolut FX: 2.1 m/s**	Device malfunction, access-site complications, tamponade, severe aortic regurgitation, ventricular tachycardiac or fibrillation, valve embolization, valve migration, complete atrioventricular block, hypotension, coronary obstruction, unplanned conversion to surgery, haemoglobin drop, stroke (procedural) Permanent pacemaker implantation, mortality, moderate or severe paravalvular leak (in-hospital) Technical success (VARC-3), device success (VARC-3), early safety (VARC-3), permanent pacemaker implantation, mortality, NYHA III or IV, stroke (CVA or TIA), aortic mean gradient, moderate or severe aortic regurgitation (30 days)
Zaid et al. 2023b Retrospective non-randomised US	- **Evolut FX (n=226)** **age, years: 80.0 years** **male: 48.2%** **STS: 3.5%** - Evolut Pro+ (n=378) Demographics of comparator arm not reported.	Commissural alignment (in-hospital, p<0.0001) - **Evolut FX: 96.5%** - Evolut Pro+: 80.2% Left coronary cusp depth (in-hospital, p<0.001) - **Evolut FX: 4.5 mm** - Evolut Pro+: 5.9 mm Device recaptures (in-hospital, p=0.004) - **Evolut FX: 26.1%** - Evolut Pro+: 39.5%	-
Gozdek et al. (2023) Systematic review with meta-analysis (N=11 observational studies)	- Evolut R (n=8,924) - **Evolut Pro (n=3,439)**	More than one valve needed (procedural, p=0.02) - **Evolut Pro: 0.87%** - Evolut R: 1.18% - RR: 0.52 [0.30 to 0.89] Moderate to severe PVL (timepoint NR, p=0.002) - **Evolut Pro: 2.4%** - Evolut R: 3.0% - RR: 0.66 [0.52 to 0.86] Major bleeding (timepoint NR, p=0.03) - **Evolut Pro: 2.63%** - Evolut R: 5.02% - RR: 0.63 [0.41 to 0.96]	Device-related complications, MI (procedural) Mild PVL, mean aortic gradient, prosthesis patient mismatch (moderate or greater), major vascular complications, PPI (timepoint NR) Mortality (30 days)
Forrest et al. (2020) Retrospective non-randomised cohort US	- CoreValve (n=5,514) - Evolut R (n=11,295) - **Evolut Pro (n=2,065)**	Major bleeding (30 days, p=0.01) - **Evolut Pro: 0.2%** - Evolut R: 0.9% - Corevalve: 0.6% Moderate or severe aortic regurgitation (30 days, p=0.03): - **Evolut Pro: 3.4%** - Evolut R: 5.4% - Corevalve: 8.3%	All-cause mortality, stroke, PPI, valve-related readmission, PCI, valve thrombosis, aortic valve reintervention, vascular complications, MI (30 days)

Abbreviations: AKI, Acute kidney injury; CVA, cerebrovascular accident; HR, Hazard ratio; ICU, Intensive care unit; NYHA, New York Heart Association; MI, Myocardial infarct; PCI, Percutaneous coronary intervention; PPI, Permanent pacemaker implantation; PVL, Paravalvular leak; RR, Risk ratio; STS, The Society of Thoracic Surgeons; TIA, Transient ischaemic attack; VARC-3, Valve Academic Research Consortium

Hydra (SMT)

The EAG did not identify any published comparative evidence for the Hydra TAVI device. The Company confirmed that there are no previous versions of the Hydra TAVI device.

The longest follow-up was from Aidietis et al. (2022) that reported 30-day (n=146) and 1-year (n=114) outcomes in 157 patients in 18 centres across Europe and Asia (Greece, Hong Kong, India, Kazakhstan, Lithuania, New Zealand, Poland, Thailand). The authors reported 5 device-related deaths (3.2%; 95% CI 1.2% to 1.7%) at 30 days. Moderate or severe paravalvular leak was 5.3%, 6.3% and 6.9% at post-procedure, 30 days and 1-year timepoints. Improvements in mean gradient were observed post-procedure (mean [SD] baseline 49.5 [18.5] mmHg to 9.2 [4.5] post-procedure, p<0.001), which were sustained at 30 days (8.1 [3.7], p<0.001) and 1 year (8.8 [4.7], p<0.001). Improvements in effective orifice area (baseline 0.7 [0.2] cm2) were also observed post -procedure (p<0.001), 30 days (p<0.001) and sustained at 1 year (p<0.001): 1.9 [0.6] cm2, 1.9 [0.6] cm2 and 1.7 [0.5] cm2 respectively. Pacemaker implantation was 10.8% and 11.5% at 30 days and 1 year. At 30 days follow up, major bleeding (4.5%), major vascular complications (4.5%), stroke (0.6%), AKI (0.6%) were reported; no increase in these events was reported at 1 year. No myocardial infarction or TIA events occurred in the cohort.

The Company did not report any ongoing studies in their standard Request for Information documentation.

Navitor (Abbott Medical)

The largest comparative evidence for TAVI devices in Scope of this late-stage assessment was not available specifically for Navitor, however was available for the predecessor device, Portico (Table 14). Comparison of Navitor and Portico (Eckel et al. 2023) is described in Table 15.

The longest follow-up identified for Navitor was 1 year reporting outcomes for 120 patients (Sondergaard et al. 2023), which included 2 UK centres (remaining US, European, Australia). The longest follow-up for device family (Portico) was 3 years, which included 803 patients (Giordano et al. 2024b).

Table 14: Key studies for Navitor (N=9)

Author (year)	Country (N centres)	Study design	Duration of follow-up	**Total no. of patients [n. after matching]**	Myval Octacor (Meril)	Sapien 3 (Edwards Lifesciences)	Sapien 3 Ultra (Edwards Lifesciences)	Navitor (Abbott Medical)	Allegra (Biosensors Int)	ACURATE neo2 (Boston Scientific)	Trilogy (JenaValve)	Evolut R (Medtronic)	Evolut Pro+ (Medtronic)	Evolut FX (Medtronic)	Hydra (SMT)	Other valves (out of scope)
Yang et al. (2023)	International	Systematic review with network meta-analysis (N=79 studies, including 5 RCTs, 19 propensity matched)	Short term (timepoint NR)	**99,725**	-	**54,691**	-	**2,001** {Portico}	-	**4,634** {included ACURATE, ACURATE neo}	-	-	**35,339** {included Evolut, Evolut R, Evolut Pro}	-	-	DFM Lotus
Rudolph et al. (2024)	Germany (N=NR, multicentre)	Retrospective non-randomised (propensity-score weighted analysis)	1 year	**24,124**	-	**13,296**	-	**878** {Portico}	-	**2,922** {ACURATE neo}	-	**7,028**	-	-	-	-
Santos-Martinez et al. (2022)†	Europe (N=9)	Retrospective non-randomised	Hospital discharge	**1,131**	**135** {Myval}	**290**	-	**125** {Portico}	**103**	**180** {ACURATE neo}	-	-	**298** {included Evolut R, Evolut Pro}	-	-	-
Costa et al. (2022)	Italy (N=28 centres)	Prospective non-randomised study (inverse propensity of treatment weighting)	1 year	**2,728**	-	**768**	-	**208** {Portico}	-	**290** {ACURATE neo}	-	**1,125**	**337** {Evolut Pro}	-	-	-
Brown et al. (2023)	US (N=1)	Retrospective non-randomised	30 days	**560**	-	-	**176**	**106** {Portico}	-	-	-	-	**278**	-	-	-
Eckel et al. (2023)	Germany (N=2)	Retrospective non-randomised	30 days	**276**	-	-	-	**137** compared with **139** {Portico}	-	-	-	-	-	-	-	
Ali et al. (2023)	UK (N=11)	Retrospective non-randomised	Median: 7 years (up to 12 years)	**214**	-	**67** {included Sapien n=40, Sapien XT n=27}	-	**4** {Portico}	-	-	-	**143** {Corevalve}	-	-	-	-
Giordano et al. 2024b	Europe (N=7)	Retrospective single arm	3 years	**803**	-	-	-	**803** {Portico}	-	-	-	-	-	-	-	
Sondergaard et al. (2023)	International (N=19)	Prospective single arm	1 year	**120**	-	-	-	**120**	-	-	-	-	-	-	-	-

Abbreviations: NR, Not reported;

Table 15: Comparative clinical evidence for Navitor or predecessor Portico (Abbott Medical) compared with other devices in Scope; latest version in bold

Author (year); design, location	Intervention arms (number of patients); demographic descriptors	Individual outcomes with **statistically significant differences** reported between comparator(s); ordered best to worst performance (at specified timepoint)	Outcomes where **no statistically significant differences** were found between comparator(s) (at specified timepoint)
Eckel et al. (2023) Retrospective non-randomised cohort Germany	- **Navitor (n=137)** **age: 83.0 years** **male: 38.7%** **EuroSCORE II: 3.6%** - Portico (n=139) age: 82.7 years male: 38.8% EuroSCORE II: 3.7	Paravalvular leak - greater than mild or requiring SAVR or valve-in-valve (in-hospital, p=0.041) - **Navitor 1.5%** - Portico 7.2% Major vascular complication (in-hospital, p=0.036) - **Navitor 0.7%** - Portico 5.8% Severe bleeding – type 2 to 4 (in-hospital, p=0.005) - **Navitor 13.1%** - Portico 27.3%	Technical success, post-dilatation, death, conversion to sternotomy, multiple valves, device migration or embolisation, all stroke, major cardiac structural complication, AKI type 2 to 4, new permanent pacemaker implantation (in-hospital). Early safety, device success, death (30-days).

Abbreviations: AKI, Acute kidney injury; SAVR, Surgical aortic valve replacement

Trilogy (JenaValve)

The EAG identified predecessor versions of the Trilogy TAVI device (referred to as JenaValve) through targeted searches. Only 1 German case report specific to the Trilogy device was identified by the EAG (Geyer et al. 2023) reporting outcomes to 1 month. Comparative evidence was only available for a predecessor device (exclusively in transapical TAVI procedures). No between-generation comparative evidence was identified.

The EAG also identified a non-comparative multicentre (Germany N=12, the Netherlands N=1, Switzerland N=1, UK N=1, NCT01598844) post-market registry for JenaValve which reported 1-year outcomes in 180 patients with aortic stenosis undergoing transapical TAVI (Silaschi et al. 2016). The EAG note that most of TAVI procedures in the UK are undertaken via percutaneous transfemoral delivery approach (96% in 2022/23 as stated in NICOR 2024 report); and that transfemoral is recommended as the default position by GIRFT in its 2021 cardiology report. As a result, transapical approach was reported in 0.5% (73 of 14,401) and 1.4% (162 of 11,681) of TAVI procedures recorded in UK TAVI Registry and HES respectively. Therefore, the EAG considers that results from the published studies may not be generalisable to a UK NHS setting. No evidence was identified comparing between generations of JenaValve devices, therefore it is unclear whether results are generalisable to the Trilogy device.

Clinical Experts have advised that JenaValve would not be used in a patient with aortic stenosis and is more appropriate for use in patients with aortic regurgitation.

The Company advised that there are two ongoing studies using JenaValve valve. The ALIGN-AS (NCT02732691) multi-centre (N=13; Germany, the Netherlands, New Zealand, US) single-arm study aimed to recruit 68 participants with severe native aortic stenosis to TAVI with the JenaValve device. The study status was classed as active not recruiting (on 11 June 2024) despite an estimated completion date of April 2024. The primary outcome measure was all-cause mortality at 30 days. The ALIGN-AR multicentre (N=30; US) study (NCT04415047) including a total of 180 participants with severe native aortic regurgitation considered to be high risk for open surgical valve replacement treated with the JenaValve Trilogy device. However, the

EAG notes that this population is out of scope for this late-stage assessment and that results are unlikely to be generalisable to a population with aortic stenosis.

5.2.3 Adverse events

During the targeted searches, the EAG identified 6 publications reporting adverse events not directly captured within the economic modelling for 2 devices (ACURATE neo2, Evolut Pro+) in Scope of this late-stage assessment (Appendix B3). The EAG acknowledge that capturing adverse events for TAVI devices is likely to be associated with breadth of use and that systematic searches for all devices in Scope of this late-stage assessment have not been undertaken. Therefore, the EAG consider these additional outcomes to be incidental findings relating to adverse events.

ACURATE neo2 (Boston Scientific)

Kim et al. (2022a) reported 68 of 448 (15.2%) cases experienced valve micro-dislodgement (VMD), which is associated with procedure technical failure, with transfemoral TAVI using ACURATE neo2 in a single German centre. VMD was defined as displacement of 2 mm or greater between the initial and valve release positions as measured on fluoroscopy. The rate of valve malposition was higher in the group with VMD than those without (4.4% compared with 0.8%, p=0.048), resulting in lower rates of technical success (p=0.026). VMD was associated with longer procedural and fluoroscopy time, more frequent device embolisation and multiple valve implantations (bailout TAVI). Additionally, transprosthetic mean gradients were lower in those with VMD than without (89.7% compared with 96.1%, p<0.001). From multi-variable logistic regression modelling, the authors reported that greater extent of oversizing (larger cover index), a higher position of the radiopaque marker band, partial detachment of the lower crown, and severe parallax prior to deployment were independent predictors of VMD. The position of the delivery system within the outer curvature was protective of VMD.

Trębacz et al. (2023) reported a single case of high-grade valve under-expansion in a 77-year-old female with an existing permanent pacemaker in a Polish setting, preventing safe removal of the delivery system. Insertion of a parallel guidewire

enabled post-dilatation with a balloon, and optimal valve position and function with limited PVL. An additional single case report by Pellicano et al. (2021) reported a rare adverse event of iatrogenic ventricular septal defect 3 days following TAVI using an ACURATE neo2 device in a 90-year-old female patient in an Italian setting. Following TAVI, new onset left bundle branch block and mild-to-moderate PVL was observed. A peri-membranous ventricular septal defect (VSD) was observed on transoesophageal echocardiogram, confirmed as an iatrogenic VSD by CT and MRI imaging. Surgical repair of the VSD was deemed unsuitable therefore a percutaneous closure was carried out with arterial and venous access. A permanent pacemaker was implanted, and pre-discharge echocardiogram confirmed a moderate PVL with the patient being discharged after 1 week in a stable condition.

Evolut Pro+ (Medtronic)

The EAG also identified 2 publications reporting valve frame infolding with the Evolut Pro+ (Rao et al. 2023; Yashige et al. 2022). Valve frame infolding is a rare occurrence during deployment, which results in distortion and malfunction of the prosthesis and typically occurs with self-expanding TAVI valves (Karrowni et al. 2020). Rao et al. (2023) reported 4 of 10 patients receiving the 34 mm Evolut Pro+ valve experienced valve frame infolding between June and October 2022 in a single Australian setting. Authors noted that while the total calcium volume between those with and without infolding was not significantly different, the distribution of calcium in the non-coronary cusp was higher in those experiencing infolding (52% compared with 37%), in the left coronary cusp was lower in those experiencing infolding (20% compared with 33%), and similar in the right coronary cusp (27% compared with 30%). The mean ellipticity index was also higher in those with infolding than without (0.22 compared with 0.14). However, no statistical analysis was reported. Yashige et al. (2022) also reported a single case of valve frame infolding with a 26 mm Evolut Pro+ in a 91-year-old female with severe aortic stenosis in a Japanese setting. Authors described procedural bailout because of infolding using balloon aortic valvuloplasty.

The EAG also identified a case report detailing surgical recovery of an Evolut Pro+ valve, which had migrated within 3 days post-discharge resulting in PVL requiring

ICU admission and surgical intervention for a 74-year-old male in a single setting in Puerto Rico (González-Bravo et al. 2022).

5.2.4 Usability

The EAG also identified 2 conference abstracts reporting outcomes from clinician surveys investigating procedural technique outcomes and feedback with Evolut FX compared with Evolut Pro+ (Bajwa et al. 2023; Chetcuti et al. 2023, Appendix B3). The abstracts overlap in authorship, timepoint (June to August or September 2022), US setting and figure used. No outcomes in Scope of this late-stage assessment were reported, however authors noted that 79% of operators rated the Evolut FX as having a more predictable deployment than the Evolut Pro+.

The EAG identified a case report describing Allegra in a failed ACURATE neo which had been put into a failed Perimount valve, that is a valve-in-valve-in-valve procedure (Miura et al. 2019).

5.2.5 Other

The EAG note previously available TAVI devices have been subject to a global voluntary recall, such as the Lotus Edge (Boston Scientific).

The EAG identified a publication that reported successful implantation of the Allegra device in 8 patients with a prior mitral valve prosthesis in situ from a single Spanish centre with no significant changes in mitral function or haemodynamics observed at 30 days, (Tébar Márquez et al. 2022). The non-inferiority RCT by Herrmann et al. 2024 (NCT04722250) compared TAVI with Evolut (R/Pro/Pro+/FX) with Sapien (3/3 Ultra) in patients with small annuli (defined as aortic annulus area of 430 mm2 or less).

5.2.6 Assessment of clinical equivalence

The EAG recognise extensive published evidence for differences in outcomes between TAVI devices in and out of Scope of this late-stage assessment, (EAG Protocol, 2024), however the quality and length of follow-up for studies comparing TAVI devices are generally low. The EAG also note that the indications for the included devices vary, such as by surgical risk group, anatomical features and clinical history. The Clinical Experts have advised that patient characteristics inform the choice of which TAVI is most suitable (Appendix G), therefore definition of what

is considered to be clinically equivalent in outcomes may differ at a patient level. Because of this, the EAG have not sought to define equivalence, nor assumed equivalence in clinical outcomes between the Class III implantable TAVI devices. Instead, the EAG considered using real-world data from an NHS setting (UK TAVI Registry, supplemented by HES data for longitudinal outcomes) to compare individual TAVI devices in Scope of this late-stage assessment using multivariate analysis when accounting for recorded confounders. Whilst long-term data is available for TAVI manufacturers (Edwards Lifesciences and Medtronic) up to 12 years, long-term data on the specific devices listed in the scope are limited.

The EAG also recognise published evidence comparing generations of devices for 4 manufacturers in Scope of this late-stage assessment (Abbott, Boston Scientific, Edwards Lifesciences, and Medtronic), noting that between-generation comparisons for Hydra (SMT) and Allegra (Biosensors) are not applicable, as these represent first generation TAVI devices. No comparisons were identified that compared JenaValve Trilogy with an earlier JenaValve device, Myval Octacor with Myval. Largely, publications focused on differences in rates of paravalvular leak (PVL), which can lead to reintervention, bailout TAVI, or conversion to SAVR (Grubb et al. 2024). Reductions in moderate or greater PVL have been observed for newer TAVI models when compared with older models by the same manufacturers:

- Sapien 3 Ultra compared with Sapien 3 (Abdelfattah et al. 2022; Nazif et al. 2021),
- ACURATE neo2 compared with ACURATE neo (Scotti et al. 2022; Buono et al. 2022a; Kim et al. 2022c),
- Evolut FX compared with Evolut Pro+ (Merdler et al. 2023), Evolut Pro compared with R (Gozdek et al. 2023, Forrest et al. 2020), Evolut R compared with CoreValve (Forrest et al. 2020),
- Navitor compared with Portico (Eckel et al. 2023).

Conversely, some publications have reported poorer outcomes with newer devices, such as Evolut FX having higher rates of VARC-3 early safety and pacemaker implantation (in-hospital and at 30 days) when compared with Evolut

Pro+ (Merdler et al. 2023). Furthermore, most publications included short follow-up periods up to 30 days; some differences may be reported later, such as higher reintervention rates for Evolut R compared with Evolut Pro and Evolut R or Pro compared with SAVR at 1 and 5 years post-procedure respectively (Grubb et al. 2024). Therefore, the EAG has not assumed equivalence between TAVI devices by the same manufacturer.

5.3 *UK TAVI Registry*

5.3.1 Quality appraisal

The EAG highlight that analysis of observed real-world data from the UK TAVI Registry includes tests for associations between recorded variables but does not establish causality.

The EAG (single reviewer) completed formal critical appraisal of the UK TAVI Registry using the Data Suitability Assessment Tool (DataSAT), Appendix C5. The UK TAVI Registry data provided to the EAG represents the latest validated data of TAVI procedures undertaken between 01 April 2021 to 31 March 2023 in England, Wales, and Northern Ireland. Data from 3 private hospitals were included in the Registry but excluded from the analysis to ensure generalisability to the NHS. Results from UK TAVI Registry are self-reported (risk of under-reporting) and not validated (risk of publication bias). There is a reliance on local data entry and clinical staff to ensure data accuracy, although NICOR may contact the submitting centre to encourage resubmission of corrected values.

Because of poor quality and completeness of TAVI device model in the registry (invalid combinations of TAVI manufacturer and model were identified, and older models not available within the time period were selected within the Registry) the EAG undertook additional cleaning and aggregated procedures in the Registry by manufacturer. However, Myval Octacor (Meril), Hydra (SMT), Allegra (Biosensors) and Trilogy (JenaValve) TAVI devices listed in the NICE Final Scope were only available to the NHS Supply Chain framework from 18 September 2023 and therefore were not available in the UK TAVI Registry extract received by the EAG. The EAG note that 3 procedures reported use of a JenaValve device (no mention of “Trilogy”) within the UK TAVI Registry extract, however 1 was used for aortic regurgitation (no mention of aortic stenosis), and 2 were used in proctored cases, and therefore all 3 were excluded from analysis.

NICOR acknowledged that there were some duplicated rows in the dataset (based on procedure start time), which were excluded by the EAG where this was obviously the case. Other duplicates may remain where the EAG was unable to identify the correct row (such as where there were data entry errors that were not apparent during cleaning). Data completeness varied by data field, and continuous variables included data outside of the limits defined in the data specification (v4.09) which were subsequently treated as missing by the EAG in its analysis. Also treated as missing were any fields left blank, or with the "Unknown" option selected.

There is a lack of direct alignment of outcomes recorded in the UK TAVI Registry with the Valve Academic Research Consortium-3 (VARC-3) consensus document (2021); however the EAG have tried to align these where possible (see Appendix C4). The EAG restricted analysis to patients with severe aortic stenosis, defined as aortic valve mean gradient greater than 40 mmHg, aortic valve area (AVA) less than 1 cm2 or peak aortic jet velocity greater than 4.0 m/s (ACC/AHA, 2006); however aortic jet velocity is not recorded in the Registry. This may mean some patients were not included in the analysis who would have met the eligibility criteria if this information was available.

The EAG was aware of potential confounders which are not captured currently within the UK TAVI Registry, and therefore could not be adjusted for in the analysis. For example:

- surgical risk group (not routinely recorded by interventional cardiologists conducting the procedure),
- patient anatomy characteristics informing device choice (for example, challenging vascular access, tortuosity, aortic valve and left ventricular outflow tract calcium burden and distribution),
- medication prior to procedure,
- operator learning curve with new valve, or level of experience.

Pre-procedural symptom scores are captured in the Registry, including Canadian Cardiovascular Society (CCS) angina status, New York Heart Association (NYHA)

dyspnoea status, Canadian Study of Health and Aging (CSHA) Frailty score, and Katz Index of Independence in Activities of Daily Living. However, only NYHA and CCS are recorded at follow-up (1 year, 3 years), with poor data completeness (less than 10%). No standardised measures of quality of life are recorded in the Registry (for example: Minnesota Living with Heart Failure Questionnaire MLHFQ, Kansas City Cardiomyopathy Questionnaire KCCQ, EQ-5D, SF health questionnaires). Therefore, the EAG was unable to determine changes in quality of life over time from the Registry.

Monitoring data quality for example missing values, flagging outliers, estimating measurement errors and sharing this information with TAVI centres could improve data completeness and accuracy, further increasing the benefit of the dataset for ongoing monitoring of TAVI valve performance in the NHS (Pongiglione et al. 2021).

5.3.2 Cohort identification

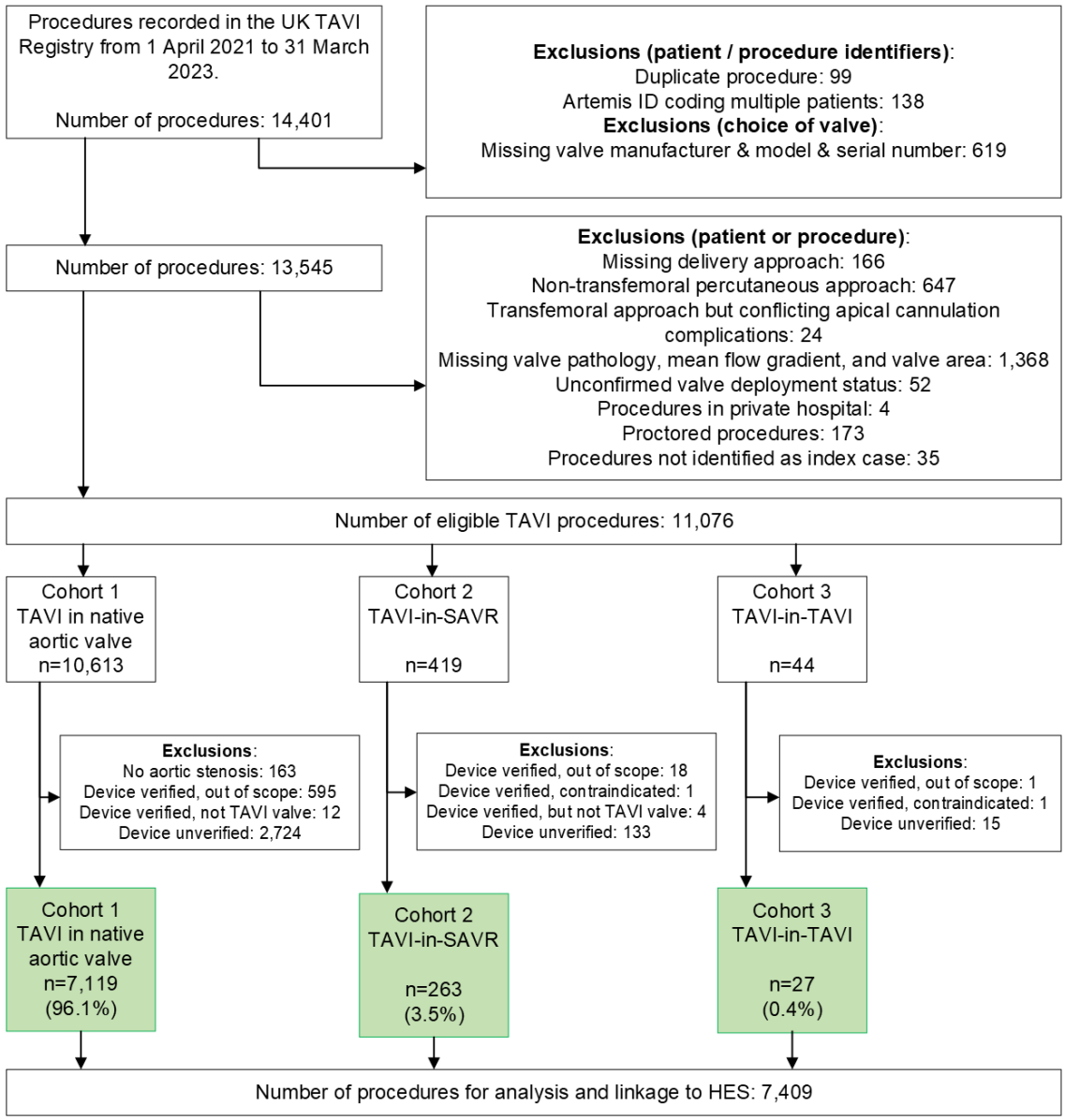
From the UK TAVI Registry, a total of 14,401 TAVI procedures were undertaken between 01 April 2021 to 31 March 2023 in England, Wales and Northern Ireland. This is broadly consistent with the figures reported in the recent NICOR report (2024) (7,669 from 01 April 2022 to 31 March 2023, 6,738 from 01 April 2021 to 31 March 2022; total of 14,407). The EAG applied cleaning rules to narrow to the population in scope, and to ensure generalisability of results. The top three reasons for exclusion were:

- missing valve pathology, mean flow gradient and valve area, such that it was not possible to confirm an aortic stenosis population (n=1,368, 9%),
- missing valve manufacturer, model, and serial number such that it was not possible to determine the device used (n=619, 4%),
- restricting to transfemoral delivery approach as per GIRFT recommendations thus excluding evidence where a non-transfemoral approach was taken (n=671, 5.0%) or where the delivery approach was not reported (n=166, 1%).

Following exclusions, 3 cohorts were identified: 10,613 TAVI in native aortic valve procedures (95.8 %), 419 TAVI-in-SAVR procedures (3.8%) and 44 TAVI-in-TAVI procedures (0.4%), Figure 1. NICOR reports that approximately 3% of people undergoing TAVI between 2022 and 2023 had a previous surgical bioprosthetic valve

(TAVI-in-SAVR), and that approximately 0.5% of procedures were TAVI-in-TAVI, which is consistent with EAG's findings. Following verification of the TAVI device using serial numbers, the EAG applied further exclusions, removing 3,667 procedures where device model could not be verified, or it was verified that an older version not in scope was used; 33%. A total of 7,409 procedures remained for analysis, comprising 7,119 native aortic valve (96.1%), 263 TAVI-in-SAVR (3.5%), and 27 TAVI-in-TAVI (0.4%).

Figure 1: Data flow diagram for UK TAVI Registry



Of the 7,119 procedures in native aortic valve:

- Sapien 3 Ultra was used in 3,919 (55%),

- Sapien 3 in 1,229 (17%),
- Evolut Pro+ in 987 (14%),
- Evolut R in 374 (5%),
- ACURATE neo2 in 347 (5%),
- Navitor in 260 (4%) and
- Evolut FX in 3 (0.04%).

Of the 263 TAVI-in-SAVR procedures:

- Sapien 3 Ultra was used in 101 (38%),
- Evolut R in 79 (30%),
- Evolut Pro+ in 51 (19%),
- Sapien 3 in 24 (9%) and
- Navitor in 8 (3%).

Of the 27 TAVI-in-TAVI procedures:

- Sapien 3 Ultra was used in 19 (70%),
- Evolut R in 3 (11%),
- Evolut Pro+ in 2 (7%),
- Sapien 3 in 2 (7%) and
- Navitor in 1 (4%).

After cleaning, there were 3 procedures in the UK TAVI Registry that used Medtronic's Evolut FX; all were in the TAVI in native aortic valve cohort. Because this was too few for meaningful statistical analysis, these procedures are not included in any tables or analyses where different models of valve are considered separately. The EAG note that 2 valve-in-valve procedures used ACURATE neo2 (1 in TAVI-in-SAVR, 1 in TAVI-in-TAVI) which is considered off-label use as this device is explicitly contraindicated in this group (likely related to clinical situation). A total of 12 hospitals used TAVI devices manufactured by Abbott Medical, 9 by Boston Scientific, 30 by Edwards Lifesciences and 23 by Medtronic. Three hospitals reported using devices from 1 manufacturer, 21 hospitals used devices from 2 manufacturers, 3 hospitals used devices from 3 manufacturers, and 5 hospitals used devices from all 4 manufacturers. Most (90.6%) had access to at least 1 balloon-

expanding and 1 self-expanding TAVI device. After cleaning and exclusions, the EAG found the centre volume (for the 32 NHS hospitals that submitted data to the UK TAVI Registry) ranged from 1 to 379 in 2022 to 2023, compared with a range of 21 to 461 reported for NHS providers in the NICOR report (2024).

The median age across all cohorts combined was 82 [IQR: 77 to 86] years; consistent with the recent NICOR report (2024). The EAG found 17.6% of procedures were in patients aged 75 years or under in 2022 to 2023, compared with 17.2% reported by NICOR for the same period. Other comparable patient characteristics and procedural data between EAG analysis (all cohorts after cleaning) and the report by NICOR (2024), respectively, for 2022 to 2023 were the proportion of urgent, emergent or salvage procedures (24.1% versus 25.4%), the proportion of procedures in female patients (42.4% versus 42.5%), the proportion of procedures in patients with previous CABG (7.9% versus 7.3%) or valve surgery (3.9% versus 4.2%), the proportion of procedures using conscious sedation (98.3% versus 93.9%), and proportion of procedures using cerebral embolic protection (11.6% versus 10.4%). The EAG summarised some additional patient characteristics that were deemed to be clinically important, aggregated across all TAVI cohorts combined including: 220 procedures with a patient body weight less than 50kg (3.1% of the 6,996 procedures with weight recorded), 688 (9.8%) greater than 100kg, and 338 with pulmonary artery systolic pressure greater than 50 (14.5% of the 2,331 procedures with this data field recorded).

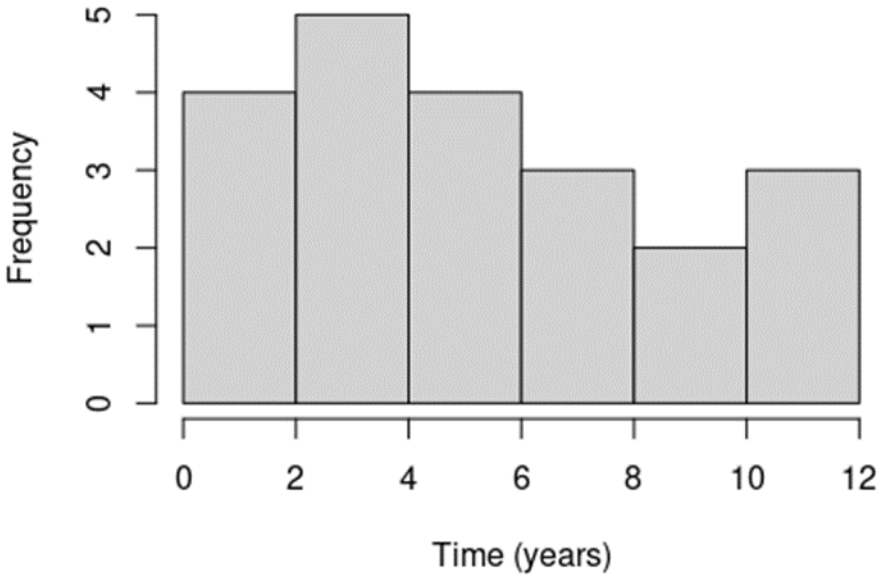
Comparable outcomes between the EAG analysis (all cohorts) and NICOR report (2024), respectively, for 2022 to 2023, were median length of stay for elective procedures (3 days, both EAG and NICOR analysis), length of stay for urgent procedures (16 days versus 15 days), in hospital mortality (1.0% versus 2.1%), in hospital stroke (1.4%, both EAG and NICOR analysis), major bleeding (0.9% versus 1.0%), major vascular access complications (1.3% versus 1.4%), moderate or severe aortic regurgitation (1.8%, both EAG and NICOR analysis), and pacemaker implantation during or after procedure (6.7% versus 6.3%).

The patient and procedural characteristics of the 3 cohorts (TAVI in native aortic valve, TAVI-in-SAVR, and TAVI-in-TAVI) with TAVI undertaken between 01 April 2021 and 31 March 2023 are reported separately (Appendix C6). Differences

between cohorts were seen for age in years, the proportion aged over 90 years, mean aortic pressure gradient (mmHg), peak pressure gradient (mmHg), valve area (cm2), annular diameter (mm), critical status pre-procedure, marked limitation of physical activity or symptoms at rest using the NYHA dyspnoea scale, or CCS Angina Score, categorical valve size (small, medium, large), non-elective procedure, planned use of general anaesthesia, previous CABG, and any cardiac or coronary comorbidity. These population differences further justify analysing these cohorts separately.

For the TAVI-in-TAVI group, 21 of 27 (77%) procedures reported a date of previous TAVI; with a median of 1,750 days (4.8 years) between TAVI procedures (range 7 to 3,913 days [10.7 years]), Figure 2. There were 2 repeated TAVI procedures within 30 days of the first, 2 occurring between 30 days and 1 year, and most (n=17) occurred more than 1 year after the first. From the data available in the UK TAVI Registry, it was not possible to calculate the time between SAVR and TAVI for the TAVI-in-SAVR group.

Figure 2: Time between TAVI procedures for the TAVI-in-TAVI cohort



5.3.3 Univariate analysis

Patient and procedural characteristics for the patients undergoing TAVI in native aortic valve for aortic stenosis (the largest cohort) were tabulated by device manufacturer, Table 16. Univariate analysis of a number of patient and procedural characteristics showed statistical differences between TAVI devices, including: age, sex, height, weight, pulmonary artery systolic pressure, aortic valve mean gradient and peak gradient, valve area, annular diameter, extensive calcification of ascending aorta pre-procedure, severe symptoms (by NYHA dyspnoea or CCS angina status), poor left ventricular ejection fraction (LVEF), history of smoking, presence of more than 50% stenosis in at least one coronary vessel, calculated creatinine clearance, extracardiac arteriopathy, size of TAVI device implanted, and use of cerebral protection.

Univariate analysis also highlighted statistical differences across a number of in-hospital outcomes between devices, Table 17, including: procedure duration, length of hospital stay, peak and mean pressure gradients post-procedure, valve area, presence of moderate to severe aortic regurgitation post-procedure, malposition of valve, major vascular complications, stroke before discharge, prescription of non-vitamin-K oral anticoagulants (NOACs), prescription of other anti-thrombotics, technical success (VARC-3). However, these results should be considered with caution because they may be influenced by the differences in characteristics between patients receiving different TAVI devices described previously.

Table 16: Summary of patient and procedural characteristics from UK TAVI Registry for TAVI in native aortic valve between 01 April 2021 and 31 March 2023, unadjusted

Patient and procedural characteristics	Edwards Sapien 3 (n=1,229)	Edwards Sapien 3 Ultra (n=3,919)	Boston Scientific ACURATE neo2 (n=347)	Medtronic Evolut R (n=374)	Medtronic Evolut Pro+ (n=987)	Abbott Navitor (n=260)	p-value (comparison across 6 valves; **unadjusted**)	p-value (comparison across 6 valves; **adjusted**)
Age, years: median [Q1,Q3]	81.0 [77.0 to 85.0] (n=1,229)	82.0 [78.0 to 86.0] (n=3,919)	83.0 [79.0 to 86.0] (n=347)	81.0 [76.0 to 85.0] (n=374)	82.0 [77.0 to 86.0] (n=987)	83.0 [79.0 to 86.0] (n=260)	0.0000000	<0.0001*
Age (90+ years)	59/1,229 (4.8%)	354/3,919 (9.0%)	25/347 (7.2%)	23/374 (6.1%)	95/987 (9.6%)	23/260 (8.8%)	0.0004998	0.021*
Male sex	1,121/1,227 (91.4%)	1,984/3,912 (50.7%)	125/346 (36.1%)	242/373 (64.9%)	553/986 (56.1%)	124/259 (47.9%)	0.0004998	0.021*
Height, m: median [Q1,Q3]	1.7 [1.7 to 1.8] (n=1,153)	1.6 [1.6 to 1.7] (n=3,669)	1.6 [1.6 to 1.7] (n=300)	1.7 [1.6 to 1.8] (n=366)	1.7 [1.6 to 1.7] (n=964)	1.6 [1.6 to 1.7] (n=241)	0.0000000	<0.0001*
Weight, kg: median [Q1,Q3]	84.0 [74.0 to 95.2] (n=1,158)	74.0 [64.0 to 85.5] (n=3,684)	71.0 [63.0 to 86.5] (n=293)	77.0 [65.6 to 90.0] (n=368)	74.0 [64.0 to 86.0] (n=968)	74.0 [63.7 to 83.4] (n=243)	0.0000000	<0.0001*
BMI, kg/m2: median [Q1,Q3]	27.7 [24.7 to 31.6] (n=1,149)	27.0 [23.9 to 30.9] (n=3653)	27.4 [24.2 to 31.2] (n=292)	26.8 [23.8 to 31.6] (n=366)	27.2 [23.8 to 30.9] (n=964)	27.2 [23.8 to 30.4] (n=240)	0.0076485	0.168
Underweight (BMI under 17.5)	13/1,149 (1.1%)	67/3,653 (1.8%)	7/292 (2.4%)	7/366 (1.9%)	24/964 (2.5%)	2/240 (0.8%)	0.1809095	1
Obese (BMI 30 or above)	388/1,149 (33.8%)	1,108/3,653 (30.3%)	98/292 (33.6%)	122/366 (33.3%)	302/964 (31.3%)	69/240 (28.8%)	0.2198901	1
Pulmonary artery systolic pressure, mmHg: median [Q1,Q3]	32.0 [25.0 to 44.0] (n=364)	33.0 [23.0 to 43.0] (n=1,191)	38.0 [31.0 to 46.0] (n=69)	40.0 [35.0 to 48.5] (n=172)	37.0 [30.0 to 49.5] (n=283)	32.0 [30.0 to 40.0] (n=111)	0.0000000	<0.0001*
Mean pressure gradient, mmHg: median [Q1,Q3]	42.0 [33.0 to 52.0] (n=1,155)	44.0 [36.0 to 55.0] (n=3,700)	43.0 [35.0 to 52.0] (n=333)	43.0 [37.5 to 55.0] (n=351)	45.0 [37.0 to 57.0] (n=915)	42.0 [35.0 to 52.0] (n=248)	0.0000000	<0.0001*
Peak pressure gradient, mmHg: median [Q1,Q3]	66.0 [50.0 to 81.0] (n=1,150)	71.0 [60.0 to 87.0] (n=3,623)	70.0 [59.0 to 85.0] (n=332)	71.0 [60.0 to 87.0] (n=339)	72.0 [62.0 to 88.0] (n=911)	72.0 [60.0 to 89.0] (n=235)	0.0000000	<0.0001*
Valve area, cm2: median [Q1,Q3]	0.8 [0.6 to 0.9] (n=1,115)	0.7 [0.6 to 0.8] (n=3,526)	0.7 [0.6 to 0.9] (n=312)	0.7 [0.5 to 0.8] (n=325)	0.7 [0.6 to 0.8] (n=834)	0.7 [0.6 to 0.8] (n=226)	0.0000000	<0.0001*
Annular diameter, mm: median [Q1,Q3]	27.5 [26.7 to 29.0] (n=1,004)	24.0 [22.4 to 25.3] (n=3,117)	23.2 [22.0 to 25.0] (n=191)	25.5 [22.8 to 27.0] (n=316)	24.2 [22.8 to 26.0] (n=804)	24.4 [23.0 to 25.6] (n=204)	0.0000000	<0.0001*
Extensive calcification of ascending aorta	30/1,140 (2.6%)	98/3,687 (2.7%)	11/254 (4.3%)	28/365 (7.7%)	56/950 (5.9%)	11/247 (4.5%)	0.0004998	0.021*
Critical status pre-procedure	26/1,192 (2.2%)	31/3,810 (0.8%)	1/324 (0.3%)	4/370 (1.1%)	11/967 (1.1%)	3/254 (1.2%)	0.0064968	0.149
CCS Angina Status (any limitation of physical activity)	254/1,188 (21.4%)	879/3,821 (23.0%)	61/320 (19.1%)	95/369 (25.7%)	194/943 (20.6%)	66/249 (26.5%)	0.0679660	0.975
CCS Angina Status (symptoms at rest)	13/1,188 (1.1%)	29/3,821 (0.8%)	5/320 (1.6%)	3/369 (0.8%)	10/943 (1.1%)	2/249 (0.8%)	0.5687156	1
NYHA dyspnoea status (marked limitation of physical activity, or symptoms at rest or minimal activity)	901/1,201 (75.0%)	2867/3844 (74.6%)	233/332 (70.2%)	285/369 (77.2%)	660/940 (70.2%)	153/251 (61%)	0.0004998	0.021*
NYHA dyspnoea status (symptoms at rest)	141/1,201 (11.7%)	372/3,844 (9.7%)	50/332 (15.1%)	63/369 (17.1%)	148/940 (15.7%)	34/251 (13.5%)	0.0004998	0.021*
Severe symptoms (symptoms at rest measured by CCS Angina Status or NYHA dyspnoea status)	149/1,207 (12.3%)	387/3,866 (10.0%)	53/333 (15.9%)	65/371 (17.5%)	154/949 (16.2%)	36/255 (14.1%)	0.0004998	0.021*
CSHA Clinical Frailty Score (moderately or severely frail)	93/1,158 (8.0%)	275/3,706 (7.4%)	19/287 (6.6%)	22/368 (6.0%)	75/911 (8.2%)	11/248 (4.4%)	0.3043478	1
Katz Index less than 3	39/1,128 (3.5%)	113/3,553 (3.2%)	5/279 (1.8%)	2/358 (0.6%)	22/875 (2.5%)	11/240 (4.6%)	0.0114943	0.241
Katz Index less than 6	153/1,128 (13.6%)	462/3,553 (13.0%)	38/279 (13.6%)	36/358 (10.1%)	142/875 (16.2%)	40/240 (16.7%)	0.0389805	0.703
Frailty composite (moderately or severely frail on CSHA, or Katz Index less than 6)	217/1,169 (18.6%)	655/3,739 (17.5%)	50/292 (17.1%)	46/373 (12.3%)	191/975 (19.6%)	46/249 (18.5%)	0.0479760	0.768
Poor LV function (LVEF<30%)	173/1,181 (14.6%)	242/3,786 (6.4%)	18/312 (5.8%)	45/364 (12.4%)	66/967 (6.8%)	18/251 (7.2%)	0.0004998	0.021*
Diabetes	307/1,196 (25.7%)	995/3,825 (26.0%)	86/325 (26.5%)	104/372 (28.0%)	240/976 (24.6%)	61/258 (23.6%)	0.7661169	1
Ever smoked (current and ex smokers)	540/988 (54.7%)	1,447/3,094 (46.8%)	134/288 (46.5%)	166/319 (52.0%)	370/822 (45.0%)	81/227 (35.7%)	0.0004998	0.021*

Patient and procedural characteristics	Edwards Sapien 3 (n=1,229)	Edwards Sapien 3 Ultra (n=3,919)	Boston Scientific ACURATE neo2 (n=347)	Medtronic Evolut R (n=374)	Medtronic Evolut Pro+ (n=987)	Abbott Navitor (n=260)	p-value (comparison across 6 valves; **unadjusted**)	p-value (comparison across 6 valves; **adjusted**)
Dialysis	18/1,191 (1.5%)	72/3,814 (1.9%)	2/334 (0.6%)	4/369 (1.1%)	16/977 (1.6%)	4/233 (1.7%)	0.5422289	1
Presence of left main stem disease	30/1,095 (2.7%)	78/3,377 (2.3%)	4/249 (1.6%)	8/325 (2.5%)	27/860 (3.1%)	9/222 (4.1%)	0.3808096	1
Presence of >50% stenosis in at least one coronary vessel, excluding left main stem disease	314/1,092 (28.8%)	840/3,340 (25.1%)	68/248 (27.4%)	95/325 (29.2%)	184/871 (21.1%)	60/216 (27.8%)	0.0034983	0.087
Valve size, mm: median [Q1,Q3]	29.0 [29.0 to 29.0] (n=1,229)	26.0 [23.0 to 26.0] (n=3,919)	25.0 [23.0 to 27.0] (n=347)	34.0 [29.0 to 34.0] (n=374)	29.0 [26.0 to 29.0] (n=987)	27.0 [25.0 to 29.0] (n=260)	0.0000000	<0.0001*
Valve size (categorical: small, medium, large)	S: 52/1,229 (4.2%); M: 72/1,229 (5.9%); L: 1,105/1,229 (89.9%)	S: 1,830/3,919 (46.7%); M: 2,089/3,919 (53.3%); L: 0/3,919 (0%)	S: 106/347 (30.5%); M: 141/347 (40.6%); L: 100/347 (28.8%)	S: 20/374 (5.3%); M: 68/374 (18.2%); L: 286/374 (76.5%)	S: 29/987 (2.9%); M: 248/987 (25.1%); L: 710/987 (71.9%)	S: 18/260 (6.9%); M: 162/260 (62.3%); L: 80/260 (30.8%)	0.0004998	0.021*
Non-elective procedure	316/1,225 (25.8%)	922/3,904 (23.6%)	63/347 (18.2%)	112/374 (29.9%)	253/986 (25.7%)	67/260 (25.8%)	0.0019990	0.054
Procedure urgency (non-elective procedure, or critical status pre-procedure)	319/1,229 (26%)	930/3,919 (23.7%)	63/347 (18.2%)	113/374 (30.2%)	255/987 (25.8%)	68/260 (26.2%)	0.0054973	0.132
Planned use of general anaesthesia	17/1,217 (1.4%)	28/3,893 (0.7%)	1/347 (0.3%)	6/374 (1.6%)	11/980 (1.1%)	3/260 (1.2%)	0.0929535	1
Previous balloon aortic valvuloplasty	29/1,216 (2.4%)	119/3,869 (3.1%)	8/336 (2.4%)	8/370 (2.2%)	32/975 (3.3%)	7/260 (2.7%)	0.7191404	1
Use of cardiopulmonary bypass	10/1,216 (0.8%)	9/3,878 (0.2%)	1/339 (0.3%)	1/369 (0.3%)	4/961 (0.4%)	2/255 (0.8%)	0.0689655	0.975
Use of cerebral circulation protection device(s)	160/1,221 (13.1%)	376/3,892 (9.7%)	63/347 (18.2%)	40/370 (10.8%)	132/977 (13.5%)	17/258 (6.6%)	0.0004998	0.021*
Creatinine clearance, mL/min: median [Q1,Q3]	64.1 [48.5 to 81.0] (n=1,117)	54.6 [40.4 to 71.1] (n=3,488)	51.6 [39.2 to 66.8] (n=277)	55.1 [41.3 to 73.5] (n=359)	53.8 [39.6 to 69.9] (n=942)	52.0 [39.0 to 66.9] (n=214)	0.0000000	<0.0001*
Creatinine clearance less than 30 mL/min	63/1,117 (5.6%)	336/3,488 (9.6%)	27/277 (9.7%)	28/359 (7.8%)	98/942 (10.4%)	19/214 (8.9%)	0.0014993	0.042*
Previous MI (ever)	154/1,218 (12.6%)	458/3,865 (11.8%)	36/334 (10.8%)	65/372 (17.5%)	109/979 (11.1%)	29/259 (11.2%)	0.0414793	0.705
Previous MI (within previous 90 days)	26/1,218 (2.1%)	80/3,865 (2.1%)	2/334 (0.6%)	12/372 (3.2%)	21/979 (2.1%)	7/259 (2.7%)	0.2028986	1
Previous PCI	162/1,208 (13.4%)	501/3,855 (13.0%)	40/335 (11.9%)	67/370 (18.1%)	123/976 (12.6%)	29/259 (11.2%)	0.1094453	1
Previous CABG	107/1,182 (9.1%)	305/3,800 (8.0%)	29/323 (9.0%)	39/370 (10.5%)	64/973 (6.6%)	28/235 (11.9%)	0.0369815	0.703
Previous stroke or TIA	131/1,209 (10.8%)	450/3,837 (11.7%)	48/335 (14.3%)	46/369 (12.5%)	107/973 (11.0%)	24/258 (9.3%)	0.4082959	1
Presence of extracardiac arteriopathy	117/1,199 (9.8%)	273/3,808 (7.2%)	34/312 (10.9%)	63/371 (17.0%)	125/973 (12.8%)	40/251 (15.9%)	0.0004998	0.021*
Any cardiac or coronary comorbidity (previous MI, PCI, or CABG, presence of extracardiac arteriopathy or Extensive calcification of ascending aorta, symptoms at rest on NYHA or CCS, poor LV function, left main stem disease or stenosis of at least 50% in one vessel)	640/1,226 (52.2%)	1748/3,907 (44.7%)	147/345 (42.6%)	213/374 (57.0%)	462/987 (46.8%)	124/260 (47.7%)	0.0004998	0.021*
Anatomical coronary comorbidity (left main stem disease, or stenosis of at least 50% in one vessel)	317/1,115 (28.4%)	847/3,422 (24.8%)	70/264 (26.5%)	96/328 (29.3%)	185/878 (21.1%)	62/222 (27.9%)	0.0029985	0.078
Clinical coronary comorbidity (previous MI, PCI or CABG)	296/1,222 (24.2%)	862/3,888 (22.2%)	74/340 (21.8%)	108/373 (29.0%)	209/981 (21.3%)	63/260 (24.2%)	0.0294853	0.59
Any non-cardiac or non-coronary comorbidity (previous stroke or TIA, diabetes, current or former smoker, extracardiac arteriopathy, current dialysis or creatinine clearance less than 30)	797/1,221 (65.3%)	2397/3,886 (61.7%)	219/339 (64.6%)	246/373 (66.0%)	623/983 (63.4%)	150/260 (57.7%)	0.0649675	0.975
Non-cardiac non-coronary other comorbidity (previous	229/1,216 (18.8%)	657/3,867 (17.0%)	75/336 (22.3%)	92/373 (24.7%)	213/979 (21.8%)	58/259 (22.4%)	0.0004998	0.021*

Patient and procedural characteristics	Edwards Sapien 3 (n=1,229)	Edwards Sapien 3 Ultra (n=3,919)	Boston Scientific ACURATE neo2 (n=347)	Medtronic Evolut R (n=374)	Medtronic Evolut Pro+ (n=987)	Abbott Navitor (n=260)	p-value (comparison across 6 valves; **unadjusted**)	p-value (comparison across 6 valves; **adjusted**)
stroke or extracardiac arteriopathy)								
Non-cardiac non-coronary risk factor (current or former smoker, or diabetes)	692/1,206 (57.4%)	2,022/3,865 (52.3%)	185/337 (54.9%)	219/372 (58.9%)	504/978 (51.5%)	117/259 (45.2%)	0.0004998	0.021*
Renal comorbidity (current dialysis or creatinine clearance less than 30)	67/1,205 (5.6%)	365/3,849 (9.5%)	28/335 (8.4%)	28/373 (7.5%)	100/980 (10.2%)	20/248 (8.1%)	0.0004998	0.021*

Key: Significance of **adjusted** p-values (using Holm-Bonferroni correction) denoted by: *** < 0.001, ** <0.01, * < 0.05
Abbreviations: CABG, Coronary artery bypass grafting; CCS, Canadian Cardiovascular Society; CSHA, Canadian Study of Health and Aging; LVEF, Left ventricular ejection fraction; MI, myocardial infarction NYHA, New York Heart Association; PCI, Percutaneous coronary intervention; TIA, Transient ischaemic attack

Table 17: Summary of results from UK TAVI Registry for TAVI in native aortic valve (01 April 2021 to 31 March 2023), unadjusted

In-hospital outcome	Edwards Sapien 3 (n=1,229)	Edwards Sapien 3 Ultra (n=3,919)	Boston Scientific ACURATE neo2 (n=347)	Medtronic Evolut R (n=374)	Medtronic Evolut Pro+ (n=987)	Abbott Navitor (n=260)	p-value (comparison across 6 values; **unadjusted**)	p-value (comparison across 6 valves; **adjusted**)
Length of procedure, minutes: median [Q1,Q3]	61.0 [55.0 to 80.0] (n=1,080)	60.0 [55.0 to 75.0] (n=3,280)	80.0 [64.5 to 102.0] (n=331)	80.0 [65.0 to 108.0] (n=351)	75.0 [60.0 to 92.0] (n=821)	71.5 [60.0 to 90.0] (n=230)	0.0000000	<0.0001*
Length of hospital stay, overnight stays: median [Q1,Q3]	3.0 [2.0 to 8.2] (n=1,008)	3.0 [2.0 to 9.0] (n=3,064)	3.0 [2.0 to 5.0] (n=305)	4.0 [2.0 to 11.0] (n=365)	4.0 [2.0 to 13.0] (n=905)	3.0 [2.0 to 11.0] (n=189)	0.0000000	<0.0001*
Peak pressure gradient, mmHg: median [Q1,Q3]	12.0 [9.0 to 18.0] (n=812)	15.0 [10.0 to 22.0] (n=2,649)	16.0 [11.1 to 22.0] (n=258)	12.0 [8.0 to 17.0] (n=269)	13.0 [9.0 to 18.0] (n=605)	14.0 [10.0 to 20.0] (n=168)	0.0000000	<0.0001*
Mean pressure gradient, mmHg: median [Q1,Q3]	6.0 [5.0 to 10.0] (n=849)	8.0 [5.0 to 12.0] (n=2,799)	8.0 [6.0 to 11.0] (n=273)	7.0 [4.0 to 11.0] (n=296)	6.0 [4.0 to 9.0] (n=672)	7.0 [5.0 to 10.0] (n=195)	0.0000000	<0.0001*
Valve area, cm2: median [Q1,Q3]	2.0 [1.6 to 2.4] (n=558)	1.8 [1.5 to 2.1] (n=1,829)	1.8 [1.4 to 2.0] (n=202)	1.9 [1.6 to 2.0] (n=215)	1.7 [1.5 to 2.0] (n=458)	1.8 [1.5 to 2.1] (n=101)	0.0000000	<0.0001*
Aortic regurgitation	11/1,183 (0.9%)	38/3,760 (1.0%)	10/309 (3.2%)	15/365 (4.1%)	42/966 (4.3%)	6/250 (2.4%)	0.0004998	0.011*
Valve failure	3/1,219 (0.2%)	7/3,896 (0.2%)	1/345 (0.3%)	1/371 (0.3%)	3/980 (0.3%)	0/256 (0%)	0.7881059	1
Unsuccessful valve deployment	16/1,229 (1.3%)	74/3,919 (1.9%)	1/347 (0.3%)	8/374 (2.1%)	30/987 (3.0%)	2/260 (0.8%)	0.0039980	0.052
Malposition of valve	4/1,185 (0.3%)	16/3,758 (0.4%)	6/345 (1.7%)	8/362 (2.2%)	11/885 (1.2%)	5/257 (1.9%)	0.0004998	0.011*
Use of post implantation balloon dilatation	56/1,181 (4.7%)	225/3,743 (6.0%)	31/343 (9.0%)	58/361 (16.1%)	150/875 (17.1%)	54/253 (21.3%)	0.0004998	0.011*
Need for permanent pacing	87/1,162 (7.5%)	229/3,681 (6.2%)	15/305 (4.9%)	33/358 (9.2%)	108/875 (12.3%)	40/253 (15.8%)	0.0004998	0.011*
Conversion to sternotomy for valve surgery	1/1,220 (0.1%)	3/3,892 (0.1%)	1/341 (0.3%)	1/368 (0.3%)	2/972 (0.2%)	0/258 (0%)	0.3073463	1
Valve reintervention before discharge	3/1,215 (0.2%)	13/3,883 (0.3%)	1/344 (0.3%)	5/361 (1.4%)	7/960 (0.7%)	1/257 (0.4%)	0.0579710	0.464
Failure of percutaneous closure device	21/1,161 (1.8%)	43/3,658 (1.2%)	4/287 (1.4%)	9/357 (2.5%)	13/853 (1.5%)	3/247 (1.2%)	0.2603698	1
Need for bailout PCI	3/1,215 (0.2%)	16/3,890 (0.4%)	0/341 (0%)	1/365 (0.3%)	0/965 (0%)	0/257 (0%)	0.3148426	1
Need for bailout TAVI-in-TAVI	4/1,188 (0.3%)	15/3,765 (0.4%)	3/346 (0.9%)	7/362 (1.9%)	9/895 (1%)	0/257 (0%)	0.0029985	0.042*
MI within 72 hours of procedure	1/1,174 (0.1%)	11/3,677 (0.3%)	2/296 (0.7%)	1/361 (0.3%)	1/917 (0.1%)	0/240 (0%)	0.3613193	1
Major, life threatening or disabling bleeding	15/1,157 (1.3%)	29/3,664 (0.8%)	8/285 (2.8%)	6/351 (1.7%)	9/842 (1.1%)	3/243 (1.2%)	0.0254873	0.255
Major vascular complications	12/1,152 (1.0%)	36/3,647 (1.0%)	9/288 (3.1%)	11/357 (3.1%)	13/850 (1.5%)	6/244 (2.5%)	0.0009995	0.018*
Tamponade during or after procedure	11/1,196 (0.9%)	35/3,851 (0.9%)	2/325 (0.6%)	0/370 (0%)	4/976 (0.4%)	0/256 (0%)	0.1489255	1
Stroke before discharge	23/1,140 (2.0%)	43/3,618 (1.2%)	2/289 (0.7%)	6/349 (1.7%)	25/850 (2.9%)	8/230 (3.5%)	0.0019990	0.03*
Modified Rankin score of 4 or above	1/152 (0.7%)	3/448 (0.7%)	1/41 (2.4%)	0/8 (0%)	2/15 (13.3%)	2/43 (4.7%)	0.0054973	0.066
Need for renal replacement therapy	0/1,155 (0%)	5/3,638 (0.1%)	0/286 (0%)	2/352 (0.6%)	1/835 (0.1%)	0/242 (0%)	0.2353823	1
Deaths	14/1,221 (1.1%)	39/3,899 (1.0%)	6/343 (1.7%)	8/372 (2.2%)	15/972 (1.5%)	7/255 (2.7%)	0.0474763	0.427
Prescribed NOACs	371/1,126 (32.9%)	916/3,556 (25.8%)	78/300 (26.0%)	128/350 (36.6%)	238/919 (25.9%)	57/229 (24.9%)	0.0004998	0.011*
Prescribed other anti-thrombotics	131/1,126 (11.6%)	314/3,556 (8.8%)	40/300 (13.3%)	27/350 (7.7%)	85/919 (9.2%)	10/229 (4.4%)	0.0014993	0.024*
Prescribed antiplatelets	676/1,109 (61.0%)	2,309/3,482 (66.3%)	195/302 (64.6%)	224/355 (63.1%)	617/925 (66.7%)	153/219 (69.9%)	0.0124938	0.137
Technical success (VARC-3)	1,129/1,168 (96.7%)	3,579/3,730 (96.0%)	319/334 (95.5%)	326/350 (93.1%)	805/864 (93.2%)	238/251 (94.8%)	0.0009995	0.018*

Key: Significance of **adjusted** p-values (using Holm-Bonferroni correction) denoted by: *** < 0.001, ** <0.01, * < 0.05
Abbreviations: MI, Myocardial infarction; NOAC, Non-vitamin K oral anticoagulants; PCI, Percutaneous coronary intervention; TAVI, transcatheter aortic valve implantation,

5.4 *Hospital Episode Statistics (HES)*

5.4.1 Quality appraisal

The EAG highlight that analysis of observed real-world data from Hospital Episode Statistics (HES) includes tests for associations between recorded variables but does not establish causality.

The EAG (single reviewer) completed formal critical appraisal of Hospital Episode Statistics using the Data Suitability Assessment Tool (DataSAT), Appendix D4. Data from the HES Admitted Patient Care (APC) dataset (which includes day cases) in this report includes NHS activity between 01 April 2021 and 31 October 2023 across all hospitals in England. Activity from private hospitals was excluded to ensure generalisability to the NHS. A key limitation is that HES source does not record device manufacturer or model. Results may include devices used outside of their indications for use (considered off-label) and potentially older devices no longer available from NHS Supply Chain. As such, HES cannot be used in isolation to determine longitudinal outcomes for the TAVI devices listed in the Final Scope. While NHS Digital previously produced data quality reports on HES data commenting on activity levels and data completeness compared with the prior month or year (no longer available), the EAG was unable to determine an estimate of overall data quality, accuracy or completeness of clinical coding when compared with patient records.

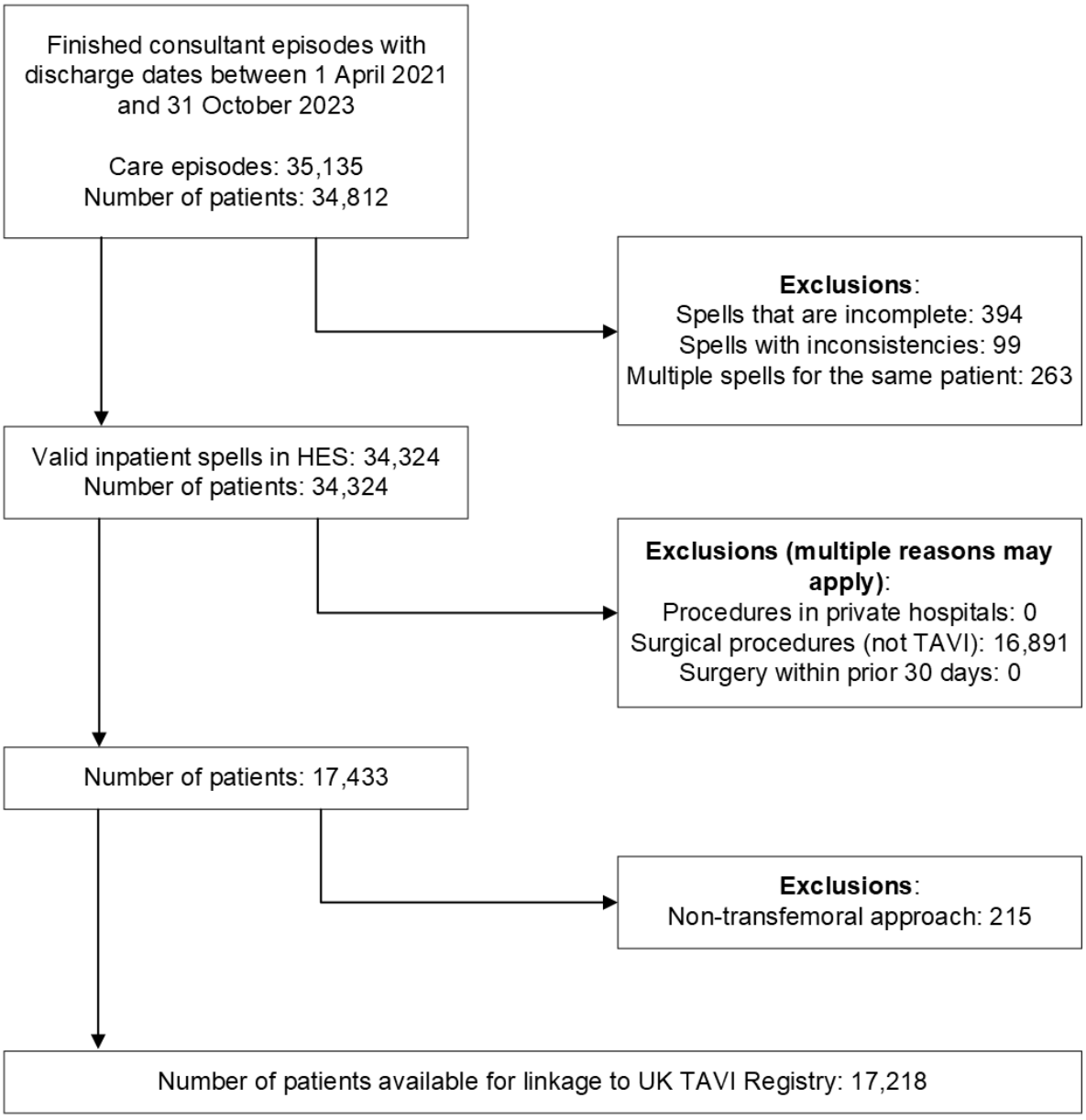
HES is an administrative database managed by NHS Digital (part of NHS England from February 2023), which is used for activity monitoring for reimbursement purposes in England. Because of this it includes routine information on length of hospital and intensive care unit stay. Linkage of HES to Civil Registration of Mortality (formerly ONS) enables longitudinal tracking of patients across England, including the date and cause of death (where applicable). A key limitation of HES is that the data source lacks clinical detail relevant to this late-stage assessment, including surgical risk, degree of calcification, haemodynamic performance (aortic valve gradients, aortic valve area), medication and quality of life measures. This results in poor translation to VARC-3 outcomes, see Appendix D2. HES does not record information on

patient mobility, prior medication, severity of complications, or operator learning curve, which may confound outcomes. HES does permit comprehensive follow-up across all hospitals in England enabling robust estimates of subsequent stroke and pacemaker implantation events, however the EAG acknowledges that late events may not be directly attributable to TAVI. Clinical coding practice varies across the NHS, which may introduce bias into both cohort identification and subsequent analysis. However, analysis of common data fields that exist in both HES and the UK TAVI Registry (for example mortality, stroke) enables some data validation of in-hospital outcomes.

5.4.2 Cohort identification

A total of 17,433 index spells (admissions) from 17,433 patients having TAVI procedures were identified in HES, with 215 excluded because their procedure used a transapical (rather than transfemoral) approach, Figure 3. This resulted in a total of 17,218 remaining for analysis. The EAG note that determining surgical history of each patient back to 2007 should capture most TAVI procedures, however it may not be sufficient to capture all prior SAVR procedures, which can occur 20 years before TAVI. Therefore, to avoid introducing bias, the procedures identified in HES were not assigned to cohorts before linkage to the UK TAVI Registry (that is, the data contained in the Registry was assumed to accurately record all prior TAVI and SAVR procedures).

Figure 3: Data flow diagram for Hospital Episode Statistics (HES)



5.4.3 Univariate analysis

The patient and procedural characteristics of 17,218 patients undergoing TAVI between 01 April 2021 and 31 October 2023 (latest data available) across 32 hospital providers (median [Q1,Q3] hospital volume of 209 [110,268] procedures annually) are presented in Table 18. A total of 19.4% were admitted as an emergency. Considering patient pathway, a total of 2,100 patients (12.2%) were admitted from another hospital but not as an emergency. A total of 234 (1.4%) had documented cerebral protection during their TAVI procedure, which is substantially lower than the proportion reported in the UK TAVI Registry (11.2% of TAVI procedures in native aortic valves used cerebral circulation protection).

Clinical outcomes for the TAVI cohort between 01 April 2021 and 31 October 2023, are reported in Table 19. The EAG note a total of 14.8% of patients (2,550 of 17,218) needed a critical care admission, with median [Q1,Q3] duration in critical care being 2 [1,4] nights (time calculated from admission to critical care, to discharge from critical care) during the TAVI procedural admission. Whilst in critical care 740 patients needed advanced cardiovascular support, 1,590 basic cardiovascular support, 595 advanced respiratory support, 760 basic respiratory support, 238 neurological support, and 295 required renal support. A total of 249 in-hospital deaths occurred during the TAVI procedural admission. Most patients were discharged to their usual place of residence (94.5%, n=16,262 patients), 494 patients (2.9%) were discharged to another hospital provider, and 47 (0.3%) to a care or nursing home.

A total of 1,884 deaths occurred after discharge, 203 within 30 days. A total of 1,681 deaths occurred after 30 days follow-up, 592 (32.4%) were because of major cardiovascular disease (Appendix D3). A total of 359 patients (2.1%) had a stroke or TIA during the TAVI procedural admission (of which 36 died in hospital). An additional 1.4% (95% CI 1.2 to 1.5%) experienced a stroke or TIA after discharge but within 30 days of the procedure. Of the total 624 patients who experienced a stroke after discharge, 217 died during follow-up, 48 were readmitted with heart failure, 28 needed a pacemaker, 5 needed TAVI reintervention, and 1 needed an SAVR during follow-up. However, it is important to note that these are crude event counts and that length of follow-up varied across patients.

Table 18: Summary of patient and procedural characteristics from HES, unadjusted

Parameter	HES: all TAVI procedures between 01 April 2021 and 31 October 2023 (n=17,218)
Age, years; median [Q1,Q3]	82.0 [77.0 to 86.0] (n=17,218)
Male sex, % [95%CI]	57.7 [57.0 to 58.5] (n=9,937)
Diabetes, % [95%CI]	26.4 [25.7 to 27.1] (n=4,546)
Emergency admission, (%)	19.4 [18.8 to 20.0] (n=3,344)
Previous CABG, % [95%CI]	6.5 [6.2 to 6.9] (n=1,126)
Previous PCI, % [95%CI]	11.8 [11.4 to 12.3] (n=2,039)
Previous dialysis, % [95%CI]	1.5 [1.3 to 1.7] (n=261)
History of stroke or TIA, % [95%CI]	7.9 [7.5 to 8.4] (n=1,368)
History of myocardial infarction, % [95%CI]	11.6 [11.1 to 12.1] (n=1,997)
History of conduction abnormalities/arrhythmia, % [95%CI]	50.7 [49.9 to 51.4] (n=8,722)

Abbreviations: CABG, Coronary artery bypass grafting; CI, Confidence interval; PCI, Percutaneous coronary intervention; TAVI, transcatheter aortic valve implantation; TIA, transient ischaemic attack

Table 19: Summary of outcomes from HES, unadjusted *[Note: complications not mutually exclusive, longitudinal events included until time to first event]*

Outcome	HES: TAVI (in native aortic valve) 01 April 2021 to 31 October 2023 (n=17,218)
Length of hospital stay, nights; median [Q1,Q3]	3.0 [2.0 to 8.0] (n=17,217)
Length of intensive care unit stay, nights; median [Q1,Q3]	2.0 [1.0 to 4.0] (n=2,398)
In-hospital pacemaker implantation, % [95%CI]	9.1 [8.7 to 9.5] (n=1,568)
In-hospital vascular complications, % [95%CI]	0.2 [0.1 to 0.3] (n=32)
In-hospital bleeding, % [95%CI]	9.7 [9.2 to 10.1] (n=1,664)
In-hospital stroke or TIA, % [95%CI]	2.1 [1.9 to 2.3] (n=359)
In-hospital stroke, % [95%CI]	1.9 [1.7 to 2.2] (n=335)
In-hospital TIA, % [95%CI]	0.1 [0.1 to 0.2] (n=24)
In-hospital death, % [95%CI]	1.4 [1.3 to 1.6] (n=249)
Median [Q1,Q3] length of follow-up from discharge until the earliest of death or 31 October 2023, days	385.0 [179.0 to 629.0]
Death, patients	1,884
30 days, % [95%CI]	0.9 [0.8 to 1.1] (n=16,382)
1 year, % [95%CI]	9.2 [8.7 to 9.7] (n=8,872)
2 years, % [95%CI]	18.1 [17.2 to 19.0] (n=2,844)
Aortic valve reintervention, patients	110
30 days, % [95%CI]	0.2 [0.1 to 0.2] (n=16,356)
1 year, % [95%CI]	0.6 [0.5 to 0.8] (n=8,814)

Outcome	HES: TAVI (in native aortic valve) 01 April 2021 to 31 October 2023 (n=17,218)
2 years, % [95%CI]	1.0 [0.8 to 1.2] (n=2,814)
Subsequent TAVI, patients	87
30 days, % [95%CI]	0.1 [0.1 to 0.2] (n=16,361)
1 year, % [95%CI]	0.5 [0.4 to 0.6] (n=8,829)
2 years, % [95%CI]	0.7 [0.5 to 0.9] (n=2,823)
Subsequent SAVR, patients	27
30 days, % [95%CI]	0.0 [0.0 to 0.1] (n=16,377)
1 year, % [95%CI]	0.2 [0.1 to 0.2] (n=8,857)
2 years, % [95%CI]	0.3 [0.2 to 0.4] (n=2,835)
Pacemaker implantation, patients	577
30 days, % [95%CI]	1.2 [1.0 to 1.4] (n=16,184)
1 year, % [95%CI]	3.3 [3.0 to 3.6] (n=8,599)
2 years, % [95%CI]	4.9 [4.4 to 5.3] (n=2,695)
Stroke or TIA, patients	624
30 days, % [95%CI]	1.4 [1.2 to 1.5] (n=16,180)
1 year, % [95%CI]	3.4 [3.1 to 3.7] (n=8,639)
2 years, % [95%CI]	5.4 [4.9 to 5.9] (n=2,742)
Stroke, patients	524
30 days, % [95%CI]	1.2 [1.0 to 1.3] (n=16,210)
1 year, % [95%CI]	2.8 [2.6 to 3.1] (n=8,692)
2 years, % [95%CI]	4.5 [4.1 to 5.0] (n=2,767)
Heart failure, patients	975
30 days, % [95%CI]	1.5 [1.3 to 1.6] (n=16,160)
1 year, % [95%CI]	5.6 [5.2 to 6.0] (n=8,475)
2 years, % [95%CI]	8.4 [7.9 to 9.0] (n=2,663)

Abbreviations: CI, Confidence interval; HES, Hospital Episode Statistics; TAVI, Transcatheter aortic valve implantation; TIA, Transient ischaemic attack

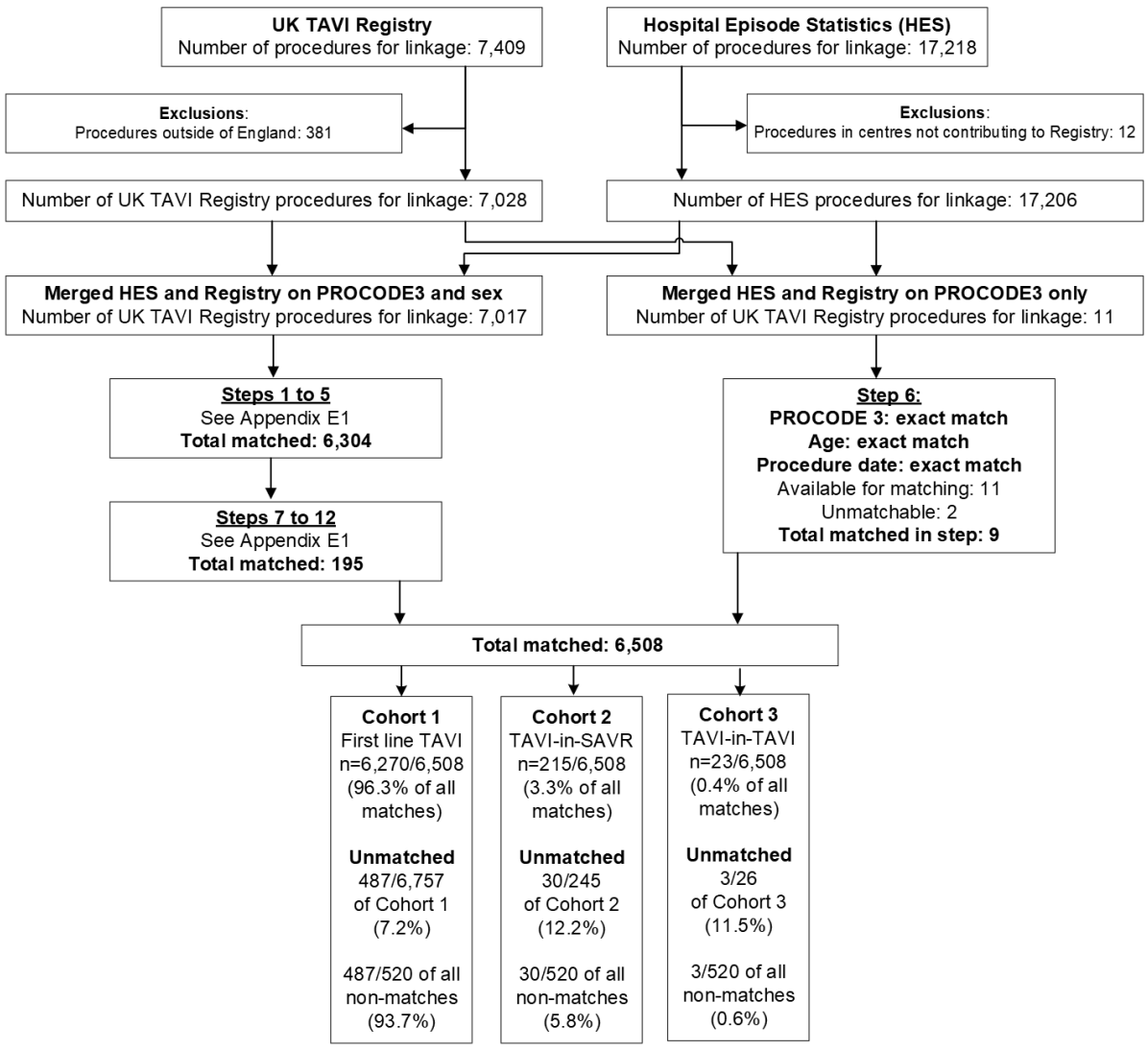
5.5 *Linkage of UK TAVI Registry and HES*

Data linkage between UK TAVI Registry and HES was only possible for 7,028 of 7,409 procedures in the Registry, which were conducted in England (the geographical coverage of HES). In total, 6,508 out of 7,028 procedures in the UK TAVI Registry (92.6%) were successfully and uniquely matched to one of the 17,218 procedures in HES, Figure 4. (breakdown of matching steps described in Appendix E1).

A match was found for 92.8% of UK TAVI Registry procedures allocated to the TAVI in native aortic valve cohort, 87.8% for the TAVI-in-SAVR cohort, and 88.5% for the TAVI-in-TAVI cohort. To ensure generalisability of the matched procedures, the characteristics of the matched and unmatched procedures were compared for each cohort (Appendix E2); no statistical differences were identified.

To make meaningful comparisons between TAVI devices (in line with the decision problem) all subsequent analysis has been restricted to TAVI procedures in native aortic valve which represented the largest cohort.

Figure 4: Summary of data linkage data flow



5.5.1 Univariate analysis

The patient and procedural characteristics across devices were tabulated (Table 20) highlighting several statistically significant differences between valves. These differences reflect the different populations treated using different valves however the clinical impact of these univariate findings remain uncertain. Key clinical differences included:

- Annular diameter: smallest with ACURATE neo2 (23.0 mm), largest with Sapien 3 (29.0 mm), which is, understandably, related to the range of valves and sizes available (that is, the ACURATE neo2 is not available in a size above 27.0 mm, so could not be used in an annular diameter of 29.0 mm).
- Male sex: highest proportion with Sapien 3 (92%), lowest with ACURATE neo2 (35.3%). As sex is associated with height, weight, age, this may explain differences in those patient characteristics across devices where different valve sizes (with different range of treatable annulus diameters) are available. One Clinical Expert also advised that this finding reflects their clinical experience, in that that female patients tend to have smaller annuli and are therefore more likely to receive a self-expanding TAVI device.
- Extensive calcification of the ascending aorta: highest proportion with Evolut R (7.9%), lowest with Sapien 3 Ultra (2.6%). If calcification of the ascending aorta was considered as a surrogate marker of calcification of the aortic valve and left ventricular outflow tract, these findings would support that self-expanding TAVI devices are used more frequently in calcified valves which reflects clinical experience (in line with Table 1).
- Poor LVEF: highest with Sapien 3 (14.3%), lowest with ACURATE neo2 (5.6%).
- Presence of extracardiac arteriopathy: highest with Evolut R (15.5%) and lowest with Sapien 3 Ultra (7.1%).
- Use of cerebral circulation protection devices: highest with ACURATE neo2 (18.2%), lowest with Navitor (6.6%). There is currently an ongoing RCT across 31 sites in the UK investigating whether cerebral circulation protection reduces stroke in TAVI patients (British Heart Foundation PROTECT-TAVI, ISRCTN16665769; Kharbanda et al. 2023). Therefore, differences in stroke outcomes may be confounded by this additional treatment. One Clinical Expert advised that use of cerebral circulation protection was likely related to the trial and was unlikely to be directly associated with choice of TAVI device.

Although statistically significant differences were found for mean and peak flow gradients, and valve area, these have not been outlined above, as a Clinical Expert stated that these would be used to define aortic stenosis only, and not to inform choice of TAVI device.

Differences in short-term in-hospital outcomes (Table 21) were also identified between devices, but should be interpreted with caution because they may be influenced by differences in the characteristics of patients receiving different TAVI devices, and not directly linked to the TAVI device itself:

- Procedure duration: longest with Evolut R (median 93 minutes), shortest with Sapien 3 and Sapien 3 Ultra (median 60 minutes), which one Clinical Expert advised reflected their clinical experience.
- Peak pressure gradient at end of procedure: highest with ACURATE neo2 (median [Q1,Q3]: 16 [11,22] mmHg) and lowest with Evolut Pro+, Evolut R, and Sapien 3 (12 [8,17] mmHg, 12 [8,19] mmHg, 12 [9,18] mmHg respectively).One Clinical Expert has advised that trial data suggest that self-expanding devices may have better haemodynamics, but this is not yet linked to clinical outcomes.
- Aortic regurgitation at end of procedure: highest with Evolut R (5.0%), lowest with Sapien 3 and Sapien 3 Ultra (1.0%),
- Need for permanent pacemaker implantation (PPI): highest with Navitor (15.8%), lowest with ACURATE neo2 (5.9%), which one Clinical Expert advised reflected their clinical experience.
- Use of a post implantation balloon dilatation: highest with Navitor (25.8%), lowest with Sapien 3 (4.8%),
- Major vascular complications: highest with Evolut R (3.9%), lowest with Sapien 3 Ultra (1.0%),
- Stroke before discharge: highest with Navitor (4.0%), lowest with ACURATE neo2 (0.8%).

Although length of hospital stay was statistically significantly different between devices, one Clinical Expert advised that this may relate to hospital policies, rather than the device itself. Another Clinical Expert stressed that the numerical difference between length of stay for different devices was not clinically significant. One Clinical Expert also advised that patients treated with self-expanding devices may be monitored for longer (due to increased likelihood of pacemaker implantation). One Clinical Expert advised that prescription of anti-thrombotics at discharge was unlikely to be related to device choice.

No statistically significant differences were identified between TAVI devices across any of the long-term outcomes considered, and the 95% confidence intervals overlapped for different devices (

Table 22, Figure 5 to Figure 9).

The EAG note that a number of patients experienced multiple adverse events during follow-up. Of the 108 patients in total with recorded aortic regurgitation at discharge:

- 3 died within 30 days, 13 within 1 year, 18 within 2 years.
- 5 had a recorded readmission with heart failure within 30 days, 8 within 1 year, 11 within 2 years.

Of the 91 patients who suffered an in-hospital stroke, 2 died within 30 days, 10 died within 1 year, 15 within 2 years. The EAG advise caution in interpreting these results as length of follow-up varied across patients, and therefore true event rates (if data were available to follow up all patients for 2 years) may be higher.

Table 20: Summary of patient and procedural characteristics from UK TAVI Registry for TAVI in native aortic valve between 01 April 2021 and 31 March 2023, only for procedures linked to a procedure in HES

Patient and procedural characteristics	Edwards Sapien 3 (n=1,121)	Edwards Sapien 3 Ultra (n=3,589)	Boston Scientific ACURATE neo2 (n=295)	Medtronic Evolut R (n=247)	Medtronic Evolut Pro+ (n=845)	Abbott Navitor (n=170)	p-value (comparison across 6 valves; **unadjusted**)	p-value (comparison across 6 valves; **adjusted**)
Age, years: median [Q1,Q3]	81.0 [77.0 to 85.0] (n=1,121)	82.0 [78.0 to 86.0] (n=3,589)	83.0 [79.0 to 86.0] (n=295)	81.0 [76.0 to 85.0] (n=247)	82.0 [77.0 to 86.0] (n=845)	83.0 [78.0 to 86.0] (n=170)	0.0000015	<0.0001*
Age (90+ years)	52/1,121 (4.6%)	330/3,589 (9.2%)	21/295 (7.1%)	15/247 (6.1%)	82/845 (9.7%)	17/170 (10.0%)	0.0004998	0.021*
Male sex	1,030/1,120 (92.0%)	1,818/3,584 (50.7%)	104/295 (35.3%)	172/246 (69.9%)	467/844 (55.3%)	72/169 (42.6%)	0.0004998	0.021*
Height, m: median [Q1,Q3]	1.8 [1.7 to 1.8] (n=1,049)	1.6 [1.6 to 1.7] (n=3,360)	1.6 [1.6 to 1.7] (n=248)	1.7 [1.6 to 1.8] (n=240)	1.7 [1.6 to 1.7] (n=823)	1.6 [1.6 to 1.7] (n=152)	0.0000000	<0.0001*
Weight, kg: median [Q1,Q3]	84.0 [74.0 to 95.7] (n=1,054)	74.0 [64.0 to 85.5] (n=3,374)	72.2 [63.6 to 86.8] (n=241)	80.0 [67.0 to 92.0] (n=241)	74.0 [64.2 to 86.0] (n=827)	75.0 [64.5 to 83.7] (n=154)	0.0000000	<0.0001*
BMI, kg/m2: median [Q1,Q3]	27.7 [24.7 to 31.6] (n=1,045)	27.0 [23.9 to 30.9] (n=3,344)	27.6 [24.2 to 31.6] (n=240)	28.0 [24.1 to 32.4] (n=240)	27.3 [24.2 to 30.9] (n=823)	27.9 [24.4 to 31] (n=151)	0.0020147	0.058
Underweight (BMI under 17.5)	13/1,045 (1.2%)	61/3,344 (1.8%)	7/240 (2.9%)	6/240 (2.5%)	17/823 (2.1%)	1/151 (0.7%)	0.3273363	1
Obese (BMI 30 or above)	354/1,045 (33.9%)	1,001/3,344 (29.9%)	86/240 (35.8%)	93/240 (38.8%)	260/823 (31.6%)	48/151 (31.8%)	0.0174913	0.367
Pulmonary artery systolic pressure, mmHg: median [Q1,Q3]	32.0 [24.0 to 43.0] (n=314)	32.0 [24.0 to 43.0] (n=1,049)	37.0 [32.0 to 46.0] (n=45)	39.0 [32.0 to 55.2] (n=64)	37.0 [30.0 to 50.0] (n=210)	32.0 [27.8 to 45.2] (n=40)	0.0000000	<0.0001*
Mean pressure gradient, mmHg: median [Q1,Q3]	42.0 [33.0 to 52.0] (n=1,052)	44.0 [36.0 to 55.0] (n=3,389)	43.0 [35.0 to 53.0] (n=281)	44.0 [37.0 to 58.0] (n=225)	44.0 [37.0 to 56.0] (n=779)	41.0 [33.0 to 50.0] (n=158)	0.0000000	<0.0001*
Peak pressure gradient, mmHg: median [Q1,Q3]	67.0 [51.0 to 81.0] (n=1,045)	71.0 [60.0 to 87.0] (n=3,316)	70.0 [57.0 to 86.2] (n=280)	71.0 [58.0 to 87.0] (n=213)	71.0 [60.2 to 87.0] (n=774)	71.0 [57.0 to 85.0] (n=145)	0.0000000	<0.0001*
Valve area, cm2: median [Q1,Q3]	0.8 [0.6 to 0.9] (n=1,014)	0.7 [0.6 to 0.8] (n=3,229)	0.7 [0.6 to 0.9] (n=263)	0.7 [0.5 to 0.8] (n=201)	0.7 [0.6 to 0.8] (n=700)	0.8 [0.6 to 0.9] (n=137)	0.0000000	<0.0001*
Annular diameter, mm: median [Q1,Q3]	27.5 [26.7 to 29.0] (n=910)	24.0 [22.4 to 25.3] (n=2,831)	23.0 [22.0 to 25.0] (n=153)	26.0 [23.0 to 27.4] (n=194)	24.0 [22.6 to 26.0] (n=675)	24.3 [22.9 to 26.0] (n=117)	0.0000000	<0.0001*
Extensive calcification of ascending aorta	30/1,041 (2.9%)	89/3,362 (2.6%)	10/211 (4.7%)	19/239 (7.9%)	47/812 (5.8%)	3/158 (1.9%)	0.0004998	0.021*
Critical status pre-procedure	25/1,084 (2.3%)	29/3,484 (0.8%)	1/272 (0.4%)	3/244 (1.2%)	10/829 (1.2%)	3/164 (1.8%)	0.0039980	0.108
CCS Angina Status (any limitation of physical activity)	235/1,083 (21.7%)	813/3496 (23.3,%)	45/268 (16.8%)	64/244 (26.2%)	170/805 (21.1%)	58/159 (36.5%)	0.0004998	0.021*
CCS Angina Status (symptoms at rest)	13/1,083 (1.2%)	26/3,496 (0.7%)	4/268 (1.5%)	3/244 (1.2%)	10/805 (1.2%)	2/159 (1.3%)	0.3318341	1
NYHA dyspnoea status (marked limitation of physical activity, or symptoms at rest or minimal activity)	820/1,095 (74.9%)	2,615/3,518 (74.3%)	204/280 (72.9%)	181/243 (74.5%)	580/803 (72.2%)	119/161 (73.9%)	0.8185907	1
NYHA dyspnoea status (symptoms at rest)	130/1,095 (11.9%)	333/3,518 (9.5%)	40/280 (14.3%)	41/243 (16.9%)	123/803 (15.3%)	21/161 (13.0%)	0.0004998	0.021*
Severe symptoms (symptoms at rest measured by CCS Angina Status or NYHA dyspnoea status)	138/1,100 (12.5%)	345/3,539 (9.7%)	42/281 (14.9%)	43/245 (17.6%)	129/811 (15.9%)	23/165 (13.9%)	0.0004998	0.021*
CSHA Clinical Frailty Score (moderately or severely frail)	85/1,053 (8.1%)	254/3,383 (7.5%)	17/237 (7.2%)	15/242 (6.2%)	62/774 (8.0%)	11/159 (6.9%)	0.9365317	1
Katz Index less than 3	33/1,024 (3.2%)	104/3,243 (3.2%)	3/229 (1.3%)	1/233 (0.4%)	18/741 (2.4%)	11/152 (7.2%)	0.0024988	0.07
Katz Index less than 6	133/1,024 (13.0%)	420/3,243 (13.0%)	33/229 (14.4%)	28/233 (12.0%)	115/741 (15.5%)	20/152 (13.2%)	0.5422289	1
Frailty composite (moderately or severely frail on CSHA, or Katz Index less than 6)	194/1,063 (18.3%)	602/3,415 (17.6%)	45/241 (18.7%)	36/246 (14.6%)	156/833 (18.7%)	26/160 (16.2%)	0.7601199	1
Poor LV function (LVEF<30%)	154/1,074 (14.3%)	220/3,458 (6.4%)	17/261 (6.5%)	33/237 (13.9%)	61/827 (7.4%)	9/161 (5.6%)	0.0004998	0.021*
Diabetes	277/1,092 (25.4%)	931/3,504 (26.6%)	76/276 (27.5%)	70/245 (28.6%)	214/835 (25.6%)	46/169 (27.2%)	0.8645677	1

Patient and procedural characteristics	Edwards Sapien 3 (n=1,121)	Edwards Sapien 3 Ultra (n=3,589)	Boston Scientific ACURATE neo2 (n=295)	Medtronic Evolut R (n=247)	Medtronic Evolut Pro+ (n=845)	Abbott Navitor (n=170)	p-value (comparison across 6 valves; **unadjusted**)	p-value (comparison across 6 valves; **adjusted**)
Ever smoked (current and ex smokers)	494/899 (54.9%)	1,332/2,845 (46.8%)	117/242 (48.3%)	103/199 (51.8%)	319/693 (46.0%)	64/137 (46.7%)	0.0009995	0.031*
Dialysis	15/1,085 (1.4%)	64/3,490 (1.8%)	2/282 (0.7%)	4/242 (1.7%)	14/837 (1.7%)	2/144 (1.4%)	0.8001000	1
Presence of left main stem disease	26/995 (2.6%)	73/3,080 (2.4%)	3/201 (1.5%)	5/202 (2.5%)	20/728 (2.7%)	4/133 (3.0%)	0.9145427	1
Presence of >50% stenosis in at least one coronary vessel, excluding left main stem disease	286/993 (28.8%)	770/3,039 (25.3%)	58/203 (28.6%)	55/202 (27.2%)	155/737 (21.0%)	40/128 (31.2%)	0.0039980	0.108
Valve size, mm: median [Q1,Q3]	29.0 [29.0 to 29.0] (n=1,121)	26.0 [23.0 to 26.0] (n=3,589)	25.0 [23.0 to 27.0] (n=295)	34.0 [29.0 to 34.0] (n=247)	29.0 [26.0 to 29.0] (n=845)	27.0 [25.0 to 29.0] (n=170)	0.0000000	<0.0001*
Valve size (categorical: small, medium, large)	S: 41/1,121 (3.7%); M: 60/1,121 (5.4%); L: 1,020/1,121 (91.0%)	S: 1,677/3,589 (46.7%); M: 1,912/3,589 (53.3%); L: 0/3,589 (0%)	S: 96/295 (32.5%); M: 116/295 (39.3%); L: 83/295 (28.1%)	S: 12/247 (4.9%); M: 35/247 (14.2%); L: 200/247 (81.0%)	S: 24/845 (2.8%); M: 214/845 (25.3%); L: 607/845 (71.8%)	S: 17/170 (10.0%); M: 105/170 (61.8%); L: 48/170 (28.2%)	0.0004998	0.021*
Non-elective procedure	282/1,118 (25.2%)	837/3,576 (23.4%)	50/295 (16.9%)	72/247 (29.1%)	210/844 (24.9%)	40/170 (23.5%)	0.0199900	0.4
Procedure urgency (non-elective procedure, or critical status pre-procedure)	285/1,121 (25.4%)	845/3,589 (23.5%)	50/295 (16.9%)	73/247 (29.6%)	212/845 (25.1%)	41/170 (24.1%)	0.0104948	0.241
Planned use of general anaesthesia	17/1,113 (1.5%)	25/3,567 (0.7%)	1/295 (0.3%)	6/247 (2.4%)	10/840 (1.2%)	2/170 (1.2%)	0.0149925	0.33
Previous balloon aortic valvuloplasty	25/1,108 (2.3%)	109/3,542 (3.1%)	6/284 (2.1%)	6/243 (2.5%)	28/835 (3.4%)	1/170 (0.6%)	0.2688656	1
Use of cardiopulmonary bypass	9/1,111 (0.8%)	7/3,551 (0.2%)	0/289 (0%)	1/242 (0.4%)	3/820 (0.4%)	0/165 (0%)	0.0664668	1
Use of cerebral circulation protection device(s)	154/1,115 (13.8%)	349/3,566 (9.8%)	54/295 (18.3%)	27/243 (11.1%)	123/837 (14.7%)	17/168 (10.1%)	0.0004998	0.021*
Creatinine clearance, mL/min: median [Q1,Q3]	64.9 [48.8 to 81.3] (n=1,013)	54.5 [40.4 to 71.2] (n=3,183)	51.7 [39.6 to 66.4] (n=226)	57.0 [40.6 to 75.9] (n=232)	53.8 [39.5 to 70.4] (n=804)	53.4 [39 to 73.8] (n=127)	0.0000000	<0.0001*
Creatinine clearance less than 30 mL/min	54/1,013 (5.3%)	312/3,183 (9.8%)	21/226 (9.3%)	19/232 (8.2%)	82/804 (10.2%)	12/127 (9.4%)	0.0004998	0.021*
Previous MI (ever)	135/1,110 (12.2%)	423/3,537 (12.0%)	33/282 (11.7%)	36/245 (14.7%)	98/839 (11.7%)	21/169 (12.4%)	0.8680660	1
Previous MI (within previous 90 days)	22/1,110 (2.0%)	72/3,537 (2.0%)	2/282 (0.7%)	9/245 (3.7%)	17/839 (2.0%)	5/169 (3.0%)	0.2468766	1
Previous PCI	145/1,104 (13.1%)	452/3,529 (12.8%)	32/283 (11.3%)	38/244 (15.6%)	104/835 (12.5%)	13/169 (7.7%)	0.2568716	1
Previous CABG	89/1075 (8.3%)	289/3476 (8.3%)	25/271 (9.2%)	27/244 (11.1%)	53/834 (6.4%)	14/147 (9.5%)	0.1809095	1
Previous stroke or TIA	121/1,102 (11.0%)	407/3,514 (11.6%)	41/283 (14.5%)	24/243 (9.9%)	95/833 (11.4%)	21/168 (12.5%)	0.6036982	1
Presence of extracardiac arteriopathy	105/1,093 (9.6%)	249/3,485 (7.1%)	27/260 (10.4%)	38/245 (15.5%)	100/834 (12.0%)	16/161 (9.9%)	0.0004998	0.021*
Any cardiac or coronary comorbidity (previous MI, PCI, or CABG, presence of extracardiac arteriopathy or extensive calcification of ascending aorta symptoms at rest on NYHA or CCS, poor LV function, left main stem disease or stenosis of at least 50% in one vessel)	580/1,118 (51.9%)	1,587/3,577 (44.4%)	124/293 (42.3%)	132/247 (53.4%)	394/845 (46.6%)	77/170 (45.3%)	0.0004998	0.021*
Anatomical coronary comorbidity (left main stem disease, or stenosis of at least 50% in one vessel)	289/1,015 (28.5%)	776/3,118 (24.9%)	59/215 (27.4%)	56/204 (27.5%)	156/743 (21.0%)	42/133 (31.6%)	0.0049975	0.125
Clinical coronary comorbidity (previous MI, PCI or CABG)	256/1,114 (23.0%)	792/3,560 (22.2%)	64/288 (22.2%)	65/246 (26.4%)	178/840 (21.2%)	35/170 (20.6%)	0.6086957	1
Any non-cardiac or non-coronary comorbidity	719/1,113 (64.6%)	2,211/3,558 (62.1%)	187/287 (65.2%)	159/246 (64.6%)	541/841 (64.3%)	109/170 (64.1%)	0.5757121	1

Patient and procedural characteristics	Edwards Sapien 3 (n=1,121)	Edwards Sapien 3 Ultra (n=3,589)	Boston Scientific ACURATE neo2 (n=295)	Medtronic Evolut R (n=247)	Medtronic Evolut Pro+ (n=845)	Abbott Navitor (n=170)	p-value (comparison across 6 valves; **unadjusted**)	p-value (comparison across 6 valves; **adjusted**)
(previous stroke or TIA, diabetes, current or former smoker, extracardiac arteriopathy, current dialysis or creatinine clearance less than 30)								
Non-cardiac non-coronary other comorbidity (previous stroke or extracardiac arteriopathy)	208/1,109 (18.8%)	594/3,540 (16.8%)	63/284 (22.2%)	54/246 (22.0%)	178/839 (21.2%)	34/169 (20.1%)	0.0064968	0.156
Non-cardiac non-coronary risk factor (current or former smoker, or diabetes)	628/1,102 (57.0%)	1,872/3,541 (52.9%)	161/286 (56.3%)	142/245 (58%)	442/837 (52.8%)	92/169 (54.4%)	0.1284358	1
Renal comorbidity (current dialysis or creatinine clearance less than 30)	57/1,097 (5.2%)	339/3,525 (9.6%)	22/283 (7.8%)	19/246 (7.7%)	84/839 (10.0%)	13/159 (8.2%)	0.0009995	0.031*

Key: Significance of **adjusted** p-values (using Holm-Bonferroni correction) denoted by: *** < 0.001, ** <0.01, * < 0.05. Abbreviations: CABG, Coronary artery bypass grafting; CCS, Canadian Cardiovascular Society; CSHA, Canadian Study of Health and Aging; LVEF, Left ventricular ejection fraction; MI, Myocardial infarction; NYHA, New York Heart Association; PCI, Percutaneous coronary intervention; TIA, Transient ischaemic attack

Table 21: Summary of in-hospital outcomes from linked dataset (UK TAVI Registry linked to HES) for TAVI in native aortic valve (01 April 2021 to 31 March 2023).

[Note: Incident rates represent raw numbers before adjusting for differences in recorded patient characteristics between devices]

In-hospital outcome	Edwards Sapien 3 (n=1,121)	Edwards Sapien 3 Ultra (n=3,589)	Boston Scientific ACURATE neo2 (n=295)	Medtronic Evolut R (n=247)	Medtronic Evolut Pro+ (n=845)	Abbott Navitor (n=170)	p-value (comparison across 6 valves; **unadjusted**)	p-value (comparison across 6 valves; **adjusted**)
Length of procedure, minutes: median [Q1,Q3]	60.0 [55.0 to 80.0] (n=985)	60.0 [55.0 to 75.0] (n=2,999)	80.0 [63.0 to 105.0] (n=280)	93.0 [69.0 to 120.0] (n=225)	75.0 [60.0 to 95.0] (n=693)	69.0 [60.0 to 90.0] (n=141)	0.0000000	<0.0001*
Length of hospital stay, nights: median [Q1,Q3]	3.0 [2.0 to 8.0] (n=917)	3.0 [2.0 to 9.0] (n=2,799)	3.0 [2.0 to 5.0] (n=263)	4.0 [2.0 to 13.0] (n=238)	4.0 [2.0 to 11.0] (n=790)	3.0 [2.0 to 10.0] (n=124)	0.0000004	<0.0001*
Peak pressure gradient, mmHg: median [Q1,Q3]	12.0 [9.0 to 18.0] (n=760)	15.0 [10.0 to 22.0] (n=2,450)	16.0 [11.0 to 22.0] (n=223)	12.0 [8.0 to 19.0] (n=167)	12.0 [8.0 to 17.0] (n=507)	13.0 [9.0 to 18.0] (n=104)	0.0000000	<0.0001*
Mean pressure gradient, mmHg: median [Q1,Q3]	6.5 [5.0 to 10.0] (n=786)	8.0 [5.0 to 12.0] (n=2,577)	8.0 [5.0 to 11.0] (n=233)	7.0 [4.0 to 11.0] (n=179)	6.0 [4.0 to 9.0] (n=566)	7.0 [4.0 to 9.0] (n=128)	0.0000000	<0.0001*
Valve area, cm2: median [Q1,Q3]	2.0 [1.6 to 2.5] (n=510)	1.8 [1.5 to 2.1] (n=1,669)	1.8 [1.5 to 2.0] (n=169)	1.7 [1.5 to 2.1] (n=103)	1.7 [1.5 to 2.0] (n=368)	2.0 [1.8 to 2.4] (n=42)	0.0000000	<0.0001*
Aortic regurgitation at end of procedure by echo or angio	11/1,077 (1.0%)	33/3,442 (1.0%)	8/257 (3.1%)	12/239 (5.0%)	38/827 (4.6%)	6/162 (3.7%)	0.0004998	0.011*
Valve failure	3/1,111 (0.3%)	6/3,569 (0.2%)	0/293 (0%)	1/245 (0.4%)	2/840 (0.2%)	0/166 (0%)	0.7051474	1
Unsuccessful valve deployment	15/1,121 (1.3%)	67/3,589 (1.9%)	1/295 (0.3%)	6/247 (2.4%)	21/845 (2.5%)	2/170 (1.2%)	0.1249375	0.756
Malposition of valve	4/1,082 (0.4%)	14/3,446 (0.4%)	4/293 (1.4%)	5/237 (2.1%)	9/753 (1.2%)	3/167 (1.8%)	0.0009995	0.018*
Use of post implantation balloon dilatation	52/1,078 (4.8%)	203/3,431 (5.9%)	26/292 (8.9%)	39/236 (16.5%)	128/744 (17.2%)	42/163 (25.8%)	0.0004998	0.011*
Need for permanent pacing	79/1,061 (7.4%)	202/3,371 (6.0%)	15/256 (5.9%)	25/233 (10.7%)	95/746 (12.7%)	26/165 (15.8%)	0.0004998	0.011*
Conversion to sternotomy for valve surgery	1/1,114 (0.1%)	2/3,564 (0.1%)	0/291 (0%)	1/242 (0.4%)	2/834 (0.2%)	0/168 (0%)	0.2313843	1
Valve reintervention before discharge	3/1,109 (0.3%)	10/3,557 (0.3%)	1/293 (0.3%)	4/237 (1.7%)	4/821 (0.5%)	1/168 (0.6%)	0.0544728	0.481
Failure of percutaneous closure device	19/1,060 (1.8%)	36/3,352 (1.1%)	4/243 (1.6%)	8/233 (3.4%)	9/729 (1.2%)	2/161 (1.2%)	0.0534733	0.481
Need for bailout PCI	3/1,108 (0.3%)	14/3,562 (0.4%)	0/291 (0%)	0/239 (0%)	0/828 (0%)	0/167 (0%)	0.4892554	1
Need for bailout TAVI-in-TAVI	4/1,085 (0.4%)	13/3,452 (0.4%)	3/294 (1.0%)	4/238 (1.7%)	9/763 (1.2%)	0/167 (0%)	0.0119940	0.156
MI within 72 hours of procedure	1/1,071 (0.1%)	11/3,360 (0.3%)	0/250 (0%)	1/236 (0.4%)	1/787 (0.1%)	0/155 (0%)	0.6556722	1
Major, life threatening or disabling bleeding	14/1,056 (1.3%)	27/3,355 (0.8%)	6/241 (2.5%)	5/227 (2.2%)	9/721 (1.2%)	2/159 (1.3%)	0.0429785	0.43
Major vascular complications	12/1,051 (1.1%)	34/3,340 (1.0%)	7/244 (2.9%)	9/232 (3.9%)	12/724 (1.7%)	4/159 (2.5%)	0.0014993	0.025*

In-hospital outcome	Edwards Sapien 3 (n=1,121)	Edwards Sapien 3 Ultra (n=3,589)	Boston Scientific ACURATE neo2 (n=295)	Medtronic Evolut R (n=247)	Medtronic Evolut Pro+ (n=845)	Abbott Navitor (n=170)	p-value (comparison across 6 valves; **unadjusted**)	p-value (comparison across 6 valves; **adjusted**)
Tamponade during or after procedure	11/1,093 (1.0%)	30/3,526 (0.9%)	1/274 (0.4%)	0/243 (0%)	4/837 (0.5%)	0/166 (0%)	0.4887556	1
Stroke before discharge	20/1,038 (1.9%)	38/3,316 (1.1%)	2/245 (0.8%)	5/227 (2.2%)	20/726 (2.8%)	6/147 (4.1%)	0.0014993	0.025*
Modified Rankin score of 4 or above	1/142 (0.7%)	3/423 (0.7%)	1/37 (2.7%)	0/6 (0%)	1/7 (14.3%)	2/39 (5.1%)	0.0179910	0.216
Need for renal replacement therapy	0/1,053 (0%)	4/3,334 (0.1%)	0/246 (0%)	2/229 (0.9%)	1/715 (0.1%)	0/159 (0%)	0.1079460	0.756
Deaths	15/1,121 (1.3%)	36/3,589 (1.0%)	5/295 (1.7%)	8/247 (3.2%)	15/845 (1.8%)	6/170 (3.5%)	0.0069965	0.105
Prescribed NOACs	336/1,032 (32.6%)	835/3,265 (25.6%)	61/254 (24.0%)	89/232 (38.4%)	204/795 (25.7%)	38/159 (23.9%)	0.0004998	0.011*
Prescribed other anti-thrombotics	126/1,032 (12.2%)	293/3,265 (9.0%)	40/254 (15.7%)	21/232 (9.1%)	77/795 (9.7%)	7/159 (4.4%)	0.0004998	0.011*
Prescribed antiplatelets	622/1,019 (61.0%)	2,114/3,197 (66.1%)	162/255 (63.5%)	140/232 (60.3%)	534/800 (66.8%)	106/151 (70.2%)	0.0209895	0.231
Technical success (VARC-3)	1,030/1,067 (96.5%)	3,285/3,422 (96.0%)	277/289 (95.8%)	210/228 (92.1%)	690/735 (93.9%)	158/167 (94.6%)	0.0099950	0.14

Key: Significance of **adjusted** p-values (using Holm-Bonferroni correction) denoted by: *** < 0.001, ** <0.01, * < 0.05. Abbreviations: MI, Myocardial infarction; NOAC, Non-vitamin K oral anticoagulants; PCI, Percutaneous coronary intervention; TAVI, transcatheter aortic valve implantation; VARC-3, Valve Academic Research Consortium-3

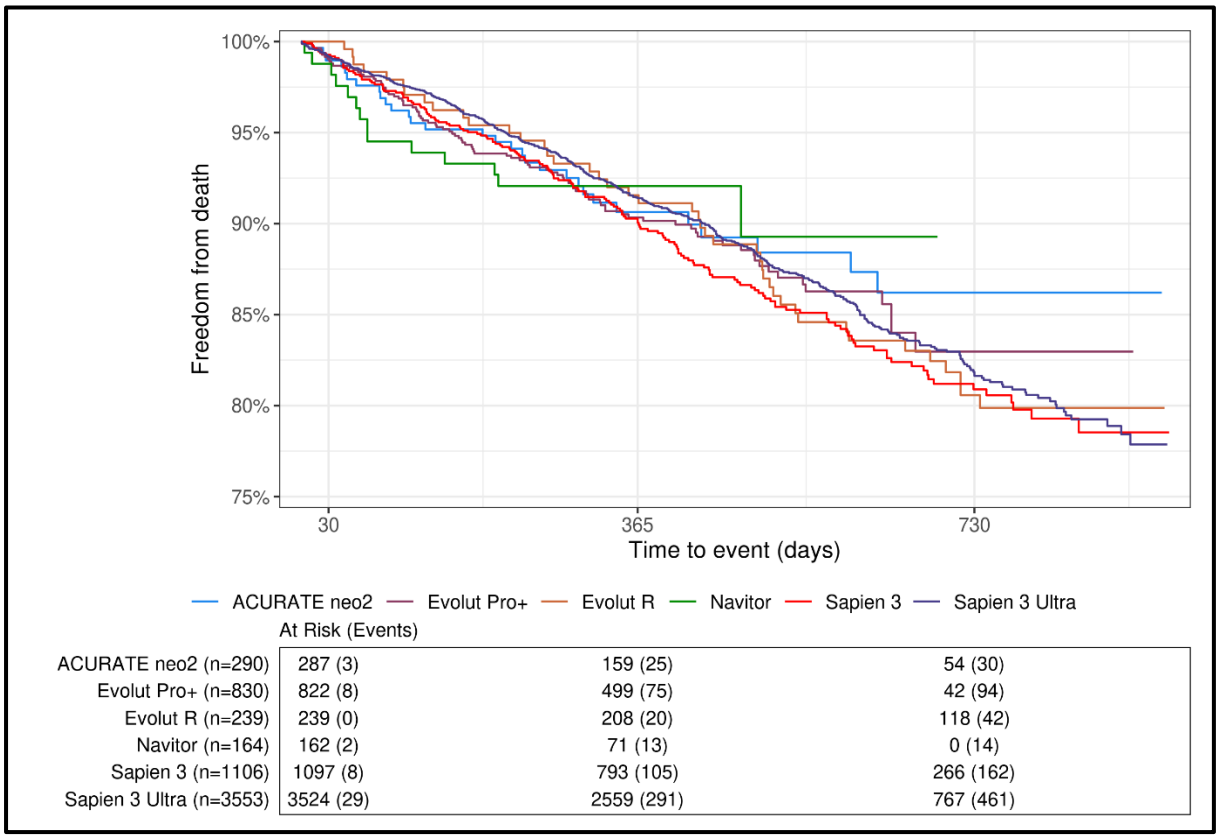
Table 22: Summary of longitudinal unadjusted outcomes for patients from linked dataset (UK TAVI Registry linked to HES) for TAVI in native aortic valve follow-up to up 31 October 2023. Reported as % [95%CI] (n=number of patients) unless explicitly reported otherwise.

[Note: Incident rates represent raw numbers before adjusting for differences in recorded patient characteristics between devices]

Parameter	Edwards Sapien 3 (n=1,121)	Edwards Sapien 3 Ultra (n=3,589)	Boston Scientific ACURATE neo2 (n=295)	Medtronic Evolut R (n=247)	Medtronic Evolut Pro+ (n=845)	Abbott Navitor (n=170)
Median [Q1,Q3] length of follow-up, days	521.5 [354,0, 725.3]	502.0 [354.0,705.0]	403.0 [275.0, 634.0]	730.0 [529.5, 832.5]	417.0 [292.0, 558.0]	343.0 [279.0, 443.3]
Death (total=827)	-	-	-	-	-	-
30 days	0.4 [0.0 to 0.7]	0.7 [0.4 to 0.9]	0.7 [0.0 to 1.6]	0.0 [0.0 to 0.0]	0.8 [0.2 to 1.5]	1.2 [0.0 to 2.9]
6 months	3.9 [2.7 to 5.0]	3.6 [3.0 to 4.2]	4.5 [2.1 to 6.0]	4.6 [1.9 to 7.2]	5.5 [4.0 to 7.1]	6.1 [2.4 to 9.7]
12 months	8.1 [6.4 to 9.7]	7.7 [6.8 to 8.6]	7.8 [4.5 to 11.0]	8.0 [4.5 to 11.4]	9.3 [7.2 to 11.3]	7.3 [3.2 to 11.2]
18 months	12.7 [10.5 to 14.8]	11.8 [10.6 to 13.0]	9.2 [5.4 to 12.8]	14.5 [9.8 to 19.0]	13.4 [10.5 to 16.2]	10.1 [3.2 to 16.6]
24 months	16.9 [14.1 to 19.6]	16.9 [15.2 to 18.5]	11.4 [6.7 to 16.0]	18.5 [13.1 to 23.6]	16.0 [11.8 to 19.9]	-
Stroke (total=267)	-	-	-	-	-	-
30 days	1.2 [0.5 to 1.8]	1.2 [0.9 to 1.6]	1.7 [0.2 to 3.2]	0.4 [0.0 to 1.2]	1.7 [0.8 to 2.6]	1.2 [0.0 to 2.9]
6 months	3.3 [2.2 to 4.4]	2.3 [1.8 to 2.8]	3.1 [1.1 to 5.1]	0.8 [0.0 to 2.0]	2.6 [1.5 to 3.6]	1.8 [0.0 to 3.9]
12 months	4.5 [3.3 to 5.8]	3.2 [2.6 to 3.8]	4.5 [2.0 to 7.0]	0.8 [0.0 to 2.0]	3.1 [1.9 to 4.3]	2.9 [0.0 to 5.8]
18 months	5.7 [4.1 to 7.1]	4.4 [3.6 to 5.1]	4.5 [2.0 to 7.0]	4.0 [1.2 to 6.6]	4.8 [3.0 to 6.6]	2.9 [0.0 to 5.8]
24 months	6.7 [4.9 to 8.5]	5.7 [4.7 to 6.7]	4.5 [2.0 to 7.0]	4.0 [1.2 to 6.6]	4.8 [3.0 to 6.6]	-
Aortic reintervention; TAVI or SAVR (total =28)	-	-	-	-	-	-
30 days	0.0 [0.0 to 0.0]	0.1 [0.0 to 0.1]	0.0 [0.0 to 0.0]	0.0 [0.0 to 0.0]	0.4 [0.0 to 0.8]	0.0 [0.0 to 0.0]
6 months	0.1 [0.0 to 0.3]	0.1 [0.0 to 0.2]	0.0 [0.0 to 0.0]	0.8 [0.0 to 2.0]	0.7 [0.1 to 1.3]	0.0 [0.0 to 0.0]
12 months	0.1 [0.0 to 0.3]	0.4 [0.2 to 0.7]	0.0 [0.0 to 0.0]	0.8 [0.0 to 2.0]	0.7 [0.1 to 1.3]	0.0 [0.0 to 0.0]
18 months	0.1 [0.0 to 0.3]	0.6 [0.3 to 0.9]	0.0 [0.0 to 0.0]	0.8 [0.0 to 2.0]	1.1 [0.2 to 2.1]	0.0 [0.0 to 0.0]
24 months	0.1 [0.0 to 0.3]	0.6 [0.3 to 0.9]	0.0 [0.0 to 0.0]	0.8 [0.0 to 2.0]	1.1 [0.2 to 2.1]	
Readmission with heart failure (total=427)	-	-	-	-	-	-
30 days	1.5 [0.8 to 2.3]	1.2 [0.9 to 1.6]	1.7 [0.2 to 3.2]	3.3 [1.0 to 5.6]	2.7 [1.6 to 3.7]	1.2 [0.0 to 2.9]
6 months	4.7 [3.4 to 5.9]	3.6 [2.9 to 4.2]	4.5 [2.1 to 6.9]	5.9 [2.9 to 8.8]	4.9 [3.4 to 6.3]	5.0 [1.6 to 8.4]
12 months	6.9 [5.4 to 8.4]	5.2 [4.5 to 6.0]	5.8 [3.0 to 8.6]	6.3 [3.2 to 9.4]	6.8 [5.0 to 8.6]	7.3 [3.0 to 11.5]
18 months	8.7 [6.9 to 10.5]	6.6 [5.7 to 7.5]	5.8 [3.0 to 8.6]	7.3 [3.9 to 10.6]	9.4 [6.9 to 11.8]	13.2 [5.2 to 20.6]
24 months	10.4 [8.1 to 12.5]	7.5 [6.5 to 8.6]	8.6 [3.8 to 13.1]	8.5 [4.7 to 12.1]	12.2 [7.2 to 16.9]	-
PPI (total=225)	-	-	-	-	-	-
30 days	1.5 [0.8 to 2.3]	1.1 [0.8 to 1.5]	1.0 [0.0 to 2.2]	0.4 [0.0 to 1.2]	1.0 [0.3 to 1.6]	1.2 [0.0 to 2.9]
6 months	2.5 [1.5 to 3.4]	2.0 [1.6 to 2.5]	2.4 [0.6 to 4.2]	2.5 [0.5 to 4.5]	2.2 [1.2 to 3.2]	1.8 [0.0 to 3.9]
12 months	3.6 [2.5 to 4.8]	3.0 [2.4 to 3.6]	2.4 [0.6 to 4.2]	3.0 [0.8 to 5.2]	3.1 [1.9 to 4.3]	3.7 [0.3 to 7.0]
18 months	4.7 [3.3 to 6.1]	3.7 [3.0 to 4.4]	2.4 [0.6 to 4.2]	4.5 [1.7 to 7.3]	4.0 [2.4 to 5.5]	3.7 [0.3 to 7.0]
24 months	5.6 [3.9 to 7.3]	4.1 [3.3 to 4.8]	3.6 [0.7 to 6.3]	4.5 [1.7 to 7.3]	5.1 [2.3 to 7.8]	-

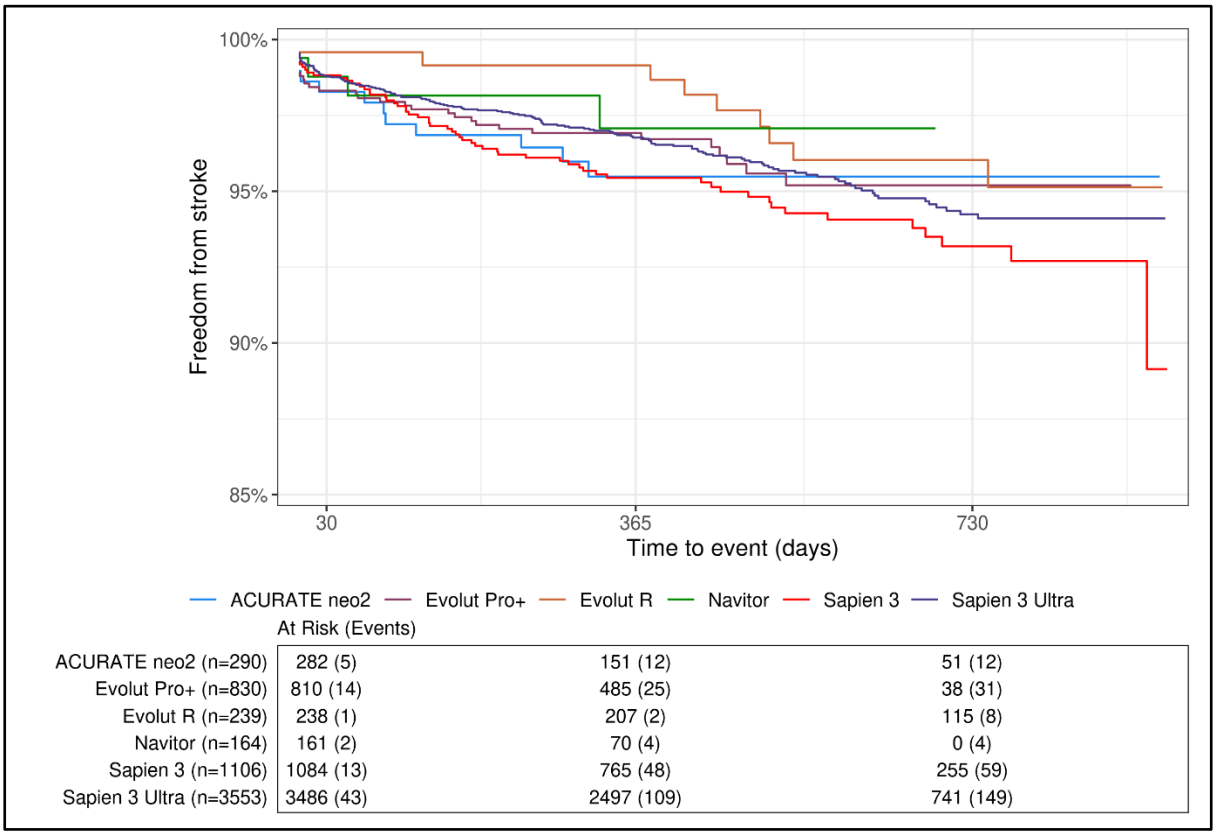
Abbreviations: PPI, Permanent pacemaker implantation; SAVR, Surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation

Figure 5: Kaplan-Meier for mortality (n=827 events): UK TAVI Registry linked to HES



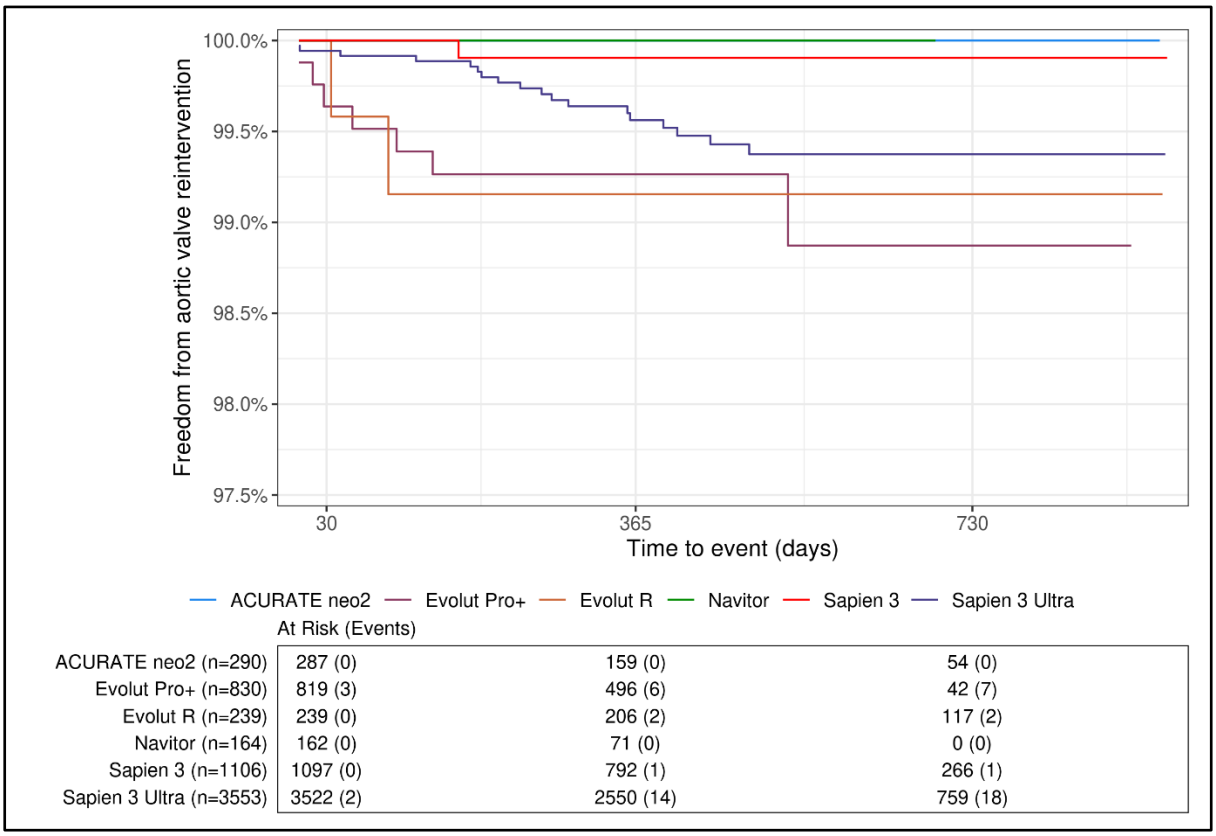
At Risk (Events)			
ACURATE neo2 (n=290)	287 (3)	159 (25)	54 (30)
Evolut Pro+ (n=830)	822 (8)	499 (75)	42 (94)
Evolut R (n=239)	239 (0)	208 (20)	118 (42)
Navitor (n=164)	162 (2)	71 (13)	0 (14)
Sapien 3 (n=1106)	1097 (8)	793 (105)	266 (162)
Sapien 3 Ultra (n=3553)	3524 (29)	2559 (291)	767 (461)

Figure 6: Kaplan-Meier for stroke (n=267 events): UK TAVI Registry linked to HES



At Risk (Events)			
ACURATE neo2 (n=290)	282 (5)	151 (12)	51 (12)
Evolut Pro+ (n=830)	810 (14)	485 (25)	38 (31)
Evolut R (n=239)	238 (1)	207 (2)	115 (8)
Navitor (n=164)	161 (2)	70 (4)	0 (4)
Sapien 3 (n=1106)	1084 (13)	765 (48)	255 (59)
Sapien 3 Ultra (n=3553)	3486 (43)	2497 (109)	741 (149)

Figure 7: Kaplan-Meier for aortic valve reintervention (n=28): UK TAVI Registry linked to HES



At Risk (Events)			
ACURATE neo2 (n=290)	287 (0)	159 (0)	54 (0)
Evolut Pro+ (n=830)	819 (3)	496 (6)	42 (7)
Evolut R (n=239)	239 (0)	206 (2)	117 (2)
Navitor (n=164)	162 (0)	71 (0)	0 (0)
Sapien 3 (n=1106)	1097 (0)	792 (1)	266 (1)
Sapien 3 Ultra (n=3553)	3522 (2)	2550 (14)	759 (18)

Figure 8: Kaplan-Meier for readmission with heart failure (n=427): UK TAVI Registry linked to HES

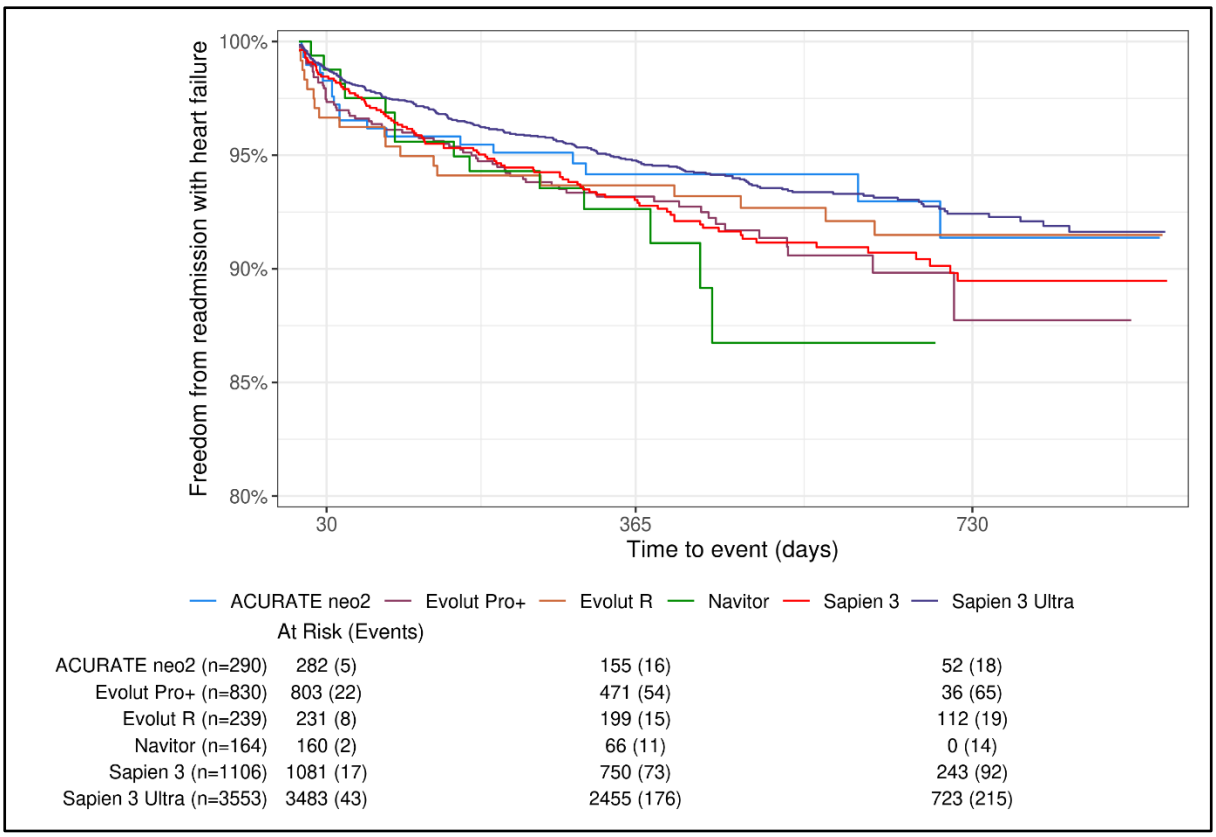
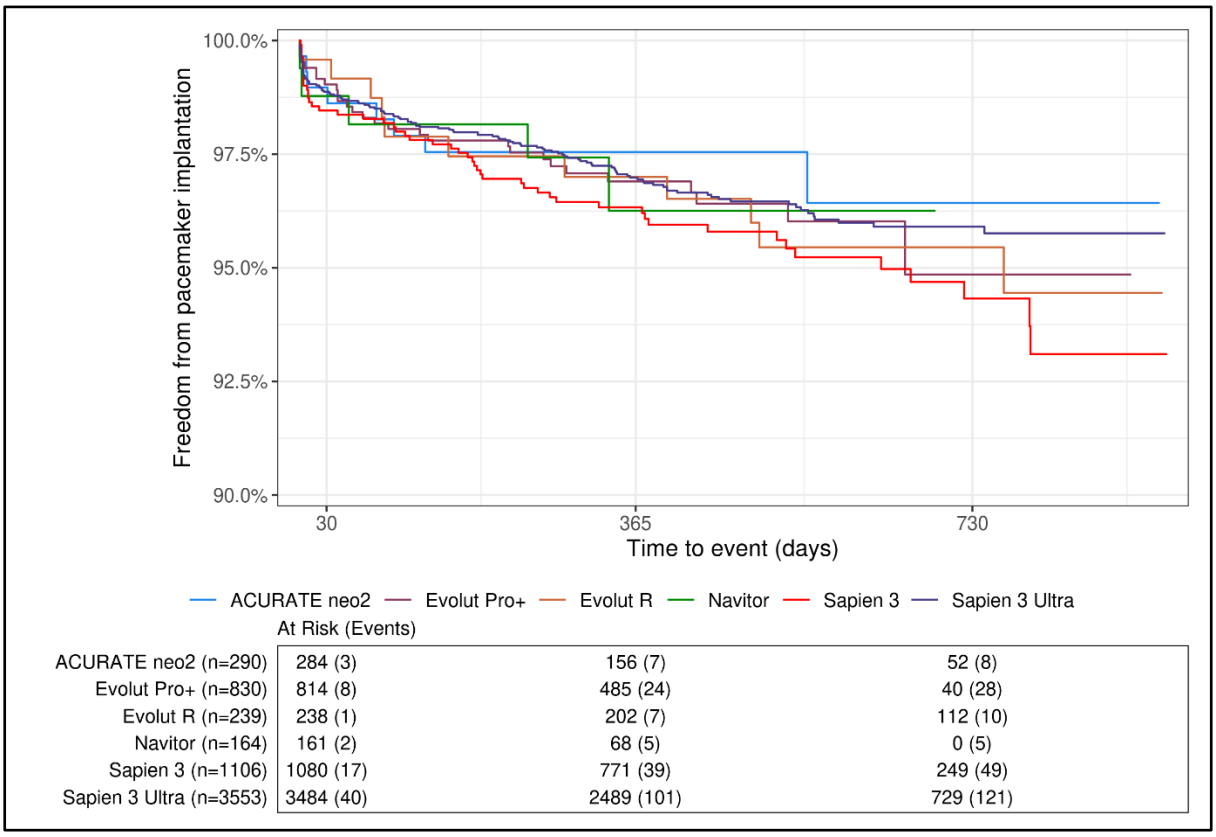


Figure 9: Kaplan-Meier for permanent pacemaker implantation (n=225): UK TAVI Registry linked to HES



At Risk (Events)			
ACURATE neo2 (n=290)	284 (3)	156 (7)	52 (8)
Evolut Pro+ (n=830)	814 (8)	485 (24)	40 (28)
Evolut R (n=239)	238 (1)	202 (7)	112 (10)
Navitor (n=164)	161 (2)	68 (5)	0 (5)
Sapien 3 (n=1106)	1080 (17)	771 (39)	249 (49)
Sapien 3 Ultra (n=3553)	3484 (40)	2489 (101)	729 (121)

5.5.2 Multivariate analysis

Preparation

Of the 6,270 patients undergoing TAVI in native aortic valve, a total of 3,917 patients (62.0%) had complete information across the covariates and outcomes which were to be used in multivariate analysis. As some covariates were potentially associated (for example: sex, height, annular diameter, valve area, size of TAVI device), multiple imputation was not used to correct for missing data for each variable in isolation. In initial univariate exploration of patient characteristics, the EAG found that no covariate differed significantly ($p<0.05$) between patients who died in-hospital and those who did not (Appendix E3). However, in complete case analysis (all patients with any missing data excluded), there was a statistically significant difference for frailty between groups, indicating that exclusion of missing data altered the patient populations. For the in-hospital stroke outcome, there were statistically significant differences in age and presence of renal comorbidity between those having a stroke and those not; although only difference in age remained statistically significant in complete case analysis. For the aortic regurgitation at discharge outcome, there were statistically significant differences in mean aortic valve gradient pre-procedure and size of TAVI device between those with and without aortic regurgitation before complete case analysis, with only size of TAVI device remaining statistically significant after. For the pacemaker outcome, sex and size of TAVI device were significantly different between those who did and did not need a permanent pacemaker before complete case analysis, with only size of TAVI device remaining statistically significant after. Complete case analysis had little impact on similar analysis undertaken for major bleeding, major vascular complications, bailout TAVI-in-TAVI, and conversion to SAVR outcomes. Furthermore, the EAG did initially construct separate multivariate models for each outcome optimising the covariates, however the significance of results was unchanged. The EAG acknowledges that limiting the model data sets to complete cases (with no missing data for any outcome or any key covariate) may have introduced a degree of bias to the analysis. However, the alternative approach of using different covariate sets for each outcome, to optimise data usage in each case, did not lend itself to using all BLR and CPH models as simultaneous inputs to the economic model. Because the EAG had ruled out the alternative approach of using Poisson or negative binomial models,

as described earlier, the EAG felt that overall, its approach minimised limitations. Improved data completeness in the Registry would improve future analyses.

Within multivariate analysis, BLR models were built for each in-hospital outcome of interest, all results are presented as odds ratios when compared with the 'reference patient' (classed as those who received an Edwards Lifesciences Sapien 3 Ultra device, representing most of the cases, 65.1%), where all binary covariates are set to zero (representing 'FALSE') and continuous covariates are at the median.

In-hospital outcomes

Only complete cases (across all key covariates and outcomes) were included in the analysis. If patients died in hospital before experiencing outcomes they were considered 'complete'; however, this causes a small variation in the number of patients included in each model (between 3,910 and 3,917). For example, if a patient died as consequence of a fatal stroke, they would have complete data for the stroke and death outcomes, but it is not known if they would have also experienced another outcome.

The EAG noted correlation between TAVI device and size of TAVI device, namely Sapien 3 Ultra showing a negative correlation with large valve size (-0.81) indicating that they are more frequently used in small and medium valves, whereas Sapien 3 showed the opposite (0.62) indicating increased usage in large valve sizes. One Clinical Expert noted that this finding reflected that Sapien 3 is available in 29 mm valve size, whereas the largest valve size for Sapien 3 Ultra is 26 mm. Evolut Pro + and Evolut R were positively correlated with large valve size (0.35 and 0.21 respectively). Notable correlations were also found between sex, height, weight, annular diameter, and size of TAVI device all of which were expected. No other significant correlations between covariates were identified (Figure 10).

The key covariates for in-hospital outcomes and their associated odds ratio (95%CI) are presented in Table 23. TAVI device was not associated with in-hospital death, major bleeding, major vascular complications, TAVI reintervention or SAVR intervention outcomes; however, the EAG note that the number of events in the latter 2 outcomes were small. Some patient characteristics were associated with an

increased odds of event (for example general anaesthesia and frailty increased the odds of in-hospital death), and others reduced the odds of an event (for example male sex was protective against in-hospital stroke). Increased weight (per kg) was found to be weakly associated with reduced rates of aortic-regurgitation and major vascular complication, likely reflecting an increased risk of these outcomes in patients with low body weight (50kg or less). One Clinical Expert advised that this result was plausible because female patients, with typically lower body weight, smaller annuli, smaller peripheral vessels, and increased risk of vascular injury, are more likely to receive a self-expanding TAVI device, which have higher risk of aortic regurgitation. The EAG investigated the possibility of applying transformations (for example log, polynomial) to the weight covariate but in all cases the association remained (to help with interpretability no transformations were applied in the final model).

TAVI device was associated with:

- in-hospital stroke: Sapien 3, Evolut R, Evolut Pro+, and Navitor were found to have significantly increased odds of in-hospital stroke relative to Sapien 3 Ultra. Conversely, ACURATE neo2 was not associated with increased odds of stroke in-hospital, relative to Sapien 3 Ultra. After adjusting for recorded covariates (including annular diameter, valve size), age, non-coronary clinical comorbidities, and non-coronary renal comorbidities were found to be associated with significantly increased odds of in-hospital stroke, and male sex with decreased odds. One Clinical Expert advised that this finding is consistent with published literature, reporting women undergoing TAVI have increased risk of stroke when compared with men.
- in-hospital aortic regurgitation: Evolut R, Evolut Pro+, ACURATE neo2, and Navitor were all found to have increased odds relative to Sapien 3 Ultra. Extensive calcification of ascending aorta (which may be considered as a surrogate marker of aortic valve calcification), patient height, and mean valve gradient were associated with increased odds. Weight was associated with decreased odds. One Clinical Expert advised that this finding is consistent with published literature, reporting increased risk of aortic regurgitation in people treated with self-expanding valves, compared with balloon-expanding

valves. The EAG did not analyse data comparing all self-expanding, with all balloon-expanding valves directly, so as not to weight the results on the older generations of devices, which understandably, may be associated with poorer outcomes.

- in-hospital permanent pacemaker implantation: Evolut R, Evolut Pro+, and Navitor were all found to have increased odds relative to Sapien 3 Ultra. ACURATE neo2 was therefore the only self-expanding valve not associated with increased odds of permanent pacemaker implantation, relative to Sapien 3 Ultra. No other recorded patient or clinical characteristics were found to be associated with this outcome. One Clinical Expert advised that pre-existing right bundle branch block may influence choice of device to one with reduced likelihood of pacemaker implantation.

Two Clinical Experts advised that statistical differences in in-hospital outcomes are likely related to unmeasured confounders. One explained that in their centre, the Sapien devices are the first line choice for straightforward anatomies, and that Evolut devices would be used for more complex cases; which may explain the higher stroke and AR rates. The other confirmed that major confounders, mostly anatomical or patient characteristics, that affect decision making, are not captured in the Registry.

The TAVI device used was not associated with major bleeding, which one Clinical Expert advised seemed clinically plausible, because major bleeding is more likely related to patient characteristics than the device itself. Male sex, small annular diameter and small valve size were associated with decreased odds of major bleeding. One Clinical Expert advised that the published literature has shown increased bleeding and vascular complications in female patients, who typically have smaller annuli. It is therefore difficult to explain the findings of the Registry analysis, in terms of annular diameter. Annular diameter was found to be associated with decreased odds as the diameter increased, which contradicts the coefficient for valve size (valve size is a categorical variable which should be proportional to annular diameter; that is, a large valve size for a large annular diameter). This is likely a consequence of the categorisation of a continuous variable. The EAG also explored transformations of the annular diameter (fractional, square-root, log, polynomial) and the association remained or became insignificant.

Due to the relative low frequency of almost all key outcomes in the final data used to train each model, the confidence intervals for coefficients are often wide, showing a degree of uncertainty in results. Under the thresholds used by the EAG the PPI model was the only model deemed to be poor at being able to discriminate between outcomes, all other models were at acceptable levels (AUC>0.7). Some confidence intervals extend infinitely due to the absence of data for categorical covariates for the outcome, for example no patients that suffered major life-threatening bleeding were recorded as having extensive calcification or anaesthesia, which causes a separation of data and so the model is unable to estimate a coefficient for the covariate. This is the case in the modelling of in-hospital SAVR intervention, where there were no recorded cases for ACURATE neo2 or Navitor therefore the model was unable to estimate the coefficient for TAVI device. One Clinical Expert confirmed that bailout SAVR is rare, and that it would be difficult to demonstrate differences between valves for this specific outcome.

To assess the impact of missing data on each outcome across TAVI devices the EAG performed chi-squared test on the proportion of patients that experienced each outcome per TAVI device type before and after exclusions. For example, the EAG tested if the proportion of patients that had Sapien 3 and died in-hospital was different to the proportion that died in-hospital after excluding incomplete cases. There was no evidence for an effect of missingness on any of the outcomes considered, except one. The exclusion of incomplete cases had a significant impact on the proportion of Sapien 3 Ultra patients that experience aortic regurgitation (p=0.029), before exclusions there were 33 patients out of 3396 (0.97%) whereas after exclusions there were 10 out of 2342 patients (0.42%). There was no evidence that the proportion of patients with aortic regurgitation with other valve types was influenced by missingness. Therefore, the exclusion of incomplete cases disproportionately affected Sapien 3 Ultra compared with other device types and caused a decrease in the proportion of patients that suffered aortic regurgitation. As Sapien 3 Ultra was used as the reference, the odds ratios observed for the other device types may be influenced by this significant decrease, although it will not influence relative differences between other devices. There was no further evidence of a significant difference in proportions across any other outcomes for all TAVI

device types, suggesting that exclusion of incomplete cases had no discernible impact on the final estimates.

The multivariate analysis accounts for patient characteristics that are known and measured risk factors. It is limited by the availability and quality of the data, and by the presence of unmeasured potential confounders. For example, if the more frequent use of Sapien 3 Ultra observed in the UK TAVI Registry is because clinicians choose that by default, and only select a different TAVI device if the patient has characteristics that need it, there may be a greater proportion of uncomplicated patients being treated with that device. One Clinical Expert advised that this reflected clinical practice where many units would have a default valve and use others in specific clinical situations and patient anatomies. They noted that it would be rare for valves to be used interchangeably by all operators in all units. Whilst the multivariate analysis can control for those characteristics that are included in the model, it cannot control for unmeasured variables.

Table 23: Results of binary logistic modelling (adjusted) of UK TAVI Registry data (TAVI in native aortic valve) for each key in-hospital outcome

[Note: Values are odds ratios (confidence intervals), representing the risk each outcome relative to the 'reference patient' that is, one that received Edwards Lifesciences Sapien 3 Ultra TAVI device, with binomial covariates set to zero and continuous variables (†) set to the median. Red indicates increased odds, green decreased odds (protective)]. In each model only main effects (i.e. no interactions) were investigated.]

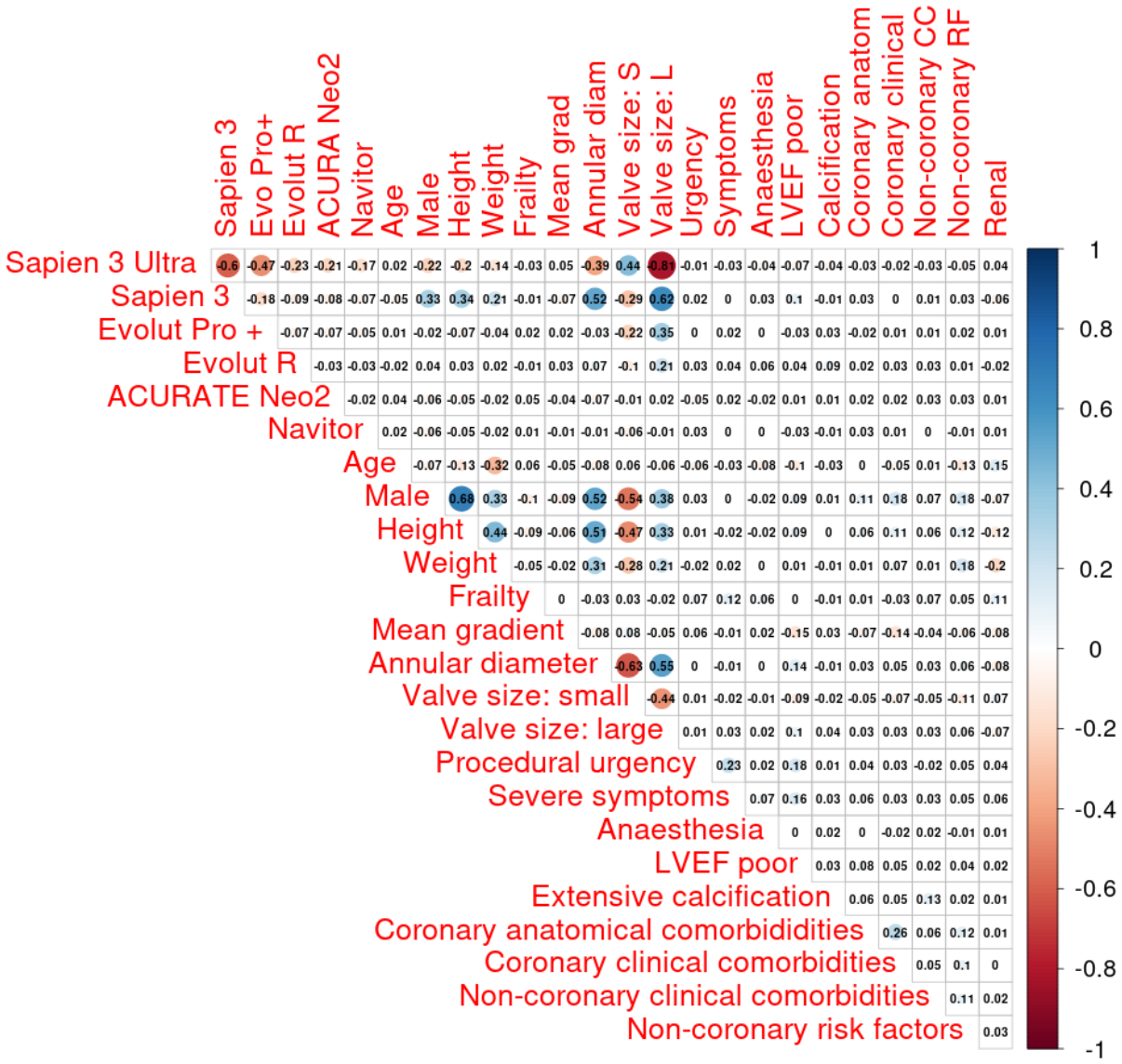
Parameter	Death (1.2%); 47 events in 3,917 patients	Stroke (1.6%); 61 events in 3,910 patients	Aortic regurgitation (1.2%); 46 events in 3,910 patients	Pacemaker (6.9%); 270 events in 3,913 patients	Major bleeding (1.2%); 47 events in 3,912	Major vascular complication (1.2%); 49 events in 3,913 patients	TAVI bailout/reintervention before discharge (0.6%); 23 events in 3,915 patients	SAVR intervention (0.2%); 7 events in 3,915 patients
Intercept	0.02 (0, 0.09)*	0.01 (0, 0.03)*	0.05 (0.01, 0.38)*	0.06 (0.03, 0.13)*	0.03 (0, 0.16)*	0.06 (0.01, 0.39)*	0.02 (0, 0.25)*	0 (0, 0.05)*
Sapien 3 Ultra	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Sapien 3	0.86 (0.25, 2.92)	3.26 (1.23, 8.64)*	1.58 (0.41, 6.1)	0.89 (0.51, 1.55)	0.97 (0.28, 3.28)	0.60 (0.17, 2.17)	0.76 (0.11, 5.38)	0 (0, Inf)
ACURATE neo2	2.35 (0.61, 9.08)	0.97 (0.13, 7.51)	5.60 (1.11, 28.32)*	0.79 (0.32, 1.92)	1.77 (0.48, 6.5)	3.10 (0.92, 10.39)	3.85 (0.74, 19.99)	0 (0, Inf)
Evolut R	3.11 (0.77, 12.57)	5.44 (1.49, 19.91)*	8.51 (2.1, 34.47)*	2.08 (1.03, 4.18)*	0.77 (0.14, 4.15)	0.66 (0.11, 4.05)	2.28 (0.22, 24)	0 (0, Inf)
Evolut Pro +	1.11 (0.31, 4.01)	5.21 (2.02, 13.46)*	9.78 (3.11, 30.76)*	1.89 (1.09, 3.28)*	0.41 (0.11, 1.52)	0.73 (0.2, 2.67)	3.28 (0.68, 15.86)	0 (0, Inf)
Navitor	0.97 (0.11, 8.28)	5.22 (1.59, 17.15)*	24.56 (7.04, 85.67)*	2.54 (1.24, 5.2)*	1.07 (0.21, 5.3)	2.54 (0.62, 10.36)	0 (0, Inf)	0 (0, Inf)
Age (per year) †	0.99 (0.95, 1.04)	1.06 (1.01, 1.11)*	0.97 (0.93, 1.01)	1.01 (0.99, 1.03)	0.98 (0.94, 1.03)	1 (0.95, 1.04)	1.05 (0.97, 1.14)	1.06 (0.93, 1.21)
Anaesthesia	4.34 (1.08, 17.55)*	0 (0, Inf)	1.32 (0.14, 12.82)	1.09 (0.32, 3.68)	0 (0, Inf)	2.02 (0.24, 16.71)	0 (0, Inf)	33.9 (2.95, 390.17)*
Annular diameter (per mm) †	1.04 (0.92, 1.18)	1.08 (0.97, 1.19)	1.02 (0.88, 1.18)	1 (0.94, 1.07)	0.81 (0.68, 0.95)*	0.93 (0.78, 1.12)	0.95 (0.74, 1.22)	1.02 (0.67, 1.56)
Extensive calcification of ascending aorta	0.53 (0.06, 4.35)	0.92 (0.21, 4.01)	4.05 (1.41, 11.6)*	0.82 (0.37, 1.83)	0 (0, Inf)	0 (0, Inf)	0 (0, Inf)	0 (0, Inf)
Coronary anatomical comorbidities	1.02 (0.51, 2.07)	1.45 (0.8, 2.61)	0.99 (0.48, 2.05)	1.17 (0.88, 1.57)	1.21 (0.61, 2.41)	1.06 (0.54, 2.11)	1.39 (0.54, 3.57)	0.35 (0.04, 3.57)
Coronary clinical comorbidities	0.91 (0.43, 1.93)	1.07 (0.57, 2.03)	1.07 (0.5, 2.28)	1.26 (0.94, 1.7)	1.11 (0.54, 2.31)	1.25 (0.62, 2.54)	0.99 (0.36, 2.73)	3.9 (0.68, 22.47)
Frailty	2.08 (1.1, 3.93)*	0.55 (0.26, 1.16)	0.97 (0.44, 2.14)	1.11 (0.8, 1.55)	1.9 (0.98, 3.67)	1.26 (0.64, 2.51)	0.23 (0.03, 1.71)	1.21 (0.13, 11.39)
Height (per 10cm) †	1.28 (0.83, 1.96)	1.05 (0.72, 1.54)	1.73 (1.1, 2.72)*	0.95 (0.79, 1.15)	1.1 (0.71, 1.7)	1.32 (0.86, 2.03)	0.99 (0.53, 1.85)	3.09 (0.94, 10.14)
LVEF poor	0.97 (0.35, 2.7)	1.23 (0.49, 3.1)	1.12 (0.35, 3.57)	0.86 (0.52, 1.42)	0.23 (0.03, 1.75)	0.52 (0.12, 2.3)	2.25 (0.59, 8.63)	0 (0, Inf)
Male	0.57 (0.23, 1.38)	0.4 (0.18, 0.91)*	0.83 (0.33, 2.08)	1.22 (0.82, 1.8)	0.4 (0.17, 0.96)*	0.57 (0.24, 1.35)	1.23 (0.35, 4.31)	0.27 (0.02, 4.14)
Aortic valve mean gradient (per mmHg) †	0.99 (0.97, 1.01)	1 (0.98, 1.01)	1.02 (1.01, 1.04)*	1 (0.99, 1.01)	1.01 (0.99, 1.02)	1.02 (1, 1.03)	0.98 (0.95, 1.01)	1.02 (0.98, 1.06)
Non-coronary clinical comorbidities	1.19 (0.59, 2.41)	2.02 (1.13, 3.62)*	0.37 (0.14, 1)	0.9 (0.65, 1.25)	1.11 (0.53, 2.31)	1.22 (0.61, 2.46)	1.04 (0.35, 3.15)	0.74 (0.08, 6.57)
Non-coronary risk factors	1 (0.54, 1.85)	0.82 (0.48, 1.41)	1.5 (0.79, 2.85)	0.98 (0.76, 1.28)	0.98 (0.53, 1.81)	1.36 (0.74, 2.51)	0.99 (0.41, 2.37)	2.12 (0.38, 11.95)
Non-coronary renal	1.61 (0.7, 3.71)	2.28 (1.14, 4.54)*	1.18 (0.43, 3.22)	1.07 (0.7, 1.65)	1.19 (0.44, 3.22)	1.37 (0.58, 3.28)	0 (0, Inf)	0 (0, Inf)
Procedural urgency	1.39 (0.72, 2.68)	1.49 (0.83, 2.67)	1.08 (0.54, 2.13)	0.82 (0.6, 1.12)	1.35 (0.68, 2.66)	1.28 (0.66, 2.47)	1.17 (0.41, 3.32)	0.48 (0.05, 4.55)
Severe symptoms	1.37 (0.64, 2.96)	0.89 (0.4, 1.98)	0.7 (0.25, 1.97)	1.24 (0.85, 1.81)	0.75 (0.28, 2.02)	0.69 (0.26, 1.87)	0 (0, Inf)	0 (0, Inf)
Valve size: small	1.09 (0.44, 2.7)	1.61 (0.71, 3.61)	1.7 (0.59, 4.91)	0.79 (0.52, 1.22)	0.17 (0.06, 0.49)*	0.81 (0.31, 2.13)	1.03 (0.27, 3.86)	0 (0, Inf)
Valve size: large	1.17 (0.37, 3.69)	0.75 (0.3, 1.85)	1.3 (0.48, 3.58)	1.5 (0.89, 2.53)	3.73 (1.2, 11.53)*	3.56 (1.13, 11.21)*	0.76 (0.16, 3.57)	24839152.21 (0, Inf)
Weight (per kg) †	0.99 (0.97, 1.01)	1 (0.99, 1.02)	0.96 (0.94, 0.98)*	1 (0.99, 1.01)	0.99 (0.97, 1.01)	0.97 (0.95, 0.99)*	0.98 (0.95, 1.02)	1.02 (0.97, 1.07)
Null deviance [degrees of freedom]	509.35 [3,914]	628.61 [3,909]	500.18 [3,909]	1,964.69 [3,912]	509.07 [3,911]	526.64 [3,912]	282.17 [3,914]	102.56 [3,914]
Residual deviance [degrees of freedom]	481.55 [3,890]	575.45 [3,885]	416.58 [3,885]	1,891.55 [3,888]	468.66 [3,887]	491.12 [3,888]	250.23 [3,890]	76.24 [3,890]

AUC	0.713 [0.639, 0.788]	0.758 [0.693, 0.823]	0.844 [0.785, 0.904]	0.647 [0.612, 0.681]	0.746 [0.679, 0.814]	0.737 [0.667, 0.809]	0.828 [0.773, 0.884]	0.903 [0.896, 1.00]
AIC	531.55	625.45	466.16	1,943.55	518.66	541.12	300.23	126.24

Abbreviations: AIC, Akaike information criterion; AUC, Area under the curve; LVEF, Left ventricular ejection fraction;

Figure 10: Correlation matrix for logistic model parameters for all outcomes (all trained on same data)

[Note that the 'correlation' between TAVI device is a consequence of converting categorical variables to 'dummy' variables, which induces a linear relationship between dummy variables, this should be ignored]



Outcomes occurring after discharge

Key covariates for late outcomes occurring post-discharge are presented in Table 24, which includes hazard ratios and 95% confidence intervals. TAVI device was not associated with any long-term outcomes. In addition to the covariates used in the in-hospital outcome models, additional variables were introduced to look at the effect of in-hospital adverse events (during TAVI procedure) on long-term outcomes, this includes in-hospital stroke on death and subsequent stroke, aortic-regurgitation on re-admission for heart failure and PPI on subsequent PPI (because this finding relied

on identification of pacemaker codes in the follow up period in HES, it simply highlights that patients who need a permanent pacemaker as a result of their TAVI procedure need ongoing pacemaker maintenance during long-term follow up, and is to be expected). Age at discharge, frailty, non-coronary renal comorbidities, and non-coronary risk-factors, procedural urgency, severe symptoms all increased the hazard of death post-discharge. Age, non-coronary clinical comorbidities, and stroke during TAVI admission increased hazard of stroke post-discharge. Procedural urgency increased the hazard of PPI post-discharge. Frailty, non-coronary clinical comorbidities, non-coronary risk factors, procedural urgency, and small valve size all increased odds of re-admission for heart failure. Mean aortic gradient measured pre-procedure was found to decrease odds of death and re-admission for heart failure. The 1-year estimated event rate predicted more than 1 in 10 [0.12, (0.07, 0.16)] will die within a year of discharge. However, the death model has the lowest concordance (0.663), which suggests that whilst the model has some predictive capability, it is lacking. Further modelling would look to include more patients and include a richer dataset which may include variables that the EAG was unable to obtain from the UK TAVI Registry.

Table 24: Results of Cox proportional hazard modelling (adjusted) of UK TAVI Registry data (TAVI in native aortic valve) for each key outcome occurring post-discharge

[Note Values are hazard ratios, representing risk relative to the 'reference patient' that is one that received Edwards Lifesciences Sapien 3 Ultra TAVI device, with binomial covariates set to zero and continuous variables set to the median]. In each model only main effects (i.e. no interactions) were investigated.]

Parameter	**Death; 512 events in 3,907 patients**	**Stroke; 124 events in 3,907 patients**	**Pacemaker; 133 events in 3,907 patients**	**Aortic reintervention (TAVI or SAVR); 18 events in 3,907**	**Readmission for heart failure; 276 events in 3,880 patients**
Sapien 3 Ultra	Reference	Reference	Reference	Reference	Reference
Sapien 3	0.81 (0.54, 1.2)	1.3 (0.61, 2.77)	1.39 (0.67, 2.86)	0 (0, Inf)	1.29 (0.79, 2.12)
ACURATE neo2	1.14 (0.68, 1.91)	0.91 (0.27, 3.01)	1.83 (0.69, 4.85)	0 (0, Inf)	1.38 (0.68, 2.82)
Evolut R	0.82 (0.47, 1.43)	0.67 (0.18, 2.45)	1.71 (0.66, 4.45)	0 (0, Inf)	1.76 (0.87, 3.53)
Evolut Pro+	0.82 (0.53, 1.26)	1.05 (0.45, 2.42)	1.23 (0.55, 2.75)	0 (0, Inf)	1.6 (0.93, 2.74)
Navitor	1.68 (0.89, 3.18)	0.92 (0.21, 4)	1.04 (0.24, 4.49)	0 (0, Inf)	1.47 (0.58, 3.73)
Age, median adjusted	1.02 (1.01, 1.04)*	1.04 (1.01, 1.07)*	1.02 (0.99, 1.05)	0.96 (0.9, 1.02)	1.02 (1, 1.04)
Anaesthesia	1.39 (0.65, 2.98)	0.96 (0.13, 7.04)	0.8 (0.11, 5.85)	0 (0, Inf)	1.93 (0.78, 4.78)
Annular, diameter median adjusted	1.01 (0.96, 1.06)	1.02 (0.93, 1.13)	1.07 (0.99, 1.16)	1.07 (0.86, 1.33)	1.03 (0.97, 1.1)
Extensive calcification of ascending aorta	0.77 (0.42, 1.42)	1.4 (0.51, 3.87)	1.33 (0.48, 3.68)	0 (0, Inf)	1 (0.49, 2.06)
Coronary anatomical comorbidities	1.11 (0.91, 1.36)	0.7 (0.44, 1.11)	0.67 (0.43, 1.04)	0.83 (0.23, 3.02)	1.17 (0.89, 1.53)
Coronary clinical comorbidities	0.93 (0.75, 1.15)	0.84 (0.53, 1.34)	1.29 (0.86, 1.94)	0.69 (0.18, 2.56)	1.18 (0.9, 1.56)
Frailty	1.39 (1.13, 1.71)*	1.52 (0.99, 2.34)	0.72 (0.43, 1.2)	0.32 (0.04, 2.53)	1.47 (1.11, 1.94)*
Height (per 10 cm), median adjusted	1.11 (0.97, 1.26)	1.15 (0.88, 1.5)	1.11 (0.86, 1.44)	1.36 (0.68, 2.71)	0.99 (0.82, 1.18)
LVEF poor	1.15 (0.86, 1.54)	1.28 (0.67, 2.42)	1.4 (0.82, 2.4)	0.67 (0.08, 5.7)	1.28 (0.89, 1.84)
Male sex	1.01 (0.77, 1.34)	1.03 (0.58, 1.83)	0.83 (0.48, 1.44)	0.67 (0.16, 2.73)	1.07 (0.73, 1.56)
Mean aortic valve gradient (measured pre-procedure) median adjusted	0.99 (0.98, 0.99)*	0.99 (0.98, 1)	0.98 (0.97, 1)	0.98 (0.95, 1.01)	0.97 (0.96, 0.97)*
Non-coronary clinical comorbidities	1.22 (0.99, 1.51)	2.1 (1.42, 3.11)*	0.84 (0.52, 1.35)	0.61 (0.14, 2.72)	1.5 (1.15, 1.97)*
Non-coronary renal	1.34 (1.11, 1.63)*	1.06 (0.73, 1.55)	0.81 (0.57, 1.16)	0.99 (0.38, 2.59)	1.27 (0.98, 1.65)
Non-coronary risk factors	1.8 (1.42, 2.3)*	0.82 (0.46, 1.48)	0.88 (0.46, 1.67)	0.75 (0.1, 5.91)	1.85 (1.32, 2.58)*
Procedural urgency	1.25 (1.02, 1.53)*	0.81 (0.51, 1.27)	1.48 (1.01, 2.18)*	0.42 (0.09, 1.92)	1.76 (1.36, 2.29)*
Severe symptoms	1.34 (1.05, 1.71)*	1.16 (0.66, 2.04)	1.27 (0.77, 2.09)	1.23 (0.27, 5.66)	1.17 (0.84, 1.62)
Valve size: small	0.99 (0.74, 1.32)	1.26 (0.71, 2.23)	1.24 (0.71, 2.16)	2.84 (0.63, 12.77)	1.57 (1.06, 2.33)*
Valve size: large	1.3 (0.88, 1.93)	0.82 (0.38, 1.75)	0.95 (0.46, 1.97)	55870994.26 (0, Inf)	0.92 (0.56, 1.52)
Weight, median adjusted	0.99 (0.99, 1)	0.99 (0.98, 1)	1 (0.99, 1.01)	0.99 (0.96, 1.02)	1.01 (1, 1.02)
In-hospital stroke	1.36 (0.73, 2.56)	16.34 (9.64, 27.71)*	-	-	-
PPI at discharge (post-TAVI)	-	-	2.34 (1.42, 3.85)*	-	-
AR at discharge (post-TAVI)	-	-	-	-	1.21 (0.38, 3.87)
Concordance	0.663	0.717	0.655	0.798	0.716
1 year event rate, 95% (CI)	0.12 (0.07, 0.16)	0.03 (0.01, 0.06)	0.03 (0.006, 0.06)	0.005 (0.004, 0.014)	0.066 (0.03, 0.10)

Abbreviations: AR, Aortic Regurgitation; TAVI, transcatheter aortic valve implantation

Device subgroups

To further explore differences between manufacturers, the EAG repeated modelling for self-expanding valves only. To do this all valves manufactured by Edwards Lifesciences were excluded, and Medtronic Evolut Pro+ was set as the reference as the most frequently used self-expanding TAVI device, to which other self-expanding devices were compared, Table 25 (in-hospital outcomes) and Table 26 (post-discharge outcomes).

Within this analysis no statistical difference between self-expanding TAVI devices was observed for any of the in-hospital outcomes, with the exception of major vascular complications where ACURATE neo2 had statistically increased odds when compared with Evolut Pro+. This may be a consequence of higher proportion of female patients being treated with ACURATE neo2, with smaller vessels and therefore increased risk of vascular complications. These results in comparison with the previous analysis comparing all 6 devices with each other (combining balloon- and self-expanding valves) further confirms that different patient populations are being treated with the different expansion types; noting that the Clinical Experts have stressed that specific anatomies inform device choice. Subgroup analysis accounts for any measured differences between those that have balloon- and self-expanding valves, however, it further reduces data from over 3000 patients in the main analysis to around 800. Consequently, events become even rarer which reduces statistical power and the increases the risk of overfitting the data, decreasing the generalisability of the results to the broader population.

Other contributory factors included:

- Annular diameter increased odds of stroke, but decreased odds of major bleeding and vascular complication.
- Coronary clinical comorbidities increased odds of major vascular complications.
- Poor LVEF increased odds of TAVI bailout or reintervention before discharge.
- Non-coronary clinical comorbidities increased odds of stroke, but decreased risk of aortic regurgitation.

- Procedural urgency increased odds of death.
- Large valve size increased odds of major bleeding and major vascular complications.
- Weight decreased odds of in-hospital aortic regurgitation.

The model for in-hospital SAVR conversion failed to converge, likely due to the extreme rarity of events (n=2). Modelling relies on sufficient data to make estimates of the likelihood of an event occurring. With only 2 events the data is too sparse to be able to make accurate inferences, which can lead to large uncertainty in estimates and the model being unable to estimate optimal parameters and thus failing to converge.

As was the case in the main analysis, TAVI device was not significantly associated with any long-term outcomes. Males had an increased hazard of death after discharge (not found in overall analysis) and as found in the main analysis renal comorbidities were associated with an increased hazard of death. In-hospital stroke (during TAVI admission) increased the hazard of a subsequent stroke after discharge and age, male sex, and procedural urgency all increased the hazard of future re-admission with heart failure. Mirroring observations from the main analysis, mean aortic pressure gradient was associated with a decreased hazard of death and re-admission with heart failure.

There was no significant difference in the odds of aortic regurgitation across self-expanding devices, which is surprising when one considers the differences between TAVI devices in the main analysis (self-expanding devices increased odds between 5 and 24 times when compared to balloon-expanding). This could be because of excluded missing data or be a further indication of difference in patient populations between the two expansion types. The EAG compared the proportion of patients with calcification (shown to increase odds of aortic regurgitation) between balloon- and self-expanding valves (chi-squared test) and found there was evidence to suggest that the proportion of patients reported to have extensive calcification differed significantly ($p<0.05$) between groups (2.1% in balloon- compared with 4.9% in self-expanding valves). The EAG investigated the effect of an interaction term between

TAVI devices and extensive calcification. None of the interaction terms were significant and all TAVI device types remained with an increased the odds of aortic regurgitation, so for simplicity the EAG did not include the interaction term in the final model. However, the quality and completeness of the extensive calcification variable is lacking. Additionally it is a dichotomisation of a continuous outcome, which reduces its statistical power and is subject to an arbitrary threshold which, if changed, will likely lead to different results.

Table 25: Odds ratios from binary logistic modelling (that is, adjusted by multivariate analysis) of UK TAVI Registry data (TAVI in native aortic valve) for all self-expanding valves for each key in-hospital outcome

Parameter	Death (1.8%); 15 events in 812 patients	Stroke (3.0%); 24 events in 810 patients	AR (3.8%); 31 events in 812	PPI (12.3%); 100 events in 810 patients	Major Bleeding (2.1%); 17 events in 809	Major Vascular Complication (2.3%); 19 events in 810	TAVI Bailout/Reintervention (1.1%)
Intercept	0 (0, 0.09)*	0.01 (0, 0.17)*	0.73 (0.06, 8.47)	0.27 (0.07, 1.04)	0 (0, 0.01)*	0.01 (0, 0.16)*	0.4 (0, 34.29)
Evolut Pro+	Reference	Reference	Reference	Reference	Reference	Reference	Reference
ACURATE neo2	1.86 (0.34, 10.11)	0.21 (0.02, 1.79)	0.78 (0.16, 3.68)	0.44 (0.18, 1.09)	4.41 (0.98, 19.82)	5.11 (1.4, 18.65)*	2.02 (0.31, 13.3)
Evolut R	2.76 (0.7, 10.9)	0.96 (0.29, 3.16)	0.99 (0.31, 3.1)	0.99 (0.54, 1.8)	1.84 (0.37, 9.08)	0.85 (0.16, 4.45)	0.85 (0.08, 8.49)
Navitor	0.49 (0.04, 5.99)	0.79 (0.2, 3.11)	2.63 (0.8, 8.59)	1.25 (0.58, 2.67)	3.34 (0.58, 19.19)	4.3 (0.93, 19.88)	0 (0, Inf)
Age (per year) †	1.01 (0.93, 1.1)	1.05 (0.97, 1.13)	0.99 (0.94, 1.04)	1.01 (0.98, 1.05)	0.96 (0.89, 1.04)	1.01 (0.94, 1.09)	1.07 (0.93, 1.23)
Anaesthesia	0 (0, Inf)	0 (0, Inf)	3.17 (0.24, 42.51)	0.73 (0.08, 6.46)	0 (0, Inf)	6.81 (0.56, 82.53)	0 (0, Inf)
Annular, diameter (per mm) †	1.13 (0.89, 1.42)	1.19 (1.04, 1.37)*	0.99 (0.82, 1.18)	1.03 (0.94, 1.14)	0.6 (0.46, 0.77)*	0.74 (0.57, 0.95)*	0.85 (0.58, 1.25)
Extensive calcification of ascending aorta	0.84 (0.09, 8.21)	0.72 (0.08, 6.34)	3.02 (0.74, 12.28)	1.26 (0.46, 3.48)	0 (0, Inf)	0 (0, Inf)	0 (0, Inf)
Coronary anatomical comorbidities	0.92 (0.26, 3.18)	1.81 (0.69, 4.78)	0.87 (0.34, 2.23)	0.98 (0.58, 1.64)	1.84 (0.58, 5.83)	1.02 (0.34, 3.04)	0.52 (0.05, 5.08)
Coronary clinical comorbidities	1.52 (0.46, 4.98)	1.15 (0.41, 3.17)	0.71 (0.26, 1.95)	1.27 (0.76, 2.12)	2.17 (0.66, 7.15)	3.76 (1.27, 11.12)*	0.4 (0.04, 3.96)
Frailty	1.15 (0.31, 4.21)	0.34 (0.09, 1.25)	1.09 (0.42, 2.86)	1 (0.57, 1.76)	1.65 (0.48, 5.66)	0.97 (0.31, 3.02)	0 (0, Inf)
Height (per 10 cm increase) †	1.09 (0.46, 2.59)	0.88 (0.47, 1.65)	1.6 (0.9, 2.82)	1.18 (0.85, 1.63)	0.77 (0.35, 1.7)	1.07 (0.51, 2.28)	1.4 (0.48, 4.09)
LVEF poor	2.12 (0.5, 9.07)	0.49 (0.06, 4.23)	1.35 (0.33, 5.6)	0.94 (0.42, 2.14)	0.62 (0.06, 6.57)	0.71 (0.07, 6.69)	9.35 (1.15, 76.29)*
Male sex	1.53 (0.24, 9.53)	0.31 (0.09, 1.12)	1.26 (0.43, 3.74)	1.05 (0.55, 2.02)	0.52 (0.11, 2.41)	0.4 (0.11, 1.53)	2.45 (0.22, 26.88)
Mean, gradient (per mmHg) †	1 (0.96, 1.03)	0.99 (0.96, 1.02)	1.02 (1, 1.04)	0.99 (0.98, 1.01)	0.98 (0.94, 1.02)	1.01 (0.98, 1.04)	1.01 (0.98, 1.05)
Non-coronary clinical comorbidities	2.28 (0.69, 7.6)	3.68 (1.43, 9.44)*	0.18 (0.04, 0.82)*	0.64 (0.35, 1.17)	0.84 (0.24, 3.01)	1.04 (0.33, 3.25)	0 (0, Inf)
Non-coronary risk factors	1.45 (0.44, 4.8)	1.14 (0.47, 2.76)	1.76 (0.77, 4.01)	0.86 (0.55, 1.34)	2.09 (0.57, 7.75)	1.09 (0.39, 3.05)	1.4 (0.32, 6.14)
Non-coronary renal	2.84 (0.65, 12.55)	2 (0.58, 6.89)	1.59 (0.48, 5.23)	0.68 (0.3, 1.54)	0.65 (0.07, 5.87)	0.82 (0.16, 4.27)	0 (0, Inf)
Procedural urgency	5.37 (1.58, 18.29)*	2.44 (0.98, 6.12)	1.75 (0.79, 3.92)	1.47 (0.9, 2.38)	1.6 (0.48, 5.35)	1.16 (0.36, 3.73)	0.84 (0.15, 4.82)
Severe symptoms	1.35 (0.36, 5.04)	0.72 (0.19, 2.73)	0.42 (0.11, 1.65)	1.47 (0.82, 2.64)	2.77 (0.79, 9.73)	1.53 (0.43, 5.46)	0 (0, Inf)
Valve size: small	1.03 (0.09, 11.87)	1.52 (0.27, 8.58)	0 (0, Inf)	0.79 (0.24, 2.55)	0.19 (0.02, 2.01)	0.25 (0.02, 2.56)	0 (0, Inf)
Valve size: large	0.41 (0.08, 2.11)	0.74 (0.22, 2.47)	1.01 (0.34, 2.99)	1.39 (0.72, 2.69)	5.48 (1.28, 23.41)*	5.05 (1.29, 19.76)*	0.4 (0.05, 3.49)
Weight (per kg) †	1 (0.96, 1.04)	1.01 (0.98, 1.04)	0.95 (0.92, 0.98)*	0.99 (0.97, 1)	1.01 (0.98, 1.05)	0.99 (0.96, 1.03)	0.96 (0.9, 1.02)
Null deviance [degrees of freedom]	149.46 [811]	216.19 [809]	263.26 [811]	605.48 [809]	164.96 [808]	180.14 [809]	98.94 [811]
Residual deviance [degrees of freedom]	124.92 [789]	192.19 [787]	227.13 [789]	578.70 [787]	127.34 [786]	156.43 [787]	71.49 [789]
AUC	0.808 [0.690, 0.926]	0.773 [0.682, 0.863]	0.789 [0.712, 0.867]	0.663 [0.610, 0.715]	0.870 [0.797, 0.943]	0.810 [0.730, 0.891]	0.908 [0.843, 0.973]
AIC	170.929	238.19	273.13	624.70	173.34	202.43	117.49

Key: †median adjusted. Abbreviations: AIC, Akaike information criterion; AUC, Area under the curve; LVEF, Left ventricular ejection fraction

Table 26: Results of cox proportional hazard modelling (adjusted) of UK TAVI Registry data (TAVI in native aortic valve) for each key outcomes occurring post-discharge, for all self-expanding valves

[Parameters included in final model and associated hazard ratio – in relation to the 'reference patient' that is one that received Evolut Pro+ device, and binomial variables are set to zero and continuous variables are set to the median.]

Parameter	**Death; 102 events in 809 patients**	**Stroke; 21 events in 809 patients**	**Pacemaker; 31 events in 809 patients**	**Aortic reintervention (TAVI or SAVR); 5 events in 809 patients**	**Readmission for heart failure; 63 events in 809 patients**
Evolut Pro+	Reference	Reference	Reference	Reference	Reference
Evolut R	1.3 (0.74, 2.29)	0.74 (0.18, 3)	1.78 (0.7, 4.54)	2.32 (0.3, 17.93)	1.02 (0.51, 2.04)
ACURATE neo2	1.62 (0.9, 2.92)	1.01 (0.24, 4.22)	1.46 (0.49, 4.37)	0 (0, Inf)	0.74 (0.32, 1.7)
Navitor	1.79 (0.88, 3.62)	0.83 (0.15, 4.7)	0.83 (0.17, 3.99)	0 (0, Inf)	0.83 (0.3, 2.31)
Age, median adjusted	1.03 (1, 1.07)	1.03 (0.94, 1.12)	1.04 (0.98, 1.1)	1.01 (0.86, 1.18)	1.05 (1.01, 1.09)*
Anaesthesia	1.06 (0.13, 8.31)	0 (0, Inf)	0 (0, Inf)	0 (0, Inf)	3.06 (0.39, 24.11)
Annular diameter, median adjusted	1.01 (0.92, 1.11)	0.89 (0.71, 1.12)	1.02 (0.85, 1.22)	1.08 (0.75, 1.56)	1.05 (0.92, 1.19)
Extensive calcification of ascending aorta	0.41 (0.1, 1.73)	0 (0, Inf)	0 (0, Inf)	0 (0, Inf)	1.19 (0.35, 4.06)
Coronary anatomical comorbidities	1.38 (0.88, 2.18)	0.21 (0.04, 1.11)	1.11 (0.49, 2.52)	1.96 (0.26, 14.68)	0.75 (0.41, 1.37)
Coronary clinical comorbidities	0.83 (0.52, 1.33)	0.47 (0.12, 1.84)	1.96 (0.88, 4.33)	2.09 (0.27, 15.91)	1.45 (0.83, 2.53)
Frailty	1.52 (0.96, 2.42)	1.99 (0.63, 6.27)	0.32 (0.07, 1.38)	0 (0, Inf)	1.48 (0.81, 2.72)
Height (per 10cm), median adjusted	0.99 (0.73, 1.35)	1.82 (0.87, 3.8)	1.04 (0.6, 1.81)	0.85 (0.19, 3.94)	1.07 (0.73, 1.56)
LVEF poor	1.19 (0.58, 2.42)	3.6 (0.85, 15.19)	0.9 (0.25, 3.24)	1.98 (0.12, 33.47)	1.03 (0.43, 2.47)
Male	2.17 (1.2, 3.95)*	1.13 (0.26, 4.9)	2.19 (0.69, 7.01)	0.3 (0.02, 4.31)	2.27 (1.01, 5.14)*
Aortic valve mean gradient, median adjusted	0.98 (0.97, 0.99)*	0.99 (0.96, 1.02)	0.98 (0.96, 1.01)	0.99 (0.95, 1.05)	0.96 (0.95, 0.98)*
Non-coronary clinical comorbidities	1.21 (0.76, 1.94)	1.68 (0.6, 4.71)	0.49 (0.16, 1.47)	1.31 (0.11, 15.12)	1.51 (0.85, 2.7)
Non-coronary risk factors	0.91 (0.6, 1.38)	0.86 (0.33, 2.25)	1.58 (0.72, 3.45)	3.02 (0.32, 28.27)	1.15 (0.67, 1.99)
Non-coronary renal	2.16 (1.27, 3.67)*	1.04 (0.26, 4.21)	1.1 (0.3, 4.02)	0 (0, Inf)	0.3 (0.09, 1.01)
Procedural urgency	1.45 (0.91, 2.3)	0.78 (0.25, 2.44)	1.42 (0.62, 3.27)	0.58 (0.04, 7.73)	2.46 (1.4, 4.3)*
Severe symptoms	1.03 (0.58, 1.83)	0.75 (0.15, 3.84)	1.75 (0.66, 4.62)	1.47 (0.11, 19.29)	1.58 (0.83, 3.01)
Valve size: small	0.6 (0.24, 1.53)	0.89 (0.16, 5.13)	0.59 (0.11, 3.13)	1.44 (0, Inf)	1.97 (0.72, 5.4)
Valve size: large	0.89 (0.51, 1.57)	0.89 (0.25, 3.13)	0.48 (0.15, 1.47)	486922464.68 (0, Inf)	0.63 (0.29, 1.39)
Weight, median adjusted	0.98 (0.97, 1)	0.96 (0.92, 1)	1 (0.98, 1.03)	0.99 (0.93, 1.06)	0.99 (0.97, 1.01)
In-hospital stroke	1.62 (0.5, 5.3)	34.3 (9.76, 120.54)*	-	-	-
In-hospital PPI	-	-	1.82 (0.76, 4.36)	-	-
In hospital AR	-	-	-	-	0.49 (0.06, 3.79)
Concordance	0.717	0.876	0.779	0.915	0.737
1 year event rate, 95% (CI)					

Abbreviations: AR, Aortic Regurgitation; TAVI, transcatheter aortic valve implantation

5.6 Strengths and limitations of the clinical evidence

The published literature has identified differences in outcomes between TAVI devices (expansion types, manufacturers and models) including those directly in scope for this late-stage assessment, however few adjusted for population differences, and few included patients recruited from a UK setting. One Clinical Expert advised that the pace of change in transcatheter therapy for heart valve disease is rapid and acknowledged that using results from older trial data (with longer-follow-up) were less generalisable. Because of limitations in length of follow up and reporting, and technical differences between different generations of TAVI device from the same manufacturer, no equivalence has been assumed. The EAG considers the multivariate analysis of linked patient level data from the UK (linking in-hospital outcomes from the UK TAVI Registry and out of hospital outcomes up to 31 months from HES) adjusting for recorded confounders, to be the strongest source of clinical evidence available. This analysis demonstrated statistically significant differences in in-hospital outcomes (stroke, moderate or severe aortic regurgitation, pacemaker implantation) between 6 TAVI devices, but no statistical difference in out-of-hospital outcomes, at 1 year. Given lack of comparability (population, pathway, adjustment for confounding, intervention compared, time points and definition of outcomes), the EAG have not presented a comparison of the results of these with the results of the literature.

The UK TAVI Registry represents data which are most generalisable to a UK NHS setting, however these results have significant limitations that need consideration:

- Data are self-reported (with only a small proportion of data fields being validated through data linkage to HES).
- Reporting of the device manufacturer and model was poor; 4% of the procedures have no information to identify the device used. Of the serial numbers provided to Companies, 26% were unverified and excluded from analysis, and complete case analysis conducted by the EAG confirmed that removal of missing data may bias results.
- Immediate procedural outcomes may be recorded in the Registry contemporaneously, however outcomes happening later in the hospital visit

(for example, bleeding) may not be recorded robustly in the Registry. Linkage to HES can only help to validate clinical complications recorded in the UK TAVI Registry where specific diagnosis (ICD-10), and procedural (OPCS) codes exist and are defined the same as in the Registry.

- Several clinically important variables which determine choice of TAVI device are not recorded in the Registry and cannot be adjusted for in multivariate analysis (for example bicuspid valves, severe left ventricular outflow tract and annular calcification, potential coronary obstruction because of patient anatomy (see Table 1).

- The main analysis did not include 5 devices listed in the Final Scope, which were added to the NHS Supply Chain framework after 31 March 2023, the latest UK TAVI Registry data released by NICOR.

As indicated by the exploratory analyses conducted by the EAG, there is evidence to suggest that differences in outcomes between TAVI devices may be a consequence of different patient populations or being treated with different manufacturer TAVI devices. Therefore, the clinical evidence, including the analysis of short-term (in-hospital only) and medium-term (up to 31 month) outcomes from this real-world data which can only adjust for recorded confounders, and review of published evidence which does not adjust for population differences, should be interpreted with caution during the decision-making process. The EAG cannot rule out important differences that could favour specific TAVI device(s). It remains unclear whether specific TAVI device design features drive differences in clinical outcomes between TAVI devices. This could be addressed by adding additional data fields in the UK TAVI Registry.

6 Economic evaluation

6.1 *Quality appraisal of economic evidence*

The economic model and summary used within NG208 which considered the cost-effectiveness of TAVI when compared with SAVR (described in the Economic analysis report, NG208) was reviewed by the EAG and critically appraised against the CHEERS 2022 checklist (Appendix F1). The EAG tabulated the assumptions from the NG208 economic report and considered their appropriateness within the context of this late-stage assessment. The EAG also identified additional assumptions incorporated into the economic model which were identified when the EAG replicated it in *rdecision* (Appendix F2). Clinical Experts informing this late-stage assessment were also consulted about the appropriateness of prior assumptions.

The EAG considered several key limitations of the NG208 model, which included but are not limited to:

- The model structure only permitted pairwise comparisons. While this is a standard approach in HTA when considering cost-effectiveness against a reference case, this structure required modification to permit clinically relevant multi-way comparisons incorporating probabilistic sensitivity analysis to be conducted.

- The model structure included decision trees nested within health states representing re-intervention to account for adverse events during repeated TAVI interventions and included two Markov models per arm (one for those whose most recent intervention was TAVI and one for those whose most recent intervention was SAVR, to account for those having both treatments at different times). This was not clear from the model description within NG208 and only became apparent when the EAG attempted replication.

- Inclusion of standardized mortality because of an ageing population was correctly applied in the model, but excess hazards associated with TAVI and SAVR were applied in a complex manner.

- The model structure did not allow modelling of multiple adverse events. The model also did not account for short-term complications impacting risk of long-term complications (for example paravalvular leak at discharge did not adjust subsequent risks of rehospitalization for heart failure or need for further aortic valve intervention). One Clinical Expert advised that rehospitalisation for heart failure is likely reflective of patient characteristics, rather than attributable to heart failure secondary to functionally significant regurgitation at discharge.

- Bailout TAVI, bailout SAVR, and aortic reintervention prior to discharge were not captured in the decision tree costs. While these events are rare, they have considerable costs. However, 1 Clinical Expert has advised that these events may reflect early experience, and that bailout interventions are less common now in established TAVI practice.

- Within NG208 (2021) the Committee considered additional outcomes such as patient prothesis mismatch and atrial fibrillation. However, there was uncertainty regarding their inclusion. The NG208 Committee concluded that atrial fibrillation developing during the intervention was a peri-procedural outcome only, unlikely to have a long-term impact, and likely captured within NHS reference costs for the procedure (NG208 Economic Analysis Report, 2021). The EAG note that the late valve failure data field in the UK TAVI Registry was only completed for 2.3% of procedures, and that no cases of prosthesis-patient size mismatch were reported.

- The model included mild paravalvular leak and dialysis as in-hospital outcomes. The Clinical Experts advised that these are not key clinical considerations in directing choice of TAVI valve.

- Only acute complications following reintervention were considered in the Markov model during the long-term follow-up. The EAG has identified late events (post discharge) which appear to differ between TAVI valves, and which may have an economic impact.

- The model did not consider additional requirements for diagnostic tests (for example for those with paravalvular leak) or quality of life differences between TAVI devices. This is likely related to lack of data.

- Transition probabilities, p, between each pair of states were calculated from the formula p = exp(-rt), where r is the transition rate and t is the cycle time. However, as Welton and Ades (2005) have shown, this only holds for a two-state model and is an approximation in more complex models, and when there would be multiple transitions per cycle. This is likely to be the case in NG208 which had a cycle length of 1 year.

- While TAVI-in-TAVI currently represents a small proportion of patients, because of the expansion of TAVI in low and intermediate surgical risk patients the uptake of TAVI-in-TAVI is likely to increase. Two devices are explicitly contraindicated for valve-in-valve procedures (ACURATE neo2, Hydra; see Table 2).

- Costs associated with TAVI were appropriately obtained from the Healthcare Resource Groups (HRGs: EY21A, EY21B). However, the use of this aggregated cost did not enable modelling of procedure durations, in-hospital complications, or length of stay which may differ between TAVI devices.

To enable comparison with the economic model used within NG208, the EAG reviewed and summarised the 11 studies with associated economic models which were published after 2020 (identified from 6 systematic reviews), which included 7 peer-reviewed papers and 4 health technology assessment reports, 2 of which were in the French language) (Appendix B6). All the economic models, including the one used within NG208, reported the key parameters such as intervention and comparators, modelling approach, cost and outcomes, perspective, time horizon, and discounting:

- Seven were set in Europe (N=3 France, N=1 Spain, N=1 Italy, N=1 Norway, N=1 UK), 2 were set in Asia (N=1 Singapore, N=1 Japan), 1 was set in Canada, 1 was set in Australia. A total of 8 compared TAVI to SAVR, 3 to

medical management and for 2 the comparator was unknown (not reported in English).

- The time horizon across the included studies ranged from 5 years to the estimated patient lifetime.

- All studies included subgroups by surgical risk, with some including multiple subgroups (N=4 inoperable, N=1 high, N=2 intermediate, N=6 low).

- Four economic evaluation studies (Inoue et al. 2020, Kuntjoro et al. 2020, Gilard et al. 2022, Haute Autorite de Sante 2021a) used a combination of a decision tree model and a Markov model, while the remaining 7 studies used a Markov model only. In the economic evaluations using the decision tree models, the decision tree model was run for the first 30 days, with exception to Inoue et al. 2020 which ran it for the first 2 years. Almost all the Markov models used a 30-day cycle length except Inoue et al. 2020 and Kuntjoro et al. 2020 which used 1-year cycles. It should be noted that the economic model used within NG208 (Economic analysis report, NG208) also used a decision tree model for the first 30 days, thereafter using a Markov model (with nested decision trees in health states identified at replication) with annual cycles. All 11 economic evaluation studies used 2 (Inoue et al. 2020), 3 (Himmels 2021, Health Technology Wales, 2020), 4 (Zhou et al. 2021, Gilard et al. 2022, Haute Autorite de Sante 2021a, Haute Autorite de Sante 2021b) or 5 (Kuntjoro et al. 2020, Tam et al. 2021a) health states in their Markov model except Pinar 2022 and Lorenzoni et al. 2021 which both used 9 mutually exclusive health states primarily defined by the 4 levels of functional state based on the New York Heart Association (NYHA) classification and the occurrence of stroke along with risk of death at the end of each monthly cycle.

- All studies reported the utility values used in their model and provided references to their sources (note that utility values from 2 HTA reports (Haute Autorite de Sante 2021a, Haute Autorite de Sante 2021b) were reported in French).

The EAG considered the largest systematic review of economic evaluations of TAVI by Heathcote et al. (2023) which included the largest number of studies (N=42 studies which reported 65 unique analyses, Appendix B5); most used Edwards balloon-expanding valves (82%) and the remaining used Medtronic self-expanding valves (18%). From multivariate analysis of the probability that TAVI is cost-effective conducted by Heathcote et al. (2023), the generation of the device and the surgical risk group were the most important factors. Access route was not found to be a contributory factor. However, a strong correlation was seen between access route and risk group ($p=0.02$), device type ($p<0.01$) and time horizon used in the economic model ($p<0.01$). The use of TAVI resulted in more QALYs on average than its comparator in 90% of analyses. The largest health benefits were observed in the inoperable risk group (where the comparator was medical management) and increased with the proportion conducted via transfemoral access route. No notable difference in QALYs was observed between device generations; however, the latest generation balloon-expanding TAVI device had the largest average QALY gain.

Because of similarities with the published literature, the EAG confirmed that the economic model structure used within NG208 was a suitable basis for economic evaluation within the context of this late-stage assessment. The EAG reproduced the economic model used within NG208 using *rdecision* in R, and replicated its base case ICER results within a 2% margin of error.

6.2 *Economic model*

The EAG adapted the NG208 economic model, building it in *rdecision* to enable comparison of multiple TAVI devices, using outcomes derived from those recorded in the UK TAVI Registry. The updated economic model incorporated feedback from Clinical Experts who were consulted during the development of the model, including the ability for patients to experience multiple adverse events.

As with the original economic model used in NG208, a cost-utility analysis was undertaken. The patient group adopted for this late-stage assessment was adults with aortic stenosis requiring intervention with TAVI. In line with the NICE reference case (PMG36), both costs and outcomes were discounted at the 3.5% annual discount rate, with costs and outcomes considered from a UK NHS and personal social services perspective. The EAG applied a base case time horizon of 15 years,

in line with NG208, with most parameters informed by UK real world evidence (Hospital Episode Statistics outcomes up to 30 months; 2.5 years, which would be categorised as ‘intermediate’ time horizon using the definition outlined by the systematic review of economic evaluations by Heathcote et al. 2023). The model can be modified in future to account for events beyond two years, as data become available. Additional time horizons were considered in sensitivity analysis, but these also needed extrapolation of results from the real-world evidence.

Because of the decision problem of this late-stage assessment, the EAG focused on comparison of TAVI devices as deemed clinically appropriate by Clinical Experts, using the most frequently used TAVI device as the reference case within each scenario. Conversion to SAVR or subsequent SAVR during follow-up was treated as an outcome, and average cost and utility decrement (disutilities) associated with SAVR adverse events were obtained from the NG208 economic model output.

The economic model was run to estimate both the costs and the outcomes for each TAVI device. Due to the potential for more than 2 alternative TAVI devices being compared, the EAG reported the net monetary benefit (NMB) for each TAVI device when compared with a suitable reference rather than focusing on the more commonly presented incremental cost effectiveness ratios (ICERs). This is because ICERs are more difficult to interpret for comparisons of multiple alternatives. The decision rule for NMB is the alternative with the highest NMB when the NMB is calculated at a specified threshold value for a QALY is the most cost-effective option. The primary benefit of NMB is that it also allows all alternative devices to be ranked and considered against both a common comparator and against each other. For example if one TAVI device was not considered to be clinically relevant to a particular clinical scenario, its results could be discarded and the probability of the remaining TAVI devices could be ranked and considered against each other. Whereas for ICERs, technologies are ordered in terms of cost and the next most costly option is compared to the least costly option. If that next most costly option is both more effective and more costly then an ICER is calculated. It this is the case then the third most costly option can now be compared to the second most costly option and it that third option is more effective than the second then a further ICER is calculated. If however the second most costly option is more costly but less effective

than the least costly option, then it is considered dominated by the least costly option. Here the third mostly costly option is compared to the least costly option and so long as that third most costly option is not dominated an ICERs is calculated. When considering several mutually exclusive option (i.e. we can only chose one out of several options) then the NMB allows a simpler presentation of results that more easily facilitates comparison between all options by providing information on the relative cost-effectiveness between alternatives capturing the magnitude of how much more or less cost-effective one alternative is compared with another (Paulden et al. 2020). In this clinical context when not all clinical devices are suitable for all people then so long as parameter values or model structure does not change then the NMB would allow the decision maker to readily compare any given set of devices. The NMB was calculated for each TAVI device as an absolute value (rather than an incremental value through comparison with another device) and presented for willingness to pay (WTP) thresholds of £20,000 per QALY using the following formula: NMB = QALYs x λ – Cost, where λ is the chosen WTP threshold. The probability of each device having the highest NMB at the WTP thresholds is also presented. Where comparisons are appropriate devices can be compared by simply looking at the difference between the NMB of the devices. The procedure with the highest NMB is the most effective and the difference in NMB is the gain to the NHS and personal social services from adopting that device over the alternative. The 95% confidence interval for the probability of having the highest NMB was estimated from 500 simulation runs using the Dirichlet distribution function from the *gtools* package in R.

6.2.1 Model structure

The EAG modified the economic model structure such that both short-term and long-term outcomes were modelled transparently within a single cohort Markov model (Figure 11). Whilst appearing complex, the EAG would consider that the model structure shown is similar to that modelled within NG208 but without hidden nested decision trees; where the allowed transitions reflect the complexity of patient journeys. Each Markov state is intended to represent a health state, as experienced by a patient. Each transition is intended to represent an event which causes patients to change health states. The starting point is a hypothetical cohort of 1,000 patients with stenosis of the native aortic valve. The costs and QALYs are calculated as

patients enter and leave the post-procedural health states (up to discharge as obtained from the UK TAVI Registry) and longitudinal states (as obtained from HES linked to the TAVI registry). All patients start in the 'TAVI Implantation' state (representing the peri-procedural phase) and move to one of the other states after their TAVI procedure. The Clinical Experts have advised that there is no difference in waiting times between TAVI devices; this model structure does permit a waiting list to be modelled by modifying the transition rate from the implantation and reimplantation states; which may be considered in future economic evaluations of TAVI. Only TAVI devices for which there are data within the UK TAVI Registry were included in economic modelling.

In contrast to the model used for NG208, the peri-procedural outcomes are modelled as transitions from implantation states to stable states, rather than as a decision tree. The modelling framework permits a cost to be assigned to making a transition. As in in the model used for NG208, the EAG have not considered atrial fibrillation as a complication, because its outcomes and costs are likely to be short term, and costs are expected to be captured by the HRG costs used for the base case. Utility decrements associated with the states are similarly applied. Modelled health states included:

- **Death**, as an absorbing state. Transition to death is possible from each state.
- **Stroke** represents aortic stenosis resolved by TAVI and having a stroke at or after the implantation phase. The model permits multiple adverse events, such that patients may also require a pacemaker, or have a paravalvular leak. The stroke state enables higher costs to be applied to the first year when compared with ongoing costs in subsequent years which are applied for the lifetime of the patient. Patients who have had a stroke are not considered eligible for a reintervention with TAVI, as per the assumption of NG208. Because the cycle duration is less than 1 year, the stroke state is not considered a tunnel state, but the transition rates to the **post-stroke** state are arranged such that the mean occupancy time is 1 year.

- **Major or severe paravalvular leak, (PVL)** represents aortic stenosis resolved by TAVI, but with a residual paravalvular leak (around the valve and between the TAVI and native valves). PVL is an acute complication which is considered a consequence of implantation or reimplantation of TAVI (following subsequent procedures). Modelling PVL as a separate health state enabled additional follow-up costs to be modelled (for example increased echocardiogram within the first 12 months). Patients with a PVL are assumed to be at increased risk of heart failure. There is an allowed transition from heart failure to reimplantation.
- **Paced** represents aortic stenosis resolved by TAVI but requiring a cardiac pacemaker. Treating this as a separate health state enabled additional follow-up costs to be modelled (associated with the pacemaker management). **Paced and PVL** was a separate health state to include the combination of both pacemaker and residual paravalvular leak.
- **Reimplantation** is the health state representing a subsequent TAVI procedure. Modelling this as a separate state enables a different subsequent valve to be used from the original TAVI valve, offering flexibility in future economic evaluations where TAVI may be used in younger or lower risk populations resulting in increases over time in the uptake of TAVI-in-valve procedures.
- **SAVR** represents aortic stenosis resolved from surgical aortic valve repair, including bailout SAVR during the initial TAVI procedure, those having SAVR prior to discharge, and SAVR as a late event. This was considered an absorbing state, with yearly accumulated costs and QALYs from the NG208 SAVR arm applied to the population in this state, which implicitly includes deaths and other adverse events of SAVR. In the base case the transition probability was set to 0, this is due to the small number of events as identified by the registry (in-hospital n=7, out of hospital n=18) and difficulty in identifying any differences between devices. However, the EAG has built the model structure such that this could be populated as evidence becomes available in the future.

- The state representing TAVI procedure and no adverse events (as described above) was incorporated (and labelled "**No complications**").

Late (that is, after the implantation phase) transitions are possible. For example, it is possible to transition from the NoComp to the Paced state. This allows for modelling of the economic effect of there being a difference between devices in the rate of late pacemaker implantation after discharge from a TAVI procedure.

At most three health conditions are assumed to be consequent to implantation; these are stroke (yes, no), requiring a pacemaker, and presence of moderate and severe paravalvular leak (PVL). Accounting for combinations of these, there are 8 possible combinations including none. The state with none of these conditions is labelled as "NoComp". In contrast, the NG208 model permitted only one of these conditions to be present in each patient and not a combination. To avoid unnecessary proliferation of Markov states, these health states and combinations are modelled as follows:

- The stroke state includes patients with multiple events (that is those experiencing stroke + PVL, stroke + pacemaker and stroke + PVL + pacemaker) with the costs and clinical impact of stroke dominating.

- The occupancy cost of the stroke state is increased by the cost of managing patients with a pacemaker multiplied by the proportion of patients who have a stroke and need a pacemaker.

- The transition cost into the stroke state is increased by the cost of a pacemaker implantation multiplied by the proportion who require it.

- The occupancy cost of the stroke state is increased by the cost of managing patients with a PVL multiplied by the proportion of patients who have a stroke and have a PVL.

- Similarly, the utility decrements associated with having a pacemaker and having a PVL are combined with the utility decrement of having a stroke in proportion to the rate of these events.

- The Markov states representing these consequential health states are therefore: NoComp, Stroke, PVL, Paced, PVL + Paced.

As in NG208, the short-term outcomes of major bleeding and major vascular complication are resolved via additional treatment before discharge, and thereafter patients having these complications are assumed to move into one of the long-term health states. Thus, there are no Markov states for those outcomes; the occupancy cost of the implantation states is increased by the cost of such an event multiplied by the proportion having an event. The additional cost and utility decrement of patients requiring a bailout TAVI (TAVI-in-TAVI) after an attempted TAVI were modelled similarly to the short-term adverse events of major bleeding and major vascular complications; that is, they are added to state occupancy costs and transition costs in proportion to their occurrence.

The EAG did not include MI or need for renal replacement therapy as acute complications of TAVI in the economic model because of the rarity of these events (0.3% and 0.1% respectively from the UK TAVI Registry). Clinical Experts advised that they did not expect differences in these outcomes between TAVI devices. The EAG also did not model technical success (VARC-3) outcome which is a composite of multiple data fields (successful access, delivery of the device and retrieval of the delivery system, correct positioning of single prosthetic heart valve into the proper anatomical location, freedom of surgery or intervention related to the device or major vascular or access-related or cardiac structural complication) and were therefore omitted to avoid double counting. One Clinical Expert also advised that patients who initially wanted to avoid SAVR and opted for TAVI with equivocal risks may opt for SAVR again if the waiting list for TAVI was too long. One Clinical Expert advised that there was variation across the NHS and that in some cases the waiting list may be shorter for TAVI than SAVR. As Clinical Experts advised that the waiting list is not different between TAVI devices, the EAG consider that the proportion opting for SAVR because of the TAVI waiting list would apply equally across device arms. It was therefore omitted from the economic model. This omission will impact total costs and QALYs but have little impact on the incremental differences in total costs and QALYs between devices arms of the economic model.

The Implantation, Reimplantation and Stroke states are effectively transition states, through which patients progress to other states. The rate at which patients leave the Implantation and Reimplantation state is set to ensure that 95% of patients leave

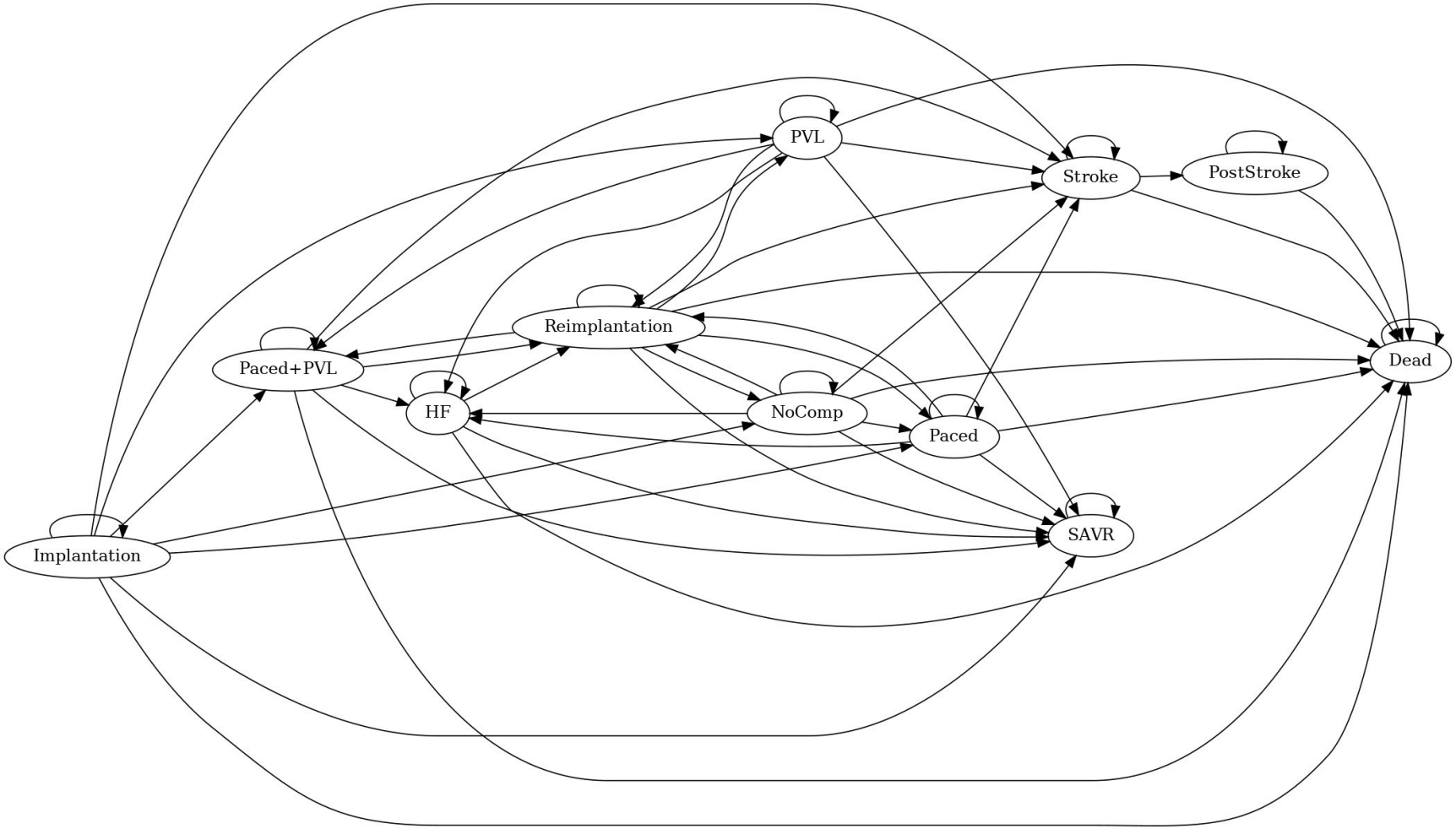
(are discharged) within 30 days. The rate at which patients leave the stroke state (for the post-stroke state) is set to ensure that the mean occupancy time is 1 year. This avoids the use of tunnel states which introduce an unwanted dependency of the Markov trace on cycle time.

Transition probabilities between states were computed from transition rates using Kolmogorov's forward equation, implemented as a matrix operation via R package "expm" (Maechler, 2024).

The cycle length is 1 month (one twelfth of a year) to permit modelling of short and longer-term term outcomes. At the end of each cycle, people either remained in their current state, or transitioned to another state or died (the arrows in Figure 11 indicate the allowed direction of transition of patients from one state to another. The method of calculation of transition probabilities allows for the possibility that patients may start and end in states between which there is no allowed transition (for example, patients moving from Implantation to Post Stroke, via Stroke, within one cycle). These probabilities were negligible due to the short cycle length and were redistributed proportionally among the allowed transitions.

The EAG calculated the hazard ratio of death for the TAVI population from the linked data set at 1 year and 2 years, relative to standard mortality for each cohort. The hazard ratio at one year was applied during year 1 and the hazard ratio at year 2 was applied for the remainder of the time horizon. This is a similar approach to NG208, which applied and extrapolated relative survival rates for years 1 to 3 estimated from the literature to the time horizon. Hazard ratios for death associated with stroke, pacemaker, PVL relative to complication-free TAVI, were taken from NG208.

Figure 11: Markov model structure developed by the EAG



Because of the small number of procedures, differences in demographics and presentation (when compared with TAVI in native aortic valve) and because not all TAVI devices are explicitly indicated for TAVI-in-TAVI or TAVI-in-SAVR, the EAG was unable to conduct multivariate analysis on these populations (to adjust for population differences). The EAG did not consider these cohorts in the economic evaluation (because of reasons stated above). However, the overall economic model structure could be applied to these cohorts when sufficient data becomes available to enable device-level comparisons within these cohorts.

The EAG considers that a combination of factors will impact economic consideration in the future: TAVI in younger cohorts, with lower surgical risk profiles, and increasing patient life expectancy. Reintervention options for a failed bioprosthesis are: 1) TAVI (valve in valve/TAVI in valve), or 2) surgery (TAVI explant) (Bapat et al. 2021). Review of the international EXPLANTORREDO-TAVR registry from May 2009 to February 2022 showed 396/66,760 (0.59%) reinterventions for failed TAVI (Tang et al. 2023). The annual numbers increased considerably over that period: 6.6% from May 2009 to 2013, 37.6% from 2014 to 2018, and 55.8% from 2019 to February 2022 (Tang et al. 2023). Increasing reinterventions have clear cost implications together with the significant procedural related morbidity (Bapat et al. 2021).

The EAG has endeavoured to model the complexity of the decision problem (where short and long-term outcomes may differ between TAVI devices) and also included transitions between states that may become relevant as further data become available but are currently assigned a 0 probability. Nevertheless, the EAG acknowledges a number of limitations with the above modelling approach:

- Patients who receive a pacemaker after their first implantation remain at risk of a second pacemaker after re-implantation. Whilst this is not clinically plausible, this is a consequence of the memoryless property of cohort Markov models and could not be avoided without adding further complexity into the model. The EAG

note that this was also an assumption implicit in the NG208 model which re-ran the decision tree representing the implantation procedure at each cycle.

- Because of the memoryless principle of cohort Markov models, third and subsequent interventions, which are rare, are not modelled differently to second interventions.

- A very small proportion of patients make more than one transition per monthly cycle. These multi-step transitions are a consequence of calculating probabilities from rates and can result in making apparent transitions that are not allowed (for example, from Implantation to PostStroke via Stroke within one cycle). At each cycle, the negligible probabilities of these disallowed transitions were set to zero, and the remaining probabilities from each state rescaled to unity.

- Because of the low rate of per-procedural conversion to SAVR and bailout TAVI-in-TAVI, the EAG was unable to incorporate this in multivariate anlaysis to determine differences between devices when accounting for covariates (model unable to converge). Therefore the rates of these specific events are assumed to be fixed and applied equally across all devices. This was not the case for subsquent aortic valve intervention following discharge (which was incorporated in multivariate modelling, and varied by device).

6.2.2 Clinical parameters

Transition probabilities between states were calculated from transition rates using Kolmogorov's forward equation (Welton and Ades, 2005) in matrix form, using the R package 'expm'. This approach accounts for the possibility of more than one transition per cycle. For example, the probability of starting a cycle in state A, say, and ending it in state C, depends not only on the rate of transitions from A to C, but also on the rates of transitions via a third state, B (that is, from A to B and from B to C within one cycle).

The characteristics of the starting population were the same for across all devices. In the base case this was set as the average age of 82 years, and 57.4% male sex, undergoing a 70-minute procedure as derived from the UK TAVI Registry. All transition probabilities and rates (including 95% confidence intervals) were predicted from the linked UK TAVI Registry and HES real world datasets, Table 27. Outcomes which statistically differed across devices (as indicated by previous multivariate analysis) were adjusted for against Sapien 3 Ultra as the reference case (the most frequently used valve) using odds ratios from the logistic regression analysis of short and long-term outcomes (as described in Section 5.5). The EAG would advise caution in interpretation of these results in isolation, due to the limitations previously stated, however the EAG would consider this data to be best estimates available from an UK NHS setting.

To avoid introducing tunnel states, the rate at which patients leave the Implantation and Reimplantation state was set to ensure that 95% of patients leave (are discharged) within 30 days (the length of one cycle); which may reflect clinical practice. The relative rates of transition to health states are given by the rate of leaving an implantation state multiplied by the proportion (absolute risk) of having an event. The EAG note that in NG208, patients spent 0 days in the intervention state and 1 year in the re-intervention state.

Table 27: Predicted event proportions (absolute risks) for base case (using binary logistic and cox proportional hazard models on linked dataset), reported as % with (95% confidence interval)

Predicted outcome	Sapien 3 (male)	Sapien 3 (female)	Sapien 3 Ultra (male)	Sapien 3 Ultra (female)	ACURATE neo2 (male)	ACURATE neo2 (female)	Evolut R (male)	Evolut R (female)	Evolut Pro+ (male)	Evolut Pro+ (female)	Navitor (male)	Navitor (female)
In-hospital death	1.22 (0.14, 10)	1.74 (0.18, 15.01)	1.42 (0.22, 8.64)	2.03 (0.27, 13.57)	3.27 (0.35, 24.65)	4.63 (0.49, 32.51)	4.29 (0.45, 30.83)	6.04 (0.63, 39.52)	1.58 (0.18, 12.76)	2.25 (0.26, 17.13)	1.38 (0.09, 18.17)	1.97 (0.13, 23.92)
In-hospital stroke	0.85 (0.12, 5.78)	1.52 (0.2, 10.79)	0.26 (0.04, 1.65)	0.47 (0.07, 3.25)	0.25 (0.02, 3.65)	0.46 (0.03, 6.52)	1.4 (0.17, 10.9)	2.52 (0.3, 18.29)	1.35 (0.19, 8.86)	2.42 (0.35, 14.73)	1.35 (0.17, 10.03)	2.42 (0.3, 16.81)
In-hospital AR	5.09 (0.48, 37.5)	6.65 (0.6, 45.62)	3.29 (0.37, 23.81)	4.32 (0.44, 31.44)	16.02 (1.35, 72.62)	20.21 (1.79, 77.9)	22.46 (2.33, 77.86)	27.78 (3.06, 82.44)	24.98 (3.14, 77.39)	30.66 (4.27, 81.42)	45.54 (7.1, 90.15)	52.61 (9.13, 92.46)
In-hospital PPI	6.9 (2.7, 16.5)	5.99 (2.24, 15.03)	7.71 (3.46, 16.3)	6.7 (2.78, 15.26)	6.16 (1.91, 18.13)	5.34 (1.63, 16.11)	14.78 (5.6, 33.64)	12.97 (4.81, 30.53)	13.66 (5.63, 29.57)	11.97 (4.91, 26.35)	17.48 (6.7, 38.46)	15.4 (5.76, 35.15)
In-hospital major bleeding	0.61 (0.06, 5.73)	2.9 (0.29, 23.56)	0.63 (0.08, 4.66)	3 (0.38, 20.08)	1.11 (0.1, 11.03)	5.17 (0.52, 36.29)	0.48 (0.03, 6.49)	2.31 (0.19, 22.86)	0.26 (0.02, 2.81)	1.24 (0.13, 10.96)	0.67 (0.05, 8.35)	3.19 (0.26, 29.38)
In-hospital vascular comp	1.38 (0.13, 13.13)	3.4 (0.3, 29.05)	2.28 (0.29, 15.69)	5.54 (0.66, 33.95)	6.73 (0.65, 44.21)	15.37 (1.66, 66.16)	1.51 (0.1, 19.21)	3.71 (0.26, 36.18)	1.67 (0.15, 16.2)	4.1 (0.41, 31.04)	5.59 (0.51, 40.47)	12.97 (1.31, 62.66)
One-year death	11.24 (3.43, 18.41)	10.8 (2.94, 18.03)	13.73 (5.75, 21.03)	13.21 (4.88, 20.81)	15.46 (3.53, 25.92)	14.88 (3.33, 25.06)	11.41 (2.24, 19.71)	10.97 (2.07, 19.06)	11.34 (3.22, 18.78)	10.9 (3.15, 18.03)	21.94 (3.5, 36.86)	21.16 (3.36, 35.68)
One-year stroke	3.57 (0, 8.03)	2.79 (0, 6.49)	3.07 (0, 6.43)	2.39 (0, 5.27)	2.37 (0, 6.1)	1.84 (0, 4.82)	1.54 (0, 4.11)	1.2 (0, 3.25)	3.48 (0, 7.91)	2.71 (0, 6.22)	3.77 (0, 9.61)	2.94 (0, 7.58)
One-year PPI	4.22 (0, 9.54)	3.78 (0, 8.77)	3.06 (0, 6.45)	2.74 (0, 6.02)	5.55 (0, 13.2)	4.98 (0, 11.89)	5.19 (0, 12.39)	4.65 (0, 11.23)	3.76 (0, 8.68)	3.37 (0, 7.77)	3.18 (0, 8.69)	2.85 (0, 7.81)
One-year heart failure	1.9 (0.18, 3.59)	1.38 (0.06, 2.69)	1.47 (0.31, 2.62)	1.07 (0.14, 1.99)	2.03 (0, 4.1)	1.47 (0, 3.01)	2.57 (0, 5.15)	1.87 (0, 3.79)	2.34 (0.17, 4.47)	1.71 (0.13, 3.26)	2.16 (0, 4.67)	1.57 (0, 3.42)
Two-year death	23.15 (7.49, 36.16)	22.32 (6.46, 35.50)	27.83 (12.30, 40.62)	26.87 (10.52, 40.23)	31.00 (7.66, 48.44)	29.96 (7.27, 47.09)	23.47 (5.00, 38.36)	22.64 (4.64, 37.24)	23.34 (6.94, 36.86)	22.51 (6.82, 35.57)	42.15 (7.32, 63.89)	40.85 (7.05, 62.36)

Abbreviations: AR, aortic regurgitation; PPI, permanent pacemaker implantation; SAVR, Surgical Aortic Valve Replacement; TAVI, Transcatheter aortic valve implantation

6.2.3 Cost parameters

Updated cost parameters are reported in Table 28. The EAG note that whilst the majority of costs remained at 2021/22, it was not consistent across each resource item. The EAG acknowledge that this will tend to underestimate costs and hence increase the NMB for each procedure. The EAG has redacted costs (and their corresponding sources) in order to prevent backwards calculation of the price of TAVI device valves, which were provided by NHS Supply Chain and confidential price agreements.

Table 28: Updated cost parameters

Parameter	Updated value	Updated source
Proportion non-elective	[redacted]	[redacted]
Median length of stay (elective)	[redacted]	[redacted]
Median length of stay (non-elective)	[redacted]	[redacted]
Length of stay, bed day cost (per day)	[redacted]	[redacted]
Proportion with ICU stay	[redacted]	
Length of ICU stay, days	[redacted]	
Additional ICU stay if bailout TAVI	[redacted]	
Additional ICU stay if SAVR (bailout, intervention before discharge, reintervention during follow-up)	[redacted]	
ICU cost (per day)	[redacted]	
Median procedure time, mins	[redacted]	[redacted]

Parameter	Updated value	Updated source
Additional minutes for bailout TAVI-in-TAVI	[redacted]	
Cardiac catheterisation laboratory costs	[redacted]	[redacted]
Proportion of procedures supported by anaesthetist and Operating Department Practitioner (ODP)	[redacted]	Clinical Experts
Staffing during procedure	[redacted]	Clinical Experts
Staff costs (hourly): consultant operator, consultant anaesthetist	[redacted]	[redacted]
Staff costs (hourly): Nurse-led sedation – Band 7	[redacted]	[redacted]
Staff costs (hourly): radiographer – Band 6	[redacted]	[redacted]
Staff costs (hourly): cardiac physiologist – Band 7	[redacted]	[redacted]
Staff costs (hourly): scrub nurse, runner nurse, ODP - Band 5	[redacted]	[redacted]
Staff costs (hourly): nurse preparing	[redacted]	[redacted]

Parameter	Updated value	Updated source
valve – Band 6		
Procedural costs TAVI (including length of stay, excluding valve and ICU stay)	[redacted]	HRG codes [redacted]
Generic TAVI valve	[redacted]	[redacted]
Valve Cost Sapien 3 (Edwards Lifesciences)	[redacted]	Net SSDP and Trust Rebate price provided by NHS Supply Chain on 22 January 2024. [redacted]
Valve Cost Sapien 3 Ultra (Edwards Lifesciences)	[redacted]	Net SSDP and Trust Rebate price provided by NHS Supply Chain on 22 January 2024. [redacted]
Valve Cost ACURATE neo2 (Boston Scientific)	[redacted]	Net SSDP and Trust Rebate price provided by NHS Supply Chain on 20 February 2024. [redacted]
Valve Cost Evolut R (Medtronic)	[redacted]	Net SSDP and Trust Rebate price provided by NHS Supply Chain on 22 January 2024. [redacted]
Valve Cost Evolut Pro+ (Medtronic)	[redacted]	Net SSDP and Trust Rebate price provided by NHS Supply Chain on 22 January 2024. [redacted]
Valve Cost Navitor (Abbott Medical)	[redacted]	Net SSDP and Trust Rebate price provided by NHS Supply Chain on 22 January 2024. [redacted]
Bailout TAVI	[redacted]	[redacted]
TAVI reintervention	[redacted]	[redacted]
SAVR (bailout, before discharge, during follow-up)	[redacted]	[redacted]
Major vascular	[redacted]	[redacted]

Parameter	Updated value	Updated source
complications		
Major bleeding	[redacted]	[redacted]
New pacemaker implantation	[redacted]	[redacted]
1 year Markov model costs Rehospitalisation with heart failure	[redacted]	[redacted]
1 year Markov model costs Stroke	[redacted]	[redacted]
Annual Markov model costs Post-stroke	[redacted]	[redacted]
CT imaging (during procedure)	[redacted]	[redacted]
Follow-up appointment (TAVI); annual	[redacted]	[redacted]
Echocardiogram	[redacted]	[redacted]
Number of echocardiograms conducted during follow-up annually	[redacted]	Clinical experts
Follow-up appointment (if permanent pacemaker implanted); annual	[redacted]	[redacted]

Abbreviations: CC, complication and comorbidity; EAG, External assessment group; HES, Hospital episode statistics; HRG, healthcare resource group; ICU, intensive care unit; NHSCII, NHS Cost Inflation Index; ODP, Operating department practitioner; PVL, paravalvular leak; SAVR, surgical aortic valve replacement; SSDP, Specialised Service Devices Programme; TAVI, transcatheter aortic valve implantation.

6.2.4 Health-related quality of life

The EAG applied utility values associated with a starting population, and increment because of successful TAVI procedure at 1 year, and decrements associated with adverse events applied in the economic model as described by the Health Information and Quality Authority (HIQA) HTA of TAVI (2019) and the Norwegian Institute of Public Health (NIPH) HTA of TAVI (2019), Table 29. Alternative utility values from HTA Wales (2020) were identified for some parameters which were considered in sensitivity analysis.

Table 29: Health-related quality of life and utility applied in the base case sourced from the HIQA HTA (2019) and NIPH HTA (2019)

Parameter	Quality of life	Lower CI	Upper CI	Distribution	Source
TAVI - baseline - 30 days - 6 months - 12 months	 0.750 0.808 0.794 0.794	 0.738 0.794 0.778 0.778	 0.762 0.822 0.809 0.809	 Beta Beta Beta Beta	Baron et al. 2017. The EAG has not identified any evidence to suggest that quality of life differs between TAVI devices longitudinally.
Complication	Utility	Lower CI	Upper CI	Distribution	Source
Stroke	-0.161	-0.267	-0.055	Normal	Kaier et al. (2016); assuming utility decrement same for post-stroke as stroke.
Major vascular complication	-0.00695	-0.00831	-0.00558	Normal	Kaier et al. (2016); EAG has assumed SE of 10%, and applied upper and lower confidence intervals assuming normal distribution.
Bailout TAVI/reintervention	-0.005	-0.007	-0.004	Normal	NIPH (2019) EAG could not retrieve primary source 'Scottish study'
SAVR intervention/bailout	-0.027	-0.035	-0.019	Normal	NIPH (2019) EAG could not retrieve primary source 'Scottish study'
Major bleeding	-0.447	-0.739	-0.155	Normal	Kaier et al. (2016)
Pacemaker	-0.003	-0.044	0.038	Normal	Lange et al. (2016)
Moderate or severe paravalvular leak	-0.003	-0.044	0.038	Normal	Lange et al. (2016) which

					assumed the same utility decrement as pacemaker
Heart failure	-0.162	-0.194	-0.130	Normal	NG17, 2022; utility decrement calculated as difference between no complications and CHF (0.839-0.677) and assumed 10% standard error

Key: * assume same as pacemaker implantation. Abbreviations: CI, Confidence interval; EAG, External Assessment Group; NIPH, Norwegian Institute of Public Health; SAVR, surgical aortic valve replacement; TAVI, Transcatheter aortic valve implantation

6.2.5 Sensitivity analysis

The model was built probabilistically to account for uncertainty around input point estimates of clinical parameters. Probability distributions were fitted to model parameters to randomly select a value for each parameter simultaneously from its respective distribution when the probabilistic sensitivity analysis (PSA) was run. The model was run repeatedly (1,000 times for the base case where mean cost and QALY estimates derived remained stable), with the same random seed used for all 12 cases (6 devices, male and female) in each run to account for correlated model parameters. The mean cost, QALY and net monetary benefit for each device was calculated for each run. The variables considered in the PSA and the distribution used are below:

- Baseline risks followed a beta distribution (beta distribution is bounded by continuous random variable between 0 and 1; this would ensure that the random probability of an event is never less than 0 or higher than 1).

- Hazard, odds, and risk ratios followed a lognormal distribution [positively skewed random variables, this would ensure only positive values are used, as negative random values (which normal distributions can allow) are not expected for these parameters].

- Utilities followed a beta distribution (continuous random variable between 0 and 1, this would ensure that the random utility value is in between 0 and 1).

- Utility decrements followed a gamma distribution (bounded at zero and positively skewed; this ensures the random utility decrement values are always positive and have skewed distributions).

Deterministic sensitivity analyses were undertaken to test the robustness of model estimates, including:

- different time horizons (2, 5, 10 years; noting the base case was 15 years),
- shorter procedure duration (45 minutes; noting that the base case was 90 minutes),
- reducing the proportion of procedures involving an anaesthetist (15%; noting that the base case was 33%),
- reducing ICU days for patients who require an ICU stay (0 days; noting that the ICU stay was 2 days in the base case),
- cost of TAVI device (to a) transacted price, b) £17,500 based on NG208, 2021 where it was noted that 80% of hospitals purchased the TAVI at a discounted costs of £17,500, c) £15,000 from threshold analysis in NG208),
- cost of stroke (base case increased by 15%),
- proportion requiring a conversion to SAVR (0.1%; noting in the base case this was set to 0 due to lack of data; rare event),
- inclusion of additional cost of a cardiac balloon catheter to conduct balloon dilatation to the TAVI procedure costs. One Clinical Expert advised that the balloon incurs additional cost (estimated to be approximately £200). The EAG note that the unadjusted crude proportion of use of balloon implantation post-procedure from the UK TAVI Registry were Sapien 3: 4.8%, Sapien 3 Ultra: 5.9%, ACURATE neo2: 8.9%, Evolut R: 16.5%, Evolut Pro+: 17.5%, Navitor: 25.8%.

6.2.6 Clinical scenarios

Given that different TAVI devices may be used in certain clinical situations the EAG has attempted to create various theoretical scenarios and comparisons guided by

Clinical Expert input. Each clinical scenario was defined using clinical data available in the UK TAVI Registry, and outcomes modelled using the results from logistic regression modelling (to adjust for population differences), to determine the impact on economic results. A total of 9 clinical scenarios were considered, Table 30. All transition probabilities and rates for these clinical scenarios were predicted from the linked UK TAVI Registry and HES real world datasets (as conducted with the base case), Appendix F5.

The EAG note that Navitor and ACURATE neo2 have the lowest probability of having the highest NMB across all scenarios. However, the EAG would advise caution in overinterpreting these numbers, as this finding is likely a consequence of those two devices having the least amount of data entered into the registry (used to power the economic model) and therefore both have the largest uncertainty which translates in the model of having low probability of net monetary benefit, or negative NMB in some scenarios.

The EAG note that the 95% confidence interval on per patient costs, QALYs and NMB may also reflect uncertainties in the data (impacting results related to ACURATE neo2 and Navitor which were used less frequently than Sapien 3 and Evolut TAVI devices). However, this may also be related to the infrequency of use for specific TAVI devices in certain clinical scenarios. For example, in an extensive or asymmetric calcified aortic valve, a clinician may choose to use a self-expanding TAVI device (making the clinical decision and balancing risk of annular rupture and risk of aortic regurgitation). While the “calcification” scenario 9 (which has used extensive calcification of the ascending aorta as a surrogate for aortic valve calcification) shows Sapien 3 Ultra to be the preferred option (58% probability of having the highest NMB), this probability has dropped significantly from the base case (76% probability of having the highest NMB). The second preferred option within this calcification scenario is Evolut R (19%).

The EAG was unable to model several clinical scenarios because of lack of data available, such as degenerative surgical bioprosthesis (as there were only 215 procedures; insufficient data for multivariate modelling), bicuspid aortic valves (morphology not recorded in the registry), severe left ventricular outflow tract and

annular calcification (not recorded in registry), and coronary height (not recorded in the registry).

Table 30: Theoretical clinical scenarios defined using clinical data available in the UK TAVI Registry

Data field	**Base case (male)**	**Base case (female)**	Scenario 1: Coronary obstruction	Scenario 2: Younger (preservation of coronary access)	Scenario 3: Small annular diameter size (<22mm)	Scenario 4 Large annular diameter size (>32mm)	Scenario 5: No severe symptoms	Scenario 6: LVEF<30	Scenario 7 Frail (based on Katz/CSHA)	Scenario 8 Urgent	Scenario 9 Calcification*
Age, years	**82**	**82**	Same as base case	70	Same as base case	Same as base case	Same as base case	Same as base case	Same as base case	Same as base case	Same as base case
Male sex	**Yes**	**No**	Same as base case	Same as base case	Same as base case	Same as base case	Same as base case	Same as base case	Same as base case	Same as base case	Same as base case
Poor LV function (LVEF<30%)	**No**	**No**	Same as base case	Same as base case	Same as base case	Same as base case	Same as base case	Yes	Same as base case	Same as base case	Same as base case
Annular diameter, mm	**26**	**23**	Same as base case	Same as base case	20	34	Same as base case	Same as base case	Same as base case	Same as base case	Same as base case
Extensive calcification of ascending aorta	**No**	**No**	Same as base case	Same as base case	Same as base case	Same as base case	Same as base case	Same as base case	Same as base case	Same as base case	Yes
Anatomical coronary comorbidity (Left main stem disease or stenosis of at least 50% in one vessel)	**No**	**No**	Yes	Same as base case	Same as base case	Same as base case	Same as base case	Same as base case	Same as base case	Same as base case	Same as base case
Severe symptoms	**Yes**	**Yes**	Same as base case	Same as base case	Same as base case	Same as base case	No	Same as base case	Same as base case	Same as base case	Same as base case
CSHA frailty score (moderate or severe) OR Katz<6	**No**	**No**	Same as base case	Same as base case	Same as base case	Same as base case	Same as base case	Same as base case	Yes	Same as base case	Same as base case
Procedural urgency	**No**	**No**	Same as base case	Same as base case	Same as base case	Same as base case	Same as base case	Same as base case	Same as base case	Yes	Same as base case

*Note: extensive calcification of the ascending aorta used as a surrogate marker of aortic valve calcification. Abbreviations: CSHA, Canadian Study of Health and Ageing; LVEF, Left ventricular ejection fraction

6.2.7 Model validation

From a practical perspective running 1000 patients in the economic model, requires running 1000 males and 1000 females each for the 6 different devices (total of 12,000 patients); the model in *rdecision* took 50 minutes to run this. As the EAG proposed several scenarios and sensitivity analyses, a pragmatic decision was made to reduce the number of simulated patients to reduce this processing time. As the results did not differ significantly (see Appendix F2), the EAG dropped the number of simulated patients to 500.

The EAG populated the model structure using data from the TAVI arm of the original NG208 economic model; results were within 2% (Appendix F2). As an additional validation exercise the results from the base case economic model were compared with raw counts of events at 1 year using the linked data set from UK TAVI Registry linked to HES. The internal validity of the NG208 and updated model was checked independently by 2 health economists within the EAG and involved varying model input parameters and assessing whether the model results are sensitive and logical. A health economist checked that values for model parameters had been incorporated within the economic model appropriately.

6.3 Results from the economic modelling

6.3.1 Base case

Deterministic results, including state occupancy and accumulated costs and QALYs over the 500 simulated patients over a 15-year time horizon using data from patients treated with Sapien 3 Ultra (as the reference case for illustration) are shown in Appendix F4. The EAG note that most of the costs per-patient (82% to 94% across devices and across males and females) were accrued from the in-hospital events and procedure costs.

Probabilistic results from the base case separated by male and female sex are shown in Table 31and Table 32 respectively. Across the 6 TAVI devices compared, Sapien 3 gave the highest probability of yielding the greatest NMB in both male (76 [67 to 84] %) and female patients (74 [65 to 82] %). However, the ranking of

subsequent devices was slightly different between female patients (where the 95% confidence interval of having the highest NMB overlapped across 3 devices; Evolut R: 11 [6 to 18]%, Sapien 3 Ultra: 9 [4 to 16]%, Evolut Pro+: 6 [2 to 12]%) and male patients (Evolut R: 16 [10 to 24]% with no overlap in confidence intervals with Sapien 3 Ultra or Evolut Pro+). Across self-expanding TAVI devices, Evolut R provided the highest probability in both male and female patients. The EAG would consider that for ACURATE neo2 and Navitor the 0% probability of having the highest NMB (consequence of both having the lowest NMB which in turn was driven by having the lowest QALYs per patient) are likely a result of these two devices having a small number of patients in the UK TAVI Registry (compared to the other 4 devices) and therefore in economic modelling ACURATE neo2 and Navitor incorporates the greatest statistical uncertainty. Additionally, from the health state occupancy of the economic model output (Appendix F4) Navitor had higher mortality at one year than the other devices, which would contribute to these results.

Table 31: Probabilistic results comparing 6 TAVI valves in the base case (male sex)

Cost items	Sapien 3	Sapien 3 Ultra	ACURATE neo2	Evolut R	Evolut Pro+	Navitor
Mean cost per patient, £ [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean QALYs per patient [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NMB at £20,000 WTP value, £ [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probability of highest NMB at £20,000 WTP Value	76 [67 to 84] %	4 [1 to 9] %	0 [0 to 0] %	16 [10 to 24] %	4 [1 to 9] %	0 [0 to 0] %

Abbreviations: CI, confidence interval; NMB, Net monetary benefit; QALY, Quality-adjusted life year; WTP, Willingness to pay

Table 32: Probabilistic results comparing 6 TAVI valves in the base case (female sex)

Cost items	Sapien 3	Sapien 3 Ultra	ACURATE neo2	Evolut R	Evolut Pro+	Navitor
Mean cost per patient, £ [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean QALYs per patient [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NMB at £20,000 WTP value, £ [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probability of highest NMB at £20,000 WTP Value	74 [65 to 82] %	9 [4 to 16] %	0 [0 to 0] %	11 [6 to 18] %	6 [2 to 12] %	0 [0 to 0] %

Abbreviations: CI, confidence interval; NMB, Net monetary benefit; QALY, Quality-adjusted life year; WTP, willingness to pay

6.3.2 Sensitivity analysis

Results from the deterministic sensitivity analysis for male and female patients are shown separately in in Table 33 and Table 34 respectively.

As the time horizon was increased from 2 years to 10 years, the accumulated costs do not increase rapidly, reflecting that most of the lifetime costs are incurred during the peri-procedural phase and in the early years post-procedure. Accumulated QALYs increase slowly after 5 years, reflecting the high mortality associated with the age of the population. The Sapien 3 achieves the highest probability of greatest NMB for all time horizons. Among the self-expanding valves, the ACURATE neo2 has the greatest probability of highest NMB over a 2-year time horizon (however the EAG note that all devices experience negative NMB within this short timeframe as operation costs are incurred but we do not allow time for QALYs to accumulate), then switching to the Evolut R over 5, 10 and 15-year time horizons.

Variations to the costs of conducting the procedure make relatively little difference to the total cost incurred over the time horizon and do not change the profile of NMB, although favours valves found to have lower reintervention rates. Setting the price of all 6 valves to the same value did not change the relative probabilities of achieving the greatest NMB. However, setting the valve price to the transacted price (that is not accounting for rebates given based on volume of sales, which did differ by valve) did change the relative probabilities. In male patients, Evolut R had the greatest probability of the highest NMB (45 [35 to 54] %) followed by Sapien 3 (30 [21 to 39] %) and Evolut Pro+ (24 [16 to 33] %). In female patients, Sapien 3 had the greatest probability of the highest NMB (42 [33 to 52] %) followed by Evolut R (31 [22 to 40] %) and Evolut Pro+ (20 [13 to 28] %).

Increasing the cost of stroke increases the probability of having greatest NMB for valves observed to have lower stroke rates, subject to the uncertainty in rates of stroke predicted by the multivariate modelling. In contrast to NG208, the model includes strokes observed after discharge, which will dominate the total number of such events. A limitation of the approach is that these events are not necessarily associated with having a TAVI, and the late stroke rates could be influenced by an unmeasured confounder associated with valve choice (for example level of surgical risk).

Table 33: Results of sensitivity analysis (mean per patient); male patients only [Note: highest probability of highest NMB in bold for each sensitivity setting]

Sensitivity settings	TAVI	Total costs [95%CI]	Total Quality Adjusted Life Years (QALYs) [95%CI]	NMB at £20,000 [95%CI]	Probability of highest NMB [95%CI]
Base case	**Sapien 3**	[redacted]	[redacted]	[redacted]	**76 [67 to 84] %**
	Sapien 3 Ultra	[redacted]	[redacted]	[redacted]	4 [1 to 9] %
	ACURATE neo2	[redacted]	[redacted]	[redacted]	0 [0 to 0] %
	Evolut R	[redacted]	[redacted]	[redacted]	16 [10 to 24] %
	Evolut Pro+	[redacted]	[redacted]	[redacted]	4 [1 to 9] %
	Navitor	[redacted]	[redacted]	[redacted]	0 [0 to 0] %
Time horizon: 2 years	**Sapien 3**	[redacted]	[redacted]	[redacted]	**48 [38 to 58] %**
	Sapien 3 Ultra	[redacted]	[redacted]	[redacted]	24 [16 to 33] %
	ACURATE neo2	[redacted]	[redacted]	[redacted]	19 [12 to 27] %
	Evolut R	[redacted]	[redacted]	[redacted]	9 [4 to 15] %
	Evolut Pro+	[redacted]	[redacted]	[redacted]	0 [0 to 0] %
	Navitor	[redacted]	[redacted]	[redacted]	0 [0 to 0] %
Time horizon: 5 years	**Sapien 3**	[redacted]	[redacted]	[redacted]	**71 [62 to 79] %**
	Sapien 3 Ultra	[redacted]	[redacted]	[redacted]	13 [7 to 20] %
	ACURATE neo2	[redacted]	[redacted]	[redacted]	0 [0 to 0] %
	Evolut R	[redacted]	[redacted]	[redacted]	13 [7 to 20] %
	Evolut Pro+	[redacted]	[redacted]	[redacted]	3 [1 to 7] %
	Navitor	[redacted]	[redacted]	[redacted]	0 [0 to 0] %
Time horizon: 10 years	**Sapien 3**	[redacted]	[redacted]	[redacted]	**77 [68 to 85] %**
	Sapien 3 Ultra	[redacted]	[redacted]	[redacted]	5 [2 to 10] %
	ACURATE neo2	[redacted]	[redacted]	[redacted]	0 [0 to 0] %
	Evolut R	[redacted]	[redacted]	[redacted]	14 [8 to 21] %
	Evolut Pro+	[redacted]	[redacted]	[redacted]	4 [1 to 9] %
	Navitor	[redacted]	[redacted]	[redacted]	0 [0 to 0] %
Procedure duration: 45 minutes	**Sapien 3**	[redacted]	[redacted]	[redacted]	**77 [68 to 85] %**
	Sapien 3 Ultra	[redacted]	[redacted]	[redacted]	4 [1 to 9] %
	ACURATE neo2	[redacted]	[redacted]	[redacted]	0 [0 to 0] %
	Evolut R	[redacted]	[redacted]	[redacted]	15 [9 to 23] %
	Evolut Pro+	[redacted]	[redacted]	[redacted]	4 [1 to 8] %
	Navitor	[redacted]	[redacted]	[redacted]	0 [0 to 0] %
Anaesthetist and ODP required in 15% of cases	**Sapien 3**	[redacted]	[redacted]	[redacted]	**73 [64 to 81] %**
	Sapien 3 Ultra	[redacted]	[redacted]	[redacted]	3 [1 to 7] %
	ACURATE neo2	[redacted]	[redacted]	[redacted]	0 [0 to 0] %
	Evolut R	[redacted]	[redacted]	[redacted]	18 [11 to 26] %
	Evolut Pro+	[redacted]	[redacted]	[redacted]	6 [2 to 11] %
	Navitor	[redacted]	[redacted]	[redacted]	0 [0 to 0] %
TAVI ICU stay: 0 days	**Sapien 3**	[redacted]	[redacted]	[redacted]	**74 [65 to 82] %**
	Sapien 3 Ultra	[redacted]	[redacted]	[redacted]	3 [1 to 7] %
	ACURATE neo2	[redacted]	[redacted]	[redacted]	0 [0 to 0] %
	Evolut R	[redacted]	[redacted]	[redacted]	18 [11 to 26] %
	Evolut Pro+	[redacted]	[redacted]	[redacted]	5 [2 to 10] %
	Navitor	[redacted]	[redacted]	[redacted]	0 [0 to 0] %
Cost of valve, transacted	Sapien 3	[redacted]	[redacted]	[redacted]	30 [21 to 39] %

Sensitivity settings	TAVI	Total costs [95%CI]	Total Quality Adjusted Life Years (QALYs) [95%CI]	NMB at £20,000 [95%CI]	Probability of highest NMB [95%CI]
	Sapien 3 Ultra	[redacted]	[redacted]	[redacted]	1 [0 to 4] %
	ACURATE neo2	[redacted]	[redacted]	[redacted]	1 [0 to 4] %
	Evolut R	[redacted]	[redacted]	[redacted]	**45 [35 to 54] %**
	Evolut Pro+	[redacted]	[redacted]	[redacted]	24 [16 to 33] %
	Navitor	[redacted]	[redacted]	[redacted]	0 [0 to 0] %
Cost of valve, £17,500	**Sapien 3**	[redacted]	[redacted]	[redacted]	**71 [62 to 79] %**
	Sapien 3 Ultra	[redacted]	[redacted]	[redacted]	2 [0 to 5] %
	ACURATE neo2	[redacted]	[redacted]	[redacted]	0 [0 to 0] %
	Evolut R	[redacted]	[redacted]	[redacted]	18 [11 to 26] %
	Evolut Pro+	[redacted]	[redacted]	[redacted]	9 [4 to 15] %
	Navitor	[redacted]	[redacted]	[redacted]	0 [0 to 0] %
Cost of valve £15,000	**Sapien 3**	[redacted]	[redacted]	[redacted]	**74 [64 to 82] %**
	Sapien 3 Ultra	[redacted]	[redacted]	[redacted]	4 [1 to 9] %
	ACURATE neo2	[redacted]	[redacted]	[redacted]	0 [0 to 0] %
	Evolut R	[redacted]	[redacted]	[redacted]	17 [11 to 25] %
	Evolut Pro+	[redacted]	[redacted]	[redacted]	5 [2 to 10] %
	Navitor	[redacted]	[redacted]	[redacted]	0 [0 to 0] %
Cost of stroke (25% increase)	**Sapien 3**	[redacted]	[redacted]	[redacted]	**63 [53 to 72] %**
	Sapien 3 Ultra	[redacted]	[redacted]	[redacted]	5 [2 to 10] %
	ACURATE neo2	[redacted]	[redacted]	[redacted]	0 [0 to 0] %
	Evolut R	[redacted]	[redacted]	[redacted]	27 [19 to 36] %
	Evolut Pro+	[redacted]	[redacted]	[redacted]	5 [2 to 10] %
	Navitor	[redacted]	[redacted]	[redacted]	0 [0 to 0] %
0.2% conversion to SAVR	**Sapien 3**	[redacted]	[redacted]	[redacted]	**62 [53 to 72] %**
	Sapien 3 Ultra	[redacted]	[redacted]	[redacted]	4 [1 to 8] %
	ACURATE neo2	[redacted]	[redacted]	[redacted]	0 [0 to 0] %
	Evolut R	[redacted]	[redacted]	[redacted]	28 [19 to 37] %
	Evolut Pro+	[redacted]	[redacted]	[redacted]	6 [2 to 11] %
	Navitor	[redacted]	[redacted]	[redacted]	0 [0 to 0] %
Cost of cardiac balloon	**Sapien 3**	[redacted]	[redacted]	[redacted]	**62 [52 to 71] %**
	Sapien 3 Ultra	[redacted]	[redacted]	[redacted]	4 [1 to 9] %
	ACURATE neo2	[redacted]	[redacted]	[redacted]	0 [0 to 0] %
	Evolut R	[redacted]	[redacted]	[redacted]	29 [20 to 38] %
	Evolut Pro+	[redacted]	[redacted]	[redacted]	5 [2 to 10] %
	Navitor	[redacted]	[redacted]	[redacted]	0 [0 to 0] %

Abbreviations: CI, confidence interval; HTA, health technology assessment; ICU, Intensive care unit; NMB, Net monetary benefit; ODP, Operating department practitioner; QALY, Quality-adjusted life year; TAVI, Transcatheter aortic valve implantation

Table 34: Results of sensitivity analysis (mean per patient); female patients only [Note: highest probability of highest NMB in bold for each sensitivity setting]

Sensitivity settings	TAVI	Total costs [95%CI]	Total Quality Adjusted Life Years (QALYs) [95%CI]	NMB at £20,000 [95%CI]	Probability of highest NMB [95%CI]
Base case	**Sapien 3**	[redacted]	[redacted]	[redacted]	**74 [65 to 82] %**
	Sapien 3 Ultra	[redacted]	[redacted]	[redacted]	9 [4 to 16] %
	ACURATE neo2	[redacted]	[redacted]	[redacted]	0 [0 to 0] %
	Evolut R	[redacted]	[redacted]	[redacted]	11 [6 to 18] %
	Evolut Pro+	[redacted]	[redacted]	[redacted]	6 [2 to 12] %
	Navitor	[redacted]	[redacted]	[redacted]	0 [0 to 0] %
Time horizon: 2 years	**Sapien 3**	[redacted]	[redacted]	[redacted]	**38 [29 to 48] %**
	Sapien 3 Ultra	[redacted]	[redacted]	[redacted]	**36 [27 to 46] %**
	ACURATE neo2	[redacted]	[redacted]	[redacted]	21 [14 to 29] %
	Evolut R	[redacted]	[redacted]	[redacted]	5 [2 to 10] %
	Evolut Pro+	[redacted]	[redacted]	[redacted]	0 [0 to 0] %
	Navitor	[redacted]	[redacted]	[redacted]	0 [0 to 0] %
Time horizon: 5 years	**Sapien 3**	[redacted]	[redacted]	[redacted]	**62 [53 to 71] %**
	Sapien 3 Ultra	[redacted]	[redacted]	[redacted]	24 [16 to 33] %
	ACURATE neo2	[redacted]	[redacted]	[redacted]	1 [0 to 4] %
	Evolut R	[redacted]	[redacted]	[redacted]	9 [4 to 15] %
	Evolut Pro+	[redacted]	[redacted]	[redacted]	4 [1 to 9] %
	Navitor	[redacted]	[redacted]	[redacted]	0 [0 to 0] %
Time horizon: 10 years	**Sapien 3**	[redacted]	[redacted]	[redacted]	**71 [62 to 79] %**
	Sapien 3 Ultra	[redacted]	[redacted]	[redacted]	10 [5 to 17] %
	ACURATE neo2	[redacted]	[redacted]	[redacted]	0 [0 to 0] %
	Evolut R	[redacted]	[redacted]	[redacted]	13 [7 to 20] %
	Evolut Pro+	[redacted]	[redacted]	[redacted]	6 [2 to 11] %
	Navitor	[redacted]	[redacted]	[redacted]	0 [0 to 0] %
Procedure duration: 45 minutes	**Sapien 3**	[redacted]	[redacted]	[redacted]	**70 [61 to 79] %**
	Sapien 3 Ultra	[redacted]	[redacted]	[redacted]	9 [4 to 15] %
	ACURATE neo2	[redacted]	[redacted]	[redacted]	0 [0 to 0] %
	Evolut R	[redacted]	[redacted]	[redacted]	13 [7 to 20] %
	Evolut Pro+	[redacted]	[redacted]	[redacted]	8 [4 to 14] %
	Navitor	[redacted]	[redacted]	[redacted]	0 [0 to 0] %
Anaesthetist and ODP required in 15% of cases	**Sapien 3**	[redacted]	[redacted]	[redacted]	**70 [61 to 78] %**
	Sapien 3 Ultra	[redacted]	[redacted]	[redacted]	14 [8 to 21] %
	ACURATE neo2	[redacted]	[redacted]	[redacted]	0 [0 to 0] %
	Evolut R	[redacted]	[redacted]	[redacted]	10 [5 to 17] %
	Evolut Pro+	[redacted]	[redacted]	[redacted]	6 [2 to 11] %
	Navitor	[redacted]	[redacted]	[redacted]	0 [0 to 0] %
TAVI ICU stay: 0 days	**Sapien 3**	[redacted]	[redacted]	[redacted]	**72 [63 to 80] %**
	Sapien 3 Ultra	[redacted]	[redacted]	[redacted]	9 [4 to 15] %
	ACURATE neo2	[redacted]	[redacted]	[redacted]	0 [0 to 0] %
	Evolut R	[redacted]	[redacted]	[redacted]	11 [6 to 18] %
	Evolut Pro+	[redacted]	[redacted]	[redacted]	8 [4 to 14] %
	Navitor	[redacted]	[redacted]	[redacted]	0 [0 to 0] %
Cost of valve, transacted	**Sapien 3**	[redacted]	[redacted]	[redacted]	**42 [33 to 52] %**
	Sapien 3 Ultra	[redacted]	[redacted]	[redacted]	4 [1 to 8] %

Sensitivity settings	TAVI	Total costs [95%CI]	Total Quality Adjusted Life Years (QALYs) [95%CI]	NMB at £20,000 [95%CI]	Probability of highest NMB [95%CI]
	ACURATE neo2	[redacted]	[redacted]	[redacted]	3 [1 to 7] %
	Evolut R	[redacted]	[redacted]	[redacted]	31 [22 to 40] %
	Evolut Pro+	[redacted]	[redacted]	[redacted]	20 [13 to 28] %
	Navitor	[redacted]	[redacted]	[redacted]	0 [0 to 0] %
Cost of valve, £17,500	**Sapien 3**	[redacted]	[redacted]	[redacted]	**72 [63 to 80] %**
	Sapien 3 Ultra	[redacted]	[redacted]	[redacted]	10 [5 to 17] %
	ACURATE neo2	[redacted]	[redacted]	[redacted]	0 [0 to 0] %
	Evolut R	[redacted]	[redacted]	[redacted]	11 [6 to 18] %
	Evolut Pro+	[redacted]	[redacted]	[redacted]	7 [3 to 13] %
	Navitor	[redacted]	[redacted]	[redacted]	0 [0 to 0] %
Cost of valve £15,000	**Sapien 3**	[redacted]	[redacted]	[redacted]	**74 [65 to 82] %**
	Sapien 3 Ultra	[redacted]	[redacted]	[redacted]	11 [6 to 18] %
	ACURATE neo2	[redacted]	[redacted]	[redacted]	0 [0 to 0] %
	Evolut R	[redacted]	[redacted]	[redacted]	9 [4 to 15] %
	Evolut Pro+	[redacted]	[redacted]	[redacted]	6 [2 to 11] %
	Navitor	[redacted]	[redacted]	[redacted]	0 [0 to 0] %
Cost of stroke (25% increase)	**Sapien 3**	[redacted]	[redacted]	[redacted]	**75 [66 to 83] %**
	Sapien 3 Ultra	[redacted]	[redacted]	[redacted]	10 [5 to 16] %
	ACURATE neo2	[redacted]	[redacted]	[redacted]	0 [0 to 0] %
	Evolut R	[redacted]	[redacted]	[redacted]	10 [5 to 16] %
	Evolut Pro+	[redacted]	[redacted]	[redacted]	5 [2 to 10] %
	Navitor	[redacted]	[redacted]	[redacted]	0 [0 to 0] %
0.2% conversion to SAVR	**Sapien 3**	[redacted]	[redacted]	[redacted]	**69 [59 to 78] %**
	Sapien 3 Ultra	[redacted]	[redacted]	[redacted]	9 [4 to 16] %
	ACURATE neo2	[redacted]	[redacted]	[redacted]	0 [0 to 0] %
	Evolut R	[redacted]	[redacted]	[redacted]	15 [9 to 23] %
	Evolut Pro+	[redacted]	[redacted]	[redacted]	7 [3 to 13] %
	Navitor	[redacted]	[redacted]	[redacted]	0 [0 to 0] %
Cost of cardiac balloon	**Sapien 3**	[redacted]	[redacted]	[redacted]	**69 [60 to 78] %**
	Sapien 3 Ultra	[redacted]	[redacted]	[redacted]	11 [6 to 18] %
	ACURATE neo2	[redacted]	[redacted]	[redacted]	0 [0 to 0] %
	Evolut R	[redacted]	[redacted]	[redacted]	12 [6 to 19] %
	Evolut Pro+	[redacted]	[redacted]	[redacted]	8 [4 to 14] %
	Navitor	[redacted]	[redacted]	[redacted]	0 [0 to 0] %

Abbreviations: CI, confidence interval; HTA, health technology assessment; ICU, Intensive care unit; NMB, Net monetary benefit; ODP, Operating department practitioner; QALY, Quality-adjusted life year; TAVI, Transcatheter aortic valve implantation

6.3.3 Clinical scenarios

The EAG ran the economic model for 9 different clinical scenarios separately for male and female patients (Table 35 and Table 36 respectively; Appendix F5). For most clinical scenarios, there is little change in the relative differences between the valves, in terms of the proportion with the greatest net monetary benefit per run, although the absolute values differ between scenarios, as expected. For example, in patients of younger age, the costs throughout the time horizon are similar to the base case, as expected, but the accumulated QALYs are higher due to the difference in standardized mortality rate (SMR) of the starting population.

In one scenario, there is a notable departure from the base case in terms of relative proportions with greatest net monetary benefit. This was related to the presence of extensive calcification in the ascending aorta (a surrogate marker of calcification in the aortic valve) in male and female patients, where the probability of having the highest NMB for Sapien reduced from 76 [67 to 84]% in the base case to 64 [51 to 70]% in males, and 74 [65 to 82]% to 57 [47 to 66]% in female patients. In these cases, this may reflect clinician choice; in that Sapien 3 may not be used frequently in this scenario. Clinical Experts have advised that in a calcified valve, that a self-expanding valve may be considered, however that this was considered a balance between annular rupture and risk of aortic regurgitation. The economic model results are a consequence of the prevalence of cases in the registry, and therefore the confidence intervals of the predictions from procedural and longer-term outcomes for these scenarios will be narrower, leading to more consistent costs and QALYs compared with devices used less frequently in those scenarios. Those with a narrow confidence interval consequently result in a greater chance of having the greatest net monetary benefit.

Table 35: Scenario results (male). [Note: highest probability of highest NMB in bold for each scenario, all included all devices in all comparison however shaded cells where device may not be used]

Scenario	Outcome	Sapien 3	Sapien 3 Ultra	ACURATE neo2	Evolut R	Evolut Pro+	Navitor
Base case	Total cost, £	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	NMB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	Highest NMB, P	**76 [67 to 84] %**	4 [1 to 9] %	0 [0 to 0] %	16 [10 to 24] %	4 [1 to 9] %	0 [0 to 0] %
Coronary obstruction **(scenario 1)**	Total cost, £	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	NMB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	Highest NMB, P	**78 [70 to 86] %**	3 [1 to 7] %	0 [0 to 0] %	15 [9 to 22] %	4 [1 to 9] %	0 [0 to 0] %
Younger age **(scenario 2)**	Total cost, £	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	NMB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	Highest NMB, P	**69 [60 to 78] %**	8 [4 to 14] %	0 [0 to 0] %	17 [10 to 25] %	6 [2 to 11] %	0 [0 to 0] %
Small annular diameter size (<22mm) **(scenario 3)**	Total cost, £	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	NMB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	Highest NMB, P	**63 [54 to 73] %**	8 [4 to 14] %	0 [0 to 0] %	24 [16 to 32] %	5 [2 to 10] %	0 [0 to 0] %
Large annular diameter size (>32mm) **(scenario 4)**	Total cost, £	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	NMB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	Highest NMB, P	**70 [61 to 78] %**	11 [6 to 18] %	1 [0 to 4] %	13 [7 to 20] %	5 [2 to 10] %	0 [0 to 0] %
No severe symptoms **(scenario 5)**	Total cost, £	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	NMB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	Highest NMB, P	**76 [67 to 84] %**	5 [2 to 10] %	0 [0 to 0] %	16 [9 to 24] %	3 [1 to 7] %	0 [0 to 0] %
LVEF<30 **(scenario 6)**	Total cost, £	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	NMB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	Highest NMB, P	**72 [63 to 80] %**	6 [2 to 11] %	0 [0 to 0] %	18 [11 to 26] %	4 [1 to 9] %	0 [0 to 0] %
Frailty (Katz/CSHA) **(scenario 7)**	Total cost, £	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	NMB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	Highest NMB, P	**73 [64 to 81] %**	7 [3 to 13] %	0 [0 to 0] %	15 [9 to 23] %	5 [2 to 10] %	0 [0 to 0] %
Urgency **(scenario 8)**	Total cost, £	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	NMB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	Highest NMB, P	**77 [68 to 85] %**	6 [2 to 12] %	0 [0 to 0] %	12 [6 to 19] %	5 [2 to 10] %	0 [0 to 0] %

Scenario	Outcome	Sapien 3	Sapien 3 Ultra	ACURATE neo2	Evolut R	Evolut Pro+	Navitor
Calcification (surrogate used) **(scenario 9)**	Total cost, £	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	NMB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	Highest NMB, P	**61 [51 to 70] %**	19 [12 to 27] %	1 [0 to 4] %	15 [9 to 23] %	4 [1 to 9] %	0 [0 to 0] %

Abbreviations: LVEF, Left ventricular ejection fraction; NMB, Net monetary benefit; QALY, Quality-adjusted life years

Table 36: Scenario results (female). [Note: highest probability of highest NMB in bold for each scenario, all included all devices in all comparison however shaded cells where device may not be used]

Scenario	Outcome	Sapien 3	Sapien 3 Ultra	ACURATE neo2	Evolut R	Evolut Pro+	Navitor
Base case	Total cost, £	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	NMB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	Highest NMB, P	**74 [65 to 82] %**	9 [4 to 16] %	0 [0 to 0] %	11 [6 to 18] %	6 [2 to 12] %	0 [0 to 0] %
Coronary obstruction **(scenario 1)**	Total cost, £	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	NMB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	Highest NMB, P	**70 [61 to 78] %**	11 [6 to 18] %	0 [0 to 0] %	12 [7 to 19] %	7 [3 to 13] %	0 [0 to 0] %
Younger age **(scenario 2)**	Total cost, £	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	NMB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	Highest NMB, P	**72 [62 to 80] %**	12 [6 to 19] %	0 [0 to 0] %	9 [4 to 15] %	7 [3 to 13] %	0 [0 to 0] %
Small annular diameter size (<22mm) **(scenario 3)**	Total cost, £	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	NMB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	Highest NMB, P	**66 [57 to 75] %**	14 [8 to 21] %	1 [0 to 4] %	11 [6 to 18] %	8 [4 to 14] %	0 [0 to 0] %
Large annular diameter size (>32mm) **(scenario 4)**	Total cost, £	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	NMB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	Highest NMB, P	**59 [50 to 69] %**	21 [13 to 29] %	2 [0 to 5] %	11 [6 to 18] %	7 [3 to 13] %	0 [0 to 0] %
No severe symptoms **(scenario 5)**	Total cost, £	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	NMB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	Highest NMB, P	**74 [65 to 82] %**	14 [8 to 21] %	0 [0 to 0] %	8 [4 to 14] %	4 [1 to 9] %	0 [0 to 0] %
LVEF<30 **(scenario 6)**	Total cost, £	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	NMB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	Outcome	Sapien 3	Sapien 3 Ultra	ACURATE neo2	Evolut R	Evolut Pro+	Navitor
-	Highest NMB, P	**71 [61 to 79] %**	10 [5 to 17] %	0 [0 to 0] %	13 [7 to 20] %	6 [2 to 11] %	0 [0 to 0] %
Frailty (Katz/CSHA) **(scenario 7)**	Total cost, £	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	NMB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	Highest NMB, P	**71 [61 to 79] %**	13 [7 to 20] %	0 [0 to 0] %	7 [3 to 13] %	9 [4 to 15] %	0 [0 to 0] %
Urgency **(scenario 8)**	Total cost, £	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	NMB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	Highest NMB, P	**72 [63 to 80] %**	14 [8 to 22] %	0 [0 to 0] %	8 [4 to 14] %	6 [2 to 11] %	0 [0 to 0] %
Calcification **(scenario 9)**	Total cost, £	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	NMB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-	Highest NMB, P	**57 [47 to 66] %**	28 [20 to 37] %	1 [0 to 4] %	9 [4 to 15] %	5 [2 to 10] %	0 [0 to 0] %

Abbreviations: LVEF, Left ventricular ejection fraction; NMB, Net monetary benefit; QALY, Quality-adjusted life years

6.4 Strengths and limitations of the economic evidence

The EAG used the economic model from NG208 and adapted it to enable comparisons of multiple TAVI devices, adding additional outcomes determined from multivariate analysis of the UK TAVI Registry linked to HES. The economic model was informed by the best available UK data to estimate short- and longer-term clinical outcomes in a UK setting, and by up-to-date NHS and social care costs. The multivariate modelling approach enabled clinical outcomes to be predicted for patients with specific characteristics and applying these to the economic model estimated net monetary benefits, as if a patient with those characteristics had received each valve. The multivariate analysis could allow cost-effectiveness to be estimated for a different sets of characteristics.

Adjusting for patient characteristics, the economic model demonstrated that the Sapien 3 device had the greatest probability of highest NMB in most analyses. The EAG note this will be influenced by Sapien 3 having lowest mortality at 1 and 5 years in the economic modelling when compared with other devices. Relating this to clinical practice, this is likely a consequence of Sapien 3 being available in a 29 mm valve size, and therefore used in a higher proportion of male patients (92% male; 1030/1120 in linked data) when compared with the other devices. Males typically have large vessels and therefore are at lower risk of stroke and major bleeding as demonstrated by the multivariate analysis. The EAG also showed that the economic model was sensitive to TAVI device costs, such that changing to transacted price meant that the device with the probability of highest NMB changed.

Modelling clinical scenarios also resulted in relative changes in NMB and likely reflected clinical practice in that not all TAVI devices are used in all clinical scenarios. This should be borne in mind when using the economic results to inform judgements as the EAG acknowledges that TAVI choice is primarily dependent upon clinical and anatomical considerations where not all TAVI devices may be suitable.

The strength of the economic analysis is that it is driven by real-world UK data representing the largest economic comparison of TAVI devices in an NHS setting, meaning it has applicability to contemporary NHS practice. These data are by their nature collected routinely, and thus not subject to the same rigorous quality control

as randomised trials, and subject to missingness, although incorporate larger numbers of cases in an NHS setting. However, the EAG was able to predict costs (from an economic model) using predicted events (from multivariate analysis of UK real-world evidence) using completed cases (3,900 out of 14,400 procedures, 27%, recorded in the UK TAVI Registry linked to HES) to determine incremental clinical and cost differences with relative cost-effectiveness between 6 TAVI devices adjusting for differences in recorded patient and procedural characteristics.

PSA was used to estimate the imprecision in estimates of NMB but may not fully reflect uncertainties caused by missing data. To overcome this the EAG made a series of assumptions and where possible tried to explore the impact of these through deterministic sensitivity analysis.

Additional limitations include that the economic modelling did not account for different quality of life increments between TAVI devices, or for severity of acute events and was limited by follow-up (restricted to 2.5 years based on latest available HES data) because of lack of data. Further, only 6 devices recorded in the registry were available for inclusion in logistic regression and cox proportional hazards and subsequent economic models, and the only balloon-expanding TAVI devices were both from the same manufacturer.

We could not include 5 TAVI devices (Myval Octacor, Allegra, Evolut FX, Hydra, JenaValve Trilogy) within the economic evaluation as there were no data (or insufficient data in the case of Evolut FX) in the UK TAVI Registry. As the EAG was unable to adjust for patient characteristics from the published literature to enable fair comparison; the relative cost, QALY, NMB differences using those 5 devices in the UK remain unknown.

7 Combined summary of the availability of clinical and economic evidence

The EAG considered a traffic light system to summarise the availability of clinical and economic evidence (Table 37) for each of the 11 TAVI devices listed in the Final Scope:

- **[GREEN]**: evidence available for device listed in Final Scope.
- **[AMBER]**: partial evidence, which could reflect evidence only available for a previous version of the device, or evidence using a combination of TAVI; evidence of no difference between TAVI devices.
- **[RED]**: no evidence available.

Table 37: Summary of availability of clinical and economic evidence included in this late-stage assessment

Device (manufacturer)	Summary of real-world evidence (UK TAVI Registry linked to HES)	Summary of published evidence (restricting to those that adjusted for population differences in study design or subsequent analysis, and findings statistically significant)	Longest available evidence	Evidence within TAVI-in-SAVR or TAVI-in-TAVI	Summary of economics (using Real World Evidence from UK)
Myval Octacor (Meril)	**[RED]** No data in UK TAVI Registry extract	**[AMBER;** mixed intervention**]** • Non-inferiority RCT of Myval and Myval Octacor (combined) against mixture of Sapien 3, Sapien 3 Ultra, Evolut R, Evolut Pro, Evolut Pro+, Evolut FX. *No difference in outcomes.* • Propensity matched non-randomised comparing Myval with Sapien 3 *Myval lower PPI, lower mean and peak aortic gradient, patient-prosthesis at 30 days.* • Propensity matched non-randomised comparing Myval with Evolut R/Pro *Myval lower PPI at 30 days*	**[AMBER]** 30 days (for Myval Octacor), 2 years (for previous version).	**[AMBER]** No data in UK TAVI Registry, but published literature identified.	**[RED]** Not included in economic model
Sapien 3 (Edwards Lifesciences)	**[GREEN]** No difference in in-hospital or out of hospital outcomes between devices within multi-variate analysis. Higher in-hospital stroke than Sapien 3 Ultra.	**[GREEN]** • 2 Network meta-analyses *Sapien 3 lowest short term mortality* • Propensity matched non-randomised comparing Sapien 3, Evolut R, ACURATE neo, Portico *Sapien 3 lowest vascular complications, dilatation post-procedure, paravalvular leak, implantation, and highest mean transvalvular gradient at discharge (difference of 3.5 mmHg likely within measurement error).*	**[GREEN]** 1 year (for Sapien 3). Longest follow-up for device family: up to 12 years.	**[GREEN]** 24 TAVI-in-SAVR, 3 TAVI-in-TAVI cases in UK TAVI Registry (within extract received by EAG)	**[GREEN]** Largest probability of highest NMB in most scenarios.
Sapien 3 Ultra (Edwards Lifesciences)	**[GREEN]** Used as the reference case in multivariate analysis. Other devices had higher in-hospital stroke, pacemaker implantation, aortic regurgitation at discharge. No differences in other in-hospital or out-of-hospital outcomes.	**[GREEN]** • Propensity matched non-randomised comparing Sapien 3 Ultra with Evolut Pro or Pro+ *Sapien 3 Ultra lowest in-hospital PPI, lowest new onset LBBB, major bleeding, lowest disabling stroke in-hospital, 30 days, 1 year. Sapien 3 Ultra highest effective orifice area, highest transprosthetic mean gradient at 30 days (5 mmHg difference likely within measurement error).* • Propensity matched non-randomised comparing Sapien 3 Ultra with ACURATE neo2 *Sapien 3 Ultra lower post-dilation, device success. Sapien 3 Ultra higher, index effective orifice area, mean gradient, but also higher severe patient-prosthesis mismatch (absolute increase of 12.1%) post procedure.* • Propensity matched non-randomised comparing Sapien 3 Ultra with Sapien 3 *Sapien 3 Ultra larger aortic valve area at discharge, fewer and less severe paravalvular regurgitation at discharge*	**[GREEN]** 1 year (for Sapien 3 Ultra). Longest follow-up for device family: up to 12 years.	**[GREEN]** 101 TAVI-in-SAVR, 19 TAVI-in-TAVI cases in UK TAVI Registry (within extract received by EAG)	**[GREEN]** Largest probability of highest NMB in when restricting to a 2-year time horizon (in females only).
ACURATE neo2 (Boston Scientific)	**[GREEN]** Only one outcome (aortic regurgitation at discharge) statistically poorer than reference (Sapien 3 Ultra). No other differences in in-hospital or out of hospital outcomes. Further, when analysis was restricted to self-expanding TAVI devices, ACURATE neo2 had statistically increased odds of major vascular complications when compared to Evolut Pro+.	**[AMBER**; based on results**]** • 2 network meta-analyses (on ACURATE or ACURATE neo) *Lowest pacemaker implantation* • 1 network meta-analyses (on ACURATE neo) *Higher odds of mortality and moderate or severe aortic regurgitation at 30 days.* • Propensity matched non-randomised comparison of ACURATE neo2 with Evolut Pro or Pro+ *ACURATE neo2 lower effective orifice area, major vascular complications at 30 days, PPI at 30 days. ACURATE neo2higher mean and peak aortic gradient at discharge (absolute differences 1.3 and 1.5 mmHg likely within measurement error), major vascular complications (procedural), cardiac hospitalisation within 30 days, more frequent*	**[GREEN]** 1 year (for ACURATE neo2). Longest follow-up for device family: median 3 years (max 7 years).	**[RED]** Contraindicated	**[AMBER]** 0% probability of highest NMB at £20,000 WTP across majority of analysis (likely related to lack of data in registry and corresponding large confidence interval on event probabilities). When considering self-expanding TAVI devices across a 2-year time horizon, ACURATE neo2 had the greatest probability of highest NMB.

Device (manufacturer)	Summary of real-world evidence (UK TAVI Registry linked to HES)	Summary of published evidence (restricting to those that adjusted for population differences in study design or subsequent analysis, and findings statistically significant)	Longest available evidence	Evidence within TAVI-in-SAVR or TAVI-in-TAVI	Summary of economics (using Real World Evidence from UK)
		intervention for cardiac structural complications and AKI at 30 days.			
Allegra (Biosensors)	**[RED]** No data in UK TAVI Registry extract	**[RED]** No comparative evidence which accounted for population differences	**[GREEN]** 3 years	**[AMBER]** No data in UK TAVI Registry, but published literature identified.	**[RED]** Not included in economic model
Evolut FX (Medtronic)	**[AMBER]** Only 3 eligible cases in UK TAVI Registry extract	**[AMBER;** mixed intervention**]** • RCT comparing Evolut (R, Pro, Pro+, FX all combined) with Sapien (3 and 3 Ultra) in small annuli. *Evolut arm had lower primary endpoint (all-cause death, disabling stroke, rehospitalisation for heart failure up to 12 months).*	**[AMBER]** 30 days (for Evolut FX). Longest follow-up for device family: up to 12 years.	**[RED]** No evidence identified describing use in TAVI-in-SAVR or TAVI	**[RED]** Not included in economic model
Evolut Pro+ (Medtronic)	**[GREEN]** Evolut Pro+ had statistically higher odds of in-hospital stroke, aortic regurgitation, and pacemaker than the reference (Sapien 3 Ultra) from multivariate analysis. However, no difference was observed in long-term outcomes. Further, when analysis was restricted to self-expanding TAVI devices, Evolut Pro+ had statistically decreased odds of major vascular complications than ACURATE neo2.	**[AMBER;** mixed intervention**]** • 1 network meta-analysis (Evolut R and Pro combined) *Lowest patient-prosthesis mismatch, mean aortic gradient post-procedure.* • 1 network meta-analysis (Evolut CoreValve, Evolut R and Pro combined) *Higher odds of pacemaker at 30 days* • RCT comparing Evolut (R, Pro, Pro+, FX all combined) with Sapien (3 and 3 Ultra) in small annuli. *Evolut arm had lower primary endpoint (all-cause death, disabling stroke, rehospitalisation for heart failure up to 12 months).*	**[GREEN]** 3 years (for Evolut Pro+). Longest follow-up for device family: up to 12 years.	**[GREEN]** 51 TAVI-in-SAVR, 2 TAVI-in-TAVI cases in UK TAVI Registry (within extract received by EAG)	**[GREEN]** Greatest probability of highest NMB for self-expanding valves in some scenarios.
Evolut R (Medtronic)	**[GREEN]** Evolut R had statistically higher odds of in-hospital stroke, aortic regurgitation, and pacemaker than the reference (Sapien 3 Ultra). However, no difference was observed in long-term outcomes. Further, when analysis was restricted to self-expanding TAVI devices, there was no statistical difference between Evolut R and Evolut Pro+ (as the reference).	**[GREEN]** • RCT comparing Evolut (R, Pro, Pro+, FX all combined) with Sapien (3 and 3 Ultra) in small annuli. Evolut arm had lower primary endpoint (all-cause death, disabling stroke, rehospitalisation for heart failure up to 12 months). • Prospective non-randomised (with propensity matching) comparing Evolut R, Evolut Pro, Sapien 3, ACURATE neo, Portico. *Hazard ratio (HR) of pacemaker implantation was higher than Sapien 3 and ACURATE neo.*	**[GREEN]** 5 years (for Evolut R). Longest follow-up for device family: up to 12 years.	**[GREEN]** 79 TAVI-in-SAVR, 3 TAVI-in-TAVI cases in UK TAVI Registry (within extract received by EAG)	**[GREEN]** Greatest probability of highest NMB in some scenarios. Highest probability of highest NMB for self-expanding valves in most scenarios.
Hydra (SMT)	**[RED]** No data in UK TAVI Registry extract	**[RED]** No comparative evidence against other manufacturers.	**[GREEN]** 1 year	**[RED]** Contraindicated	**[RED]** Not included in economic model
Navitor (Abbott Medical)	**[GREEN]** Navitor had statistically higher odds of in-hospital stroke, aortic regurgitation, and pacemaker than the reference (Sapien 3 Ultra). However, no difference was observed in long-term outcomes. Further, when analysis was restricted to self-expanding TAVI devices, there was no statistical difference between Navitor and Evolut Pro+ (as the reference).	**[AMBER;** based on results**]** • 1 network meta-analysis (Portico) *Lowest AKI* • Propensity matched adjusted logistic regression comparing Portico, Evolut R, Sapien 3 with ACURATE neo as the reference *Portico had the highest procedural death, vascular complications, post-procedural dilatation, paravalvular leak at discharge.*	**[GREEN]** 1 year (for Navitor). Longest follow-up for device family: 3 years.	**[AMBER]** 8 TAVI-in-SAVR, 1 TAVI-in-TAVI cases in UK TAVI Registry (within extract received by EAG)	**[AMBER]** 0% probability of highest NMB at £20,000WTP (likely related to lack of data in registry with available data reporting less favourable results (possibly purely by chance).
Trilogy (JenaValve)	**[RED]** No data in UK TAVI Registry extract	**[RED]** No comparative evidence which accounted for population differences; exclusively in transapical approach.	**[AMBER]** 30 days (for Trilogy). Longest follow-up for device family: 1 year	**[RED]** No evidence identified describing use in TAVI-in-SAVR or TAVI	**[RED]** Not included in economic model

Abbreviations: NMB, Net monetary benefit; TAVI, Transcatheter aortic valve implantation; WTP, Willingness to pay

8 Discussion

For this Late-stage assessment, the EAG has considered evidence from a number of sources, each with strengths and limitations.

There is a wealth of published evidence on the TAVI devices included in the Final Scope of this late-stage assessment. The main limitation is the inability to combine multiple studies to conduct indirect comparisons of multiple TAVI devices. This is related to patient characteristics informing the device choice, and therefore breaks the transitivity assumption which is also why results from 4 network meta-analyses are not considered by the EAG to be reliable. The EAG considered additional primary evidence which compared more than 2 TAVI devices also to be at high risk of bias. Few studies adjusted for population differences, none were conducted in a UK setting, the majority did not explore multivariate analysis, typically short-term outcomes were reported and Company sponsorship or funding was common. The main strengths of the published evidence are the identification of results from other non-UK national TAVI registries and capture of rare adverse events, and early evidence for the TAVI devices that do not yet have much (Evolut FX) or any (Allegra, Hydra, Myval Octacor, Trilogy) data available in the UK TAVI Registry. Clinical Experts have advised that Trilogy is used in aortic regurgitation which may explain the lack of evidence for the context of this late-stage assessment on aortic stenosis. Due to the above limitations, the EAG was not able to use the published literature to assume equivalence or difference between TAVI devices in a UK NHS setting.

Real world data from the UK TAVI Registry was considered most generalisable to NHS practice, and when linked to Hospital Episode Statistics (HES) data for multivariate analysis, has allowed longer term outcomes (up to 31 months) for 6 TAVI devices (from 4 manufacturers) to be assessed. However, there are clinically important variables (for example clinical risk, calcium burden and distribution, coronary height, and valve morphology) that can determine choice of TAVI device for an individual patient, that are not recorded in the Registry and therefore could not be adjusted for in multivariate analysis. Clinical Experts have indicated that the majority of TAVI procedures in the UK NHS continue to be performed in those considered high risk for surgery, so this is unlikely to have confounded the results of the analysis

of the EAG, although this may be a consideration for future analysis, if the case mix changes over time. The EAG considered extensive calcification in the ascending aorta as a surrogate for aortic valve calcification within its analysis, noting that calcification was broadly higher in cases using self-expanding than balloon-expanding TAVI devices, which reflects Clinical Expert experience. The EAG also note, that non-tricuspid morphology occurs in the minority of cases, and that some devices are explicitly contraindicated in bicuspid valves which would preclude appropriate comparison of TAVI devices. The EAG notes that the data in the UK TAVI Registry are self-reported by centres, and that data completeness and lack of validation at data entry also resulted in the exclusion of 30% of cases reported in the Registry, which also introduces bias. Acknowledging these limitations, we undertook multivariate analysis to provide evidence of differences in clinical outcomes between valves. Analysis focused on the 6 separate TAVI devices and did not group by manufacturer to prevent older devices, likely to have been used more frequently in the UK TAVI Registry, weighting the results towards poorer outcomes. Overall event rates are low, however when comparing all 6 TAVI devices (adjusting for recorded confounders) the EAG found evidence of differences in in-hospital outcomes (stroke, moderate or severe aortic regurgitation, pacemaker implantation), but no statistical difference in out-of-hospital outcomes, at 1 year. The clinical significance of the these differences remains uncertain. Clinical Experts advised that differences seen may be related to device selection in patients with certain characteristics which are not recorded in the UK TAVI Registry. For example, patients with underlying conduction disturbances may be given a TAVI device associated with less likelihood of needing a subsequent pacemaker. Comparing 4 self-expanding TAVI devices showed only differences in in-hospital major vascular complications. The EAG also note that choice of TAVI device (expansion type, size, access route, use of general anaesthesia) is dependent upon patient characteristics. Therefore, on a patient by patient basis, the suitable TAVI devices to consider and compare, may change, with some being entirely inappropriate. The EAG note that all results may be influenced by the less frequent use of some devices (ACURATE neo2 and Navitor) in the UK TAVI Registry, and that data were only available from 2 balloon-expanding valves (2 generations from Edwards Lifescience, the Sapien 3 and Sapien 3 Ultra).

Predicted values from the multivariate analysis were used as input parameters for the economic model, which compared the 6 devices using data from the UK TAVI Registry linked to HES. Where applicable, confidence intervals of odds and hazard ratios were used to inform the uncertainty distributions of model inputs. A strength of this analysis was that the model used was structured similarly to that used in NG208, which had previously compared the cost-effectiveness of TAVI with SAVR. The EAG reconstructed the economic model to enable multiple TAVI devices to be compared, and used the model to calculate net monetary benefit, assuming a willingness to pay threshold of £20,000, for several scenarios and sensitivity settings. The probability of providing the highest net monetary benefit was calculated for each device from probabilistic sensitivity analysis. This approach enables results to be compared across arms (as inappropriate comparators for any clinical scenario can be omitted and the remaining options ranked) so long as the model structure and input parameters remain unchanged. For the base case and most scenarios and sensitivity settings, one balloon-expanding device was found to be most likely to provide the highest net monetary benefit; however, this too has some associated uncertainty. The results were influenced by the prevalence of use of each TAVI device in the NHS, with those used less frequently rarely achieving the highest probability of net monetary benefit. This may be an artifact of the sparser data or reflective of the relatively poorer performance of these devices. The EAG note that multivariate and economic analysis adjusted for patient characteristics which varied between devices would enable fairer head-to-head comparison of devices; this analysis is most applicable to patients where any TAVI device could be used. However, the EAG acknowledges that in clinical practice the patient population treated by each device is clinically significantly different.

Results of the EAG analysis (clinical and economic) were limited by unmeasured confounders arising from the real-world evidence underpinning the model. This evidence could be further improved with minor changes to the UK TAVI Registry to record characteristics known to influence clinician choice of valve. Greater understanding of these factors and their related outcomes could support use of alternative modelling approaches, such as an individual patient simulation rather than a Markov cohort model, to determine the range of TAVI devices needed to serve a UK NHS population in a cost-effective, and more importantly, safe manner.

Should improved real world data become available then the analysis pipeline used by the EAG (analysis of national registry, linkage to HES for longer-term outcomes, multivariate analysis to adjust for potential confounders, prediction of outcomes assuming the same patient characteristics used to populate an economic model) could be repeated. This would also allow both active surveillance of TAVI devices to gain further long-term data when available, and also analysis of the 5 TAVI devices (and potentially newer devices) added to the NHS Supply Chain framework after 31 March 2023.

Despite the acknowledged and inherent limitations associated the underlying data from the UK TAVI registry, the analysis by the EAG represents the largest comparison of TAVI devices being used in the NHS setting, translating observed data from the UK into economic outcomes while adjusting for differences in some patient characteristics in the populations using the difference devices. As with any economic evaluation, which should be seen as an aid to decision making, the results of the economic analysis should be considered alongside the analysis of the linked UK TAVI Registry data (which represents the largest device comparison in the UK NHS setting), and the MCDA conducted by NICE (to consider other differences between devices which have not been considered in either the clinical or economic evidence) to determine whether the price variation of devices is justified.

EAG Recommendations: The UK TAVI Registry could be minimally adapted to record risk (using an appropriate clinical risk score) and additional data fields to capture characteristics that affect clinician choice of valve (for example valve morphology, calcium burden and distribution, coronary height) and additional detail on outcomes (disabling stroke) to support subgroup analysis in future and without substantially increasing the burden of data collection and data management. Data validation rules could be implemented at data collection into the Registry (for example serial number checking) and TAVI device names synchronised to NHS Procurement List, to ensure reflection of what is currently available in the NHS. Linkage to HES could be repeated as part of data quality monitoring and would enable active surveillance of TAVI devices to gain further long-term data. Future evaluation could be repeated using UK data to incorporate device-specific outcomes for all devices including the 5 additional TAVI devices that were added to the NHS

Supply Chain framework after 31 March 2023 (latest validated data available from UK TAVI Registry). These data could be used to estimate the relative clinical effectiveness and costs-effectiveness of all TAVI devices used within the NHS. Longer follow-up is essential to determine whether, and if, clinical outcomes remain similar across TAVI devices, and how these clinical outcomes affect cost-effectiveness. Longer follow-up, would also address uncertainties in the economic model that result from extrapolations from short-term clinical data.

References

Abdelfattah OM, Sayed A, Ghonim M et al. (2022) Meta-Analysis of Transcatheter Aortic Valve Implantation Using the Sapien 3 Versus Sapien 3 Ultra Valves. Am J Cardiol. 168:170-172

Ahlström MG, Thyssen JP, Wennervaldt M, et al. (2019) Nickel allergy and allergic contact dermatitis: A clinical review of immunology, epidemiology, exposure, and treatment. Contact Dermatitis. 81(4): 227-41

Aidietis A, Srimahachota S, Dabrowski M, et al. (2022) 30-day and 1-year outcomes with HYDRA self-expanding transcatheter aortic valve: the Hydra CE Study. JACC Cardiovasc Interv. 15(1): 93-104

Ali N, Blackman DJ. (2019) TAVI: Which valve for which patient? Cardiac Interventions Today. 13(2): 72-78

Ali N, Hildick-Smith D, Parker J, et al. (2023) Long-term durability of self-expanding and balloon-expandable transcatheter aortic valve prostheses: UK TAVI registry. Catheter Cardiovasc Interv. 101(5): 932-42

Anderson C, Derbas L, Kavinsky CJ. (2023) Is your heart a metal detector? J Am Coll Cardiol. 81(8_Supplement); 1018

Archbold A, Akowuah E, Banning AP, et al. (2022) Getting the best from the Heart Team: guidance for cardiac multidisciplinary meetings. Heart. 108(11): e2

Azraai M, Gao L, Ajani AE. (2020) Cost-Effectiveness of Transcatheter Aortic Valve Intervention (TAVI) Compared to Surgical Aortic Valve Replacement (SAVR) in Low- to Intermediate-Surgical-Risk Patients. Cardiovasc Revasc Med. 21(9):1164-1168

Baggio S, Pagnesi M, Kim WK et al. (2023) Comparison of transcatheter aortic valve replacement with the ACURATE neo2 versus Evolut PRO/PRO+ devices. EuroIntervention. 18(12):977-986

Bajwa T, Attizzani G, Gada H et al. (2023) LB-8 Performance and use of the Evolut FX transcatheter aortic valve system: updated results from the Evolut FX limit marker release clinical survey. J Soc Cardiovasc Angio Interv

Bapat VN, Zaid S, Fukuhara S et al. (2021) Surgical Explantation After TAVR Failure: Mid-Term Outcomes From the EXPLANT-TAVR International Registry. JACC Cardiovasc Interv. 14(18):1978-1991

Baron SJ, Arnold SV, Wang K et al. (2017) Health Status Benefits of Transcatheter vs Surgical Aortic Valve Replacement in Patients With Severe Aortic Stenosis at Intermediate Surgical Risk: Results From the PARTNER 2 Randomized Clinical Trial. JAMA Cardiol. 2(8):837-845

Baumbach A, van Royen N, Amat-Santos IJ et al. (2024) LANDMARK comparison of early outcomes of newer-generation Myval transcatheter heart valve series with contemporary valves (Sapien and Evolut) in real-world individuals with severe symptomatic native aortic stenosis: a randomised non-inferiority trial. Lancet. S0140-6736(24)00821-3

Beaver T, Bavaria JE, Griffith B, et al. (2023) Seven-year outcomes following aortic valve replacement with a novel tissue bioprosthesis. J Thorac Cardiovasc Surg. S0022-5223(23)00873-5

Bennette C, Vickers A. (2012) Against quantiles: categorization of continuous variables in epidemiologic research, and its discontents. BMC Med Res Methodol. 12:21

Bowdish ME, Habib RH, Kaneko T, et al. (2024) Cardiac surgery after transcatheter aortic valve replacement: trends and outcomes. Ann Thorac Surg. S0003-4975(24): 00254-6

Brown JA, Yousef S, Toma C, et al. (2023) Self-expanding transcatheter aortic valves optimise transvalvular hemodynamics independent of intra-versus supra-annular design. Am J Cardiol. 207: 48-53

Buono A, Gorla R, Ielasi A et al. (2022b) Transcatheter Aortic Valve Replacement With Self-Expanding ACURATE neo2: Postprocedural Hemodynamic and Short-Term Clinical Outcomes. JACC Cardiovasc Interv. 15(11):1101-1110

Cannata S, Gandolfo C, Ribichini FL, van Mieghem N, Buccheri S, Barbanti M et al. (2023) One-year outcomes after transcatheter aortic valve implantation with the

latest-generation SAPIEN balloon-expandable valve: the S3U registry. EuroIntervention. 18(17):1418-1427

Capodanno D, Petronio AS, Prendergast B, et al. (2017) Standardized definition of structural deterioration and valve failure in assessing long-term durability of transcatheter and surgical aortic bioprosthetic valves: a consensus statement from the European Association of Percutaneous Cardiovascular Interventions (EAPCI) endorsed by the European Society of Cardiology (ECS) and the European Association of Cardio-Thoracic Surgery (EACTS). Eur Heart J. 38(45): 3382-90

Chetcuti S, Bajwa T, Attizzani G. et al. (2023) CRT-700.33 Performance and Use of the Evolut FX Transcatheter Aortic Valve System: Results From the Evolut FX Limited Market Release Clinical Survey. J Am Coll Cardiol Intv (4_Supplement) S92

Chiarito M, Spirito A, Nicolas J et al. (2022) Evolving Devices and Material in Transcatheter Aortic Valve Replacement: What to Use and for Whom. J Clin Med. 11(15):4445

Chotnoppharatphatthara P, Yoodee V, Taesotikul S et al. (2023) Transcatheter aortic valve implantation in patients with severe symptomatic aortic valve stenosis: systematic review of cost-effectiveness analysis. Eur J Health Econ. 24(3):359-376

Costa G, Barbanti M, Rosato S et al. (2022) Real-World Multiple Comparison of Transcatheter Aortic Valves: Insights From the Multicenter OBSERVANT II Study. Circ Cardiovasc Interv. 15(12):e012294

Dogosh AA, Adawi A, El Nasasra A, Cafri C, Barrett O, Tsaban G et al. (2022) Comparison of Transcatheter Aortic Valve Implantation Devices in Aortic Stenosis: A Network Meta-Analysis of 42,105 Patients. J Clin Med. 11(18):5299

Dvir D, Webb J, Brecker S, et al. (2012) Transcatheter aortic valve replacement for degenerative bioprosthetic surgical valves: results from the global valve-in-valve registry. Circulation. 126(19): 2335-44

Eckel CE, Kim WK, Grothusen C et al. (2023) Comparison of the New-Generation Self-Expanding NAVITOR Transcatheter Heart Valve with Its Predecessor, the PORTICO, in Severe Native Aortic Valve Stenosis. J Clin Med. 12(12):3999

Edlinger C, Krizanic F, Butter C et al. (2021) Economic assessment of traditional surgical valve replacement versus use of transfemoral intervention in degenerative aortic stenosis. Minerva Med. 112(3):372-383

Efthimiou O, Mavridis D, Debray TP, Samara M, Belger M, Siontis GC, Leucht S, Salanti G; GetReal Work Package 4. (2017) Combining randomized and non-randomized evidence in network meta-analysis. Stat Med. 36(8):1210-1226

Elkoumy A, Jose J, Gunasekaran S, et al. (2023) Angiographic quantification of aortic regurgitation following myval octacor implantation; independent core lab adjudication. Int J Cardiol. 382: 68-75

Elkoumy A, Jose J, Terkelsen CJ, Nissen H, Gunasekaran S, Abdelshafy M et al. (2022) Safety and Efficacy of Myval Implantation in Patients with Severe Bicuspid Aortic Valve Stenosis-A Multicenter Real-World Experience. J Clin Med. 11(2):443

Elze MC, Gregson J, Baber U et al. (2017) Comparison of Propensity Score Methods and Covariate Adjustment: Evaluation in 4 Cardiovascular Studies. J Am Coll Cardiol. 69(3):345-357

Forrest JK, Kaple RK, Tang GHL, et al. (2020) Three generations of self-expanding transcatheter aortic valves: a report from the STS/ACC TVT Registry. JACC Cardiovasc Interv. 13(2): 170-9

Geyer M, Tamm AR, Münzel T, et al. (2023) 3-dimensional CT planning for TAVR with a novel self-expandable valve in a calcified anatomy. JACC Case Rep. 28: 102116

Gilard M, Eltchaninoff H, Iung B, et al. (2022) Cost-Effectiveness Analysis of SAPIEN 3 Transcatheter Aortic Valve Implantation Procedure Compared With Surgery in Patients With Severe Aortic Stenosis at Low Risk of Surgical Mortality in France. Value Health. 25(4): 605-13

Giordano A, Corcione N, Barbanti M et al. (2024a) Features and outcomes of bailout repeat transcatheter aortic valve implantation (TAVI): the Bailout Acute TAVI-in-TAVI to Lessen Events (BATTLE) international registry. Clin Res Cardiol. 113(1):68-74

Giordano A, Mas-Peiro S, Fichtlscherer S et al. (2024b) Long-term outcomes following transcatheter aortic valve implantation with the Portico self-expanding valve. Clin Res Cardiol. 113(1):86-93

González-Bravo DH, Colón-Hernández, P, Quintana-Serrano M, et al. (2022) Successful treatment of severe paravalvular leak by repositioning a self-expandable percutaneous aortic valve bioprosthesis (Evolut Pro+) using the “double snare” technique. Case Rep Cardiol. 4458109]

Gozdek M, Kuźma Ł, Dąbrowski EJ et al. (2023) Outcomes of Transcatheter Aortic Valve Implantation Comparing Medtronic's Evolut PRO and Evolut R: A Systematic Review and Meta-Analysis of Observational Studies. Int J Environ Res Public Health. 20(4):3439

Grubb KJ, Lisko JC, O’Hair D, et al. (2024) Reinterventions after CoreValve/Evolut transcatheter or surgical aortic valve replacement for treatment of severe aortic stenosis. JACC Cardiovasc Interv. 17(8): 1007-16

Guéroult AM, Al-Balah A, Davies AH, Shalhoub J. (2022) Nickel hypersensitivity and endovascular devices: a systematic review and meta-analysis. Heart. 108(21): 1707-15

Haute Autorité de Santé, HAS. (2021a) SAPIEN 3 MODEL 9600 TFX AORTIC VALVE BIOPROSTHESIS WITH EDWARDS COMMANDER™ PLACEMENT SYSTEM. Saint-Denis La Plaine [online; accessed 26 January 2024]

Haute Autorité de Santé, HAS. (2021b) COREVALVE EVOLUT PRO. Saint-Denis La Plaine [online; accessed 26 January 2024]

Hawkins RB, Deeb GM, Sukul D, et al. (2023) Redo surgical aortic valve replacement after prior transcatheter versus surgical aortic valve replacement. JACC Cardiovasc Interv. 16(8): 942-53

Health Technology Wales. (2020) Transcatheter Aortic Valve implantation to treat people with severe symptomatic aortic stenosis, who are at intermediate surgical risk. Evidence Appraisal Report [online; accessed 26 January 2024]

Heathcote L, Srivastava T, Sarmah A et al. (2023) A Systematic Review and Statistical Analysis of Factors Influencing the Cost-Effectiveness of Transcatheter Aortic Valve Implantation for Symptomatic Severe Aortic Stenosis. Clinicoecon Outcomes Res. 15:459-475

Herrmann HC, Mehran R, Blackman DK, et al. (2024) Self-expanding or balloon-expandable TAVR in patients with a small aortic annulus. N Engl J Med. Online ahead of print; doi: 10.1056/NEJMoa2312573

Higgins J, Altman D, Gøtzsche P, et al. (2011) The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ (Clinical research ed.). 343: d5928

Hiltner E, Shah M, Schwabe-Warf D, Haik B, Hakeem A, Russo M et al. (2022) [Pre-print]. Comparison of various transcatheter aortic valves for aortic stenosis – a network meta-analysis of randomised controlled trials. MedRxix.

Himmels JPW, Flottorp S, Stoinska-Schneider A, et al. (2021) Transcatheter aortic valve implantation (TAVI) versus surgical aortic valve replacement (SAVR) for patients with severe aortic stenosis and low surgical risk and across surgical risk groups: a health technology assessment. Oslo: Norwegian Institute of Public Health [online; accessed 26 January 2024]

Hoffman J, Kaplan S. (2002) The incidence of congenital heart disease. JACC. 39(12): 1890-1900

Hosmer, Lemshow, and Sturdivant (2013) Applied Logistic Regression, 3rd Edition, Ch.5; 174-177

Ielasi A, Caminiti R, Pellegrini D, et al. (2024) Technical aspects for transcatheter aortic valve replacement with the novel balloon-expandable Myval Octacor. JACC Cardiovasc Interv. 17(1): 101-103

Inoue S, Nakao K, Hanyu M, et al. (2020) Cost-Effectiveness of Transcatheter Aortic Valve Implantation Using a Balloon-Expandable Valve in Japan: Experience From the Japanese Pilot Health Technology Assessment. Value Health Reg Issues. 21: 82-90

Jansen JP, Fleurence R, Devine B, Itzler R, Barrett A, Hawkins N et al. (2011) Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 1. Value Health. 14(4):417-28

Joanna Briggs Institute. (2020) Critical Appraisal Checklist for Systematic Reviews and Research Syntheses. https://jbi.global/sites/default/files/2020-08/Checklist_for_Systematic_Reviews_and_Research_Syntheses.pdf

Joanna Briggs Institute. (2017) Critical Appraisal Checklist for Cohort Studies. https://jbi.global/sites/default/files/2019-05/JBI_Critical_Appraisal-Checklist_for_Cohort_Studies2017_0.pdf

Jose J, Mandalay A, Cholenahally MN et al. (2024) Safety and effectiveness of the novel Myval Octacor transcatheter heart valve in severe, symptomatic aortic valve stenosis - A real-world Indian experience (The OCTACOR India Study). Cardiovasc Revasc Med. S1553-8389(24)00017-4. [Epub ahead of print]

Joshy G, Korda RJ, Abhayaratna WP et al. (2015) Categorising major cardiovascular disease hospitalisations from routinely collected data. Public Health Res Pract. 25(3):e2531532

Jung YJ, Choi JW, Kang Y, et al. (2023) Long-term results of a stented bioprosthetic valve in the aortic position: structural valve deterioration and valve haemodynamic deterioration of bovine pericardial and porcine valves. Eur J Cardio-thoracic Surg. 63(2): ezac506

Kaier K, Gutmann A, Baumbach H et al. (2016) Quality of life among elderly patients undergoing transcatheter or surgical aortic valve replacement- a model-based longitudinal data analysis. Health Qual Life Outcomes. 14(1):109

Karrowni W, Fakih S, Nassar P. (2020) Infolding of self-expandable transcatheter heart valve: case report and review of literature. Cureus. 12(8): e10093

Keltie K, Cognigni P, Gross S et al. (2021) Comparison of identifiable and non-identifiable data linkage: health technology assessment of MitraClip using registry, administrative and mortality datasets. BMJ Health Care Inform. 28(1):e100223

Kharbanda RK, Perkins AD, Kennedy J, et al. (2023) Routine cerebral embolic protection in transcatheter aortic valve implantation: rationale and design of the randomised British Heart Foundation PROTECT-TAVI trial. EuroIntervention. 18(17): 1428-35

Kim WK, Eckel C, Renker M et al. (2022c) Comparison of the ACURATE neo Vs Neo2 Transcatheter Heart Valves. J Invasive Cardiol. 2022 Nov;34(11):E804-E810

Kim W-K, Möllmann H, Montorfano M, et al. (2024) Outcomes and performance of the ACURATE neo2 transcatheter heart valve in clinical practice: one-year results of the ACURATE neo2 PMCF study. EuroIntervention. 20(1): 85-94

Kim W-K, Renker M, Dörr O, et al. (2022a) Micro-dislodgement of a self-expanding transcatheter heart valve: incidence, predictors, and outcomes. Int J Cardiol. 358: 77-82

Kuntjoro I, Tay E, Hon J, et al. (2020) Cost-Effectiveness of Transcatheter Aortic Valve Implantation in Intermediate and Low Risk Severe Aortic Stenosis Patients in Singapore. Ann Acad Med Singap. 49(7): 423-33

Landes U, Webb JG, De Backer O et al. (2020) Repeat Transcatheter Aortic Valve Replacement for Transcatheter Prosthesis Dysfunction. J Am Coll Cardiol. 75(16):1882-1893

Lange R, Beckmann A, Neumann T et al. (2016). Quality of Life After Transcatheter Aortic Valve Replacement: Prospective Data From GARY (German Aortic Valve Registry). JACC Cardiovasc Interv. 9(24):2541-2554

Lorenzoni V, Barbieri G, Saia F, et al. (2021) The cost-effectiveness of transcatheter aortic valve implantation: exploring the Italian National Health System perspective and different patient risk groups. Eur J Health Econ. 22(9): 1349-63

Maechler M, Dutang C, Goulet V (2024). _expm: Matrix Exponential, Log, 'etc'_. R package version 0.999-9, https://CRAN.R-project.org/package=expm

Merdler I, Case B, Bhogal S, et al. (2023) Early experience with the Evolut FX self-expanding valve vs. Evolut PRO+ for patients with aortic stenosis undergoing TAVR. Cardiovasc Revasc Med. 56: 1-6

Moscarella E, Ielasi A, Montonati C et al. (2024) Comparing two-year outcomes of balloon-expandable Myval and self-expanding Evolut R in severe aortic valve stenosis. Int J Cardiol. 1;400:131701

Mubarik A, Sharma S, Law MA. (2023) Bicuspid aortic valve. In: StatPerls. Treasure Island, Florida, US: StatPearls Publishing

Nazif TM, Cahill TJ, Daniels D et al. (2021) Real-World Experience With the SAPIEN 3 Ultra Transcatheter Heart Valve: A Propensity-Matched Analysis From the United States. Circ Cardiovasc Interv. 14(9):e010543

Otto CM, Nishimura RA, Bonow RO, et al. (2021) 2020 American College of Cardiology and American Heart Association Guideline for the Management of Patients with Valvular Heart Disease. J Am Coll Cardiol. 77(4): e25-197

Paulden M. (2020) Why it's Time to Abandon the ICER. Pharmacoeconomics. 38(8):781-784

Pellicano M, Ielasi A, Spagnolo P, et al. (2021) Successful percutaneous closure of an iatrogenic ventricular septal defect following TAVR with the ACURATE neo2. JACC Cardiovasc Interv. 14(14): e173-6

Phillips MR, Steel DH, Wykoff CC, Busse JW, Bannuru RR, Thabane L, Bhandari M, Chaudhary V; Retina Evidence Trials InterNational Alliance (R.E.T.I.N.A.) Study Group. (2022) A clinician's guide to network meta-analysis. Eye (Lond). 36(8):1523-1526

Pinar E, García de Lara J, Hurtado J, et al. (2022) Cost-effectiveness analysis of the SAPIEN 3 transcatheter aortic valve implant in patients with symptomatic severe aortic stenosis. Rev Esp Cardiol (Engl Ed). 75(4): 325-33

Pongiglione B, Torbica A, Blommestein H et al. (2021) Do existing real-world data sources generate suitable evidence for the HTA of medical devices in Europe? Mapping and critical appraisal. Int J Technol Assess Health Care. 37(1):e62, 1-8

Rao K, Baer A, Hansen P, Bhindi R. (2023) Recurrent valve frame infolding in the 34 mm self-expanding Medtronic Evolut Pro+ transcatheter valve system: a single centre experience. Heart Lung Circ. 32(12): 1482-1488

Reardon MJ. (2021) The ACURATE neo™ and neo2™ Valve Systems. Heart Int. 15(1):37-41

Rice CT, Barnett S, O'Connell SP et al; (2023) Impact of gender, ethnicity and social deprivation on access to surgical or transcatheter aortic valve replacement in aortic stenosis: a retrospective database study in England. Open Heart. 10:e002373.

Rogers R, Thourani VH. (2018) Transcatheter aortic valve replacement after mitral valve surgery: synergistic or incompatible? J Thorac Cardiovasc Surg. 155(1): 66-7

Royston P, Altman DG, Sauerbrei W. (2006) Dichotomizing continuous predictors in multiple regression: a bad idea. Stat Med. 25(1):127-41

Rudolph, TK, Herrmann E, Bon D, et al. (2024) Comparison of contemporary transcatheter heart valve prostheses: data from the German Aortic Valve Registry (GARY). Clinical Research in Cardiology. 113(1): 75-85

Ruggeri M, Donatella M, Federica C et al. (2022) The transcatheter aortic valve implantation: an assessment of the generalizability of the economic evidences following a systematic review. Int J Technol Assess Health Care. 38(1):e27

Russo MJ, McCabe JM, Thourani VH et al. (2019) Case Volume and Outcomes After TAVR With Balloon-Expandable Prostheses: Insights From TVT Registry. J Am Coll Cardiol. 73(4):427-440.

Salaun E, Pibarot P. (2019) Transcatheter aortic valve implantation after mitral valve replacement: insights from the OPTIMAL registry. Can J Cardiol. 35(7): 805-8

Santangelo G, Ielasi A, Pellicano M, et al. (2022) An update on new generation transcatheter aortic valves and delivery systems. J Clin Med. 11(3): 499

Santos-Martinez S, Halim J, Castro-Mejía A, et al. (2022) Myval versus alternative balloon- and self-expandable transcatheter heart valves: a central core lab analysis of conduction disturbances. Int J Cardiol. 351: 25-31

Schuttelaar MLA, Ofenloch RF, Bruze M, et al. (2018) Prevalence of contact allergy to metals in the European general population with a focus on nickel and piercings: The EDEN Fragrance Study. Contact Dermatitis. 79(1): 1-9

Scotti A, Pagnesi M, Kim WK et al. (2022) Haemodynamic performance and clinical outcomes of transcatheter aortic valve replacement with the self-expanding ACURATE neo2. EuroIntervention. 18(10):804-811

SEC Working Group for the 2017 ESC/EACTS Guidelines for the Management of Valvular Heart Disease. (2018) Comments on the 2017 ESC/EACTS Guidelines for the Management of Valvular Heart Disease. Rev Esp Cardiol (Engl Ed). 71(2):67-73

Seiffert M, Conradi L, Kloth B et al. (2015) Single-centre experience with next-generation devices for transapical aortic valve implantation. Eur J Cardiothorac Surg. 47(1):39-45; discussion 45

Silaschi M, Treede H, Rastan AJ et al. (2016) The JUPITER registry: 1-year results of transapical aortic valve implantation using a second-generation transcatheter heart valve in patients with aortic stenosis. Eur J Cardiothorac Surg. 50(5):874-881

Singh S, Ghayal P, Mathur A, et al. (2015) Unicuspid unicommissural aortic valve: an extremely rare congenital anomaly. Tex Heart Inst J. 42(3): 273-6

Siqueira DA, Simonato M, Ramos AA et al. (2021) Mid- to long-term clinical and echocardiographic outcomes after transcatheter aortic valve replacement with a new-generation, self-expandable system. Catheter Cardiovasc Interv. 97(1):167-174

Sondergaard L, Walton AS, Worthley SG et al. (2023) Thirty-day and one-year outcomes of the Navitor transcatheter heart valve in patients with aortic stenosis: the prospective, multicentre, global PORTICO NG Study. EuroIntervention. 19(3):248-255

Sterne JA, White IR, Carlin JB et al. (2009) Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ. 338:b2393

Strange GA, Stewart S, Curzen N, et al. (2022) Uncovering the treatable burden of severe aortic stenosis in the UK. Open Heart. 9(1): e001783

Takagi H, Hari Y, Nakashima K, Kuno T, Ando T; ALICE (All-Literature Investigation of Cardiovascular Evidence) Group. (2019) Network meta-analysis of new-generation valves for transcatheter aortic valve implantation. Heart Vessels. 34(12):1984-1992

Tam DY, Azizi PM, Fremes SE et al. (2021a). The cost-effectiveness of transcatheter aortic valve replacement in low surgical risk patients with severe aortic stenosis. Eur Heart J Qual Care Clin Outcomes.7(6):556-563

Tam DY, Miranda RN, Elbatarny M et al. (2021b) Real-World Health-Economic Considerations Around Aortic-Valve Replacement in a Publicly Funded Health System. Can J Cardiol. 37(7):992-1003

Tamm AR, Geyer M, Kreidel F et al. (2021) Long-Term Outcome with New Generation Prostheses in Patients Undergoing Transcatheter Aortic Valve Replacement. J Clin Med. 10(14):3102

Tang GHL, Sengupta A, Alexis SL et al. (2021). Outcomes of Prosthesis-Patient Mismatch Following Supra-Annular Transcatheter Aortic Valve Replacement: From the STS/ACC TVT Registry. JACC Cardiovasc Interv. 14(9):964-976

Tang GHL, Zaid, S, Kleiman NS et al. (2023). Explant vs Redo-TAVR After Transcatheter Valve Failure: Mid-Term Outcomes From the EXPLANTORREDO-TAVR International Registry. JACC Cardiovasc Interv. 16(8):927-941

Tanner R, Giacoppo D, Saber H et al. (2024) Trends in transcatheter aortic valve implantation practice and clinical outcomes at an Irish tertiary referral centre. Open Heart. 11(1):e002610

Tébar Márquez D, Moreno R, Galeote G, et al. (2022) Transcatheter aortic valve with a novel self-expandable device in patients with previous mechanical mitral valve prosthesis. Catheter Cardiovasc Interv. 100(7): 1286-90

Trębacz J, Konstanty-Kalandyk J, Sobczyński R, et al. (2023) Successful treatment of severe ACURATE neo2 valve under expansion in a setting of severe aortic stenosis with massive calcifications. Kardiol Pol. 81(5): 515-6

Treede H, Rastan A, Ferrari M et al. (2012) JenaValve. EuroIntervention. 8 Suppl Q:Q88-93

Ueshima D, Fovino LN, Brener SJ, et al. (2020) Transcatheter aortic valve replacement for bicuspid aortic valve stenosis with first- and new-generation bioprostheses: a systematic review and meta-analysis. Int J Cardiol. 298: 76-82

Voigtländer L, Kim WK, Mauri V, Goßling A, Renker M, Sugiura A et al. (2021) Transcatheter aortic valve implantation in patients with a small aortic annulus: performance of supra-, intra- and infra-annular transcatheter heart valves. Clin Res Cardiol. 110(12):1957-1966

Welton NJ, Ades AE. (2005) Estimation of markov chain transition probabilities and rates from fully and partially observed data: uncertainty propagation, evidence synthesis, and model calibration. Med Decis Making.25(6):633-45

Wilkinson JD, Mamas MA, Kontopantelis E. (2022) Logistic regression frequently outperformed propensity score methods, especially for large datasets: a simulation study. J Clin Epidemiol. 152:176-184

Wolfrum M, Moccetti F, Piuhola J, et al. (2021) The Allegra transcatheter heart valve: short term results from a multicentre registry. Catheter Cardiovasc Interv. 98(6): 1204-9

Wolfrum M, Moccetti F, Conrad N, et al. (2023) The Allegra transcatheter heart valve: long-term clinical and echocardiographic outcomes. J Invasive Cardiol. 35(12)

Yang Y, Liu X, Fu Y et al. (2023) Comparisons of different new-generation transcatheter aortic valve implantation devices for patients with severe aortic stenosis: a systematic review and network meta-analysis. Int J Surg; 109(8): 2414-2426

Yashige M, Zen K, Takamatsu, K, Matoba S. (2022) Additional balloon aortic valvuloplasty to overcome the difficult removal of a self-expandable transcatheter aortic valve system due to valve infolding. Catheter Cardiovasc Interv. 100(7):1331-5

Zaid S, Atkins MD, Kleiman NS et al. (2023) What's New with TAVR? An Update on Device Technology. Methodist Debakey Cardiovasc J. 19(3):4-14

Zaid S, Attizzani GF, Krishnamoorthy P. et al. (2023b) First-in-human multicentre experience of the newest generation supra-annular self-expanding Evolut FX TAVR System. JACC Cardiovasc Interv. 16(13): 1626-35

Zhou JY, Liew D, Duffy SJ, Walton A, Htun N, Stub D. (2021) Cost-Effectiveness of Transcatheter Versus Surgical Aortic Valve Replacement in Low-Risk Patients With Severe Aortic Stenosis. Heart Lung Circ. 30(4): 547-54

Appendices

Appendix A: Literature search

Appendix A1: Scoping searches

Scoping searches were conducted as described in the Protocol (June 2024) to identify both systematic reviews of clinical effectiveness and systematic reviews of economic evaluations and economic models.

Search filters to identify systematic reviews of clinical effectiveness and systematic reviews of economic evaluations and models were applied. The search was limited by date from 01 January 2020 to the most recently available date in the relevant database to update the search and capture additional records added to the relevant database since the searches for NG208 in October 2020. This search identified 764 titles and abstracts, which were screened by a single reviewer for relevance to the decision problem. No publication directly addressed the decision problem or objectives of this assessment.

Database:

Ovid MEDLINE(R) ALL <1946 to November 28, 2023>

Date searched: 29 November 2023

#	Query	Results from 29 Nov 2023
1	exp Heart Valve Diseases/	137,939
2	Heart Diseases/	74,953
3	exp Aortic Valve Stenosis/	52,160
4	Aortic Valve/	40,391
5	severe aortic stenosis.ab,ti,kw.	6,131
6	((primary or secondary) adj valv* disease*).ab,ti,kw.	53
7	((mitral valv* or aortic valv* or tricuspid valv* or pulmon* valv*) adj (disease* or disorder* or fail* or dysfunction* or insufficien* or damage* or leak*)).ab,ti,kw.	11,114
8	((mitral leaflet* or aortic leaflet*) adj (disease* or disorder* or fail* or dysfunction* or insufficien* or damage* or leak*)).ab,ti,kw.	5
9	(aortic valv* adj (disease* or disorder* or fail* or dysfunction* or insufficien* or damage* or leak*)).ab,ti,kw.	5,177
10	(aortic leaflet* adj (disease* or disorder* or fail* or dysfunction* or insufficien* or damage* or leak*)).ab,ti,kw.	1
11	((heart or cardiac) adj (disease* or disorder* or fail* or dysfunction* or insufficien* or damage* or leak*)).ab,ti,kw.	431,280

#	Query	Results from 29 Nov 2023
12	((mitral or aortic or tricuspid or pulmon*) adj3 (prolaps* or regurgitation or stenosis or atresia or insufficien*)).ti,ab.	91,428
13	or/1-12	631,607
14	Heart Valve Prosthesis/	40,602
15	Heart, Artificial/	5,426
16	Implants, Experimental/	3,460
17	exp Heart Valve Prosthesis Implantation/	37,067
18	(percutan* aortic valve* adj (implant* or repair* or replace*)).ab,ti,kw.	329
19	(transcath* aortic valve* adj (implant* or repair* or replace*)).ab,ti,kw.	14,238
20	(aortic valve* adj (implant* or repair* or replace*)).ab,ti,kw.	29,946
21	((experimental or artificial or mechanical or artificial or prosthe* or bioprosthe* or biological or tissue) adj (heart or valv* or flap* or leaflet* or implant*)).ab,ti,kw.	28,035
22	((balloon-expand* or self-expand* or balloon expand* or self expand*) adj (TAVI or TAVR or PAVR)).ab,ti,kw.	238
23	((balloon-expand* or self-expand* or balloon expand* or self expand*) adj (transcatheter aortic valve implantation or transcatheter aortic valve replacement or percutaneous aortic valve replacement)).ab,ti,kw.	323
24	(TAVI or TAVR or PAVR).ab,ti,kw.	12,157
25	(transcatheter aortic valve implantation or transcatheter aortic valve replacement or percutaneous aortic valve replacement).ab,ti,kw.	15,011
26	or/14-24	94,856
27	(systematic review or meta-analysis).pt.	330,789
28	meta-analysis/ or systematic review/ or systematic reviews as topic/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/ or network meta-analysis/	371,259
29	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf.	341,061
30	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf.	16,458
31	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf.	40,609
32	(data synthes* or data extraction* or data abstraction*).ti,ab,kf.	42,708
33	(handsearch* or hand search*).ti,ab,kf.	11,367

#	Query	Results from 29 Nov 2023
34	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf.	36,990
35	(met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf.	12,586
36	(meta regression* or metaregression*).ti,ab,kf.	15,379
37	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.	491,979
38	(medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.	360,633
39	(cochrane or (health adj2 technology assessment) or evidence report).jw.	21,758
40	(comparative adj3 (efficacy or effectiveness)).ti,ab,kf.	18,217
41	(outcomes research or relative effectiveness).ti,ab,kf.	11,493
42	((indirect or indirect treatment or mixed-treatment or bayesian) adj3 comparison*).ti,ab,kf.	4,469
43	[(meta-analysis or systematic review).md.]	0
44	(multi* adj3 treatment adj3 comparison*).ti,ab,kf.	304
45	(mixed adj3 treatment adj3 (meta-analy* or metaanaly*)).ti,ab,kf.	179
46	umbrella review*.ti,ab,kf.	1,703
47	(multi* adj2 paramet* adj2 evidence adj2 synthesis).ti,ab,kf.	14
48	(multiparamet* adj2 evidence adj2 synthesis).ti,ab,kf.	18
49	(multi-paramet* adj2 evidence adj2 synthesis).ti,ab,kf.	12
50	or/27-49	716,632
51	Economics/	27,517
52	exp "Costs and Cost Analysis"/	267,609
53	Economics, Nursing/	4,013
54	Economics, Medical/	9,261
55	Economics, Pharmaceutical/	3,114
56	exp Economics, Hospital/	25,768
57	Economics, Dental/	1,921
58	exp "Fees and Charges"/	31,431
59	exp Budgets/	14,168
60	budget*.ti,ab,kf.	36,958

#	Query	Results from 29 Nov 2023
61	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf.	288,307
62	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2	393,266
63	(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf.	216,559
64	(value adj2 (money or monetary)).ti,ab,kf.	3,130
65	exp models, economic/	16,249
66	economic model*.ab,kf.	4,337
67	markov chains/	16,055
68	markov.ti,ab,kf.	29,914
69	monte carlo method/	32,528
70	monte carlo.ti,ab,kf.	61,558
71	exp Decision Theory/	13,518
72	(decision* adj2 (tree* or analy* or model*)).ti,ab,kf.	40,123
73	or/51-72	920,727
74	13 and 26 and 50 and 73	60
75	13 and 26 and 50	1,572
76	limit 75 to yr="2020 -Current"	725
77	limit 74 to yr="2020 -Current"	21

Line 76: records were downloaded into an EndNote 21 library and exported to the clinical effectiveness reviewers for screening. Line 77: records were downloaded separately into an EndNote 21 library and sent for screening for systematic reviews of economic evaluations and relevant economic models.

Lines 1-25 inclusive were adapted from the search for Evidence Review H in NG208 (line 25 was not used as it was redundant for this search). Line 43 was included in the scoping search for efficiency, it would have been removed for a more formal search as it is only relevant for APA PsycInfo on Ovid (as it is part of a multifile search this line is only relevant for APA PsycInfo on Ovid, which was not searched for this project).

Two search filters were applied to the search:

- *Systematic reviews - filter used*: A filter developed by the Canadian Agency for Drugs and Technologies in Health (CADTH) (CADTH, 2021) to identify systematic reviews, meta-analyses, health technology assessments and indirect treatment comparisons was used. The CADTH filter is for multifile use on Ovid and was adapted for single database use in MEDLINE on Ovid.
- *Economic evaluations and economic models - filter used*: A filter developed by CADTH designed to identify economic evaluations and models was applied to the search strategy to identify systematic reviews in MEDLINE on Ovid (CADTH, 2016).

Appendix A2: Clinical and technological literature search and study selection

Additional targeted searches of PubMed were done by 1 of the EAG team (PL) for the following 8 TAVI devices which were listed in the NICE Final Scope, currently available on the NHS Supply Chain, but where data on the device model were unavailable or incomplete within the TAVI Registry: Navitor (Abbott), Allegra (Biosensors), ACURATE neo2 (Boston Scientific), Trilogy (JenaValve), Evolut FX, Evolut Pro+ (Medtronic), Myval Octacor (Meril UK), and Hydra (SMT). The EAG note that these literature searches were conducted before the device models were verified by the Companies, which subsequently confirmed that Navitor, ACURATE neo2, Evolut Pro+ were included in the Registry analysis.

PubMed (National Library of Medicine, US) was chosen as a broad (bio)medical bibliographic database, which includes MEDLINE and PubMed Central among other resources. The TAVI device model name was searched and combined with other terms (as indicated by using the Boolean operator 'AND') where the search retrieved a large number of results. Searches were done in 'All Fields' and no search filters were applied. The searches for Myval Octacor, Hydra, and Trilogy were run on 01 February 2024. The search for Evolut FX was run on 06 February 2024. The searches for ACURATE neo2, Allegra, and Evolut Pro+, were run on 20 February 2024. The search for Navitor was run on 03 April 2024. The newest generation valve Trilogy (JenaValve) had minimal evidence, therefore additional searches were run for the predecessor ('Jenavalve') on 05 April 2024.

The title and abstracts were exported into a PDF which was sifted by a single reviewer (PL, RP) according to the Final Scope, where mitral valve intervention, non-cardiac intervention, off-label use (for example, based on aortic valve morphology and TAVI-in-valve when considering the contraindications stated in the instructions for use, as provided by the Companies, Table 2), animal studies, laboratory studies, non-research items, and duplicate items were excluded. Decisions for inclusions an exclusion were documented in an Excel spreadsheet. Following screening of titles and abstracts, full papers were retrieved and reviewed by a single reviewer, QA by a second reviewer (RP, KK).

In addition, the Companies were asked to provide published comparative evidence and evidence with the longest follow-up duration specific to the TAVI device models listed within the Final Scope. Company submissions were reviewed by a single reviewer (RP, KK) for relevance. Duplicates with the targeted searches described above were removed. Included and excluded papers were reviewed by a second reviewer (PL, KK, DM).

Literature search terms used in PubMed

Note that these targeted searches were for devices not available in the UK TAVI Registry (conducted prior to device model being verified by Companies using serial numbers).

Device	Main search term(s) in [All Fields]	Combined with term shown (using AND) in [All Fields]	Number of records in PubMed (title/abstracts screened)	Full text articles retrieved and screened	Included after full paper review
Myval Octacor by Meril UK	Myval	-	62	39	2
	Octacor	-	Zero new after deduplication	-	-
ACURATE neo2 by Boston Scientific	ACURATE neo2	-	54	25	22
Allegra by Biosensors	Allegra	Valve	42	23	15
Evolut FX by Medtronic	Evolut FX, EvolutFX, Evolute FX	-	7	2	2
Evolut Pro+ by Medtronic	Evolut Pro+	-	38	11	7
Hydra by SMT	Hydra	Valve	6	5	2
	Sahajanand Medical Technologies	Valve	8	-	-
	SMT	Hydra	0	-	-
Navitor by Abbott Medical	Navitor	Valve	25	5	2
JenaValve by JenaValve	JenaValve	[Search restricted to Title/Abstract]	66	9	3
Trilogy by JenaValve	Trilogy	JenaValve	7	5	1

Appendix B: Published evidence

Appendix B1: Study characteristics of included evidence

Study name, design and location	Intervention(s) and comparator	Participants and setting length of follow-up	Population characteristics	Relevant outcomes	Limitations
Abdelfattah et al. (2022) Systematic review and meta-analysis observational studies (N=7), stratified into propensity score matched and non-propensity matched [PROSPERO CRD: 42021258301] *Funding*: funding source not reported *Declaration of interests:* one author with Abbott Medical, Medtronic	*Intervention*: TAVI with Sapien 3 Ultra (n=1,996) *Comparator*: TAVI with Sapien 3 (n=2,111)	*Inclusion:* observational comparative studies, comparison of clinical and hemodynamic outcomes between S3 and S3U. *Setting*: NR *Search dates:* inception to June 2021; search update undertaken in November 2021.	Surgical risk: - STS mean 4.4 (Sapien 3 Ultra: 4.2; Sapien 3: 4.5). Aortic valve aetiology: NR Delivery approach: NR	*Primary outcome:* all-cause mortality *Secondary outcomes:* stroke, major bleeding, permanent pacemaker implantation, mild PVL, and moderate/severe PVL (VARC-2 criteria).	Non-UK. Letter; therefore lacks detailed methodology and results (image quality of forest plots makes difficult to interpret, unclear how many included studies were propensity matched, timepoint of outcomes reported unclear).
Aidietis et al. (2022) Prospective single arm cohort [NCT02434263] *Funding:* Authors declared funding from SMT *Declaration of interests:* one author with SMT.	*Intervention*: TAVI with Hydra (n=157) *Comparator*: N/A	*Inclusion*: adults aged ≥55 years with NYHA functional class ≥2, symptomatic severe calcified aortic stenosis (aortic valve area <1.0 cm2 and either a mean aortic gradient >40 mmHg or a peak aortic valve velocity >4.0 m/s), deemed at high or extreme surgical risk by heart team, eligible for TAVI via transfemoral access, aortic annulus diameter between 18 to 27 mm as measured by CT within past 180 days or echocardiogram if medically contraindicated to CT, willing and able to comply with the needed follow-up. *Exclusion:* unicuspid, bicuspid or quadricuspid aortic valve, non-calcified aortic valve as seen by echocardiography, severe mitral or tricuspid regurgitation (≥grade III), moderate-to-severe mitral stenosis, LVEF <20%, MI, TIA or stroke within 6 months, carotid artery disease requiring intervention, hypertrophic cardiomyopathy, severe basal septal hypertrophy, percutaneous intervention or other invasive cardiac or peripheral procedure within the past 14 days (does not apply for diagnostic angiography or angio-CT), history of or active endocarditis, echocardiographic evidence of	Surgical risk: - 100% deemed high or extreme risk of surgery by heart team. - STS, mean (SD): 4.7 (3.4) - EuroSCORE II, mean (SD): 5.1 (4.9) Aortic valve aetiology: 100% native Delivery approach: 100% transfemoral	*Primary outcome*: device success (VARC-2 criteria), mortality at 30 days. *Secondary outcomes:* haemodynamic performance (mean gradient, effective orifice area), cardiovascular death, device-related death, major vascular complications, life-threatening/major bleeding, stroke, TIA, AKI, pacemaker implantation, MI, change in NYHA functional class, six-minute walk test, PVL.	Non-comparative, non-UK pre-market study therefore results may not be generalisable to UK NHS setting.

Study name, design and location	Intervention(s) and comparator	Participants and setting length of follow-up	Population characteristics	Relevant outcomes	Limitations
		intracardiac mass, thrombus or vegetation, features of haemodynamic instability (requiring inotropic support or mechanical heart assistance), acute pulmonary oedema or requiring intravenous diuretic therapy to stabilize heart failure, significant pulmonary disease (Forced expiratory volume<30% as predicted), significant chronic steroid use, known hypersensitivity or contraindication to anticoagulant or antiplatelet medication, renal insufficiency (serum creatinine >3.0 mg/dL), or end-stage renal disease requiring chronic dialysis, iliofemoral arteries have severe calcification, tortuosity (> two 90 degree bends), diameter<6mm, or patient has had an aorto-femoral bypass that preclude safe placement of 18 Fr sheath, blood dyscrasia, current autoimmune disease that precludes participation (in opinion of the principal investigator), significant aortic disease, pre-existing endovascular stent graft in the supra- or infrarenal aorta or pre-existing stent grafts in the iliofemoral arteries, active peptic ulcer or has had gastrointestinal bleeding within the past 90 days prior to the procedure, life expectancy <12 months, other medical, social or psychological conditions that preclude participation (in opinion of principal investigator), known allergy to contrast media, nitinol alloys or bovine tissue, history of any cognitive or mental health status that would interfere with study participation, currently participating in another trial, pre-existing prosthetic valve or prosthetic ring in any position. *Setting*: International (N=18 centres; 11 in India, 1 Lithuania, 1 Thailand, 1 Poland, 1 Hong Kong,			

Study name, design and location	Intervention(s) and comparator	Participants and setting length of follow-up	Population characteristics	Relevant outcomes	Limitations
		1 New Zealand, 1 Kazakhstan, 1 Greece) *Recruitment period*: May 2014 to November 2018. *Follow-up*: outcomes to 1 year reported.			
Ali et al. (2023) Retrospective non-randomised analysis of UK TAVI Registry, linked to centre data (clinical outcome and echocardiographic follow-up data not captured in registry) and NHS Spine mortality database (for vital status). *Funding:* Authors declared funding received from NIHR. *Declaration of interests*: multiple authors with Abbott Medical, Boston Scientific, Edwards Lifesciences, Medtronic	*Intervention*: TAVI with: • Corevalve (n=143) • Sapien or Sapien XT (n=67) • Portico (n=4)	*Inclusion*: All patients undergoing TAVI in UK, with baseline echocardiogram done no more than 6 months after TAVI and follow-up echocardiogram no earlier than 4 years and 6 months after TAVI. *Exclusion:* NR *Setting*: UK multicentre (N=11) *Recruitment period*: 2007 to 2011. *Follow-up*: at least 5 years post TAVI.	Surgical risk: Logistic EuroSCORE, mean (SD): 20.0 (12.5) Aortic valve aetiology: 92.3% native 5.9% TAVI-in-SAVR Delivery approach: 79% transfemoral	Aortic regurgitation (moderate and severe), major vascular complications, stroke, new permanent pacemaker, peak gradient, severe structural valve deterioration.	Valve type not reported by the implanting centre for 7 patients (3.2%, 7/221). Includes 5.9% TAVI-in-SAVR. Paired echocardiogram available in 221/371 (60%) of patients alive at 5 years. Since the cause of death is unknown in most of the cases, cannot exclude death because of structural valve deterioration. As all TAVI procedures took place between 2007 and 2011, results reflect older NHS practice (79% transfemoral, transapical 14.5%, subclavian 3.7%, transaortic 2.8%) and pertain to earlier generation valves than included in the NICE Final Scope. Only peak gradient and aortic regurgitation reported by balloon- and self-expanding devices. Portico contributed to self-expanding group (4/147, 2.7%) but data not reported.
Baggio et al. (2023) Retrospective non-randomised analysis of NEOPRO-2 Registry* *Funding:* Authors declared no funding received. *Declaration of interests*: multiple authors with Abbott Medical, Biosensors, Boston Scientific, Edwards Lifesciences, Medtronic, Meril, SMT	*Intervention*: TAVI with ACURATE neo2 (n=763) [n=452 after propensity matching] *Comparator*: TAVI with Evolut Pro (n=1,254) or Evolut Pro+ (n=158) [n=452 after propensity matching] Propensity score matched (1:1) based on 13 variables: age, sex, body mass index, chronic obstructive pulmonary disease, estimated glomerular filtration rate, prior percutaneous coronary intervention, peripheral vascular disease, atrial	*Inclusion*: Consecutive patients who underwent transfemoral TAVI for severe symptomatic aortic stenosis with one of the TAVI devices. *Exclusion:* NR *Setting*: International multicentre (N=20); Germany, Italy, Switzerland, Austria, Brazil, Israel, Denmark, the Netherlands, Belgium, Canada, Ireland, Spain *Recruitment period*: September 2020 to December 2021 (Intervention), August 2017 to October 2021 (Comparator)	Surgical risk: - STS, mean (SD): 4.2 (2.8) - EuroSCORE II, mean (SD): 4.5 (4.2) Aortic valve aetiology: 100% native Delivery approach: 100% transfemoral	*Primary outcome*: device success defined according to VARC-3 criteria (technical success, pre-discharge performance of valve, 30-day safety). *Secondary outcomes*: presence and severity of paravalvular leak, mortality, stroke, rehospitalisation, pacemaker implantation, bleeding, AKI, vascular and non-vascular complications.	Non-UK. Evolut Pro and Pro+ not reported exclusively. Only short-term outcomes reported. Significantly higher proportion conscious sedation, pre- and post-dilatation in ACURATE neo2 arm. Overlap with Scotti et al. (2022); same number of patients, similar demographics. Author acknowledge that many centres contributed with nearly exclusively one valve type to the registry, adding potential selection and centre-specific bias which may not have been completely mitigated with propensity matching.

Study name, design and location	Intervention(s) and comparator	Participants and setting length of follow-up	Population characteristics	Relevant outcomes	Limitations
	fibrillation/flutter, (NYHA) Functional Class III-IV, left ventricular ejection fraction (LVEF), (EuroSCORE) II, moderate-to-heavy AV calcification, and AV annulus perimeter	*Follow-up*: Outcomes to 30 days reported.			
Baumbach et al. (2024) RCT (non-inferiority, covariate-adaptive randomisation 1:1) [LANDMARK trial; NCT04275726; EudraCT 2020-000137-40] *Funding*: authors declared funding from Meril Life Sciences who provided all financial support to conduct the trial and designed the trial protocol in consultation with the steering committee, but had no role in data analysis, data interpretation, or writing of the report. *Declaration of interests:* multiple authors with Abbott Medical, Biosensors, Boston Scientific, Edwards Lifesciences, Medtronic, Meril Life Sciences, and SMT	*Intervention*: TAVI with Myval Series (n=384 randomised, 381 ITT, 363 PP, included Myval, Myval Octacor) *Comparator:* TAVI (n=384 randomised, 381 ITT, 372 PP, included Evolut R , Evolut Pro, Evolut Pro+, Evolut FX, Sapien 3, Sapien 3 Ultra)	*Inclusion*: Adults (aged 18 years or greater) with severe symptomatic native aortic stenosis who were deemed eligible by the local heart team to undergo TAVI with any of the three study devices were considered suitable for enrolment. *Exclusion*: participants who were not willing to give informed consent. Participants with an aortic annulus mean diameter exceeding 29 mm were excluded from randomisation but included in the XL Nested registry for extra-large diameter Myval (ie, 30·5 and 32 mm). *Setting:* International (31 hospitals in 16 countries), Brazil (N=1), Croatia (N=2), Estonia (N=1), France (N=2), Germany (N=4), Greece (N=2), Hungary (N=1), Italy (N=3), New Zealand (N=1), Poland (N=1), Portugal (N=1), Slovakia (N=1), Slovenia (N=1), Spain (N=4), Sweden (N=1), the Netherlands (N=5) *Recruitment:* 06 January 2021 to 05 December 2023 *Follow-up:* 30 days	Surgical risk: STS: Myval 2·6% (1·7–4·0) Comparator 2·6% (1·7–4·0) Aortic valve aetiology: 100% native Delivery approach: Myval 378/379 (>99%) transfemoral, Comparator series 376/377 (>99%) transfemoral	Primary outcome: combined safety and effectiveness endpoint at 30 days was a composite of VARC-3 defined endpoints (all-cause mortality, all stroke, bleeding types 3 and 4, AKI stages 2 to 4, major vascular complications, moderate or severe prosthetic valve regurgitation, and conduction system disturbances resulting in a new PPI). *Secondary outcomes*: individual components of the primary endpoint, technical success, device success, and early safety endpoints at 30 days, as defined in VARC-3, conversion to open surgery, implantation of multiple TAVI valves, valve malposition, hospitalisation for valve-related symptoms or worsening congestive heart failure, patient-prothesis mismatch, effective orifice area, mean gradient, NYHA functional class, 6-min walk test, SF-12	Non-UK study. Number of valves used across both arms included: 336 Myval, 32 Myval Octacor, 108 Sapien 3, 87 Sapien 3 Ultra, 71 Evolut R, 106 Evolut Pro, 10 Evolut Pro+, 5 Evolut FX. Comparator arm combined balloon- and self-expanding TAVI devices. At stakeholder consultation, the Company confirmed that the generation of valves implanted in the randomised patients was at the investigator's discretion. Both intervention and comparator arms included different generation TAVI devices. EAG note 16 crossovers in the Myval arm (including 1 to Portico device), and 5 crossovers in the contemporary arm. Differences in NYHA, 6-minute walk test and SF-12 appear to compare each arm with baseline (not compared between arms).
Brown et al. (2023) Retrospective non-randomised cohort (analysis of existing database) *Funding:* Authors declared no funding received. *Declaration of interests:* one author with Medtronic.	*Intervention*: TAVI with: • Evolut Pro+ (n=278) • Sapien 3 Ultra (n=176) • Portico (Abbott Medical, n=106)	*Inclusion*: Consecutive symptomatic patients with severe aortic stenosis, at high or extreme risk for open-heart surgery, who underwent TAVI and data held within the institutional database. *Exclusion*: NR *Setting*: US (N=1)	Surgical risk: 100% deemed high or extreme risk Aortic valve aetiology: NR Delivery approach: 92.3% transfemoral	*Primary:* Mean transvalvular pressure gradients *Secondary:* in-hospital mortality, paravalvular leak, pacemaker implantation, stroke, major vascular access site complications.	Non-UK study. Includes comparison between valve expansion types; statistical differences in demographics observed between groups (age, sex, aortic valve annular size, vascular access site, implanted valve size). Short-term outcomes reported. Study conducted multivariable mixed effect modelling, however did not

Study name, design and location	Intervention(s) and comparator	Participants and setting length of follow-up	Population characteristics	Relevant outcomes	Limitations
		Recruitment period: September 2021 to October 2022. *Follow-up*: Secondary outcomes in-hospital, primary outcomes reported up to 30 days.			adjust for age which was statistically different between arms.
Buono et al. (2022) Retrospective non-randomised (with propensity matching on 26 variables) using data from the Italian ACURATE neo registry *Funding*: authors declared no funding received. *Declaration of interests*: authors declared no conflicts.	*Intervention:* ACURATE neo2 (n=220; 205 after propensity matching) *Comparator:* ACURATE neo (n=680; 205 after propensity matching) Propensity matching based on 26 variables.	*Inclusion:* consecutive patients with symptomatic severe aortic valve stenosis *Exclusion:* valve-in-valve procedures, pure aortic regurgitation, non-transfemoral *Setting:* Italy (N=13) *Recruitment period:* 01 September 2018 to 31 May 2021 *Follow-up:* 90 days	Surgical risk EuroSCORE II, median (UQR) ACURATE neo2: 3.01 (2.00 to 5.81) ACURATE neo: 3.07 (2.29 to 4.65) Aortic valve aetiology 100% native Delivery approach 100% transfemoral or transubclavian.	*Primary outcomes:* paravalvular leak (discharge) *Secondary outcomes:* Postprocedural technical success, 90-day device success, 90-day safety, and the single components of the prespecified composite endpoints. Device success was defined as the composite of technical success, freedom from mortality, freedom from surgery or intervention related to the device or to a major vascular or access-related or cardiac structural complication and intended performance of the valve (mean gradient <20 mmHg, peak velocity <3 m/s, Doppler velocity index ≤0.25, and less than moderate AR) at 90 days. The safety endpoint was defined as the composite of freedom from all-cause mortality; all stroke; Valve Academic Research Consortium types 2 to 4 bleeding; major vascular, access-related, or cardiac complication; acute kidney injury stage 3 or 4; moderate or severe AR; new permanent pacemaker because of procedure-related conduction abnormalities; and need for surgery or intervention related to the device at 90 days.	Non-UK study. Majority tricuspid (97.1% in matched arms). Differences in LVOT calcification after matching.
Cannata et al. (2023) Retrospective non-randomised cohort (with propensity score matching)	*Intervention: TAVI with:* • Sapien 3 Ultra (n=519; 496 after matching) • Sapien 3 (n=1,173; 496 after matching)	*Inclusion:* consecutive patients with symptomatic severe aortic stenosis undergoing transfemoral TAVI *Exclusion:* any patients who underwent TAVI with 29mm Sapien	Surgical risk: STS score: 4.65 Aortic valve aetiology:	*Primary outcomes:* all-cause mortality, composite (all-cause mortality, disabling stroke, repeat hospitalisation for heart failure at 1 year).	Non-UK study. Comparator arm includes historical cases. Authors acknowledge that two different delivery systems were used in the Sapien 3 Ultra which may confound results, and that

Study name, design and location	Intervention(s) and comparator	Participants and setting length of follow-up	Population characteristics	Relevant outcomes	Limitations
Funding: authors declared that Manufacturer did not have any role in data collection, analysis, manuscript drafting, and did not provide any financial support for the study. *Declaration of interests*: Multiple authors with Abbott, Boston Scientific, Medtronic, Edwards Lifesciences.	Propensity matching (1:1 nearest neighbour) where 36 variables were considered.	3, any alternative approaches other than transfemoral, those who had undergone TAVI for failed surgical aortic valve replacement (valve-in-valve), patients with bicuspid aortic stenosis. *Setting:* Italy (N=9 centres), the Netherlands (N=1), Portugal (N=1), Spain (N=1) *Recruitment period:* Sapien 3 Ultra between October 2018 and December 2020. Sapien 3 between October 2016 and December 2020. *Follow-up:* 1 year	NR (TAVI-in-SAVR excluded, but not clear if TAVI-in-TAVI included) Delivery approach: 100% transfemoral	*Secondary outcomes:* cardiac death, new pacemaker implantation, repeat procedure, all components of primary composite at 1 year. Procedural complications, clinical outcomes at 30 days. Echocardiographic outcomes at discharge and at 1 year.	residual confounding may remain (even after propensity matching).
Costa et al. (2022) Prospective non-randomised cohort, Italian national registry, inverse propensity of treatment weighting (OBSERVANT II study). *Funding*: authors declared funding from the Italian Ministry of Health (PE-2016-02364619). *Declaration of interests:* multiple authors with Boston Scientific, Edwards Lifesciences, and Medtronic.	*Intervention:* TAVI with: • Evolut R (n=1,125) • Evolut Pro (n=337) • Sapien 3 (n=768) • ACURATE neo (n=290) • Portico (n=208)	*Inclusion*: consecutive aortic stenosis patients *Exclusion*: NR *Setting*: Italy (N=28) *Recruitment period*: December 2016 to September 2018. *Follow-up*: In-hospital adverse events, echocardiogram outcomes to 30 days. Primary and secondary outcomes up to 1 year.	Surgical risk: EuroSCORE II, median (IQR) Overall 5.1 (3.1, 8.0) Evolut R: 5.0 (3.0,8.0) Evolut Pro: 5.2 (3.3, 7.6) Sapien 3: 4.8 (3.0, 7.7) ACURATE neo: 5.1 (3.0, 7.7) Portico: 5.1 (3.2, 7.7) Aortic valve aetiology: NR Delivery approach: 91.4% transfemoral.	*Primary outcomes:* composite of all cause death, stroke, and rehospitalization for HF at 1 year. *Secondary outcomes:* MI, annulus rupture, interventricular defect, cardiac tamponade, conversion o surgery, cardiogenic shock, vascular injury, post-procedural LBBB, post-procedural AF, PPI, neurological event, bleeding, AKI, ICU stay, post-procedural hospital stay, Moderate or severe paravalvular regurgitation, transvalvular mean gradient (at discharge). Individual components of the primary end point as well as PPI and MI (1 year). Outcomes were adjudicated through a linkage with administrative databases.	Non-UK study. Inverse probability treatment weighting-based multiple adjustment produced 5 treatment groups with homogeneous baseline characteristics. Authors acknowledge that unmeasured confounders (left ventricular outflow tract or leaflet calcifications and implantation height) might affect results, and that small sample size of groups was underpowered for detecting clinically relevant differences of rare outcomes between devices (such as stroke and MI). Echocardiographic data were not independently adjudicated. Absence of echocardiographic follow-up. A sensitivity analysis including only transfemoral procedures was also undertaken, confirming the outcomes obtained in the main analysis.
Eckel et al. (2023) Retrospective non-randomised cohort. *Funding:* Authors declared no funding received.	*Intervention*: TAVI with Navitor (n=137) *Comparator*: TAVI with Portico (n=139) Both arms treated with the same delivery system.	*Inclusion*: consecutive symptomatic patients with severe aortic stenosis of the native valve, undergoing transfemoral TAVI. *Exclusion*: Patients with type 0 native bicuspid valves, first-generation delivery system,	Surgical risk: - EuroSCORE median [Q1,Q3]: 13.9 [9.5,22.4] 12.1 [8.4,19.7] between arms - EuroSCORE II median [Q1,Q3]:3.7 [2.2, 6.2] 3.6 [2.1, 5.1] between arms	*Primary outcome*: technical success according to VARC-3. *Secondary outcomes*: 30-day all-cause mortality, device success at 30 days, early, safety combined endpoint at 30 days, haemodynamic	Non-UK study. Navitor arm likely to include learning curve, Portico arm likely retrospective; both may confound results.

Study name, design and location	Intervention(s) and comparator	Participants and setting length of follow-up	Population characteristics	Relevant outcomes	Limitations
Declaration of interests: multiple authors with Boston Scientific.		previous surgical aortic valve replacement, prior valvuloplasty. *Setting*: Germany multicentre (N=2, high-volume). *Recruitment period*: May 2012 to September 2022. *Follow-up*: outcomes to 30 days reported.	Aortic valve aetiology: 100% native Delivery approach: 100% transfemoral	performance, paravalvular leak, permanent pacemaker implantation, major vascular complication, stroke, AKI.	
Elkoumy et al. (2023) Retrospective single arm cohort *Funding:* Authors declared funding from Meril. Authors acknowledge Meril coordination team for data collection and MSCT Core Lab-Meril for detailed CT analysis. *Declaration of interests:* multiple authors with Abbott Medical, Boston Scientific, Medtronic, Meril, SMT.	*Intervention*: TAVI with Myval Octacor (n=103) *Comparator*: N/A	*Inclusion*: Consecutive patients with severe symptomatic aortic stenosis, who underwent TAVI with Myval Octacor. *Exclusion:* NR *Setting*: India multicentre (N=18) *Recruitment period*: July 2021 to June 2022. *Follow-up*: Post-procedural outcomes only.	Surgical risk: STS, median [Q1,Q3]: 3.5 [2.1 to 7.1] Aortic valve aetiology: 100% native Delivery approach: 100% transfemoral	Post-procedural residual aortic regurgitation, oversizing ratio.	Non-comparative, non-UK, first in human study therefore results may not be generalisable to UK NHS setting. Only 1 outcome in Scope reported and short follow-up. Included 62% with tricuspid anatomy, 37% with biscuspid anatomy, 1% unicuspid anatomy.
Elkoumy et al. (2022)	*Intervention:* TAVI with Myval (n=68) *Comparator*: N/A	*Inclusion:* confirmed bicuspid artic valve, treated with Myval. *Exclusion:* *Setting:* India (N=7), Denmark (N=2), Italy (N=2), Croatia (N=1). *Recruitment period:* Between 2018 and 2021. *Follow-up:* 30 days	Surgical risk: - STS, mean (SD): 3.5 (2.1)% Aortic valve aetiology: 100% native Delivery approach: 98.5% transfemoral	Technical success, procedural mortality, need for second valve implantation, conversion to surgery, life-threatening bleed, major vascular complications, device migration or embolisation, device success at 30 days, mortality within 30 days, new permanent pacemaker implantation, strokes, AKI, reintervention, early safety (30 days), echocardiographic outcomes (30 days)	Non-comparative, non-UK, 100% bicuspid (phenotype not collected). Short-term outcomes (to 30 days).
Forrest et al. (2020) Retrospective non-randomised cohort from STS/ACC TVT Registry. *Funding:* Authors declared funding received from Medtronic. *Declaration of interests*: multiple authors with Abbott Medical, Boston Scientific, Edwards Lifesciences, Medtronic.	*Intervention*: TAVI with: • CoreValve (n=5,514) • Evolut R (n=11,295) • Evolut Pro (n=2,065) Propensity score matching on 28 variables; with Evolut Pro as common reference (n=1,500) Note: CoreValve no longer available in US so direct comparison with Evolut R or Evolut Pro is not reported.	*Inclusion*: native tricuspid aortic valve stenosis treated with Medtronic self-expanding transcatheter aortic valves. *Exclusion*: primary aortic insufficiency, with pre-existing surgical or transcatheter valves, and with bicuspid or other non-trileaflet native aortic anatomy. Data for 31mm CoreValve and 24mm Evolut R excluded because	Surgical risk: STS, mean (SD): 8.7 (5.3), 7.7 (5.3), 6.7 (4.4) across unmatched groups Aortic valve aetiology: 100% native Delivery approach: 91.2% transfemoral	In-hospital outcomes (conversion to open heart surgery), 30-day outcomes (mortality, stroke, permanent pacemaker implantation or implantable cardioverter defibrillator, major bleeding, vascular complications, aortic valve intervention, valve-related readmission, moderate or severe regurgitation, haemodynamic performance).	Non-UK study. Results will include learning curve of new valves as introduced over time. Authors acknowledge that operator experience with TAVI not accounted for within propensity matching. The EAG note that despite propensity matching, differences in baseline use of general anaesthesia, moderate to severe aortic regurgitation, direct aortic

Study name, design and location	Intervention(s) and comparator	Participants and setting length of follow-up	Population characteristics	Relevant outcomes	Limitations
		of no equivalent Evolut Pro for comparison. *Setting*: US multicentre (N=381) *Recruitment period*: January 2014 to September 2017 (CoreValve from January 2014, Evolut R from July 2015 and Evolut Pro from March 2017). *Follow-up*: in hospital and outcomes at 30 days reported.			access, 23 mm valve size implanted, procedure time, and median length of stay were noted between devices. Exclusion of valve sizes led to bias in population (authors acknowledge higher proportion of females than general TAVI population, which may impact outcomes).
Geyer et al. (2023) Case report *Funding:* Funding source not reported. *Declaration of interests:* multiple authors with Abbott Medical, Edwards Lifesciences, JenaValve, Medtronic.	*Intervention*: TAVI with Trilogy (n=1) *Comparator*: N/A	*Participant*: 84-year-old female with symptomatic severe aortic stenosis undergoing TAVI with Trilogy device, annular calcification, and low left coronary with rather low origin (7 mm above annular plane, left coronary cusp length 10 mm, mean diameter of sinus of valsalva 28 mm), protruding supracoronary solid calcium deposit (8 mm wide) above the left coronary ostium. *Setting*: Germany (N=1) *Recruitment period*: NR. *Follow-up*: Outcomes to 30 days reported.	Surgical risk: EuroSCORE II: 11.1 Aortic valve aetiology: 100% native Delivery approach: 100% transfemoral	*Primary outcome:* haemodynamic performance, physical capacity, PVL, LVEF.	Single case report with narrative summary of outcomes (no quantitative data reported). Non-comparative, non-UK study. Short term outcomes reported. .
Giordano et al. (2024b) Retrospective non-randomized cohort. [NCT02713932] *Funding:* Authors declared funding received for Open access from Universita degli Studi di Roma La Sapienza within the CRUI-CARE Agreement. *Declaration of interests*: two authors with Abbott Medical.	*Intervention:* TAVI with Portico (n=803) *Comparator:* N/A	*Inclusion*: patients receiving Portico at participating centres, who were theoretically eligible for 3 or more years of follow-up. *Exclusion*: individuals unwilling to allow anonymized data collection. *Setting*: Europe multicentre (N=7 high volume >100 case per year); Denmark (N=1), Germany (N=2), Italy (N=3), Portugal (N=1) *Recruitment period*: included 2016, 2017, and 2018 (dates not specified) *Follow-up*: outcomes at 1 month and then minimum of 3 (mean 3.1, SD 1.5) years reported.	Surgical risk: EuroSCORE II, median [Q1,Q3]: 3.1 [2.0,5.8] Aortic valve aetiology: Not reported Delivery approach: 98.2% transfemoral	*Primary outcomes*: all-cause death and major adverse events (the composite of all-cause death, stroke, myocardial infarction, and reintervention for valve degeneration).	Non-UK study. Authors acknowledge voluntary participation of high-volume, established-expertise institutions familiar with the Portico valve, thus results should not be extrapolated without thought to centres without such experience.

Study name, design and location	Intervention(s) and comparator	Participants and setting length of follow-up	Population characteristics	Relevant outcomes	Limitations
Gozdek et al. (2023) Systematic review and meta-analysis (N=11 observational studies) *Funding:* authors declared no funding received. *Declaration of interests*: authors declared no conflicts.	*Intervention*: TAVI with Evolut Pro (n=3,439) *Comparator*: TAVI with Evolut R (n=8,924)	*Inclusion*: human studies; study or study arms directly comparing strategies for TAVI with Evolut R and Evolut Pro. *Exclusion*: in-vitro studies, single arm studies; outcomes of interest not reported. *Setting*: NR *Search dates:* until November 2022 *Follow-up*: Procedural, other short term (time point not reported), 30-day mortality reported.	Surgical risk: STS Score recorded in 6 studies, mean (SD): Evolut Pro: 6.79 (6.4) Evolut R: 7.34 (5.6) Aortic valve aetiology: NR Delivery approach: Evolut Pro: 95.5% transfemoral Evolut R: 94.1% transfemoral	Outcomes defined using VARC-2. *Procedural outcome:* more than one prosthesis used and other TAVI-related complications (pooled together: conversion to surgery, coronary obstruction, ventricular septal perforation, mitral valve apparatus damage/dysfunction, endocarditis, cardiac tamponade, prosthetic valve thrombosis or malpositioning–migration, embolization or ectopic deployment). *Functional outcomes*: moderate-to-severe PVL, mild PVL, mean transprosthetic gradient and prosthesis–patient mismatch. *Clinical outcomes:* serious bleeding (life-threatening or major), major vascular complications, cerebrovascular accident (stroke or TIA), peri-procedural MI, PPI and 30-day mortality.	Non-UK study. Baseline characteristics differed for patients' age, sex, STS–PROM risk profile, effective orifice area, and mean valve size which may confound outcomes. Studies reported short-term outcomes. Authors acknowledge that with the experience gained over the years during which the Evolut R was being implanted, some complications may have been avoided in the Evolut Pro generation. Two of the included studies constituted over 70% of the included population. However, sensitivity analyses, in which each individual study was successively excluded, and the calculation repeated in its absence, changed neither the direction nor the magnitude of the estimates.
Herrmann et al. (2024) RCT (non-inferiority) [SMART trial, NCT04722250] *Funding:* Authors declared funding from Medtronic. Authors acknowledged that the sponsor (Medtronic) developed the protocol in collaboration with the principal investigators and executive committee. Medtronic was responsible for clinical site selection, data monitoring, and statistical analyses. A steering committee provided oversight with regard to the scientific content and execution of the trial. The lead principal investigators had full access to the data and wrote the first draft of the manuscript, Employee of	*Intervention*: TAVI with: - Evolut R (n=2) - Evolut Pro (n=60) - Evolut Pro+ (n=273) - FX (n=15) *Comparator*: TAVI with - Sapien 3 (n=70) - Sapien 3 Ultra (n=295)	*Inclusion*: - Symptomatic subjects with predicted risk of operative mortality < 15% at 30 days per multidisciplinary local heart team assessment - Severe aortic stenosis, defined as: aortic valve area ≤1.0 cm2 (or aortic valve area index of ≤0.6 cm2/m2), OR mean gradient ≥40 mmHg, OR maximal aortic valve velocity ≥4.0 m/sec by transthoracic echocardiography at rest - Aortic valve annulus area ≤ 430 mm2 based on MDCT - Subject's anatomy is appropriate for both Medtronic and Edwards TAV Systems used within the conduct of the trial	Surgical risk: STS-PROM,% mean (SD): Evolut: 3.3 (1.9); Sapien: 3.2 (1.7) Aortic valve aetiology: 100% native Delivery approach: 100% transfemoral	*Primary outcomes*: Clinical outcome composite end point (12 months: mortality, disabling stroke or heart failure rehospitalisation), valve function composite end point of bioprosthetic valve dysfunction (12 months: haemodynamic structural valve dysfunction, non-structural valve dysfunction, clinical valve thrombosis, endocarditis, aortic valve intervention). *Secondary (powered) outcomes*: moderate or severe prothesis-patient mismatch (30 days) and hemodynamic mean gradient, effective orifice area, hemodynamic structural valve dysfunction, bioprosthetic valve	The study was set in 83 sites in 13 countries including 2 UK sites recruiting 1 and 35 patients respectively. Results apply to small aortic annulus and may not be generalisable to all patients undergoing TAVI with these valves. 3 cross-overs between arms.

Study name, design and location	Intervention(s) and comparator	Participants and setting length of follow-up	Population characteristics	Relevant outcomes	Limitations
Medtronic prepared earlier generations of the figures and tables and provided editorial assistance with the submitted manuscript under the direction of the first author. *Declaration of interests*: multiple authors with Abbott Medical, Boston Scientific, Edwards Lifesciences, JenaValve, Medtronic.		- Subject's anatomy is suitable for transcatheter aortic valve replacement via transfemoral vessel access - Commercial indication for transcatheter aortic valve replacement, in conformity with both local regulations and Instructions for Use (IFU) - Subject and the treating physician agree that the subject will return for all needed post-procedure follow-up visits. *Exclusion*: - Estimated life expectancy of less than 2 years - Multivessel coronary artery disease with a Syntax score >32 or unprotected left main coronary artery (Syntax score calculation is not needed for subjects with history of previous revascularization if repeat revascularization is not planned) - Participating in another trial that may influence the outcome of this trial - Need for an emergent procedure for any reason - Contraindicated for treatment with the Medtronic and Edwards TAV Systems in accordance with the Instructions for Use - Other medical, social, or psychological conditions that, in the opinion of the Investigator, preclude the subject from appropriate consent or adherence to the protocol needed follow-up exams - Pregnant, nursing or planning to be pregnant - Subject is less than legal age of consent, legally incompetent, unable to provide his/her own informed consent, or otherwise vulnerable		dysfunction in females (12 months), *Secondary (non-powered) outcomes*: device success (30 days), early safety composite (30 days), new pacemaker implantation (30 days, 1 year).	

Study name, design and location	Intervention(s) and comparator	Participants and setting length of follow-up	Population characteristics	Relevant outcomes	Limitations
		- Subject has an active COVID-19 infection or relevant history of COVID-19 - Previous aortic valve replacement *Setting:* International (N=83 sites in 13 countries): Canada (N=5), Denmark (N=1), Finland (N=1), France (N=3), Germany N=8), Israel (N=2), Italy (N=3), the Netherlands (N=2), Portugal (N=1), Spain (N=1), Switzerland (N=1), UK (N=2), US (N=53) *Recruitment period*: April 2021 to September 2022 *Follow-up*: 1 year			
Ielasi et al. (2024) Case report *Funding:* Funding source not reported. *Declaration of interests*: authors declare no conflicts.	*Intervention*: TAVI with Myval Octacor (n=1) *Comparator*: N/A	*Participant*: 83-year-old male with symptomatic severe aortic stenosis undergoing TAVI with Myval Octacor device. *Setting*: Italy (N=1) *Recruitment period*: NR. *Follow-up*: peri-procedural outcomes only reported.	Surgical risk: Not reported Aortic valve aetiology: 100% native Delivery approach: Not reported	*Primary outcomes:* PVL, commissural alignment, conduction abnormalities.	Single case report with narrative summary of outcomes (no quantitative data reported) and limited outcomes in Scope. Non-comparative, non-UK study.
Jose et al. (2024) Retrospective single arm registry (powered to detect composite outcome, combination of all-cause mortality, stroke, AKI, major vascular complications, moderate or severe PVL, new PPI at 30 days of 23.9%) *Funding:* Funded by Meril. *Declaration of interests:* multiple authors with Meril.	*Intervention:* TAVI with Myval Octacor (n=123) *Comparator:* N/A	*Inclusion:* patients with severe symptomatic native aortic stenosis, who underwent TAVI with Myval Octacor. *Exclusion:* None. *Recruitment period:* NR *Setting:* India multicentre (N=16) *Follow-up*: 30 days reported.	Surgical risk: STS, median [Q1,Q3]: 3.2 [1.8 to 5.0] Aortic valve aetiology: 100% native Delivery approach: 100% transfemoral	All-cause mortality, all stroke, AKI (stage 2 or 3 including renal replacement therapy), pacemaker implantation, PVL (moderate or severe), procedure- or valve-related hospitalization, bleeding complications (type 3 or 4), vascular or access-related complications, major cardiac structural complications, conversion to open surgery, implantation of multiple (>1) valves, valve malposition, MI, bioprosthetic valve dysfunction, technical success, device success, haemodynamic performance.	Non-comparative, non-UK study. Short term follow-up. Included 60% tricuspid, and 40% bicuspid. Potential overlap with Elkoumy et al. 2023.
Kim et al. (2022c) Retrospective non-randomised cohort.	*Intervention*: TAVI with ACURATE neo2 (n=810)	*Inclusion*: consecutive patients with severe native aortic stenosis who underwent transfemoral TAVI using	Surgical risk: EuroSCORE II median [Q1,Q3]:	*Primary outcomes:* incidence of relevant PVR (≥ moderate on echocardiography	Non-UK study. Eccentric aortic valve calcification differed

Study name, design and location	Intervention(s) and comparator	Participants and setting length of follow-up	Population characteristics	Relevant outcomes	Limitations
Funding: funding source not reported. *Declaration of interests*: multiple authors with Abbott Medical, Boston Scientific, Edwards Lifesciences, Medtronic, Meril.	*Comparator*: TAVI with ACURATE neo (n=2.055)	the ACURATE neo2 or ACURATE neo device *Exclusion*: NR *Setting*: Germany (N=2) *Recruitment period*: May 2012 to December 2021 *Follow-up*: 30 days	ACURATE neo2: 3.3 [2.2, 5.3] ACURATE neo: 3.4 [2.5, 5.2] Aortic valve aetiology: 100% Delivery approach: 100% transfemoral	at discharge), the implantation of a second valve, or surgical AV replacement for PVR ≥ moderate within 30 days of the index procedure. *Secondary outcomes:* 30-day all-cause mortality, technical success, device success at 30 days, and the early safety combined endpoint at 30 days according to VARC-3	between arms. Included 2.7% bicuspid valves. From January 2019 a protocol regarding low amounts of contrast and single arterial access was established in one centre which may confound results.
Kim et al. (2024) Prospective (post-market surveillance) single arm cohort [NCT04655248] *Funding:* Authors declared funding and sponsorship from Boston Scientific. Authors acknowledge Boston Scientific for study management, statistical analysis, and manuscript preparation. *Declaration of interests*: multiple authors with Abbott Medical, Boston Scientific, Edwards Lifesciences, JenaValve, Medtronic, Meril.	*Intervention*: TAVI with ACURATE neo2 (n=250), transfemorally. *Comparator*: N/A	*Inclusion:* patients with severe aortic stenosis. *Exclusion:* previous bioprosthesis in aortic position, chronic kidney disease stage IV or V, uncontrolled atrial fibrillation, expected to undergo chronic anticoagulation therapy after TAVI. *Setting*: Europe multicentre (N=NR); Denmark, Germany, Italy, the Netherlands, Spain, Sweden, Switzerland, UK *Recruitment period*: 16 December 2020 to 10 January 2022. *Follow-up*: Clinical outcomes to 1 year reported.	Surgical risk: - Deemed by heart team high risk: 31.2% int risk: 31.6% low risk: 37.2% - STS, mean (SD): 2.9 (2.0) - EuroSCORE II, mean (SD): 3.3 (2.8) Aortic valve aetiology: 100% native Delivery approach: 100% transfemoral	All-cause and cardiovascular mortality, stroke, major vascular complications, myocardial infarction, reintervention for valve-related dysfunction, hospitalization for valve-related symptoms or worsening congestive heart failure, major or life-threatening bleeding, newly implanted permanent pacemaker, paravalvular leak, change in NYHA functional classification, haemodynamic performance (mean valve area, mean aortic valve gradient).	Non-comparative study. Mixed population in terms of surgical risk as assessed by heart team assessment: 31.2% high; 31.6% intermediate; 37.2% low. 30-day outcomes reported in Kim et al. (2022b), which reported 1 UK participant. Study reports that the evaluation will continue annually up to 5 years.
Merdler et al. (2023) Retrospective non-randomised cohort *Funding:* Authors declared majority funded by the participating centres. Medtronic provided a research grant to support Academic Research Organization activities. Medtronic had no role in data collection, data analysis, data interpretation, or writing of the manuscript. *Declaration of interests:* two authors with Abbott Medical, Boston Scientific, Edwards Lifesciences, Medtronic.	*Intervention*: TAVI with Evolut FX (n=100; first patients to be treated with this device) *Comparator*: TAVI with Evolut Pro+ (n=100; last patients to be treated with this device)	*Inclusion*: Consecutive patients who underwent TAVI with one of the TAVI devices. *Exclusion:* NR *Setting*: US (N=1, tertiary referral) *Recruitment period*: February 2022 to August 2022 (Evolut Pro+) and August 2022 to February 2023 (Evolut FX). *Follow-up*: Outcomes reported up to 30 days.	Surgical risk: STS, mean (SD): 3.4 (2.4) Aortic valve aetiology: 95% native 5% TAVI-in-Valve Delivery approach: 95% transfemoral	*Primary*: VARC-3 definition of technical success (procedural), device success (30 days), early safety (30 days) *Secondary:* procedural duration, access-site complications, severe aortic regurgitation, valve migration, complete atrioventricular block, ventricular tachycardia or fibrillation, unplanned conversion to surgery, stroke, moderate or severe aortic regurgitation, haemodynamic changes (mean gradient, peak velocity).	Includes 4.5% valve-in-valve procedures (undefined). Evolut FX is indicated in TAVI-in-SAVR but not TAVI-in-TAVI valve-in-valve procedures, therefore the EAG are unable to define the proportion of off-label use, however remains less than threshold considered by EAG. Non-UK study. Retrospective comparator group, authors acknowledge that because of variation in operators and limited sample size that the potential presence of a learning curve was not assessed. Short-term outcomes only.

Study name, design and location	Intervention(s) and comparator	Participants and setting length of follow-up	Population characteristics	Relevant outcomes	Limitations
Moscarella et al. (2024) Retrospective non-randomised cohort *Funding:* funding source not reported. *Declaration of interests:* authors declared no conflicts.	*Intervention*: TAVI with Myval (n=58) *Comparator*: TAVI with Evolut R (n=108)	*Inclusion*: consecutive symptomatic severe native aortic stenosis. *Exclusion*: NR *Setting*: Italy (N=1) *Recruitment period*: March 2019 to March 2021. *Follow-up*: outcomes at 30 days, 1 year, and 2 years reported.	Surgical risk: Not reported Aortic valve aetiology: 100% native Delivery approach: 98.2% transfemoral	*Primary outcomes*: early device success as defined by VARC-3. 30-day, 1-year and 2-year outcomes (all-cause and cardiovascular mortality, all-cause and cardiovascular hospitalisation, NYHA class III or greater, neurological events, major bleeding, permanent pacemaker implantation, structural valve deterioration, redo procedure, moderate or severe aortic regurgitation, haemodynamic performance).	Non-UK study. Baseline patient and procedure characteristics not reported. Authors acknowledge that echocardiographic data was only available in 67% at 2 years.
Nazif et al. (2021) Retrospective non-randomised cohort from STS/ACC TVT Registry. *Funding:* Authors declared no funding received. *Declaration of interests*: multiple authors with Abbott Medical, Boston Scientific, Edwards Lifesciences, Medtronic.	*Intervention*: TAVI with Sapien 3 Ultra (n=1,324) *Comparator*: TAVI with Sapien 3 (n=32,982) Propensity score matching (1:1) based on 27 covariates including baseline characteristics, valve size, and anaesthesia type (n=1,324 pairs)	*Inclusion*: patients undergoing elective, transfemoral TAVI. *Exclusion*: prior prosthetic aortic valve, non-transfemoral arterial access, non-elective TAVI, and missing 30-day data. *Setting*: US multicentre (N=NR) *Recruitment period*: January 2019 to February 2020. *Follow-up*: in-hospital and outcomes at 30 days reported.	Surgical risk: STS, mean (SD): 4.3 (3.1), 4.6 (3.5) across unmatched groups) Aortic valve aetiology: 100% native Delivery approach: 100% transfemoral	Procedural outcomes (device success, conversion to open surgery, embolization), in-hospital (hospital and ICU length of stay, discharge location), and clinical outcomes in-hospital and 30-days (clinical, all-cause mortality, stroke, aortic valve reintervention, life-threatening bleeding, major vascular complication, new need for dialysis, new pacemaker, all-cause readmission, NYHA III and greater, KCCQ, moderate or severe paravalvular regurgitation).	Non-UK study. Authors acknowledge that pre-procedural CT data were not available reliably and therefore it was not possible to match for annular size, left ventricular outflow tract, oversizing, calcium location and burden in the analysis.
Rudolph et al. (2024) Retrospective non-randomized cohort from the German Aortic Valve Registry (propensity-score weighted analysis) *Funding:* Authors declared open access funding was enabled and organized by Projekt DEAL, and that the registry received funding from unrestricted grants from medical device companies (Edwards Lifesciences, Medtronic, Abbott Medical, Boston Scientific), the German Center for Cardiovascular	*Intervention*: TAVI with: • Sapien 3 (n=13,296) • Evolut R (n=7,028) • ACURATE neo (n=2,922) • Portico (n=878)	*Inclusion*: patients who underwent transfemoral TAVI. *Exclusion*: NR *Setting*: Germany multicentre (N=NR) *Recruitment period*: 2014 to 2019. *Follow-up*: outcomes at 30 days and 1 year reported.	Surgical risk: STS, mean (SD): 5.6 (4.4) Aortic valve aetiology: 100% native Delivery approach: 100% transfemoral	Procedural (procedural success, vascular complications, conversion to surgery, bailout valve-in-valve, intraoperative death, stroke, MI), 30-days (all-cause mortality, haemodynamic performance, paravalvular leakage), 1-year (all-cause mortality, MI, stroke, TIA, new pacemaker or implantable cardioverter defibrillator, PCI, hospitalization, reintervention)	Non-UK study. Propensity score matched adjusted logistic regression analysis used to determine average treatment effect (ACURATE neo used as reference). Propensity score matched adjusted model (based on: age, sex, STS score and LV function). The EAG note that a number of significant differences were noted between devices (for example: BMI, mean transvalvular gradient, aortic annulus diameter, hypertension,

Study name, design and location	Intervention(s) and comparator	Participants and setting length of follow-up	Population characteristics	Relevant outcomes	Limitations
Research (DZHK), the German Heart Foundation, the German Ministry of Health and donations from Dr Rolf M. Schwiete Foundation. *Declaration of interests*: multiple authors with Abbott Medical, Boston Scientific, Edwards Lifesciences, Medtronic, SMT.					renal insufficiency, frailty, previous surgery).
Russo et al. (2019) Retrospective non-randomised cohort from STS/ACC TVT Registry. *Funding:* Statistical analyses done by Edwards Lifesciences. Other funding source not reported. *Declaration of interests:* multiple authors with Abbott Medical, Boston Scientific, Edwards Lifesciences, Meril.	*Intervention*: TAVI with: • Sapien (n=18,192) • Sapien XT (n=15,530) • Sapien 3 (n=28,227)	*Inclusion*: severe aortic stenosis native valve, treated with Sapien TAVI devices. *Exclusion*: valve-in-valve procedures, emergent cases, and patients with primary aortic insufficiency or bicuspid valves. *Setting*: US multicentre (N=450) *Recruitment period*: November 2011 to January 2017. *Follow-up*: Outcomes to 30 days.	Surgical risk: STS, mean (SD): 8.4 (5.3), 8.1 (5.1), 7.6 (5.0), 7.4 (4.8) across case sequence quartiles Aortic valve aetiology: 100% native Delivery approach: 78.1% transfemoral	Only composite outcome (death or stroke) reported by device.	Non-UK study. Main aim of analysis is association of case volume and outcomes. Baseline characteristics not reported for each device separately. Significant differences in patient characteristics (for example age, sex, previous aortic valve intervention) and procedural characteristics (for example device used, valve size, valve sheath access site, type of anesthesia) over time (by case sequence quartile).
Santos-Martinez et al. (2022) Non-randomised comparative analysis of the European TAVI Registry *Funding:* Authors declared no funding received. *Declaration of interests:* multiple authors with Abbott Medical, Biosensors, Boston Scientific, Medtronic, Meril.	*Intervention*: TAVI with Myval (n=135) *Comparator*: TAVI with: • Allegra (n=103) • Evolut R or Pro (n=298), • ACURATE neo (n=180), • Sapien 3 (n=290), or • Portico (n=125)	*Inclusion*: Consecutive patients with symptomatic severe tricuspid aortic stenosis, who underwent TAVI with one of the TAVI devices. *Exclusion:* Patients with prior pacemakers, and missing ECG recordings at baseline, post-procedure or discharge excluded from ECG analysis. *Setting*: Europe multicentre (N=9); location NR *Recruitment period*: January 2017 to December 2020 *Follow-up*: Outcomes to hospital discharge only.	Surgical risk: EuroSCORE II, mean (SD): 4.6 (4.6) Aortic valve aetiology: Not reported Delivery approach: Not reported	Permanent pacemaker implantation, new onset AF.	Non-UK study. Minimal outcomes in Scope reported. Only in-hospital outcomes reported. All comparators include older generation devices with exception of Sapien 3, which has a different expansion type. Statistical analysis of each included device was done against Myval only (not between other devices). Possible overlap with Castro-Mejía et al. (2022) and Vera Vera et al. (2021) associated with authorship, setting and recruitment period.
Scotti et al. (2022) Retrospective non-randomised analysis of NEOPRO and NEOPRO-2 registries* *Funding:* Funding source not reported.	*Intervention*: TAVI with ACURATE neo2 (n=763) *Comparator*: TAVI with ACURATE neo (n=1,263)	*Inclusion*: Consecutive patients who underwent transfemoral TAVI for symptomatic, severe aortic stenosis of the native aortic valve. *Exclusion:* NR *Setting*: International multicentre (N=29; 16 in intervention arm, 18 in	Surgical risk: - STS, median [Q1,Q3]: 4.0 [2.8,5.8] - EuroSCORE II, median [Q1,Q3]: 3.9 [2.5,6.6] Aortic valve aetiology: 100% native	Procedural complications (death, valve embolisation, need for second valve, annular rupture, pericardial tamponade, aortic dissection, coronary occlusion, conversion to open heart surgery), 30-day outcomes: death, technical	Comparator arm included 2 UK sites (device not in Scope). Overlap in the intervention arm with Baggio et al. (2023); same number of patients, similar demographics. The EAG note differences in baseline characteristics (prior CABG,

Study name, design and location	Intervention(s) and comparator	Participants and setting length of follow-up	Population characteristics	Relevant outcomes	Limitations
Declaration of interests: multiple authors with Abbott Medical, Biosensors, Boston Scientific, Edwards Lifesciences, Medtronic, Meril.		comparator arm): Germany, Italy, Switzerland, Austria, Brazil, Israel, Denmark, the Netherlands, Belgium, Canada, Ireland, Spain, UK *Recruitment periods*: September 2020 to December 2021 (Intervention), January 2012 to March 2018 (Comparator) *Follow-up*: Clinical outcomes to 30 days reported, Kaplan-Meier survival estimate for all-cause mortality reported to 1 year.	Delivery approach: 100% transfemoral	success, device success, pacemaker implantation, vascular complications, bleeding complications, haemodynamic performance (mean aortic gradient, aortic valve area), moderate or severe aortic regurgitation.	eGFR, previous pacemaker, NYHA class III or IV, EuroSCORE II, STS score, LVEF, aortic valve perimeter, aortic valve calcification, left ventricular outflow tract calcification) and procedural characteristics (general anaesthesia, femoral access) between arms, which may confound results.
Seiffert et al. (2015) Retrospective, non-randomised cohort. *Funding:* Funding source not reported. *Declaration of interests*: multiple authors with JenaValve, Medtronic, Symetis.	*Intervention*: TAVI with: • Engager (Medtronic) (n=50) • JenaValve (n=88) • Symetis Acurate (n=62)	*Inclusion*: Consecutive patients who underwent transapical TAVI with Engager, JenaValve or Symetis, with severe aortic valve disease, with severe comorbidities precluding them from SAVR as determined by an interdisciplinary heart team of interventional cardiologists and cardiovascular surgeons. *Exclusion*: NR *Setting*: Germany (N=1) *Recruitment period*: March 2011 to August 2013. *Follow-up*: outcomes at 30 days and 1 year reported.	Surgical risk: - MDT considered severe comorbidities precluding SAVR - STS, mean (SD): 6.6 (5.3) - Logistic EuroSCORE, mean (SD): 20.2 (16.5) Aortic valve aetiology: 100% native Delivery approach: 0% transfemoral	Procedural (valve-in-valve, conversion to SAVR, paravalvular aortic regurgitation, mean gradient, hospital stay, MI, major stroke, major or life-threatening bleed, AKI stage 3, major access site complication, permanent pacemaker implantation, device success), 30 days (all-cause and cardiac mortality, NYHA functional class, aortic regurgitation grade) and 1 year (all-cause and cardiac mortality)	Non-UK study, all TAVI procedures undertaken using a transapical approach, approximately 50% of the cohort were part of the CE mark approval studies and included aortic disease (not specific as aortic stenosis or regurgitation), therefore results may not be generalisable to UK NHS setting.
Silaschi et al. (2016) JUPITER (post-market registry for JenaValve), retrospective, single arm cohort. [NCT01598844] *Funding:* Registry funded by JenaValve Technology. *Declaration of interests*: multiple authors with JenaValve.	*Intervention*: TAVI with JenaValve (n=180)	*Inclusion:* severe symptomatic aortic stenosis eligible for TAVI as per existing contraindications for surgery or considered high surgical risk (logistic EuroSCORE I 20% or greater, or on consensus of the heart team). *Exclusion:* unsuitable aortic annulus diameter, bicuspid aortic valve, previous SAVR, ascending aortic aneurysm, low origin of the left-main stem, evidence of thrombus, history of recent MI, concomitant coronary artery	Surgical risk: - Consensus of heart team: contraindications for surgery or considered high surgical risk - STS, mean (SD): 7.3 (6.8) - EuroSCORE, mean SD: 21.2 (14.7) - EuroSCORE II, mean SD: 7.5 (8.0) Aortic valve aetiology: 100% native Delivery approach: 0% transfemoral	Procedural (procedural success, severe paravalvular regurgitation, open SAVR, valve-in-valve, device success, hospital stay, ICU stay, haemodynamic performance), 30-day (combined safety end-point, all-case mortality, major stroke, new onset TIA, permanent pacemaker implantation, moderation paravalvular regurgitation, life-threatening or disabling bleed, major bleed, AKI stage 3, periprocedural MI, major vascular complication, repeat	Non-UK study, all TAVI procedures undertaken using a transapical approach, therefore results may not be generalisable to UK NHS setting. Authors acknowledge missing echocardiography data at 1 year, which may influence results.

Study name, design and location	Intervention(s) and comparator	Participants and setting length of follow-up	Population characteristics	Relevant outcomes	Limitations
		disease and the need for simultaneous revascularization. *Setting*: Europe multicentre (N=15); location NR *Recruitment period*: May 2012 to 2014. *Follow-up*: outcomes at 30 days and 1 year reported.		procedure for valve-related dysfunction), 1 year (all-cause mortality, moderate paravalvular regurgitation, permanent pacemaker implantation, AKI, major bleed, MI, new onset TIA, rehospitalization for valve-related symptoms or valve-related dysfunction, haemodynamic performance).	
Siqueira et al. (2021) Prospective single arm cohort *Funding:* Not reported. *Declaration of interests*: Not reported	Intervention: TAVI with ACURATE neo (n=104)	*Inclusion:* Consecutive patients with symptomatic aortic stenosis, considered inoperable or high surgical risk. Patients selected by care team. *Exclusion:* NR *Setting*: Brazil (N=1) *Recruitment period:* January 2012 to December 2018 *Follow-up:* 30 day and annual outcomes reported (median 3 years, maximum 7 years)	Surgical risk: - considered inoperable or high surgical risk deemed by heart team - STS, mean (SD): 6.0 (4.0) - EuroSCORE II, mean (SD): 6.6 (4.9) Aortic valve aetiology: Not reported Delivery approach: 97% transfemoral	Procedural (mismatch, device success, moderate or severe paravalvular aortic regurgitation), 30 day (all-cause mortality, MI, stroke, bleeding, AKI, vascular complication, new permanent pacemaker), late (mortality, stroke, MI, cardiovascular hospitalization, infection)	Non-UK and includes first in-human procedures using the ACURATE transfemoral TAVI system, therefore results may not be generalisable to UK NHS setting. The authors acknowledge that multivariate predictor of late mortality could not be identified (regression analysis was attempted with age, sex, BMI, history of syncope, previous MI, hyperlipidemia, smoking, hypertension, CCS class IV angina, previous stroke, diabetes, chronic obstructive pulmonary disease, STS and EuroSCORE II covariates).
Sondergaard et al. (2023) [NCT04011722] Prospective single arm *Funding:* No funding source reported, sponsored by Abbott Medical. *Declarations of interests:* multiple authors with Abbott Medical, Boston Scientific, Edwards Lifescience, Medtronic, Meril, SMT.	*Intervention:* TAVI with Navitor (n=120)	*Inclusion:* patients with severe symptomatic (NYHA of II or greater) aortic stenosis, heart team considered: high or extreme surgical risk. *Exclusion:* unicuspid or bicuspid native valve anatomy, or non-calcified native aortic valve, evidence of MI, any coronary or peripheral interventional procedure done within 30 days prior, gastrointestinal bleeding preventing the use of anti-thrombotic therapy, blood dyscrasias, pre-existing prosthetic heart valve, other implant in any valve position, life expectancy less than 1 year.	Surgical risk: - Heart team considered: high or extreme surgical risk. - STS, mean (SD): 4.0 (2.0) - EuroSCORE II, mean (SD): 3.6 (2.5)) Aortic valve aetiology: 100% native Delivery approach: 99.2% transfemoral	Procedural (procedural success, mortality, TAVI-in-TAVI, conversion to SAVR, length of hospital stay, haemodynamic performance, NYHA), 30-day and 1-year (composite safety endpoint, all-cause and cardiovascular mortality, neurological events, bleeding, AKI, major vascular complications, new permanent pacemaker, haemodynamic performance, NYHA)	Non-comparative study.

Study name, design and location	Intervention(s) and comparator	Participants and setting length of follow-up	Population characteristics	Relevant outcomes	Limitations
		Setting: International (N=19, including 12 US, 3 Australia, 2 UK, 1 Italy, 1 Denmark). *Recruitment period:* September 2019 and November 2020. *Follow-up:* outcomes reported at 30 day and 1 year.			
Tamm et al. (2021) Retrospective non-randomised *Funding:* Authors declared no external funding received. *Declaration of interests*: multiple authors with Abbott Medical, Edwards Lifesciences, Medtronic.	*Intervention:* TAVI with: • Sapien 3 (n=215) • Evolut R (n=144)	*Inclusion:* consecutive patients with severe degenerative aortic valve stenosis, treated via transfemoral access using new generation devices. *Exclusion:* transapical access, valve-in-valve procedure, use of other device (not Evolut R or Sapien 3). *Setting:* Germany (N=1) *Recruitment Period:* between June 2014 and May 2016. *Follow-up:* outcomes at 30 days and annually up to 5 (median 3.8) years reported.	Surgical risk: - STS, mean (SD): 7.3 (8.9) - EuroSCORE II, mean (SD): 8.0 (8.1) Aortic valve aetiology: 100% native Delivery approach: 100% transfemoral	Procedural (conversion to open heart surgery, stroke, major vascular complication, life-threatening or disabling bleeding, MI, AKI, permanent pacemaker implantation, haemodynamic performance,), 30-day (mortality, early safety, haemodynamic performance), late (all-cause mortality, haemodynamic performance).	Non-UK study. Differences in baseline characteristics (age, LVEF, aortic valve area) and procedural characteristics (prothesis size, balloon post-dilation) between arms. Study conducted multivariate analysis to determine predictor of all-cause mortality (with prothesis considered as a covariate). Authors acknowledge that choice of valve was determined by individual patient factors (including calcification of the cusps, annulus, left ventricular outflow tract, valve size, possible need for future coronary intervention or beneficial femoral access), which were not accounted for in multivariate analysis.
Tang et al. (2021) Retrospective non-randomised analysis of STS/ACC TVT Registry [NCT01737528] *Funding:* Medtronic obtained the data from the registry and funded the analysis. *Declaration of interests*: multiple authors with Abbott Medical, Boston Scientific, Edward Lifesciences, Medtronic, Meril.	TAVI with: • Evolut Pro or Pro+ (n=18,141) • Evolut R (n=14,401)	*Inclusion:* patients with native aortic stenosis *Exclusion:* patients with native aortic valve insufficiency, previous TAVI. *Setting:* US multicentre (N=NR) *Recruitment period:* Between July 2015 and March 2020 (Evolut R 23, 26, 29 mm added to registry from July 2015, 34 mm from October 2016, Evolut Pro from March 2017, Evolut Pro+ from October 2019). *Follow-up:* median (Q1,Q3) follow-up of 349 (38,382) days.	Surgical risk: STS, mean (SD): 6.2(5.0), 6.1 (4.7) across subgroups with and without prosthesis-patient mismatch Aortic valve aetiology: 100% native Delivery approach: Not reported	*Primary outcomes*: patient-prosthesis mismatch (none, moderate, severe) reported by device, 1-year all-cause mortality and valve related readmissions. *Secondary outcomes*: predictors of severe patient prosthesis mismatch and assess the severity of the mean aortic valve gradient in patients with severe patient prosthesis mismatch at 30 days and 1 year by echocardiography.	Non-UK study. Median follow-up 349 days. Baseline characteristics not reported by device; only severity of patient-prosthesis mismatch outcome reported by device post-procedure. Device not included in multivariate analysis.
Voigtländer et al. (2021) Retrospective non-randomised (with multivariable analysis)	*Intervention:* TAVI with: - Sapien 3 (n=288) - Evolut/Evolut R/Evolut Pro (n=179)	*Inclusion:* transfemoral TAVI procedures, patients with annulus area	Surgical risk: STS mean range between 4.0%-4.9% across devices.	Severe to moderate patient-prosthesis mismatch	Non-UK. Short-term outcome. Includes comparison between valve expansion types; statistical

Study name, design and location	Intervention(s) and comparator	Participants and setting length of follow-up	Population characteristics	Relevant outcomes	Limitations
Funding: authors declared Open access funding enabled and organised by Projekt DEAL. Research received no grant from any funding agency. *Declaration of interests:* Multiple authors with Abbott, Boston Scientific, Edwards Lifesciences, JenaValve, Medtronic, Meril.	- ACURATE neo (n=428) - Portico (n=110) - Lotus (n=64)	less than 400m2 as measured by MDCT. *Exclusion:* Patients with valve-in-valve procedures, treatment of predominant aortic regurgitation, procedures with non-transfemoral access routes. *Setting:* Germany (N=4) *Recruitment period:* between May 2012 and April 2019. *Follow-up:* Post-procedural	Aortic valve aetiology: 100% native Delivery approach: 100% transfemoral		differences in demographics observed between groups (coronary artery disease, chronic obstructive lung disease, diabetes, previous stroke, LVEF less than 30%, stroke volume index, annulus area, annulus perimeter, aortic valve complex calcification, left ventricular outflow tract calcification, valve size, local anaesthesia or conscious sedation, procedure time, contrast media, pre-dilatation, post-dilatation). Multivariable analysis on PPM outcome only; only age and post-dilatation of TAVI included as covariates (where p<0.05 in univariate analysis).
Wolfrum et al. (2023) Retrospective analysis (subset of the Swiss TAVI Registry) [NCT01368250] *Funding:* Funding source not reported. *Declaration of interests:* multiple authors with Abbott Medical, Biosensors, Boston Scientific, Edwards Lifesciences, Medtronic.	*Intervention*: TAVI with Allegra (n=103); all transfemoral *Comparator*: N/A	*Inclusion*: Consecutive patients with severe symptomatic aortic stenosis who underwent TAVI using the Allegra device. *Exclusion: NR* *Setting*: Switzerland (N=1) *Recruitment period*: April 2015 to March 2022 *Follow-up*: Clinical outcomes to 1 year reported, Kaplan-Meier survival estimate for all-cause and cardiovascular death reported to 3 years.	Surgical risk: EuroSCORE II, median [Q1,Q3]: 4.1 [1.8,4.2] Aortic valve aetiology: 97.1% native 2.9% TAVI-in-Valve Delivery approach: 100% transfemoral	Device success (including reporting of mechanisms of device failure), length of stay, paravalvular regurgitation, major vascular complication, major or life-threatening bleeding, all-cause mortality at 1 year and 3 years, cardiovascular mortality at 3 years.	2.9% underwent valve-in-valve procedure, TAVI-in-SAVR within CE-mark indications for this device. Non-UK study. Non-comparative study, unable to compare clinical performance of TAVI device with other devices in Scope. Possible overlap with Wolfrum et al. (2021) associated with authorship, setting and recruitment period.
Wyler von Ballmoos et al. (2021) Retrospective, single cohort [NCT02738853] *Funding:* Funded and sponsored by Medtronic. *Declaration of interests:* multiple authors with Abbott Medical, Boston Scientific, Edwards Lifesciences, Medtronic, Meril.	*Intervention*: TAVI with Evolut Pro (n=60). *Comparator*: N/A	*Inclusion:* severe symptomatic aortic stenosis and were deemed to be at high or extreme risk of early surgical mortality based on local heart team assessment, confirmed by national screening committee. *Exclusion:* NR. *Setting:* US multicentre (N=8) *Recruitment period:* June 2016 to November 2016. *Follow-up:* 30 days and 3 years reported.	Surgical risk: - Deemed to be at high or extreme risk of early surgical mortality based on local heart team assessment, confirmed by national screening committee - STS, mean (SD): STS: 6.4 (3.9) Aortic valve aetiology: 100% native Delivery approach: 100% transfemoral	*Primary outcomes*: incidence of no or trace PVR. *Secondary outcomes*: all-cause mortality, disabling stroke, quality of life and the echocardiographic assessment of transcatheter aortic valve function including mean effective orifice area (EOA) and valve gradient.	Non-UK study. Authors acknowledge small sample size chosen to demonstrate the early safety and effectiveness of the Evolut PRO valve. Because of the significant morbidities at baseline, and associated mortality during follow-up, echocardiographic data including assessment of PVR and haemodynamics was only available in 34 patients at 3 years.
Yang et al. (2023) Systematic review with network meta-analysis (N=79 studies;	*Intervention:* TAVI with: • Sapien (N=66 studies, n=54,691 patients)	*Inclusion:* patients with severe aortic stenosis, RCTs, prospective or retrospective cohort study	Surgical risk: STS, EuroSCORE II, Logistic EuroSCORE reported for	*Primary outcome:* Device success	Unclear how many studies were from UK.

Study name, design and location	Intervention(s) and comparator	Participants and setting length of follow-up	Population characteristics	Relevant outcomes	Limitations
including 5 RCTs, 74 observational of which 19 were propensity matched) [PROSPERO; CRD42021224646] *Funding:* Ministry of Science and Technology of the People's Republic of China, Clinical Incubation Program of Beijing Chaoyang Hospital *Declaration of interests:* authors declared no conflicts.	• Evolut R/Pro (N=51, n=35,339) • ACURATE (N=26, n=4,634) • Portico (N=17, n=2,001) • Lotus (N=22, n=2,610) • DFM (N=9, n=450)	design, sample size greater than 30, study comparing the in-hospital or 30day outcomes among new generation TAVI devices (Evolut R, Evolut Pro, ACURATE, Portico, Sapien 3, Lotus and DFM). *Exclusion:* patients with previous aortic valve replacement (valve-in-valve TAVI procedures), bicuspid aortic valve, pure aortic regurgitation, sample size in each treatment group less than 10, study was not comparing outcomes among the new-generation TAVI devices, outcomes of interest were not clearly reported or impossible to extract from the published results, case reports, abstracts and comments study designs, non-English language. *Setting:* NR *Literature search period:* inception of databases to 01 February 2022 *Follow-up:* 30 days for primary outcome.	included studies (where available). Aortic valve aetiology: 100% native Delivery approach: Range between 44% and 100% transfemoral across studies, with some NR.	*Secondary outcome:* mortality, stroke, major or life-threatening bleed, major vascular complications, AKI, PPI, no correct position, moderate to severe paravalvular leak, prosthesis patient mismatch, mean aortic valve gradient [definitions in line with VARC-2]	Authors acknowledge limitations: majority observational studies (confounding inherent), differences in aortic valve area, annulus diameter, annulus perimeter, annulus area, aortic angle and extent of aortic valve calcification and surgeon experience may explain heterogeneity (could not perform subgroup analysis on these because of lack of data, may modify treatment benefits), limited analysis to short term outcomes. Only discussed device related factors contributing to findings not patient related factors.
Zaid et al. (2023b) Retrospective non-randomised comparative cohort (analysis of US TAVI Registry, and institutional databases) *Funding:* Funding source not reported. *Declaration of interests:* multiple authors with Abbott Medical, Boston Scientific, Edwards Lifesciences, JenaValve, Medtronic.	*Intervention*: TAVI with Evolut FX (n=226) *Comparator*: TAVI with Evolut Pro+ (n=378)	*Inclusion*: Consecutive patients with symptomatic aortic stenosis or prosthetic aortic valve degeneration who underwent transfemoral TAVI with one of the TAVI devices. *Exclusion*: NR *Setting*: US multicentre (N=9 Evolut FX, N=1 Evolut Pro+) *Recruitment period*: 01 January 2020 to 31 December 2021 (Evolut Pro+) and 27 June 2022 to 16 September 2022 (Evolut FX) *Follow-up*: Outcomes to 30 days reported.	Surgical risk: STS, median [Q1,Q3]: 3.5 [2.2,5.6] Aortic valve aetiology: 89% native 1% TAVI-in-TAVI 10% TAVI-in-SAVR Delivery approach: 100% transfemoral	Commissural alignment, technical success, valve migration, mortality, stroke, reintervention, major vascular complication, pacemaker implantation, PVL, length of hospital stay, haemodynamic performance (mean gradient, peak gradient, aortic valve area).	First multicentre human multicentre experience of Evolut FX (used as part of the initial limited market release); learning curve. Study included 0.9% TAVI-in-TAVI procedures (off-label use), not reported exclusively. EAG considered paper as small sample and likely to reflect real-world practice. Unclear whether this indication precluded in a US setting. Study also included 9.7 TAVI-in-SAVR procedures and 4.0% in bicuspid anatomy, not reported exclusively. Comparative outcomes included commissural alignment only. Short term outcomes reported. Non-UK study.

Study name, design and location	Intervention(s) and comparator	Participants and setting length of follow-up	Population characteristics	Relevant outcomes	Limitations
					Retrospective comparator group, authors do not report possible confounders.

Key: *comparator out of Scope, treated as single arm study by EAG
Abbreviations: ACC, American College of Cardiology; AF, Atrial fibrillation; AKI, Acute Kidney Injury; AR, Aortic regurgitation; CCS, Canadian Cardiovascular Society; eGFR, Estimated glomerular filtration rate; HF, Heart failure; ICU, Intensive care unit; KCCQ, Kansas City Cardiomyopathy Questionnaire; LBBB, Left bundle branch block; LVEF, Left ventricular ejection fraction; LVOT, Left ventricular outflow; MI, Myocardial infarction; N/A, Not Applicable; NICE, National Institute for Health and Care Excellence; NIHR, National Institute for Health and Care Research; NR, Not reported; NYHA, New York Heart Association; PCI, Percutaneous coronary intervention; PP, per protocol; PPI, permanent pacemaker implantation; PVL, Paravalvular leak; PVR, Paravalvular regurgitation; Q1, Quartile 1; Q3, Quartile 3; RCT, Randomised controlled trial; SAVR, Surgical aortic valve replacement; SD, Standard deviation; STS, The Society of Thoracic Surgeons; TAVI, Transcatheter aortic valve implantation; TIA, Transient ischaemic attack; VARC-2, Valve Academic Research Consortium-2; VARC-3, Valve Academic Research Consortium-3

Appendix B2: Critical appraisal

Network meta-analysis (N=4)

Using ISPOR good research practices (Jansen et al. 2011)

Checklist Items	Dogosh et al. (2022)	Hiltner et al. (2022) [pre-print]	Takagi et al. (2019)	Yang et al. (2023)
1. Are the rationale for the study and the study objectives stated clearly?	Yes	Yes	Yes	Yes
2. Does the methods section include the following?	-	-	-	-
Description of eligibility criteria	Yes	Yes	Yes	Yes
Information sources	Yes	Yes	Yes	Yes
Study selection process	Yes	Yes	Yes	Yes
Data extraction	Yes	No	Yes	Yes
Validity (risk of bias) of individual studies	Yes	Yes	Yes	Yes
3. Are the outcome measures described?	No	Yes	Yes	Yes
4. Is there a description of methods for analysis/synthesis of evidence?	-	-	-	-
Description of analyses methods/models	Yes	Yes	Yes	Yes
Handling of potential bias/inconsistency	No	Yes	Yes	Yes
Analysis framework	Yes	Yes	Yes	Yes
5. Are sensitivity analyses presented?	Yes	No	No	Yes
6. Do the results include a summary of the studies included in the network of evidence?	-	-	-	-
Individual study data?	No	No	Yes	Yes
Network of studies?	Yes	Yes	Yes	Yes
7. Does the study describe an assessment of model fit? Are competing models being compared?	Yes	Yes	Yes	Yes
8. Are the results of the evidence synthesis presented clearly?	Yes	Yes	Yes	No
9. Are sensitivity/scenario analyses conducted?	Yes	No	No	Yes
10. Does the discussion include the following?	-	-	-	-
Description/summary of main findings	Yes	Yes	Yes	Yes
Internal validity of analysis	No	Yes	No	No
External validity	Yes	Yes	Yes	Yes
Implications of results for target audience	Yes	No	Yes	No

RCT (N=1)

Cochrane tool for assessing risk of bias (Higgins et al. 2011).

Baumbach et al. (2024)

Reviewer 1: KK, Reviewer 2: PL

Bias domain	Source of bias	Support for Judgement	Review authors' judgement (assess as low, unclear, or high risk of bias)
Selection bias	Random sequence generation	1:1 assignment using an interactive web response system. Minimisation and equal allocation were undertaken for each valve in the contemporary group. Covariate-adaptive randomised used to minimise imbalances	Low
	Allocation concealment	Open-label (physician and participant aware of treatment allocation)	High
Performance bias	Blinding of participants and personnel*	Participants not blinded. Clinical staff not blinded (not practical) however, 15/379 in Myval group had contemporary valve implanted 1 had non-protocol valve fitted, and 1 had Myval and Sapien because of suboptimal placement. 5/377 in contemporary group had Myval implanted. Masked clinical events committee adjudicated primary endpoint and composite secondary endpoints related to technical and device success (VARC-3). Statistician masked to treatment allocation.	High
Detection bias	Blinding of outcome assessment*	None	High
Attrition bias	Incomplete outcome data*	Few patients (n=6) lost to follow-up (short follow-up).	Low
Reporting bias	Selective reporting	Power calculation reported. Study protocol published. ITT and PP reported.	Low
Other bias	Anything else, ideally pre-specified.	Funded by Meril Life Sciences	High

*Assessments should be made for each main outcome or class of outcomes.
Abbreviations: ITT, intention-to-treat; PP, per protocol;

Comments: LANDMARK trial (NCT04275726; EudraCT 2020-000137-40). Non-inferiority trial. Inconsistencies in the number of each valve used (small number of Evolut Pro+ and Evolut FX), combined self- and balloon-expanding TAVI valves in

comparator arm as well as combined generations in both intervention and comparator arms. Statistical differences in mean gradient, effective orifice area, NYHA, six-minute walk test, quality of life by physical and mental health components of SF-12 for each arm with baseline (not between arms). Published protocol by Kawashima et al. (2021) states intention for 10 year follow-up.

Cohort studies (N=9)

Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Cohort Studies (Joanna Briggs Institute, 2017)

Brown et al. (2023)

Reviewer 1: KK, Reviewer 2: PL

#	Question	Yes	No	Unclear	Not applicable
1.	Were the two groups similar and recruited from the same population?	✓	-	-	-
2.	Were the exposures measured similarly to assign people to both exposed and unexposed groups?	-	-	-	✓
3.	Was the exposure measured in a valid and reliable way?	✓	-	-	-
4.	Were confounding factors identified?	✓	-	-	-
5.	Were strategies to deal with confounding factors stated?	✓	-	-	-
6.	Were the groups/participants free of the outcome at the start of the study (or the moment of exposure)?	-	-	✓	-
7.	Were the outcomes measured in a valid and reliable way?	✓	-	-	-
8.	Was the follow up time reported and sufficient to be long enough for outcomes to occur?	-	✓	-	-
9.	Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	-	-	✓	-
10.	Were strategies to address incomplete follow up utilised?	-	-	✓	-
11.	Was appropriate statistical analysis used?	-	-	✓	-

Comments: Non-UK. Conducted multivariable mixed effects model; timepoint at random effect, and TAVI device as fixed effect, while adjusting for aortic annular diameter. Unclear why multivariable modelling does not adjust for age (which was statistically different between arms).

Buono et al. (2022)

Reviewer 1: KK, Reviewer 2: PL

#	Question	Yes	No	Unclear	Not applicable
1.	Were the two groups similar and recruited from the same population?	✓	-	-	-
2.	Were the exposures measured similarly to assign people to both exposed and unexposed groups?	-	-	-	✓
3.	Was the exposure measured in a valid and reliable way?	✓	-	-	-
4.	Were confounding factors identified?	✓	-	-	-
5.	Were strategies to deal with confounding factors stated?	✓	-	-	-

#	Question	Yes	No	Unclear	Not applicable
6.	Were the groups/participants free of the outcome at the start of the study (or the moment of exposure)?	✓	-	-	-
7.	Were the outcomes measured in a valid and reliable way?	✓	-	-	-
8.	Was the follow up time reported and sufficient to be long enough for outcomes to occur?	-	✓	-	-
9.	Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	✓	-	-	-
10.	Were strategies to address incomplete follow up utilised?	-	✓	-	-
11.	Was appropriate statistical analysis used?	-	✓	-	-

Comments: Applied propensity matching using 26 variables; statistical difference in annular calcification and Left Ventricular Outflow Tract calcification observed post-matching. Additional stratification by valve size. No correction for multiple hypothesis testing. Power calculation reported in methods; appears powered to detect 10% reduction in moderate or severe PVL.

Cannata et al. (2023)

Reviewer 1: KK, Reviewer 2: PL

#	Question	Yes	No	Unclear	Not applicable
1.	Were the two groups similar and recruited from the same population?	-	✓	-	-
2.	Were the exposures measured similarly to assign people to both exposed and unexposed groups?	-	-	-	✓
3.	Was the exposure measured in a valid and reliable way?	✓	-	-	-
4.	Were confounding factors identified?	✓	-	-	-
5.	Were strategies to deal with confounding factors stated?	✓	-	-	-
6.	Were the groups/participants free of the outcome at the start of the study (or the moment of exposure)?	-	-	✓	-
7.	Were the outcomes measured in a valid and reliable way?	✓	-	-	-
8.	Was the follow up time reported and sufficient to be long enough for outcomes to occur?	-	✓	-	-
9.	Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	-	-	✓	-
10.	Were strategies to address incomplete follow up utilised?	-	✓	-	-
11.	Was appropriate statistical analysis used?	✓	-	-	-

Comments: Non-UK. Historical cases included in the comparator arm. Risk of adverse events at 1 year compared using Cox proportional hazards regression and Kaplan Meier analysis. SAPIEN 3 Ultra Delivery System was issued with a class I recall by the U.S. Food and Drug Administration (FDA). Following the recall, the S3U THV was implanted with the same delivery system used for the S3 THV (Commander Delivery System and eSheath; Edwards Lifesciences) – unclear how many were affected by this the recall impacts those who used the system from 3 Jan 2019, recall posted 21 Aug 2019 and ended 15 Sept 2020.

Costa et al. (2022)

Reviewer 1: KK, Reviewer 2: PL

#	Question	Yes	No	Unclear	Not applicable
1.	Were the two groups similar and recruited from the same population?	✓	-	-	-
2.	Were the exposures measured similarly to assign people to both exposed and unexposed groups?	-	-	-	✓
3.	Was the exposure measured in a valid and reliable way?	✓	-	-	-
4.	Were confounding factors identified?	✓	-	-	-
5.	Were strategies to deal with confounding factors stated?	✓	-	-	-
6.	Were the groups/participants free of the outcome at the start of the study (or the moment of exposure)?	-	-	✓	-
7.	Were the outcomes measured in a valid and reliable way?	✓	-	-	-
8.	Was the follow up time reported and sufficient to be long enough for outcomes to occur?	✓	-	-	-
9.	Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	-	✓	-	-
10.	Were strategies to address incomplete follow up utilised?	✓	-	-	-
11.	Was appropriate statistical analysis used?	✓	-	-	-

Comments: Used inverse propensity of treatment weighting (using package in R); characteristics appear similar across groups (authors acknowledge left ventricular outflow tract, leaflet calcification, implantation height as additional unmeasured confounders which could not be adjusted for). Used Cox proportional hazards model; HR reported. Death, stroke, Heart Failure reported to 1 year. Sensitivity analysis included only transfemoral procedures.

Forrest et al. (2020)

Reviewer 1: RP, Reviewer 2: KK

#	Question	Yes	No	Unclear	Not applicable
1.	Were the two groups similar and recruited from the same population?	-	-	✓	-

#	Question	Yes	No	Unclear	Not applicable
2.	Were the exposures measured similarly to assign people to both exposed and unexposed groups?	-	-	-	✓
3.	Was the exposure measured in a valid and reliable way?	✓	-	-	-
4.	Were confounding factors identified?	✓	-	-	-
5.	Were strategies to deal with confounding factors stated?	✓	-	-	-
6.	Were the groups/participants free of the outcome at the start of the study (or the moment of exposure)?	✓	-	-	-
7.	Were the outcomes measured in a valid and reliable way?	-	-	✓	-
8.	Was the follow up time reported and sufficient to be long enough for outcomes to occur?	-	✓	-	-
9.	Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	✓	-	-	-
10.	Were strategies to address incomplete follow up utilised?	-	-	-	✓
11.	Was appropriate statistical analysis used?	-	✓	-	-

Comments: Unclear whether all centres recruited patients to all arms of the study, large number of recruiting centres (N=381) across the US so may have minimal impact. Propensity score matching used to adjust for confounders. Outcomes only reported to 30 days from registry (assume part of routine follow-up). No correction for multiple hypothesis testing.

Kim et al. (2022c)

Reviewer 1: KK, Reviewer 2: PL

#	Question	Yes	No	Unclear	Not applicable
1.	Were the two groups similar and recruited from the same population?	✓	-	-	-
2.	Were the exposures measured similarly to assign people to both exposed and unexposed groups?	-	-	-	✓
3.	Was the exposure measured in a valid and reliable way?	✓	-	-	-
4.	Were confounding factors identified?	✓	-	-	-
5.	Were strategies to deal with confounding factors stated?	-	✓	-	-
6.	Were the groups/participants free of the outcome at the start of the study (or the moment of exposure)?	✓	-	-	-
7.	Were the outcomes measured in a valid and reliable way?	-	-	✓	-

#	Question	Yes	No	Unclear	Not applicable
8.	Was the follow up time reported and sufficient to be long enough for outcomes to occur?	-	✓	-	-
9.	Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	-	-	✓	-
10.	Were strategies to address incomplete follow up utilised?	-	-	✓	-
11.	Was appropriate statistical analysis used?	✓	-	-	-

Comments: Change in protocol for some patients regarding contrast agent and single arterial access; unclear in how many patients, no adjustment. 30 day outcomes only. Outcomes collected from outpatient visits, telephone interview or recent medical reports; potential reliance on patient recall. Conducted multivariate logistic regression.

Nazif et al. (2021)

Reviewer 1: RP, Reviewer 2: KK

#	Question	Yes	No	Unclear	Not applicable
1.	Were the two groups similar and recruited from the same population?	✓	-	-	-
2.	Were the exposures measured similarly to assign people to both exposed and unexposed groups?	-	-	-	✓
3.	Was the exposure measured in a valid and reliable way?	✓	-	-	-
4.	Were confounding factors identified?	✓	-	-	-
5.	Were strategies to deal with confounding factors stated?	✓	-	-	-
6.	Were the groups/participants free of the outcome at the start of the study (or the moment of exposure)?	-	-	✓	-
7.	Were the outcomes measured in a valid and reliable way?	-	-	✓	-
8.	Was the follow up time reported and sufficient to be long enough for outcomes to occur?	-	✓	-	-
9.	Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	✓	-	-	-
10.	Were strategies to address incomplete follow up utilised?	-	-	-	✓
11.	Was appropriate statistical analysis used?	-	✓	-	-

Comments: Propensity score matching used to adjust for confounders. Unclear whether centres recruited to both arms during the same time periods (arms

represent subsequent iterations of a TAVI device). Outcomes only reported to 30 days. No correction for multiple hypothesis testing.

Rudolph et al. (2024)

Reviewer 1: RP, Reviewer 2: KK

#	Question	Yes	No	Unclear	Not applicable
1.	Were the two groups similar and recruited from the same population?	✓	-	-	-
2.	Were the exposures measured similarly to assign people to both exposed and unexposed groups?	-	-	-	✓
3.	Was the exposure measured in a valid and reliable way?	✓	-	-	-
4.	Were confounding factors identified?	-	-	✓	-
5.	Were strategies to deal with confounding factors stated?	✓	-	-	-
6.	Were the groups/participants free of the outcome at the start of the study (or the moment of exposure)?	-	-	✓	-
7.	Were the outcomes measured in a valid and reliable way?	✓	-	-	-
8.	Was the follow up time reported and sufficient to be long enough for outcomes to occur?	✓	-	-	-
9.	Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	✓	-	-	-
10.	Were strategies to address incomplete follow up utilised?	-	-	✓	-
11.	Was appropriate statistical analysis used?	-	✓	-	-

Comments: Propensity score model from boosted logistic regression analysis, however differences in baseline characteristics remain. No correction for multiple hypothesis testing. Cox proportional hazard analysis undertaken (95%CI not reported).

Voigtländer et al. (2021)

Reviewer 1: KK, Reviewer 2: PL

#	Question	Yes	No	Unclear	Not applicable
1.	Were the two groups similar and recruited from the same population?	✓	-	-	-
2.	Were the exposures measured similarly to assign people to both exposed and unexposed groups?	-	-	-	✓
3.	Was the exposure measured in a valid and reliable way?	✓	-	-	-
4.	Were confounding factors identified?	✓	-	-	-

#	Question	Yes	No	Unclear	Not applicable
5.	Were strategies to deal with confounding factors stated?	✓	-	-	-
6.	Were the groups/participants free of the outcome at the start of the study (or the moment of exposure)?	✓	-	-	-
7.	Were the outcomes measured in a valid and reliable way?	✓	-	-	-
8.	Was the follow up time reported and sufficient to be long enough for outcomes to occur?	-	✓	-	-
9.	Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	-	-	-	✓
10.	Were strategies to address incomplete follow up utilised?	-	-	-	✓
11.	Was appropriate statistical analysis used?	-	-	✓	-

Comments: Multivariable analysis on single outcome only (patient-prosthesis mismatch). Methods section reports that univariate results with $p<0.05$ were included in multivariable analysis, however minimal covariates reported (Figure 2).

Appendix B3: In Scope but not included as key evidence (N=58)

#	Author (year)	Country (centres, N)	Study design	Duration of follow-up	**Total no. of TAVI patients [n after matching]**	Meril (BE)	Edwards (BE)	Abbott (SE)	Biosensors (SE)	Boston Scientific (SE)	JenaValve (SE)	Medtronic (SE)	SMT (SE)
1.	Akyüz et al. (2022)	Turkey (N=1)	Prospective, single arm	30 day	**25**	Myval (n=25)	-	-	-	-	-	-	-
2.	Al-abcha et al. (2021)	NR	Systematic review and meta analysis (N=9 studies)	NR	**3,442**	-	Sapien (n=1,576)	-	-	-	-	Evolut R (n=1,866)	-
3.	Amat-Santos et al. (2023)	International (N=12)	Multicentre registry with propensity matching	30 days	**360**	Myval (n=122)	Sapien 3 (n=129)	-	-	-	-	Evolut Pro+ (n=109)	-
4.	Arslan et al. (2020)	Turkey (N=1)	Prospective, single arm	In-hospital	**9**	Myval (n=9)	-	-	-	-	-	-	-
5.	Ayhen et al. (2022)	Turkey (N=1)	Prospective case study	In-hospital	**1**	Myval (n=1)	-	-	-	-	-	-	-
6.	Baggio et al. (2023)	International multicentre (N=20); Germany, Italy, Switzerland, Austria, Brazil, Israel, Denmark, the Netherlands, Belgium, Canada, Ireland, Spain	Retrospective non-randomised analysis of NEOPRO02 Registry	30 days	**2,175 [904]**	-	-	-	-	ACURATE neo2 (n=763)	-	Evolut Pro/Pro+ (n=1,412)	-
7.	Bajwa et al. (2023) †	US (N=69)	Survey study	N/A	**539**	-	-	-	-	-	-	Evolut FX (n=539 physicians)	-
8.	Barki et al. (2022)	Italy (N=1)	Italian EVAL registry	6 months	**166**	Myval (n=58)	-	-	-	-	-	Evolut R (n=108)	-
9.	Barki et al. (2023) †	Italy (N=13)	Italian ACURATE neo registry	30 days	**407**	-	-	-	-	ACURATE neo (n=300); ACURATE neo2 (n=107)	-	-	-
10.	Bieliauskas et al. (2021)	Denmark (N=1)	Non-randomised	Hospital discharge	**60**	-	-	Portico (n=20)	-	ACURATE neo2 (n=20)	-	Evolut Pro/R (n=20*)	-
11.	Castro-Mejía et al. (2022)†	Spain (N=5)	Non-randomised	Hospital discharge	**344**	-	-	Portico (n=75)	Allegra (n=60)	ACURATE neo (n=79)	-	Evolut Pro/R (n=130*)	-

#	Author (year)	Country (centres, N)	Study design	Duration of follow-up	**Total no. of TAVI patients [n after matching]**	Meril (BE)	Edwards (BE)	Abbott (SE)	Biosensors (SE)	Boston Scientific (SE)	JenaValve (SE)	Medtronic (SE)	SMT (SE)
			(European registry)										
12.	Chandra et al. (2021)†	India (N=11)	Prospective non-comparative cohort	6 months	**40**	-	-	-	-	-	-	-	Hydra (n=40)
13.	Chetcuti et al. (2023) †	US (N=23)	Survey study	N/A	**285**	-	-	-	-	-	-	Evolut FX (n=285 physicians)	-
14.	Costa et al. (2024)	Europe and US (N=15)	Retrospective non-randomised analysis of OPERA-TAVI Registry (propensity score matched)	1 year	**1,897 [1,174]**	-	Sapien 3 Ultra (n=799)	-	-	-	-	Evolut Pro/Pro+ (n=1,098)	-
15.	Delgado-Arana et al. (2022)	Europe (N=9)	Prospective non-randomised (with propensity score matching)	30 days	**206**	Myval (n=103)	Sapien 3 (n=103)	-	-	-	-	-	-
16.	Elkoumy et al. (2024)†	Europe (N=9)	European registry with propensity matching	Hospital discharge	**499 [168]**	-	-	-	-	ACURATE neo2 (n=499)	-	-	-
17.	Eltchaninoff et al. (2018)	France (N=1)	Prospective, non-randomised	Up to 8 years	**378**	-	Cribier (n=79); Sapien (n=83), Sapien XT (n=216*)	-	-	-	-	-	-
18.	García-Gómez et al. (2022)	Europe (N=9)	Single arm (European registry)	30 days	**100**	Myval (n=100)	-	-	-	-	-	-	-
19.	González-Bravo et al. (2022)	Puerto Rico (N=1)	Case report	3 days	**1**	-	-	-	-	-	-	Evolut Pro+ (n=1)	-
20.	Grubb et al. (2024)	NR	Pooled analysis from	5 years	**5,925**	-	-	-	-	-	-	Corevalve (n=4,478);	-

#	Author (year)	Country (centres, N)	Study design	Duration of follow-up	**Total no. of TAVI patients [n after matching]**	Meril (BE)	Edwards (BE)	Abbott (SE)	Biosensors (SE)	Boston Scientific (SE)	JenaValve (SE)	Medtronic (SE)	SMT (SE)
			RCTs and single arm									Evolut Pro (n=1,447*)	
21.	Halim et al. (2022)	the Netherlands (N=1)	Prospective, single arm cohort	1 year	**60**	Myval (n=60)	-	-	-	-	-	-	-
22.	Halim et al. (2023a)	the Netherlands (N=1)	Retrospective non-randomised (propensity matching)	30 days	**223 [182]**	Myval (n=120)	-	-	-	-	-	Evolut R or Pro (n=103)	-
23.	Halim et al. (2023b)	the Netherlands (N=1)	Prospective, single arm	6 months	**120**	Myval (n=120)	-	-	-	-	-	-	-
24.	Holzamer et al. (2023)	Germany, India, Italy, Poland, South Africa, Spain (N=8)	Retrospective, single arm	30 days	**10**	Myval (n=10)	-	-	-	-	-	-	-
25.	Kim et al. (2022a)	Germany (N=1)	Retrospective non-comparative cohort	30 days	**448**	-	-	-	-	ACURATE neo2 (n=448)	-	-	-
26.	Lerman et al. (2023)	International (N=2), Cyprus (N=1), France (N=1), Germany N=6), Israel (N=2), Italy (N=3), Japan (N=2), Spain (N=1), US (N=3)	Systematic review and meta-analysis (N=21; 1 RCT, 13 non-randomised, 6 propensity matched, 1 case matched)	In-hospital to 3.8 years across included studies	**35,338**	-	Sapien 3 (n=19,987)	-	-	-	-	Evolut R or Pro (n=15,351)	-
27.	Loewenstein et al. (2022)	Israel (N=4)	Retrospective non-randomised with propensity matching (Israeli national TAVR registry)	1 month	**2,486 [647]**	-	-	-	-	-	-	Corevalve (n=1,115); Evolut R (n=1,149); Evolut Pro (n=222)	
28.	Magyari et al. (2023)	Hungary (N=1)	Retrospective, single arm	1 year	**100**	Myval (n=100)	-	-	-	-	-	-	-

#	Author (year)	Country (centres, N)	Study design	Duration of follow-up	**Total no. of TAVI patients [n after matching]**	Meril (BE)	Edwards (BE)	Abbott (SE)	Biosensors (SE)	Boston Scientific (SE)	JenaValve (SE)	Medtronic (SE)	SMT (SE)
29.	Meduri et al. (2023)	Sweden (N=1)	Prospective cohort	30 days	**170**	-	-	-	-	ACURATE neo2 (n=170)	-	-	-
30.	Milan et al. (2021)	Poland (N=1)	Retrospective single arm	1 year	**27**	-	-	-	Allegra (n=27)	-	-	-	-
31.	Miura et al. (2019)	Switzerland (N=1)	Case report	Procedural	**1**	-	-	-	Allegra (n=1)	-	-	-	-
32.	Miyashita et al. (2023)	Finland (N=1)	Retrospective non-randomised with propensity matching	30 days	**449 [188]**	-	-	-	-	ACURATE neo (n=348); ACURATE neo2 (n=100)	-	-	-
33.	Möllmann et al. (2021)	Switzerland, Denmark, Germany (N=9)	Prospective single arm	1 year	**120**	-	-	-	-	ACURATE neo2 (n=120)	-	-	-
34.	Moreno et al. (2021)	Spain (multicentre, N=NR)	Retrospective single arm (Spanish Allegra valve-in-valve Registry)	30 days	**29**	-	-	-	Allegra (n=29)	-	-	-	-
35.	Mosquera et al. (2023)	Spain (N=1)	Retrospective single arm	1 month	**40**	-	-	-	-	ACURATE neo2 (n=40)	-	-	-
36.	Neuser et al. (2022)	Germany (N=1)	Retrospective single arm	3 months	**93**	-	-	-	Allegra (n=93)	-	-	-	-
37.	Nijenhuis et al. (2015)	the Netherlands (N=1)	Retrospective single arm	6 months	**24**	-	-	-	-	-	JenaValve (n=24)	-	-
38.	Nikolayevska et al. (2023)	Germany (N=1)	Retrospective non-randomised	Hospital discharge	**112**	-	Sapien, Sapien XT, Sapien 3 (n=24*)	-	Allegra (n=24)	-	-	Corevalve/EvolutR (n=64*)	-
39.	Olasińska-Wiśniewska et al. (2021)	Poland (N=1)	Case report	Immediate post-procedure only	**1**	-	-	-	-	ACURATE neo2 (n=1)	-	-	-
40.	Pellegrini et al. (2023)	Germany (N=4)	Retrospective non-randomised (with propensity	30 days	**1,356 [994]**	-	Sapien Ultra (n=748)	-	-	ACURATE neo2 (n=608)	-	-	-

#	Author (year)	Country (centres, N)	Study design	Duration of follow-up	**Total no. of TAVI patients [n after matching]**	Meril (BE)	Edwards (BE)	Abbott (SE)	Biosensors (SE)	Boston Scientific (SE)	JenaValve (SE)	Medtronic (SE)	SMT (SE)
			score matching)										
41.	Pellicano et al. (2021)	Italy (N=1)	Case report	Hospital discharge	**1**	-	-	-	-	ACURATE neo2 (n=1)	-	-	-
42.	Rao et al. (2023)	Australia (N=1)	Retrospective single arm	Procedural only	**10**	-	-	-	-	-	-	Evolut Pro+ (n=10)	-
43.	Reuthebuch et al. (2014)	Switzerland (N=1)	Prospective single arm	30 days	**27**	-	-	-	-	-	JenaValve (n=27)	-	-
44.	Rheude et al. (2024)	Germany (N=7)	Retrospective non-randomised comparative cohort	30 days	**709 [310]**	-	-	-	-	ACURATE neo2 (n=496)	-	Evolut Pro (n=213)	-
45.	Rück et al. (2021)†	Germany, Sweden (N=2)	European Registry	Hospital discharge (mortality to 30 days)	**228**	-	-	-	-	ACURATE neo (n=108); ACURATE neo2 (n=120)	-	-	-
46.	Rück et al. (2023)†	Europe (N=12)	Early Neo2 Registry, single arm	30 days	**554**	-	-	-	-	ACURATE neo2 (n=554)	-	-	-
47.	Sathananthan et al. (2021)	Canada (N=1)	Retrospective, non-randomised	Up to 10 years	**235**	-	Cribier (n=49); Sapien (n=182)	-	-	-	-	Corevalve (n=4)	-
48.	Schäfer et al. (2018)†	Germany (N=1)	Case report	2 months	**1**	-	-	-	Allegra (n=1)	-	-	-	-
49.	Schäfer et al. (2022)†	Germany (N=5)	Prospective single arm	1 year	**30**	-	-	-	Allegra (n=30)	-	-	-	-
50.	Seiffert et al. (2016)	Germany (N=2)	Retrospective, non-randomised comparative cohort	Hospital discharge	**537**	-	Sapien XT (n=254)	-	-	ACURATE neo (n=42)	JenaValve (n=62)	Engager (n=56); Corevalve (n=123)	-
51.	Sharma et al. (2020) [MyVal-1 study]	India (N=14)	Prospective, non-randomised, non-comparative cohort	1 year	**30**	Myval (n=30)	-	-	-	-	-	-	-

#	Author (year)	Country (centres, N)	Study design	Duration of follow-up	**Total no. of TAVI patients [n after matching]**	Meril (BE)	Edwards (BE)	Abbott (SE)	Biosensors (SE)	Boston Scientific (SE)	JenaValve (SE)	Medtronic (SE)	SMT (SE)
52.	Stolte et al. (2023)	Switzerland (N=1)	Case report	1 month	**1**	-	-	-	-	-	-	Evolut Pro+ (n=1)	-
53.	Tang et al. (2019)	US (N=NR)	Retrospective, non-randomised with propensity matching STS/ACC TVT Registry	30 days	**7,581 [3,626 PM]**	-	-	-	-	-	-	Corevalve (n=4,545); Evolut R (n=3,036)	-
54.	Tébar Márquez et al. (2022)	Spain (N=1)	Retrospective single arm	30 days	**8**	-	-	-	Allegra (n=8)	-	-	-	-
55.	Testa et al. (2023)	Italy (N=2)	Italian Registry SAPPHIRE	2 years	**100**	Myval (n=100)	-	-	-	-	-	-	-
56.	Thyregod et al. (2024) [NCT01057173]	Denmark, Sweden (N=3)	RCT (TAVI, SAVR)	Up to 10 years	**145**	-	-	-	-	-	-	Corevalve (n=145)	-
57.	Toggweiler et al. (2022)	Switzerland (N=1)	Prospective non-randomised comparative cohort	30 days	**60**	-	-	-	-	ACURATE neo (n=30); ACURATE neo2 (n=30)	-	-	-
58.	Toggweiler et al. (2018)	Switzerland (N=1)	Case report	Hospital discharge	**1**	-	-	-	Allegra (n=1)	-	-	-	-
59.	Trębacz et al. (2023)	Poland (N=1)	Case report	Hospital discharge	**1**	-	-	-	-	ACURATE neo2 (n=1)	-	-	-
60.	Treede et al. (2012)	Germany (N=7)	Prospective single arm	30 days	**73**	-	-	-	-	-	JenaValve (n=73)	-	-
61.	Vera Vera et al. (2021)†	Spain (N=4)	European Registry	30 days	**514**	-	-	Portico (n=88)	Allegra (n=102)	ACURATE neo (n=107)	-	Evolut R/Pro (n=217*)	-
62.	Vondran et al. (2021)	Germany (N=1)	Case report	Hospital discharge	**1**	-	-	-	Allegra (n=1)	-	-	-	-
63.	Wenaweser et al. (2016)	Switzerland, Germany (N=2)	Prospective single arm	30 days	**21**	-	-	-	Allegra (n=21)	-	-	-	-
64.	Wolfrum et al. (2021)	Switzerland, Finland, Spain, the Netherlands (N=4)	Single arm (European Registry)	30 days	**255**	-	-	-	Allegra (n=255)	-	-	-	-

#	Author (year)	Country (centres, N)	Study design	Duration of follow-up	**Total no. of TAVI patients [n after matching]**	Meril (BE)	Edwards (BE)	Abbott (SE)	Biosensors (SE)	Boston Scientific (SE)	JenaValve (SE)	Medtronic (SE)	SMT (SE)
65.	Yashige et al. (2022)	Japan (N=1)	Case report	Procedural only	**1**	-	-	-	-	-	-	Evolut Pro+ (n=1)	-

*Included other generations (not reported separately), †Overlap with other included studies
Abbreviations: BE, balloon-expanding; N/A, Not applicable; NR, Not reported; PM, propensity matched; RCT, Randomised controlled trial; SAVR, Surgical aortic valve replacement; SE, self-expanding; STS, The Society of Thoracic Surgeons; TAVI, Transcatheter aortic valve implantation

Appendix B4: Excluded studies (N=59)

#	Technology	Author (year); country †Abstract	Reasons for exclusion
1.	Trilogy (JenaValve)	Adam et al. (2023) Germany	*Population*: patients with severe symptomatic aortic regurgitation.
2.	Allegra (Biosensors)	Akodad et al. (2021) Canada, Germany	*Intervention:* Off-label use of TAVI device; TAVI-in-TAVI *Study design:* bench testing
3.	Allegra (Biosensors)	Ancona et al. (2020) Italy	*Intervention:* Off-label use of TAVI device; TAVI-in-TAVI *Population:* Aortic regurgitation
4.	Trilogy (JenaValve)	Angellotti et al. (2023) Italy	*Intervention:* transthoracic ECG following TAVI (device not specified) *Outcomes:* No outcomes reported. Narrative description of use of transthoracic ECG following TAVI
5.	Evolut FX (Medtronic)	Attizzani et al. (2023) US	*Outcomes:* Commissural and coronary alignment with post-procedural computed tomography.
6.	Trilogy (JenaValve)	Baumbach et al. (2023) UK / Germany	*Population*: patients with severe symptomatic aortic regurgitation.
7.	Evolut Pro+ (Medtronic)	Bielecki et al. (2022) US	*Intervention:* chimney stenting technique alongside TAVI. *Study design:* simulation/bench testing
8.	Trilogy (JenaValve)	Bourantas et al. (2019) UK	*Outcomes:* No outcomes reported. *Study design*: Narrative description of technological developments in TAVI
9.	Hydra (SMT)	Buono et al. (2022b) Italy	*Outcomes:* No outcomes reported. Narrative description of surgical technique for valve commissural alignment.
10.	Sapien 3 Ultra (Edwards Lifesciences)	Chatfield et al. (2021)	*Study type*: Narrative review and synthesis.
11.	Trilogy (JenaValve)	Constanzo et al. (2022) Canada, UK	*Population*: patients with severe symptomatic aortic regurgitation. *Study design:* Review
12.	Allegra (Biosensors)	Corcione et al. (2022)† Italy	*Intervention*: Limited information on group characteristics, and definition of comparator *Study design*: Abstract only
13.	Evolut Pro+ (Medtronic)	Dargan et al. (2022) UK	*Outcomes:* No outcomes in Scope reported, use of computer simulation prior to TAVI.
14.	Trilogy (JenaValve)	De Backer et al. (2018) International	*Population*: patients with severe symptomatic aortic regurgitation.
15.	Evolut Pro+ (Medtronic)	Eikelboom et al. (2022) Canada, US	*Study design:* Narrative review and synthesis.
16.	Trilogy (JenaValve)	Elbadawi et al. (2023) US	*Population*: patients with severe symptomatic aortic regurgitation.
17.	Combination	Elgendy et al. (2020)	*Intervention: mixed (results not separated by device)*
18.	Trilogy (JenaValve)	Geyer et al. (2022) Germany	*Population*: patients with severe symptomatic aortic regurgitation.

#	Technology	Author (year); country †Abstract	Reasons for exclusion
			Intervention: Off-label use of TAVI device; TAVI-in-TAVI
19.	Trilogy (JenaValve)	Goncharov et al. (2023) Germany	*Population*: patient with severe symptomatic aortic regurgitation.
20.	Trilogy (JenaValve)	Hamid et al. (2021) US	*Population*: mixed population (n=27) with patients with severe symptomatic aortic regurgitation (56%) or aortic stenosis (44%), results not reported by subgroup. *Outcomes*: No outcomes in Scope reported. *Study type*: Research correspondence letter.
21.	Allegra (Biosensors)	Hatoum et al. (2021) US	*Study design:* in-vitro or bench testing.
22.	Allegra (Biosensors)	Hatoum et al. (2022) US	*Study design:* in-vitro or bench testing.
23.	Evolut Pro+ (Medtronic)	Herrmann et al. (2022) International	*Study design*: Study protocol.
24.	Hydra (SMT)	Ielasi et al. (2023) Italy	*Population*: case report for a patient with severe symptomatic aortic regurgitation. *Outcomes:* no outcomes in Scope reported.
25.	Myval Octacor (Meril)	Kawashima et al. (2021a) International	*Study design:* Survey to determine clinical size selection. *Outcome:* No clinical outcomes reported.
26.	Myval Octacor (Meril)	Kawashima et al. (2021b) International	*Study design:* study protocol, no outcomes reported.
27.	Evolut FX (Medtronic) and Evolut Pro+ (Medtronic)	Khera et al. (2023) US	*Study type*: Research correspondence letter, full publication included (Zaid et al. 2023).
28.	ACURATE neo2 (Boston Scientific)	Kim et al. (2022b) International	*Outcomes:* 30-day outcomes from post-market surveillance study reported, 12-month outcomes included within Kim et al. (2024).
29.	Trilogy (JenaValve)	Lebehn et al. (2023) US	*Population*: patients with severe symptomatic aortic regurgitation. *Study design:* narrative review of condition and current treatment options.
30.	Combination	Myat et al. (2021)	*Intervention: mixed (results not separated by device)*
31.	Trilogy (JenaValve)	Ng et al. (2021) US	*Population*: case report for a patient with severe symptomatic aortic regurgitation. *Intervention:* not explicitly Trilogy generation of device. Editorial commentary in Inglessis-Azuaje (2021)
32.	Trilogy (JenaValve)	Noble and Mauler-Wittwer (2024) Switzerland	*Population*: patients with severe symptomatic aortic regurgitation.

#	Technology	Author (year); country †Abstract	Reasons for exclusion
			Study design: narrative review of condition and current treatment options.
33.	Evolut Pro+ (Medtronic)	Nuis et al. (2023) International	*Study design:* Study protocol.
34.	ACURATE neo2 (Boston Scientific) and Evolut Pro+ (Medtronic)	Pagnesi et al. (2023) International	*Intervention:* Results aside from pacemaker implantation not reported exclusively for devices in Scope (ACURATE neo and ACURATE neo2 compared with Evolut Pro and Evolut Pro+).
35.	Evolut FX (Medtronic)	Panagides et al. (2022) Canada	*Study type*: Narrative review and synthesis.
36.	Allegra (Biosensors)	Pighi et al. (2019) Italy	*Study design:* editorial
37.	Trilogy (JenaValve)	Poletti et al. (2023) International	*Population*: patients with severe symptomatic aortic regurgitation.
38.	Trilogy (JenaValve)	Poschner et al. (2021) Italy, Austria	*Intervention:* not explicitly Trilogy generation of device. *Study type*: Narrative review and synthesis.
39.	Myval Octacor (Meril)	Rao et al. 2021 India	*Intervention*: Devices used: Evolut R, Corevalve, Sapien 3, and Myval; outcomes not reported separately for each device.
40.	Myval Octacor (Meril)	Revaiah et al. (2023)† 	*Study design:* narrative summary of methods to achieve commissural alignment, no outcomes reported.
41.	Trilogy (JenaValve)	Rudolph and Baldus (2013) Germany	*Intervention:* not explicitly Trilogy generation of device. *Study type*: Narrative review of device.
42.	Myval Octacor (Meril)	Santos-Martínez et al. (2020) Spain	*Study design*: letter to editor (reports 2 case reports).
43.	Allegra (Biosensors)	Sathananthan et al. (2020) Canada	*Study design:* in-vitro or bench testing.
44.	Allegra (Biosensors)	Sathananthan et al. (2021) Canada	*Intervention:* Off-label use of TAVI device; TAVI-in-TAVI. *Study design:* bench testing
45.	Allegra (Biosensors)	Schäfer et al. (2019) Germany	*Outcomes:* 30-day outcomes from VIVALL study reported, 12-month outcomes included within Schäfer et al. (2022).
46.	Trilogy (JenaValve)	Schlingloff et al. (2014) Germany	*Population*: patients with severe symptomatic aortic regurgitation. *Intervention:* not explicitly Trilogy generation of device.
47.	Evolut Pro+ (Medtronic)	Scotti et al. (2023) International	*Intervention:* Results for Evolut Pro+ not reported exclusively.
48.	Allegra (Biosensors)	Sedaghat et al. (2018) Germany	*Study design:* in-vitro or bench testing.

#	Technology	Author (year); country †Abstract	Reasons for exclusion
49.	Trilogy (JenaValve)	Seiffert et al. (2014) Germany	*Population*: patients with severe symptomatic aortic regurgitation. *Intervention:* not explicitly Trilogy generation of device.
50.	Trilogy (JenaValve)	Silaschi et al. (2018) Europe	*Population*: patients with severe symptomatic aortic regurgitation.
51.	ACURATE neo2 (Boston Scientific)	Soriano et al. (2022) Italy	*Intervention:* TAVI and concomitant percutaneous coronary intervention (unable to attribute outcomes to TAVI). *Outcomes:* No outcomes in Scope reported.
52.	ACURATE neo2 (Boston Scientific)	Tarantini et al. (2022) Italy	*Outcomes:* Commissural and coronary alignment with post-procedural computed tomography.
53.	Evolut Pro+ (Medtronic)	Tsuda et al. (2023) Japan	*Outcomes:* surgical techniques described, no outcomes in Scope reported
54.	Trilogy (JenaValve)	Vahl et al. (2024) US	*Population*: patients with severe symptomatic aortic regurgitation.
55.	Trilogy (JenaValve)	Vora et al. (2023) US	*Population*: patients with severe symptomatic aortic regurgitation. *Study type*: Editorial comment.
56.	ACURATE neo2 (Boston Scientific)	Wong et al. (2021) Denmark	*Outcomes:* No outcomes in Scope reported, narrative for technical considerations.
57.	Trilogy (JenaValve)	Yokoyama et al. (2023) Germany	*Population*: case report for a patient with severe symptomatic aortic regurgitation. *Outcomes*: No outcomes in Scope reported.
58.	Trilogy (JenaValve)	Yoon et al. (2017) International	*Population*: case report for a patient with severe symptomatic aortic regurgitation. *Intervention:* not explicitly Trilogy generation of device.
59.	Evolut FX (Medtronic)	Yoon et al. (2023) US	*Outcomes:* Commissural and coronary alignment with post-procedural computed tomography. *Study type*: Research correspondence letter.

Abbreviations: ECG, Electrocardiogram; TAVI, Transcatheter aortic valve implantation

Appendix B5: Overview of systematic reviews of economic evaluations

#	Study	Azraai et al. 2020 (N=8)	Edlinger et al. 2021 (N=7)	Tam et al. 2021b (N=7)	Chotnoppharatphatthara et al. 2023 (N=29)	Ruggeri et al. 2022 (N=30*)	Heathcote et al. 2023 (N=42)	EAG comment
1.	Armeni et al. 2016	-	-	-	-	✓	-	Out of scope: MitraClip & MM
2.	Asgar et al. 2017	-	-	-	-	✓	-	Out of scope: Mitral leaflet repair heart failure
3.	Baron et al. 2019	✓	✓	-	✓	✓	✓	-
4.	Bayón et al. 2014	-	-	-	-	-	✓	-
5.	Neyt et al. 2011	-	-	-	-	✓	-	-
6.	Borisenko 2015	-	-	-	-	✓	-	Out of scope: Percutaneous mitral mitral regurgitation
7.	Brecker et al. 2014	-	-	-	✓	✓	✓	
8.	Cameron 2014	-	-	-	-	✓	-	Out of scope: MitraClip & mitral regurgitation
9.	Doble et al. 2013	-	✓	✓	✓	✓	✓	-
10.	Fagerlund et al. 2019	-	-	-	-	-	✓	-
11.	Fairbairn et al. 2013	-	✓	-	✓	✓	✓	-
12.	Ferreira-Gonzalez 2013	-	-	-	-	-	✓	-
13.	Freeman et al. 2016	-	-	-	✓	✓	-	-
14.	Gada et al. 2012a	-	-	-	✓	-	✓	-
15.	Gada et al. 2012b	-	✓	-	✓	✓	✓	-
16.	Geisler et al. 2017	✓	-	-	✓	-	✓	-
17.	Geisler et al. 2019	-	-	-	✓	-	✓	-
18.	†Gilard et al. 2021	-	-	-	-	-	✓	-
19.	Goodall et al. 2019	✓	-	-	✓	✓	✓	-
20.	Guerin 2016	-	-	-	-	✓	-	Out of scope: MitraClip & mitral regurgitation
21.	Hancock-Howard 2013	-	-	✓	✓	✓	✓	-
22.	Haute Autorite de Sante (HAS) 2017	-	-	-	-	-	✓	-
23.	†Haute Autorite de Sante (HAS) 2021a	-	-	-	-	-	✓	-
24.	†Haute Autorite de Sante (HAS) 2021b	-	-	-		-	✓	-
25.	Health Qual Ontario 2016	-	-	✓	✓	-	✓	-
26.	†Himmels 2021	-	-	-	-	-	✓	-
27.	Healthcare Improvement Scotland, 2019	-	-	-	-	-	✓	-
28.	Health Information and Quality Authority 2019	-	-	-	-	✓	✓	-
29.	†Health Technology Wales, 2020	-	-	-	-	-	✓	-
30.	†Inoue et al. 2020	-	-	-	✓	-	✓	-
31.	Kaier et al. 2019	-	-	-	-	✓	-	-
32.	Kodera et al. 2018	-	-	-	✓	✓	✓	-
33.	†Kuntjoro et al. 2020	-	-	-	✓	-	✓	-
34.	†Lorenzoni et al. 2021	-	-	-	-	-	✓	-
35.	Mealing et al. 2013	-	-	-	-	✓	-	Out of scope: Everest II Mitraclip mitral regurgitation
36.	MSAC 2016	-	-	-	-	-	✓	-
37.	Murphy et al. 2013	-	-	-	✓	✓	✓	-
38.	Neyt et al. 2012	-	✓	-	✓	✓	-	-
39.	Orlando et al. 2013	-	-	-	✓	✓	✓	-
40.	Osnabrugge 2012	✓	✓	-	-	-	-	-
41.	†Pinar 2021	-	-	-	-	-	✓	-
42.	Reynolds et al. 2012a	-	-	-	✓	✓	-	-
43.	Reynolds et al. 2012b	-	-	-	✓	✓	✓	-
44.	Reynolds et al. 2016	-	✓	-	✓	✓	✓	-
45.	Ribera et al. 2015	-	-	-	✓	✓	-	-
46.	‡Scottish HTA 2010	-	-	-	-	✓	-	-
47.	Sehatzadeh et al. 2012	-	-	✓	-	✓	✓	-
48.	Simons et al. 2013	-	-	-	✓	✓	✓	-
49.	Tam et al. 2018a	✓	-	✓	✓	-	✓	-
50.	Tam et al. 2018b	✓	-	✓	✓	✓	✓	-
51.	†Tam et al. 2021a	-	-	✓	-	-	✓	-
52.	Tarride et al. 2019	-	-	-	✓	-	✓	-

#	Study	Azraai et al. 2020 (N=8)	Edlinger et al. 2021 (N=7)	Tam et al. 2021b (N=7)	Chotnoppharatphatthara et al. 2023 (N=29)	Ruggeri et al. 2022 (N=30*)	Heathcote et al. 2023 (N=42)	EAG comment
53.	Watt et al. 2012	-	-	-	✓	✓	✓	-
54.	Zhou et al. 2019a	✓	-	-	✓	-	✓	-
55.	†Zhou et al. 2021	✓	-	-	✓	-	✓	-

Key: *1 paper duplicated (Orlando et al. 2013); ‡ paper redacted and no longer available; †economic models reviewed post 2020

Appendix B6: Economic evaluation models published after 2020 (N=11)

Study name, design; location	Intervention(s) and comparator	Trial name, surgical risk groups, time horizon and perspective of evaluation	Relevant outcomes and key findings	EAG comments
Inoue et al. 2020, Decision tree and Markov; Japan	*Intervention:* Transfemoral TAVI using SAPIEN XT *Comparator:* SAVR for high-risk patients, Standard of Care (mainly supportive care with pharmacotherapy) for inoperable patients	SOURCE XT Registry, PARTNER 1 and 2 (cohort B) High risk and inoperable *Time horizon:* Lifetime *Perspective:* Public Healthcare Payer's Perspective	QALY All-cause mortality	Initial age of patients in each analysis was set as 81 years for high risk patients, and 83 years for inoperable patients (based on selected clinical studies). The decision tree model was used for the first 2 years. The decision tree end points were: All cause death; myocardial infarction; stroke; renal failure; new pacemaker implantation; new atrial fibrillation; hospitalisation because of heart failure; and no event. The Markov model used annual cycle lengths and had two states: Survival; and all cause death.

Study name, design; location	Intervention(s) and comparator	Trial name, surgical risk groups, time horizon and perspective of evaluation	Relevant outcomes and key findings	EAG comments
Kuntjoro et al. 2020: Decision tree and Markov; Singapore	*Intervention:* Transfemoral TAVI using older BE (SAPIEN XT), latest BE (SAPIEN 3) *Comparator:* SAVR	PARTNER 2 (cohort A), PARTNER 2 S3 Low to intermediate risk *Time horizon:* 8 years *Perspective:* National University Health System perspective	Postoperative mortality rates	They considered the starting age as 82 years old (matching the average age of the PARTNER 2A trial). The life expectancy for those 82 years old is about 8 years according to the Singapore life tables, they used an 8-year time horizon, which is inappropriate as the 8 years represents median survival. A decision tree model was used for the first 30 days. The decision tree end points were: Alive without complications; acute complications; stroke; Myocardial Infarction (MI); Acute Kidney Injury (AKI); and death. The Markov model used annual cycle lengths and had five states: Alive without complications; stroke; MI; AKI; and death. Probabilities for MI, AKI and stroke in the first year and subsequent years after the first year were varied.

Study name, design; location	Intervention(s) and comparator	Trial name, surgical risk groups, time horizon and perspective of evaluation	Relevant outcomes and key findings	EAG comments
Zhou et al. 2021: Markov; Australia	*Intervention:* Latest BE (SAPIEN 3), Latest SE (Evolut) *Comparator:* SAVR	PARTNER 3, Evolut, Low risk *Time horizon:* Lifetime (maximum 100 years of age) *Perspective:* Australian Healthcare System perspective	Life years gained, mortality and stroke events	The Markov model used 30-day cycles and had four health states: Procedure; alive and well; alive with previous stroke; and dead. In the procedure state, acute complications were accounted for and included: Vascular injury; bleeding; myocardial infarction; acute kidney injury; permanent pacemaker implantation; atrial fibrillation; and paravalvular leak.
Lorenzoni et al. 2021: Markov Italy	*Intervention*: Latest BE *Comparator:* MM	PARTNER 2A Inoperable *Time horizon:* 15 years *Perspective:* Italian National Health System perspective	Life years gained, QALYs	The Markov model used 30-day cycles and had 9 health states: NYHA I; NYHA I with history of stroke; NYHA II; NYHA II with history of stroke; NYHA III; NYHA III with history of stroke; NYHA IV; NYHA IV with history of stroke; and death.

Study name, design; location	Intervention(s) and comparator	Trial name, surgical risk groups, time horizon and perspective of evaluation	Relevant outcomes and key findings	EAG comments
Pinar 2021: Markov; Spain	*Intervention:* SAPIEN 3 *Comparator:* SAVR/conservative medical treatment	PARTNER 1B Inoperable *Time horizon:* 15 years *Perspective:* Spanish National Health System perspective	Life years gained, QALYs	The Markov model used 30-day cycles and had 9 health states: NYHA I; NYHA I with history of stroke; NYHA II; NYHA II with history of stroke; NYHA III; NYHA III with history of stroke; NYHA IV; NYHA IV with history of stroke; and death.
Tam et al. 2021a: Markov; Canada	*Intervention:* Sapien 3, Evolut R, Evolut Pro *Comparator:* SAVR	PARTNER 3 and Evolut low risk trial. Low risk *Time horizon:* Lifetime *Perspective:* Third party payer's (Ministry of health and long-term care) perspective	All-cause mortality, stroke/disabling stroke, re-hospitalisation QALYs	The Markov model used 30- day cycles, and had 5 states: Procedure; Alive/Well; Disabling stroke; moderate PVL; and Dead. At the procedural state, patients were at risk of short-term complications (peri-operative death, non-disabling stroke, disabling stroke, major bleeding, major vascular complication, atrial fibrillation, new permanent pacemaker implantation, paravalvular leak >moderate, and rehospitalisation). Repeat hospitalisation was a tunnel state.

Study name, design; location	Intervention(s) and comparator	Trial name, surgical risk groups, time horizon and perspective of evaluation	Relevant outcomes and key findings	EAG comments
Gilard et al. 2022: Decision tree and Markov; France	*Intervention:* Sapien 3 *Comparator:* SAVR	PARTNER 3 low/high/intermediate risk *Time horizon:* Lifetime (30 years) *Perspective:* French National Hospital Claim database perspective	QALYs	The decision tree model was used for the first 30 days. The decision tree captured early adverse events linked to the TAVI procedure with end points: No adverse events; short term adverse events; disabling stroke; treated atrial fibrillation; and dead. Short term adverse events included new permanent pacemaker, hospitalisation, nondisabling stroke, transient ischemic attacks, myocardial infarction, bleeding, acute kidney injury with renal replacement therapy, and aortic interventions. The Markov model used 30-day cycles and had four states: Alive and well; treated atrial fibrillation; disabling stroke; and dead.
Himmels 2021: Markov; Norway	*Intervention:* TAVI (devices not specified) *Comparator:* SAVR	Systematic review of evidence Low risk *Time horizon:* 15 years *Perspective:* National Healthcare perspective	All-cause mortality QALYs	The model used 30-day cycles and had three major states: Alive and well; post major complications; and dead. However, an additional tunnel state “other complications” was also used. The major complications considered were: Stroke; acute kidney injury; and myocardial infarction. The other complications considered were: Major vascular complications; new pacemaker implantation; life threatening bleeding; paravalvular regurgitation; and new-onset atrial fibrillation.

Study name, design; location	Intervention(s) and comparator	Trial name, surgical risk groups, time horizon and perspective of evaluation	Relevant outcomes and key findings	EAG comments
Health Technology Wales, 2020: Markov; Wales	*Intervention:* Edwards Lifesciences SAPIEN, CoreValve Evolut *Comparator:* SAVR	PARTNER 2 Intermediate risk *Time horizon:* Lifetime *Perspective:* UK National Health Services and Personal Social Services perspective	QALYs	The model used 30-day cycles and had three major states: Alive with no complications; disabling stroke; and dead. However, the additional state “complications” was also used as a one-off event where patients transitioned for one cycle before returning to the “alive with no complications” health state. The complications considered were: Transient ischemic attack; non-disabling stroke; myocardial infarction; major vascular complication; life threatening or disabling bleeding; acute kidney injury (Stage III); new atrial fibrillation; new permanent pacemaker; endocarditis; aortic valve re-intervention; coronary obstruction; disabling stroke; and death from any cause.

Study name, design; location	Intervention(s) and comparator	Trial name, surgical risk groups, time horizon and perspective of evaluation	Relevant outcomes and key findings	EAG comments
Haute Autorite de Sante 2021a: Decision tree, Markov; France	*Unknown*	*Unknown*	*Unknown*	The document was in French, therefore only the model structure was checked. However, this publication appears the same as Gilard et al. 2022. The decision tree model was used for the first 30 days. The decision tree captured early adverse events linked to the TAVI procedure with end points: No adverse events; short term adverse events; disabling stroke; treated atrial fibrillation; and dead. Short term adverse events included: New permanent pacemaker; hospitalisation; non-disabling stroke; transient ischemic attacks; myocardial infarction; bleeding; acute kidney injury with renal replacement therapy; and aortic interventions. The Markov model used 30-day cycles and had four states: Alive and well; disabling stroke; atrial fibrillation; and dead.
Haute Autorite de Sante 2021b: Markov; France	*Unknown*	*Unknown*	*Unknown*	The document was in French, therefore only the model structure was checked. The Markov model used 30-day cycles and had four states: No stroke; stroke; post stroke; and death.

Abbreviations: AKI, Acute Kidney Injury; BE, Balloon expanding; EAG, External Assessment Group; MI, Myocardial infarction; MM, Medical Management; NYHA, New York Heart Association; QALY, Quality-adjusted life year; SAVR, Surgical aortic valve replacement; TAVI, Transcatheter aortic valve implantation

Appendix C: UK TAVI Registry

Appendix C1: Cohort definition

Data field [data field reference number]	Additional notes
Cohort Definition Inclusion: • All procedures within UK TAVI Registry with a procedure date [7.010] between 01 April 2021 to 31 March 2023. • including aortic stenosis valve pathology [6.060=0.Stenosis], or mean gradient >40 mmHg [6.014], or aortic valve area <1.0 cm2 [6.030]. Exclusion: • Valve manufacturer [7.130] and valve model [7.140] both unknown or missing. • Invalid combination of valve manufacturer [7.130] and valve model [7.140] • Older generation of device (Centera) not listed in NICE Final Scope • missing confirmation of successful/unsuccessful deployment [8.010=9.Unknown AND 8.021=99.Unknown]	Aortic valve pathology is a multi-choice variable, therefore cohort may include patients with stenosis AND regurgitation. Definition of aortic stenosis from (American College of Cardiology/American Heart Association; ACC/AHA 2006). The Registry Clinical Lead advised that the older generation devices being selected are a likely consequence of local data systems not updating their TAVI device selection to newer valves.
Subgroups TAVI in native aortic valve: • Previous TAVI [4.023]=”0. No” or empty AND date of previous TAVI [4.024] empty • Previous cardiac surgery [4.010] is empty OR does not include “2. Previous valve surgery” TAVI-in-TAVI: • Previous TAVI [4.023]=”1. Yes” OR date of previous TAVI [4.024] is not empty Note: Time between TAVI procedures will be calculated [4.024-7.010] TAVI-in-SAVR: • Previous cardiac surgery [4.010] includes “2. Previous valve surgery” • Previous TAVI [4.023]=”0. No” or empty AND date of previous TAVI [4.024] empty	EAG note that previous valve surgery may not be specific to aortic valve (for example may include mitral valves). Therefore results from this subgroup should be interpreted with caution.

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; EAG, External Assessment Group; NICE, National Institute for Health and Care Excellence; SAVR, Surgical aortic valve replacement; TAVI, Transcatheter aortic valve implantation

Appendix C2: Cleaning

UK TAVI Registry data field cleaning

Data field [Data field reference]	Available options	Cleaning rule
Age (years) [calculated by NICOR]	Continuous variable, calculated by NICOR using date of birth and date of procedure.	No cleaning applied
Sex [1.070]	0. Not known 1. Male 2. Female	Patient is male: Option 1 = TRUE Option 2 = FALSE Option 0 = NA
Ethnic origin [1.080]	[Blank] 1. White 2. Black 3. Asian 4. Chinese 8. Other 9. Unknown	No cleaning applied
Diabetes [3.010]	[Blank] 0. Not Diabetic 1. Diabetes (dietary control) 2. Diabetes (oral medicine) 3. Diabetes (insulin) 4. Newly diagnosed diabetes 9. Unknown	Patient has diabetes: Options 1, 2, 3, 4 = TRUE Option 0 = FALSE Option 9 or [Blank] = NA
Smoking status [3.020]	[Blank] 0. Never smoked 1. Ex smoker 2. Current smoker 9. Unknown	Patient has ever smoked: Options 1, 2 = TRUE Option 0 = FALSE Option 9 or [Blank] = NA
Creatinine (micromol per L) [3.030]	Continuous variable	According to NICOR data specification, entries less than 0.1 and greater than 1,050 reclassified as NA.
On dialysis [3.041]	[Blank] 0. No 1. Yes 9. Unknown	Patient is on dialysis: Option 1 = TRUE Option 0 = FALSE Option 9 or [Blank] = NA
Previous MI and interval between procedure and last MI [3.050]	[Blank] 0. No previous MI 1. MI < 6 hours 2. MI 6-24 hours 3. MI 1-30 days 4. MI 31-90 days 5. MI > 90 days	Patient has previous MI (ever): Options 1, 2, 3, 4, 5 = TRUE Option 0 = FALSE [Blank] = NA Patient has previous MI (within last 90 days): Options 1, 2, 3, 4 = TRUE Options 0, 5 = FALSE [Blank] = NA
History of pulmonary disease [3.060]	[Blank] 0. No pulmonary disease 1. Chronic Obstructive Airways Disease/emphysema 2. Asthma 3. Other significant pulmonary disease 9. Unknown	Patient has pulmonary disease: Options 1, 2, 3 = TRUE Option 0 = FALSE Option 9 or [Blank] = NA

Data field [Data field reference]	Available options	Cleaning rule
Severe liver disease [3.071]	[Blank] 0. No 1. Yes 9. Unknown	Patient has liver disease: Option 1 = TRUE Option 0 = FALSE Option 9 or [Blank] = NA
History of neurological disease [3.080]	[Blank] 0. No history of neurological disease 1. TIA or RIND 2. CVA with full recovery 3. CVA with residual deficit 4. Other history of neurological dysfunction 9. Unknown	Patient has previous stroke: Options 1, 2, 3 = TRUE Options 0, 4 = FALSE Option 9 or [Blank] = NA
Extracardiac arteriopathy [3.090]	[Blank] 0. No 1. Yes 9. Unknown	Patient has extracardiac arteriopathy: Option 1 = TRUE Option 0 = FALSE Option 9 or [Blank] = NA
Poor mobility [3.091]	[Blank] 0. No 1. Yes 9. Unknown	Patient has poor mobility: Option 1 = TRUE Option 0 = FALSE Option 9 or [Blank] = NA
Extensive calcification of ascending aorta [3.100]	[Blank] 0. No 1. Yes (grade 3 or 4 - see classification) 9. Unknown	Patient has aortic calcification: Option 1 = TRUE Option 0 = FALSE Option 9 or [Blank] = NA
Pre-operative heart rhythm [3.110]	[Blank] 0. Sinus rhythm 1. Atrial fibrillation/flutter 2. 1st degree heart block 3. RBBB 4. LBBB 5. Complete heart block 6. Paced rhythm 7. Ventricular fibrillation or ventricular tachycardia 8. Other abnormal rhythm 9. Other abnormal conduction 10. Unknown Note: multiple selections may be made	Patient has right bundle branch block (RBBB): Option 3 = TRUE Option 0, 1, 2, 4, 5, 6, 7, 8, 9 without option 3 = FALSE Option 10 or [Blank] = NA
Previous cardiac surgery [4.010]	[Blank] 0. No 1. Previous CABG 2. Previous valve operation 3. Other operation requiring opening of the pericardium 9. Unknown Note: multiple selections may be made	Patient has previous cardiac surgery: Options 1, 2, 3 = TRUE Option 0 = FALSE Option 9 or [Blank] = NA Patient has previous valve surgery: Option 2 = TRUE Option 0, 1, 3 without option 2 = FALSE Option 9 or [Blank] = NA Patient has previous CABG: Option 1 = TRUE

Data field [Data field reference]	Available options	Cleaning rule
		Option 0, 2, 3 without option 1 = FALSE Option 9 or [Blank] = NA
Balloon aortic valvuloplasty prior to date of TAVI [4.021]	[Blank] 0. No 1. Yes 9. Unknown	Patient has previous balloon aortic valuvuloplasty: Option 1 or date entered = TRUE Option 0 and no date entered = FALSE Option 9 or [Blank] and no date entered = NA
Date of previous balloon aortic valvuloplasty [4.022]	Date	-
Previous TAVI [4.023]	[Blank] 0. No 1. Yes 9. Unknown	Patient has previous TAVI: Option 1 or date entered = TRUE Option 0 and no date entered = FALSE Option 9 or [Blank] and no date entered = NA
Date of previous TAVI [4.024]	Date	-
Previous PCI [4.030]	[Blank] 0. No 1. Yes - previous standalone PCI (NOT as part of staged or hybrid procedure) 2. Yes - as part of a staged or hybrid procedure 9. Unknown	Patient has previous PCI: Options 1, 2 = TRUE Option 0 = FALSE Option 9 or [Blank] = NA
Height (m) [5.010]	Continuous variable	According to NICOR data specification, entries less than 1.0 reclassified as NA. Three digit entries greater than 2.44 assumed to be in centimetres, so divided by 100 to get into metres.
Weight (kg) [5.020]	Continuous variable	According to NICOR data specification, entries less than 30 and greater than 190 reclassified as NA.
Critical pre-operative status [5.031]	[Blank] 0. No 1. Yes 9. Unknown	Patient has critical pre-operative status: Option 1 = TRUE Option 0 = FALSE Option 9 or [Blank] = NA
CCS angina status (Pre-procedure; stable only) [5.040]	[Blank] 0. No angina 1. No limitation of physical activity 2. Slight limitation of ordinary activity 3. Marked limitation of ordinary physical activity 4. Symptoms at rest or minimal activity	Patient has any limitation of physical activity: Options 2, 3, 4 = TRUE Options 0, 1 = FALSE Option 9 or [Blank] = NA

Data field [Data field reference]	Available options	Cleaning rule
	9. Unknown	
NYHA dyspnoea status (Pre-procedure; stable only) [5.050]	[Blank] 1. No limitation of physical activity 2. Slight limitation of ordinary physical activity 3. Marked limitation of ordinary physical activity 4. Symptoms at rest or minimal activity 9. Unknown	Patient has NYHA dyspnoea score of 3 or 4: Options 3, 4 = TRUE Options 1, 2 = FALSE Option 9 or [Blank] = NA
CSHA Frailty Scale score [5.051]	[Blank] 1. Very fit 2. Well 3. Well - with treated comorbid disease 4. Apparently vulnerable 5. Mildly frail 6. Moderately frail 7. Severely frail 9. Unknown	Patient is moderately or severely frail: Options 6, 7 = TRUE Options 1, 2, 3, 4, 5 = FALSE Option 9 or [Blank] = NA
Katz Index of Independence in Activities of Daily Living [5.052]	0, 1, 2, 3, 4, 5, 6	According to NICOR data specification, entries outside of allowed options reclassified as NA. 0, 1, 2 = TRUE 3, 4, 5 = FALSE
Admission date for procedure (first hospital in chain if there is one) [5.060]	Date	No cleaning applied, but consistency of timeline (admission, then procedure, then discharge) checked when calculating length of stay. Length of stay not calculated where timeline was inconsistent.
PA systolic pressure measured [6.011]	[Blank] 0. Not measured 1. Yes - measured 9. Unknown	No cleaning applied
PA systolic pressure (mmHg) [6.012]	Continuous variable	According to NICOR data specification, entries less than 5 and greater than 250 reclassified as NA. As a result of poor completeness and quality, the EAG have not used this field for analysis.
Aortic valve mean gradient (mmHg) [6.014]	Continuous variable	According to NICOR data specification, entries less than 0 and greater than 200 reclassified as NA.

Data field [Data field reference]	Available options	Cleaning rule
Aortic valve peak gradient (mmHg) [6.020]	Continuous variable	According to NICOR data specification, entries less than 5 and greater than 350 reclassified as NA.
Aortic valve area (cm^2) [6.030]	Continuous variable	According to NICOR data specification, entries less than 0.1 and greater than 6 reclassified as NA.
Aortic annular diameter (mm) [6.040]	Continuous variable	According to NICOR data specification, entries less than 10 and greater than 55 reclassified as NA.
Aortic annular measurement method [6.050]	[Blank] 0. TTE 1. TOE 2. Angiographic 3. CT 4. MRI 5. Other 9. Unknown	No cleaning applied
Aortic valve pathology [6.060]	[Blank] 0. Stenosis 1. Regurgitation 9. Unknown Note: multiple selections may be made	Patient has stenosis: Option 0 with anything else = TRUE Option 1 alone = FALSE Option 9 or [Blank] = NA Patient has regurgitation: Option 1 = TRUE Option 0 without option 1 = FALSE Option 9 or [Blank] = NA
Aortic valve aetiology [6.070]	[Blank] 0. Congenital 1. Degenerative 2. Rheumatic 3. Bioprosthetic 4. Previous infective endocarditis 5. Other 9. Unknown Note: multiple selections may be made	Patient has bioprosthetic aortic valve: Option 3 = TRUE Options 0, 1, 2, 4, 5 without option 3 = FALSE Option 9 or [Blank] = NA
Mitral regurgitation [6.071]	[Blank] 0. None 1. Mild 2. Moderate 3. Severe 9. Unknown	No cleaning applied
LV function [6.080]	[Blank] 1. Good (LVEF >=50%) 2. Fair (LVEF = 30-49%) 3. Poor (LVEF <30%) 8. Not measured 9. Unknown	Patient has good LV function: Option 1 = TRUE Options 2, 3 = FALSE Options 8,9 or [Blank] = NA Patient has poor LV function: Option 3 = TRUE Options 1, 2 = FALSE

Data field [Data field reference]	Available options	Cleaning rule
		Options 8,9 or [Blank] = NA
Extent of coronary vessel disease (ignoring LMS disease which is scored in a separate field) [6.090]	[Blank] 0. No vessel with >50% diameter stenosis 1. One vessel with >50% diameter stenosis 2. Two vessels with >50% diameter stenosis 3. Three vessels with >50% diameter stenosis 9. Not investigated	Patient has any vessel with >50% stenosis: Options 1, 2, 3 = TRUE Option 0 = FALSE Option 9 or [Blank] = NA
Left main stem disease [6.100]	[Blank] 0. No LMS disease or LMS disease <= 50% diameter stenosis 1. LMS >50% diameter stenosis 9. Not known	Patient has left main stem disease: Option 1 = TRUE Option 0 = FALSE Option 9 or [Blank] = NA
Per-procedural imaging [7.050]	[Blank] 0. None 1. TTE 2. TOE 3. Other 4. ICE Note: multiple selections may be made	No cleaning applied
Procedure urgency [7.060]	[Blank] 1. Elective 2. Urgent 3. Emergency 4. Salvage	Procedure was not elective: Options 2, 3, 4 = TRUE Option 1 = FALSE [Blank] = NA
Anaesthesia (intended treatment) [7.071]	[Blank] 0. All types except for general anaesthesia 1. General anaesthesia 9. Unknown	General anaesthesia was planned: Option 1 = TRUE Option 0 = FALSE Option 9 or [Blank] = NA This field also used to derive field for whether general anaesthesia was used at all (planned or unplanned).
Unplanned conversion to general anaesthesia [7.072]	[Blank] 0. No 1. Yes 9. Unknown	Patient received unplanned general anaesthesia: Option 1 = TRUE Option 0 = FALSE Option 9 or [Blank] = NA This field also used to derive field for whether general anaesthesia was used at all (planned or unplanned).
Cerebral circulation device(s) used [7.073]	[Blank] 0. No 1. Yes 9. Unknown	Procedure used cerebral circulation device: Option 1 = TRUE Option 0 = FALSE Option 9 or [Blank] = NA

Data field [Data field reference]	Available options	Cleaning rule
Aortic balloon valvuloplasty before valve deployment [7.074]	[Blank] 0. Not done 1. Completed 2. Failed 9. Unknown	Balloon aortic valvuloplasty was attempted before valve deployment: Options 1, 2 = TRUE Option 0 = FALSE Option 9 or [Blank] = NA
Use of cardiopulmonary bypass [7.121]	[Blank] 0. No 1. Yes - elective 2. Yes - emergency 9. Unknown	Cardiopulmonary bypass used: Options 1, 2 = TRUE Option 0 = FALSE Option 9 or [Blank] = NA
Valve size [7.160]	Integer value	Cleaned according to known availability of valves from each manufacturer (Table 2). Valve sizes outside of these limits reclassified as NA: Valve size also represented as small, medium, large and so on: Edwards: 20 (S), 23 (S), 26 (M), 29 (L) Medtronic: 23 (S), 26 (M), 29 (L), 34 (L) Abbott Medical: 23 (S), 25 (M), 27 (M), 29 (L) Boston Scientific: 23 (S), 25 (M), 27 (L)
Valve manufacturer [7.130] Valve model [7.140]	-	Cleaning of valve manufacturer and model is described in 4.1.1
Device failure (refers to valve only) [7.170]	[Blank] 0. No failure 1. Probably iatrogenic 2. Probably intrinsic 9. Unknown	Valve failed: Options 1, 2 = TRUE Option 0 = FALSE Option 9 or [Blank] = NA
Vascular closure technique [7.180]	[Blank] 0. Manual pressure 2. Device closure 3. Surgical closure as planned 4. Surgical closure as bail out from failed percutaneous attempt	No cleaning applied
Procedure time (mins) [7.181]	Continuous variable	On expert opinion, values of zero or less, or greater than 1440 (24 hours) reclassified as NA.
Valve successfully deployed [8.010]	[Blank] 0. No 1. Yes 9. Unknown	Valve was successfully deployed: Option 1 [8.010] or Option 0 [8.021] = TRUE Option 0 [8.010] or Options 1, 2, 3, 4, 5, 6, 7, 8, 9 [8.021] = FALSE Option 99 or [Blank] ([8.010] and [8.021]) = NA

Data field [Data field reference]	Available options	Cleaning rule
Valve not deployed successfully reason [8.021]	[Blank] 0. N/A (successful) 1. Access site complication 2. Failure to negotiate iliac vessels or aorta 3. Unable to cross aortic arch 4. Unable to cross aortic valve 5. Aborted due to vessel perforation/dissection 6. Aborted due to anticipated coronary obstruction 7. Aborted for other reason 8. Not deployed for technical reason 9. Other failure to deploy 99. Unknown	-
Post deployment aortic valve peak gradient (mmHg) [8.022]	Continuous variable	According to NICOR data specification, entries less than 0 and greater than 350 reclassified as NA.
Post deployment aortic valve mean gradient (mmHg) [8.023]	Continuous variable	According to NICOR data specification, entries less than 5 and greater than 350 reclassified as NA.
Post deployment aortic valve area (cm^2) [8.024]	Continuous variable	According to NICOR data specification, entries less than 0.1 and greater than 6 reclassified as NA.
Aortic regurgitation at end of procedure by echo or angio [8.025]	[Blank] 0. None 1. Mild 2. Moderate 3. Severe 9. Unknown	Patient has moderate or severe regurgitation: Options 2, 3 = TRUE Options 0, 1 = FALSE Option 9 or [Blank] = NA
Valve malpositioning [8.026]	[Blank] 0. None 1. Valve migration 2. Valve embolisation 3. Ectopic valve deployment 9. Unknown	Valve was malpositioned: Options 1, 2, 3 = TRUE Option 0 = FALSE Option 9 or [Blank] = NA
Bail out valve-in-valve [8.027]	[Blank] 0. No 1. Emergency during index procedure 2. Non-emergency during index procedure for suboptimal result	Bailout valve in valve for any reason: Options 1, 2 = TRUE Option 0 = FALSE [Blank] = NA
Post implantation balloon dilatation of implanted valve [8.028]	[Blank] 0. No 1. Yes 8. Not applicable 9. Unknown	Balloon dilatation was used post-implantation: Option 1 = TRUE Options 0, 8 = FALSE Option 9 or [Blank] = NA
Further valve intervention not during index procedure but before discharge [8.029]	[Blank] 0. None 1. TAVI (must complete a new procedure record) 2. Surgical AVR 3. Balloon aortic valvuloplasty	Reintervention needed before discharge: Options 1, 2, 3, 4, 5 = TRUE Option 0 = FALSE Option 9 or [Blank] = NA

Data field [Data field reference]	Available options	Cleaning rule
	4. Intervention on another valve 5. Other 9. Unknown	
Tamponade during/post procedure [8.030]	[Blank] 0. No 1. Yes - requiring surgical intervention 2. Yes - requiring percutaneous intervention	Tamponade needed: Options 1, 2 = TRUE Option 0 = FALSE [Blank] = NA
Conversion to full sternotomy during procedure for any reason [8.081]	[Blank] 0. No 1. Yes - valve surgery 2. Yes - CABG 3. Yes - Haemorrhage 4. Yes - other reason 9. Unknown	Conversion to full sternotomy needed: Options 1, 2, 3, 4 = TRUE Option 0 = FALSE Option 9 or [Blank] = NA This field also used to update whether general anaesthesia or cardiopulmonary bypass was used.
Bailout PCI [8.090]	[Blank] 0. No 1. Yes 9. Unknown	Bailout PCI needed: Option 1 = TRUE Option 0 = FALSE Option 9 or [Blank] = NA
Peri-procedural MI (< = 72 hrs after index procedure) [8.091]	[Blank] 0. No 1. Yes 9. Unknown	Patient had MI within 72 hours: Option 1 = TRUE Option 0 = FALSE Option 9 or [Blank] = NA
Permanent pacing [9.070]	[Blank] 0. No 1. Yes-pre-procedure therapeutic (including distant past) 2. Yes-pre-procedure prophylactic 3. Yes-per-procedure 4. Yes-post-procedure 9. Unknown	New pacemaker because of procedure: Options 3, 4 = TRUE Options 0, 1, 2 = FALSE Option 9 or [Blank] = NA
CVA up to Dx [9.081]	[Blank] 0. No 1. Yes Ischaemic 2. Yes Haemorraghic 3. Yes undetermined 9. Unknown	Patient had stroke before discharge: Options 1, 2, 3 = TRUE Option 0 = FALSE Option 9 or [Blank] = NA
If CVA has occurred, modified Rankin score at 90 days [9.082]	0, 1, 2, 3, 4, 5, 6	According to NICOR data specification, entries outside of allowed options reclassified as NA. 4, 5, 6 = TRUE 0, 1, 2, 3 = FALSE
Vascular access site and access related complications [9.083]	[Blank] 0. None 1. Major 2. Minor 9. Unknown	Patient had major vascular complications: Option 1 = TRUE Options 0, 2 = FALSE Option 9 or [Blank] = NA

Data field [Data field reference]	Available options	Cleaning rule
Percutaneous closure device failure [9.084]	[Blank] 0. No 1. Yes 2. Not applicable 9. Unknown	Closure device failed: Option 1 = TRUE Options 0, 2 = FALSE Option 9 or [Blank] = NA
Bleeding [9.085]	[Blank] 0. No 1. Yes - Life threatening or disabling 2. Yes - Major 3. Yes - Minor 9. Unknown	Patient had life threatening, disabling or major bleeding: Options 1, 2 = TRUE Options 0, 3 = FALSE Option 9 or [Blank] = NA
Number of units of blood transfused [9.086]	Continuous variable	According to NICOR data specification, entries less than 0 and greater than 50 reclassified as NA.
Acute Kidney Injury within 7 days of procedure [9.087]	[Blank] 0. No AKI 1. Stage 1 2. Stage 2 3. Stage 3 9. Unknown	Patient had acute stage 2 or 3 kidney injury within 7 days: Options 2, 3 = TRUE Options 0, 1 = FALSE Option 9 or [Blank] = NA
New renal replacement therapy up to discharge [9.130]	[Blank] 0. No 1. Yes 9. Unknown	Patient had new renal replacement therapy before discharge: Option 1 = TRUE Option 0 = FALSE Option 9 or [Blank] = NA
Death to hospital discharge [9.141]	[Blank] 0. No 1. Yes 9. Unknown	Patient died in hospital: Option 1 = TRUE Option 0 = FALSE Option 9 or [Blank] = NA
Discharge destination from cardiothoracic ward [10.020]	[Blank] 1. Home 2. Convalescence 3. Other hospital 4. Not applicable - patient deceased	No cleaning applied, but Option 4 used to update previous field to TRUE if it had been missing.
Date of discharge or death [10.010]	Date	No cleaning applied, but consistency of timeline (admission, then procedure, then discharge) checked when calculating length of stay. Length of stay not calculated where timeline was inconsistent.
Drugs at discharge – antithrombotic [10.031]	[Blank] 0. None 1. Warfarin 2. Dabigatran 3. Rivaroxaban 4. Apixaban 8. Other 9. Unknown	Antithrombotic drugs prescribed: Options 2, 3, 4 = NOAC Options 1, 8 = Other Option 0 = None Option 9 or [Blank] = N/A
Drugs at discharge - anti-platelet [10.032]	[Blank] 0. None 1. Aspirin 2. Clopidogrel 3. Prasugrel	Antiplatelet drugs prescribed: Options 1, 2, 3, 4, 8 = TRUE Option 0 = FALSE Option 9 or [Blank] = NA

Data field [Data field reference]	Available options	Cleaning rule
	4. Ticagrelor 8. Other 9. Unknown	

Abbreviations: AKI, Acute Kidney Injury; AVR, Aortic valve replacement; CABG, Coronary artery bypass grafting; CSHA, Canadian Study of Health and Aging; CVA, Cerebrovascular accident; EAG, External Assessment Group; ICE, Intracardiac Echocardiography; LBBB, Left bundle branch block; LMS, Left Main Stem disease; LV, Left Ventricular; LVEF, Left ventricular ejection fraction; MI, Myocardial infarction; NA, Not applicable; NICOR, National Institute for Cardiovascular Outcomes Research; NOAC, non-vitamin-K oral anticoagulants;NYHA, New York Heart Association; PA, Pulmonary Artery; PCI, prior percutaneous coronary intervention; RBBB, Right bundle branch block; RIND, Reversible ischemic neurologic deficit; TIA, Transient ischaemic attack; TOE, Transoesophageal echocardiogram; TTE, Transthoracic echocardiogram

The EAG also calculated or derived additional fields using the fields cleaned as described previously. BMI was calculated for all cases with both valid height and weight. Length of stay was calculated only in cases where the timeline was plausible. That is, the date of admission was not after the date of the procedure, and the date of the procedure was not after the date of discharge. Creatinine clearance was calculated according to the Cockcroft-Gault equation using the raw creatinine result, weight, age, and sex of the patient, only where all data items were available and valid.

Because of poor completeness or quality the EAG did not use the following data fields:

- If alive: CCS angina status 1Y [11.020], 3Y [12.020]
- If alive, NYHA dyspnoea status 1Y [11.030], 3Y [12.030]
- Late stenosis [13.012]
- Date of diagnosis of significant stenosis [13.012]
- Late intrinsic valve regurgitation (not paravalvular) [13.013]
- Date of diagnosis of clinically significant regurgitation [13.014]
- Valve failure mode [13.015]
- Late paravalvular regurgitation [13.016]
- Date of diagnosis of clinically significant paravalvular regurgitation [13.017]
- Intervention for paravalvular regurgitation [13.018]

- Date of intervention for paravalvular leak [13.019]
- EuroScore (calculated by NICOR)

Simplification of key variables for incorporation within multivariate modelling

[Note Groupings were informed by UK TAVI Registry Clinical Lead and prior published multivariate analysis of TAVI (Puls et al. 2014)]

Group	Data field	Field type
Sex	Male	Binary (Yes/No)
Age	Age, years	Continuous
Height	Height, m	Continuous
Weight	Weight, kg	Continuous
Frailty (Composite)	CSHAClinicalFrailtyPre (Mod/Severe)	Binary (Yes/No)
	KatzIndex non-independent (<6)	Binary (Yes/No)
Aortic valve mean gradient	Mean gradient, mmHg	Continuous
Annular diameter	Annular diameter, mm	Continuous
Valve size	Valve Size, mm	3 categories: Small, Medium, Large
Urgency (composite)	Critical Status Pre-procedure	Binary (Yes/No)
	Urgent, Emergency, Salvage procedure	Binary (Yes/No)
Anaesthesia	Intended general anaesthesia	Binary (Yes/No)
Severe symptoms (composite)	NYHA Dyspnoea Pre-procedure (symptoms at rest: Class 4)	Binary (Yes/No)
	CCS Angina Pre-procedure (symptoms at rest, class 4)	Binary (Yes/No)
Comorbid:LVEFpoor	Poor LVEF pre-procedure (LVEF <30%)	Binary (Yes/No)
Calcification	Extensive Aortic Calcification (grade 3 or 4)	Binary (Yes/No)
Coronary Comorbidities: Anatomical (composite)	Left main stem disease (LMS >50% diam stenosis)	Binary (Yes/No)
	Extent of coronary vessel disease (any vessel with >50% diam stenosis)	Binary (Yes/No)
Coronary Comorbidites: Clinical (composite)	Previous MI	Binary (Yes/No)
	Previous PCI	Binary (Yes/No)
	Previous CABG	Binary (Yes/No)

Group	Data field	Field type
Non-cardiac comorbidities: Clinical	Previous stroke or TIA	Binary (Yes/No)
	Extracardiac arteriopathy	Binary (Yes/No)
Non-cardiac comorbidities: Risk factors (composite)	Diabetes	Binary (Yes/No)
	Ever smoked	Binary (Yes/No)
Non-cardiac comorbidities: Renal impairment (composite)	Dialysis	Binary (Yes/No)
	Calculated creatinine clearance (<30, renal impairment)	Binary (Yes/No)

Abbreviations: CABG, Coronary artery bypass grafting; CCS, Canadian Cardiovascular Society; CSHA, Canadian Study of Health and Aging; LVEF, Left ventricular ejection fraction; MI, Myocardial Infarction; NYHA, New York Heart Association; PCI, Percutaneous Coronary Intervention; TIA, Transient ischaemic attack

Valve sizes by manufacturer

The EAG categorised valves size (mm) into categories to simplify analyses. These were based on information from manufacturer websites, and assumptions from the EAG. Extra small and small were combined into one group, and extra large and large were combined into one group.

Manufacturer	**Device**	Available valve sizes (mm)	Extra small (XS, mm)	Small (S, mm)	Medium (M, mm)	Large (L, mm)	Extra Large (XL, mm)
Edwards Lifesciences	**Sapien 3** **Sapien 3 Ultra**	20, 23, 26, 29	20	23	26	29	-
Meril UK	**Myval Octacor**	20, 21.5, 23, 24.5, 26, 27.5, 29, 30.5, 32	20, 21.5	23, 24.5	26, 27.5	29, 30.5, 32	-
Abbott	**Navitor**	23, 25, 27, 29	-	23	25, 27	29	-
Biosensors	**Allegra**	23, 27, 31	-	23	27	31	-
Boston Scientific	**ACURATE neo2**	23, 25, 27	-	23	25	27	-
JenaValve	**Trilogy**	23, 25, 27	-	23	25	27	-
Medtronic	**Evolut R** **Evolut Pro+** **Evolut FX**	23, 26, 29, 34	-	23	26	29	34
SMT	**Hydra**	22, 26, 30	-	22	26	30	-

Appendix C3: Comparison of patient characteristics by financial year

Summary of statistical comparisons between 2021/22 and 2022/23 financial years across variables which contribute to EuroSCORE II (noting pulmonary hypertension and active hypertension are not recorded within the UK TAVI Registry), unadjusted

Parameter	All TAVI Between 01 April 2021 to 31 March 2022 (n=3,286)	All TAVI Between 01 April 2022 and 31 March 2023 (n=4,123)	p-value
Age, years; median [Q1,Q3]	82.0 [77.0 to 86.0] (n=3,286)	82.0 [77.0 to 86.0] (n=4,123)	1
Male sex (%, [95%CI])	1,965/3,281 (59.9% [58.2%, 61.6%])	2,374/4,115 (57.7% [56.2%, 59.2%])	0.476
Chronic lung disease (%, [95%CI])	687/3,231 (23.1%, 22.7%])	874/4,016 (21.8% [20.5%, 23.1%])	1
Extracardiac arteriopathy (%, [95%CI])	273/3,232 (8.4% [7.5%, 9.5%])	408/3,973 (10.3% [9.4%, 11.3%])	0.096
Poor mobility (%, [95%CI])	621/659 (94.2% [92.1%, 95.8%])	705/811 (86.9% [84.4%, 89.1%])	<0.0001*
Previous cardiac surgery (%, [95%CI])	466/3,239 (14.4% [13.2%, 15.7%])	458/3,935 (11.6% [10.7%, 12.7%])	0.008*
Active endocarditis (%, [95%CI])	Not recorded in registry	Not recorded in registry	-
Critical preoperative status (%, [95%CI])	50/3,233 (1.5% [1.2%, 2.1%])	48/3,971 (1.2% [0.9%, 1.6%])	1
†Creatinine clearance, median [Q1,Q3]	55.3 [40.7 to 73.0] (n=3,003)	55.9 [41.5 to 72.8] (n=3,665)	1
Diabetes on insulin (%, [95%CI])	144/3,198 (4.5% [3.8%, 5.3%])	211/4,044 (5.2% [4.6%, 6%])	1
CCS angina class 4 (%, [95%CI])	30/3,230 (0.9% [0.6%, 1.3%])	37/3,949 (0.9% [0.7%, 1.3%])	1
LVEF not good (%, [95%CI])	2,273/3,167 (71.8% [70.2%, 73.3%])	2,996/3,983 (75.2% [73.8%, 76.5%])	0.013*
Recent MI (within 90 days) (%, [95%CI])	69/3,265 (2.1% [1.7%, 2.7%])	89/4,053 (2.2% [1.8%, 2.7%])	1
Pulmonary hypertension	Not recorded in registry	Not recorded in registry	-
NYHA class (categories 3 and 4) (%, [95%CI])	2,451/3,240 (75.6% [74.1%, 77.1%])	2,892/3,983 (72.6% [71.2%, 74%])	0.041*
Surgery on thoracic aorta	Not applicable	Not applicable	-
Non-elective operation (%, [95%CI])	870/3,275 (26.6% [25.1%, 28.1%])	994/4,114 (24.2% [22.9%, 25.5%])	0.175

†Calculated field (GP notebook, 2023): ((140 - age in years) x (wt in kg)) x 1.23) / (serum creatinine in micromol/l). For female sex multiple the result of calculation by 0.85. Note that this calculation is unreliable if the patient has unstable renal function, is very obese, or is oedematous.
*Significant when adjusting for multiple hypothesis testing using Holm-Bonferroni correction
Abbreviations: CCS, Canadian Cardiovascular Society; CI, Confidence interval; LVEF, left ventricular ejection fraction; MI, Myocardial infarction; NYHA, New York Heart Association; Q1, Quartile 1; Q3, Quartile 3; TAVI, transcatheter aortic valve implantation

Appendix C4: VARC-3 endpoints

Summary of alignment of UK TAVI Registry data fields to VARC-3 endpoints

VARC3 outcome [green=full alignment, amber=partial alignment, red=no alignment]	Outcome definition	UK TAVI Registry [Data fields reference number]
Mortality	Causes: • All-cause mortality but should be classified as cardiovascular or non-cardiovascular where possible. Timings: • Periprocedural: if within 30 days (or >30 days if the patient is still hospitalized), • Early: if within 30 days and 1 year, • Late: if beyond 1 year.	Death to hospital discharge [9.141]
Neurologic events	Categories: • Overt CNS injury (all strokes: ischaemic, haemorrhagic, stroke not otherwise specified), • Covert CNS injury (covert CNS infarction or haemorrhage) • Neurological dysfunction without CNS injury (TIA and delirium without CNS injury). Timings: • Peri-procedural or within 30 days of discharge. • Early: within 30 days and 1 year of discharge. • Late: and after 1 year of discharge	CVA up to discharge [9.081] – Note does not include TIA.
Hospitalisation (or re-hospitalisation)	Heart failure related hospitalisations including A&E attendances.	Not recorded
Bleeding and transfusions	Categories: • Type 1 (minor) • Type 2 (major) • Type 3 (life-threatening) • Type 4 (leading to death) Timings: • Peri-procedural. • Early: within 48 hours of discharge. • Late: and after 48 hours of discharge	Bleeding up to discharge [9.085; None, minor, major, life-threatening] including number of units of blood transfused [9.086]
Vascular and access-related complications	Categories: • Major • Minor	Vascular access site and access related complications up to discharge [9.083; major and minor]
Cardiac structural complications	Categories: • Major • Minor	Not recorded
Other procedural or	Conversion to open surgery OR unplanned use of mechanical circulatory support, OR implantation of	Conversion to full sternotomy during

VARC3 outcome [green=full alignment, amber=partial alignment, red=no alignment]	Outcome definition	UK TAVI Registry [Data fields reference number]
valve-related complications	multiple TAVI valves during index hospitalisation, OR valve malposition OR paravalvular regurgitation.	procedure [8.081] OR Use of cardiopulmonary bypass [7.121] OR Bail out valve-in-valve [8.027] OR Valve malpositioning [8.026] OR Aortic regurgitation at end of procedure by echo or angio [8.025; none, mild, moderate, severe]. All up to discharge
New conduction disturbances and arrhythmias	Conduction disturbances OR permanent pacemaker OR atrial fibrillation Timepoints differ across event	Permanent pacing up to discharge [9.070=4. Yes=Post-procedure]
Acute kidney injury	Categories: • Stage 1 • Stage 2 • Stage 3 • Stage 4	AKI within 7 days of procedure [9.087]; New renal replacement therapy up to discharge [9.130]
Myocardial infarction	Categories: • Type 1 • Type 2 • Type 3 • Type 4A • Type 4B • Type 5	Peri-procedural MI (< = 72 hrs after index procedure) recorded as Yes/No (type not recorded)
Bioprosthetic valve dysfunction	Including structural valve deterioration (Stages: 1, 2, 3), non-structural valve dysfunction, thrombosis, endocarditis	Not recorded
Leaflet thickening and reduced motion	Including hypo-attenuated leaflet thickening, reduced leaflet motion Timing: • Acute: within 24 hours of procedure • Subacute: between 24 hours and 30 days • Late: between 30 days and 1 year • Very late: more than 1 year	Not recorded
Clinically significant valve thrombosis	Timing: • Acute: within 24 hours of procedure • Subacute: between 24 hours and 30 days • Late: between 30 days and 1 year • Very late: more than 1 year	Not recorded
Patient reported outcomes and health status	Minnesota Living with Heart Failure Questionnaire (MLHFQ) Kansas City Cardiomyopathy Questionnaire (KCCQ or short version KCCQ-12) 36-item Short-Form Health Survey (SF-36) 12-item Short-Form Health Survey (SF-12) EuroQoL 5-Dimension (EQ-5D)	Not recorded
[Composite]	Freedom from mortality AND	Death to hospital discharge [9.141] 0. No

VARC3 outcome [green=full alignment, amber=partial alignment, red=no alignment]	Outcome definition	UK TAVI Registry [Data fields reference number]
Technical success (at exit from procedure room)	Successful access, delivery of the device and retrieval of the delivery system AND	Valve successfully deployed [8.010] 1. Yes
	Correct positioning of a single prosthetic heart valve into the proper anatomical location AND	Valve malpositioning [8.026] 0. None
	Freedom of surgery or intervention related to the device or to a major vascular or access-related or cardiac structural complication.	Bailout V-I-V [8.027] 0. No AND Further valve intervention not during index procedure but before discharge [8.029] 0. No AND Conversion to full sternotomy during procedure for any reason [8.081] 0. No AND Bailout PCI [8.09] 0. No
[Composite] Device success (at 30 days)	Technical success	As above
	Freedom from mortality	As above
	Freedom from surgery or intervention related to the device or to a major vascular or access-related or cardiac structural complication	As above
	Intended performance of the valve (aortic valve mean gradient <20 mmHg, peak velocity <3m/s,)	Post deployment aortic valve mean gradient, mmHg [8.023]
[Composite] Early safety (at 30 days)	Freedom from all-cause mortality	Outcomes post-discharge not recorded
	Freedom from all stroke	
	Freedom from VARC type 2-4 bleeding	
	Freedom from major vascular, access-related or cardiac structural complication	
	Freedom from acute kidney injury stage 3 or 4	
	Freedom from moderate or severe aortic regurgitation	
	Freedom from new permanent pacemaker due to the procedure-related conduction abnormalities	
	Freedom from surgery or intervention related to the device	
[Composite] Clinical efficacy (at 1 year and thereafter)	Freedom from all-cause mortality	Outcomes post-discharge not recorded
	Freedom from all stroke	
	Freedom from hospitalisation for procedure- or valve-related causes	
	Freedom from KCCQ overall summary score	
[Composite] Valve-related long-term clinical efficacy (at 5 years and thereafter)	Freedom from bioprosthetic valve failure	Outcomes post-discharge not recorded
	Freedom from stroke or peripheral embolism	
	Freedom from VARC type 2-4 bleeding	

Abbreviations: A&E, Accident and Emergency; AKI, Acute Kidney Injury; CNS, central nervous system; CVA, cerebrovascular accident; KCCQ, Kansas City Cardiomyopathy Questionnaire; MI, Myocardial infarction; MLHFQ, Minnesota Living with Heart Failure Questionnaire; TAVI, transcatheter aortic valve implantation; TIA, Transient ischaemic attack; VARC-3, Valve Academic Research Consortium-3; V-I-V, Valve-in-Valve

Appendix C5: Data Suitability Assessment Tool (DataSAT) for UK TAVI Registry

Reviewer: KK

Research question: to define the patient and procedural characteristics, and outcomes of a population undergoing TAVI within UK NHS setting.

Data provenance

Item	Response
Data sources	UK TAVI Registry
Data linkage and data pooling	Provided to EAG as unlinked (EAG conducted data linkage thereafter – described in Section 4.1.4).
Type of data source	Clinical health and outcome data.
Purpose of data collection	One of four structural heart intervention registries within the National Cardiac Audit Programme. The UK TAVI program was established to capture and report outcomes on TAVI procedures undertaken in the UK.
Data collection	Patient identifiers and demographics, occurrence of MDT meeting, medical history and risk factors for coronary disease, previous interventions, pre-procedure clinical status, results of cardiac investigations, procedural data, procedural outcome and complications, discharge status and destination (including medication at discharge), quality of life at follow-up (1,3 years), late events.
Care setting	Secondary care (NHS and private)
Geographical setting	32 NHS centres in England, Wales and Northern Ireland; Scotland no longer participated in the UK audit (NICOR report, 2024)
Population coverage	7669 cases in 2022/23, and 6738 in 2021/22. Estimated 114 TAVI procedures per million population in the UK. The BCIS latest audit report for 2021-2022 reported that as of 27 September 2022, coverage by centre was 88.1% (37 of 42 centres submitted data), and coverage by procedure was 85.8% (6,520 TAVI procedures entered in the registry compared with the 7,601 procedures declared by centres within a survey).
Time period of data	Procedure date between 01 April 2021 to 31 March 2023
Data preparation	Pseudonymised patient-level data shared by NICOR; NICOR calculated age (such that DOB was not needed), NICOR calculated EuroSCORE II (advised poor quality and instructed not to use).
Data governance	UK TAVI Registry is managed by NICOR, clinical direction and strategy provided by the British Cardiovascular Interventional Society, BCIS, and the Society for Cardiothoracic Surgeons, SCTS)

Data specification	Full data specification (v4.09) available on NICOR website (which NICOR confirmed was rolled out in 2012).
Data management plan and quality assurance methods	Annual reports with recommendations. NICOR Outlier policy details partnership with UCL to develop methodology for outlier identification and monitoring of institutional or clinician performance an overview of statistical methods and application to national audit data. This applied to positive and negative outliers. Data completeness stated as 88%; poorest data quality in date of discharge, ethnicity and post-valve indices (NICOR report, 2024).
Other documents	Publications using UK TAVI Registry data (published 2020 onwards): - Ali et al. (Catheter Cardiovasc Interv, 2023) - Hilling-Smith et al. (Heart Vessels, 2021) - Myat et al. (Catheter Cardiovasc Interv, 2021a) - Myat et al. (Catheter Cardiovasc Interv, 2021b) - Myat et al. (Int J Cardiol, 2020)

Data quality

Study variable	Target concept	Operational definition	Quality dimension	How assessed	Assessment result
Population	Patients undergoing TAVI	Date and time TAVI procedure conducted	Completeness	Procedure date was part of query conducted by NICOR therefore implied 100%, however total number of rows received (n=14,401) was compared with figures reported in NICOR annual reports	NICOR report: 7,669 in 2022/23 and 6,738 in 2021/22; total 14,407 Completeness of registry extract to expected >99.9% (14,401/14,407)
Intervention	Device serial number; device model, device	Free text serial number, drop down options for	Completeness	Missingness	3472 missing serial number; 2250 missing device model; 643 missing device

Study variable	Target concept	Operational definition	Quality dimension	How assessed	Assessment result
	manufacturer	manufacturer and model			manufacturer. Total of 619 missing all three.
Intervention	Device serial number	Free text	Accuracy	Serial numbers returned to manufacturers	2902 not verified by company, or older version not in scope.
Outcome	Quality of life measures	CCS angina status 1 year, NYHA dyspnoea status 1 year	Completeness	Missingness	CCS and NYHA: 91.2% missing, 5.2% unknown
Covariate (confounder)	Aortic annular diameter	Measured in millimeters (measurement method captured separately)	Completeness and accuracy	Missingness and range	1540 (20.8%) missing, Range 0 to 560. A total of 12 procedures had measurement greater than 55.

Abbreviations: CCS, Canadian Cardiovascular Society; NICOR, National Institute for Cardiovascular Outcomes Research; NYHA, New York Heart Association TAVI, transcatheter aortic valve implantation

Data relevance

Item	Response
Population	Submission to UK TAVI Registry is mandated. Additional cleaning steps applied to restrict to confirmed population in scope accounting for missing data, then additional exclusions applied to narrows to devices listed in scope (verified model numbers). Of 14,401 TAVI procedures, a total of 7,409 (51.4%) remained in analysis. Lacking unique patient identifier.
Care setting	Appropriate. TAVI are conducted in secondary care setting, while relevant events may be observed in primary or secondary care.

Item	Response
Treatment pathway	The data represents routine practice in the NHS.
Availability of key study elements	Peak aortic jet velocity not recorded therefore unable to fully confirm patients with aortic stenosis using the ACC/AHA, 2006) definition. No information recorded on surgical risk group, annular calcification (burden or distribution), coronary height, valve morphology (bicuspid), left ventricular outflow tract or other risk factors which may inform choice of TAVI valve. Does not directly align to VARC-3 standardised endpoints for aortic valve clinical research.
Study period	Latest 2 years of data, reflective of NHS practice.
Timing of measurements	In-hospital outcomes only.
Follow up	None; completion of data post-discharge extremely poor.
Sample size	Sample size represents the largest UK sample of TAVI patients using latest generation TAVI devices.

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; TAVI, transcatheter aortic valve implantation, VARC-3; Valve Academic Research Consortium-3

Appendix C6: Additional analysis

Valve size

Number of valves used, by size, across all eligible UK TAVI Registry procedures (TAVI in native aortic valve, TAVI-in-SAVR, and TAVI-in-TAVI

TAVI device	20 mm	23 mm	25 mm	26 mm	27 mm	29 mm	34 mm
ACURATE neo2	-	106	141	-	100	-	-
Evolut FX	-	0	-	1	-	0	2
Evolut Pro+	-	49	-	275	-	484	232
Evolut R	-	67	-	96	-	105	188
Navitor	-	20	65	-	103	81	-
Sapien 3	4	59	-	76	-	1116	-
Sapien 3 Ultra	194	1722	-	2123	-	-	-

A dash (-) denotes that a valve and size combination is not available.

Patient and procedural characteristics across cohorts

Patient and procedural characteristics between TAVI in native aortic valve (n=7,119), TAVI-in-SAVR (n=263), TAVI-in-TAVI (n=27) cohorts, unadjusted.

Patient and procedural characteristics	Cohort 1, TAVI in native aortic valve (n=7,119)	Cohort 2, TAVI in SAVR (n=263)	Cohort 3, TAVI in TAVI (n=27)	p-value (comparison between three cohorts, **unadjusted**)	p-value (comparison between three cohorts, **adjusted**)
Age, years: median [Q1,Q3]	82.0 [77.0 to 86.0] (n=7,119)	78.0 [73.5 to 82.0] (n=263)	78.0 [73.0 to 83.0] (n=27)	0.0000000	<0.0001*
Age (90+ years)	579/7,119 (8.1%)	3/263 (1.1%)	0/27 (0%)	0.0004998	0.024*
Male sex	4,152/7,106 (58.4%)	170/263 (64.6%)	17/27 (63.0%)	0.1219390	1
Height, m: median [Q1,Q3]	1.7 [1.6 to 1.7] (n=6,696)	1.7 [1.6 to 1.8] (n=253)	1.7 [1.6 to 1.8] (n=26)	0.1201460	1
Weight, kg: median [Q1,Q3]	76.0 [65.5 to 88.0] (n=6,717)	78.0 [66.0 to 88.0] (n=253)	79.6 [66.2 to 89.0] (n=26)	0.1431855	1
BMI, kg/m2: median [Q1,Q3]	27.2 [24.1 to 31.1] (n=6,667)	27.0 [23.6 to 30.5] (n=251)	28.3 [24.8 to 30.7] (n=26)	0.5319930	1
Underweight (BMI under 17.5)	120/6,667 (1.8%)	3/251 (1.2%)	1/26 (3.8%)	0.3373313	1
Obese (BMI 30 or above)	2,088/6,667 (31.3%)	69/251 (27.5%)	9/26 (34.6%)	0.4092954	1
Pulmonary artery systolic pressure, mmHg: median [Q1,Q3]	35.0 [25.0 to 45.0] (n=2,191)	40.0 [31.2 to 48.0] (n=126)	43.5 [32.0 to 53.2] (n=14)	0.4077774	1
Mean pressure gradient, mmHg: median [Q1,Q3]	44.0 [36.0 to 55.0] (n=6,705)	36.0 [23.0 to 49.0] (n=233)	36.0 [19.0 to 44.0] (n=23)	0.0001213	0.006*
Peak pressure gradient, mmHg: median [Q1,Q3]	70.0 [58.0 to 86.0] (n=6,593)	60.0 [39.0 to 81.0] (n=230)	64.0 [43.8 to 77.8] (n=22)	0.0000000	<0.0001*
Valve area, cm2: median [Q1,Q3]	0.7 [0.6 to 0.9] (n=6,341)	0.9 [0.7 to 1.2] (n=172)	0.8 [0.6 to 1.5] (n=18)	0.0000000	<0.0001*
Annular diameter, mm: median [Q1,Q3]	24.5 [23.0 to 26.0] (n=5,639)	22.0 [20.0 to 23.3] (n=197)	23.0 [22.0 to 24.0] (n=17)	0.0000000	<0.0001*
Extensive calcification of ascending aorta	234/6,646 (3.5%)	12/251 (4.8%)	2/25 (8.0%)	0.1664168	1
Critical status pre-procedure	76/6,920 (1.1%)	21/257 (8.2%)	1/27 (3.7%)	0.0004998	0.024*
CCS Angina Status (any limitation of physical activity)	1,550/6,893 (22.5%)	48/259 (18.5%)	8/27 (29.6%)	0.2158921	1
CCS Angina Status (symptoms at rest)	62/6,893 (0.9%)	4/259 (1.5%)	1/27 (3.7%)	0.1109445	1
NYHA dyspnoea status (marked limitation of physical activity, or symptoms at rest or minimal activity)	5,102/6,940 (73.5%)	219/256 (85.5%)	22/27 (81.5%)	0.0004998	0.024*
NYHA dyspnoea status (symptoms at rest)	809/6,940 (11.7%)	60/256 (23.4%)	7/27 (25.9%)	0.0004998	0.024*
Severe symptoms (symptoms at rest measured by CCS Angina Status or NYHA dyspnoea status)	845/6,984 (12.1%)	62/260 (23.8%)	8/27 (29.6%)	0.0004998	0.024*
CSHA Clinical Frailty Score (moderately or severely frail)	496/6,681 (7.4%)	16/256 (6.2%)	3/23 (13%)	0.3603198	1
Katz Index less than 3	192/6,435 (3.0%)	7/243 (2.9%)	0/22 (0%)	1.0000000	1
Katz Index less than 6	871/6,435 (13.5%)	36/243 (14.8%)	5/22 (22.7%)	0.3198401	1
Frailty composite (moderately or severely frail on CSHA, or Katz Index less than 6)	1,206/6,800 (17.7%)	49/259 (18.9%)	5/24 (20.8%)	0.7346327	1
Poor LV function (LVEF<30%)	563/6,864 (8.2%)	27/259 (10.4%)	4/27 (14.8%)	0.1729135	1
Diabetes	1,795/6,955 (25.8%)	53/261 (20.3%)	9/26 (34.6%)	0.0699650	1
Ever smoked (current and ex smokers)	2,740/5,740 (47.7%)	96/236 (40.7%)	13/24 (54.2%)	0.0894553	1
Dialysis	116/6,921 (1.7%)	7/262 (2.7%)	2/26 (7.7%)	0.0369815	1
Presence of left main stem disease	156/6,129 (2.5%)	9/245 (3.7%)	2/23 (8.7%)	0.0809595	1
Presence of >50% stenosis in at least one coronary vessel	1,562/6,094 (25.6%)	54/244 (22.1%)	6/24 (25%)	0.4627686	1
Valve size, mm: median [Q1,Q3]	26.0 [23.0 to 29.0] (n=7,119)	23.0 [23.0 to 26.0] (n=263)	26.0 [23.0 to 26.0] (n=27)	0.4685109	1
Valve size (categorical: small, medium, large)	S: 2,055/7,119 (28.9%); M: 2,781/7,119 (39.1%); L: 2,283/7,119 (32.1%)	S: 155/263 (58.9%); M: 89/263 (33.8%); L: 19/263 (7.2%)	S: 11/27 (40.7%); M: 10/27 (37%); L: 6/27 (22.2%)	0.0004998	0.024*
Non-elective procedure	1,735/7,099 (24.4%)	118/263 (44.9%)	11/27 (40.7%)	0.0004998	0.024*
Procedure urgency (non-elective procedure, or critical status pre-procedure)	1,750/7,119 (24.6%)	120/263 (45.6%)	11/27 (40.7%)	0.0004998	0.024*
Planned use of general anaesthesia	67/7,074 (0.9%)	13/262 (5.0%)	2/26 (7.7%)	0.0004998	0.024*

Patient and procedural characteristics	Cohort 1, TAVI in native aortic valve (n=7,119)	Cohort 2, TAVI in SAVR (n=263)	Cohort 3, TAVI in TAVI (n=27)	p-value (comparison between three cohorts, **unadjusted**)	p-value (comparison between three cohorts, **adjusted**)
Previous balloon aortic valvuloplasty	203/7,029 (2.9%)	3/262 (1.1%)	1/27 (3.7%)	0.1434283	1
Use of cardiopulmonary bypass	27/7,021 (0.4%)	2/257 (0.8%)	0/26 (0%)	0.3378311	1
Use of cerebral circulation protection device(s)	789/7,068 (11.2%)	37/261 (14.2%)	6/26 (23.1%)	0.0424788	1
Creatinine clearance, mL/min: median [Q1,Q3]	55.8 [41.2 to 73.0] (n=6,400)	53.2 [39.2 to 69.6] (n=244)	64.0 [47.4 to 72.8] (n=24)	0.0529435	1
Creatinine clearance less than 30 mL/min	571/6,400 (8.9%)	23/244 (9.4%)	3/24 (12.5%)	0.6456772	1
Previous MI (ever)	851/7,030 (12.1%)	35/262 (13.4%)	7/26 (26.9%)	0.0629685	1
Previous MI (within previous 90 days)	148/7,030 (2.1%)	8/262 (3.1%)	2/26 (7.7%)	0.0669665	1
Previous PCI	922/7,006 (13.2%)	29/262 (11.1%)	7/27 (25.9%)	0.1049475	1
Previous CABG	572/6,886 (8.3%)	75/262 (28.6%)	7/26 (26.9%)	0.0004998	0.024*
Previous stroke or TIA	806/6,984 (11.5%)	33/261 (12.6%)	3/25 (12%)	0.7761119	1
Presence of extracardiac arteriopathy	652/6,917 (9.4%)	25/262 (9.5%)	4/26 (15.4%)	0.5182409	1
Any cardiac or coronary comorbidity (previous MI, PCI, or CABG, presence of extracardiac arteriopathy or aortic calcification, symptoms at rest on NYHA or CCS, poor LV function, left main stem disease or stenosis of at least 50% in one vessel)	3,335/7,102 (47.0%)	166/263 (63.1%)	20/27 (74.1%)	0.0004998	0.024*
Anatomical coronary comorbidity (left main stem disease, or stenosis of at least 50% in one vessel)	1,578/6,231 (25.3%)	55/248 (22.2%)	6/24 (25.0%)	0.5312344	1
Clinical coronary comorbidity (previous MI, PCI or CABG)	1,612/7,067 (22.8%)	93/263 (35.4%)	13/27 (48.1%)	0.0004998	0.024*
Any non-cardiac or non-coronary comorbidity (previous stroke or TIA, diabetes, current or former smoker, extracardiac arteriopathy, current dialysis or creatinine clearance less than 30)	4,435/7,065 (62.8%)	156/263 (59.3%)	19/27 (70.4%)	0.3733133	1
Non-cardiac non-coronary other comorbidity (previous stroke or extracardiac arteriopathy)	1,324/7,033 (18.8%)	51/263 (19.4%)	6/26 (23.1%)	0.7796102	1
Non-cardiac non-coronary risk factor (current or former smoker, or diabetes)	3,742/7,020 (53.3%)	129/263 (49.0%)	17/26 (65.4%)	0.1874063	1
Renal comorbidity (current dialysis or creatinine clearance less than 30)	608/6,993 (8.7%)	27/262 (10.3%)	3/26 (11.5%)	0.4997501	1

Key: Significance of **adjusted** p-values (using Holm-Bonferroni correction) denoted by: *** < 0.001, ** <0.01, * < 0.05

Abbreviations: CABG, Coronary artery bypass grafting; CCS, Canadian Cardiovascular Society; CSHA, Canadian Study of Health and Aging; LV, Left ventricular; MI, Myocardial infarction; NYHA, New York Heart Association; PCI, Percutaneous coronary intervention; SAVR, Surgical aortic valve replacement; TAVI, Transcatheter aortic valve implantation; TIA, Transient ischaemic attack

In-hospital outcomes across cohorts

In-hospital outcomes between TAVI in native aortic valve (n=7,119), TAVI-in-SAVR (n=263), TAVI-in-TAVI (n=27) cohorts, unadjusted.

In-hospital outcome	TAVI in native aortic valve (n=7,119)	TAVI in SAVR (n=263)	TAVI in TAVI (n=27)	p-value (comparison between three cohorts, **unadjusted**)	p-value (comparison between three cohorts, **adjusted**)
Length of procedure, minutes: median [Q1,Q3]	64.0 [57.0 to 83.0] (n=6,096)	77.5 [60.0 to 97.0] (n=234)	80.0 [62.5 to 104.8] (n=22)	0.0000000	<0.0001*
Length of hospital stay, overnight stays: median [Q1,Q3]	3.0 [2.0 to 10.0] (n=5,839)	6.0 [2.0 to 19.0] (n=230)	16.0 [3.0 to 30.0] (n=21)	0.0000000	<0.0001*
Peak pressure gradient, mmHg: median [Q1,Q3]	14.0 [10.0 to 20.0] (n=4,762)	22.0 [15.0 to 30.0] (n=198)	19.5 [12.8 to 26.2] (n=20)	0.0000000	<0.0001*
Mean pressure gradient, mmHg: [Q1,Q3]	7.0 [5.0 to 11.0] (n=5,086)	12.0 [8.0 to 19.0] (n=200)	10.0 [6.0 to 16.0] (n=21)	0.0000000	<0.0001*
Valve area, cm2: median [Q1,Q3]	1.9 [1.5 to 2.1] (n=3,364)	1.6 [1.4 to 2.0] (n=151)	1.8 [1.4 to 2] (n=10)	0.0000296	0.001**
Aortic regurgitation	122/6,835 (1.8%)	10/258 (3.9%)	1/26 (3.8%)	0.0369815	0.74
Valve failure	15/7,070 (0.2%)	2/263 (0.8%)	0/26 (0%)	0.1699150	1
Unsuccessful valve deployment	131/7,119 (1.8%)	7/263 (2.7%)	2/27 (7.4%)	0.0514743	0.875
Malposition of valve	50/6,794 (0.7%)	6/254 (2.4%)	0/26 (0%)	0.0409795	0.779
Use of post implantation balloon dilatation	575/6,759 (8.5%)	71/251 (28.3%)	1/26 (3.8%)	0.0004998	0.011*
Need for permanent pacing	512/6,636 (7.7%)	8/249 (3.2%)	1/26 (3.8%)	0.0149925	0.315
Conversion to sternotomy for valve surgery	8/7,053 (0.1%)	0/260 (0%)	0/27 (0%)	1.0000000	1
Valve reintervention before discharge	30/7,022 (0.4%)	1/260 (0.4%)	0/27 (0%)	1.0000000	1
Failure of percutaneous closure device	93/6,565 (1.4%)	8/245 (3.3%)	0/26 (0%)	0.1059470	1
Need for bailout PCI	20/7,035 (0.3%)	1/259 (0.4%)	0/27 (0%)	0.5637181	1
Need for bailout TAVI-in-TAVI	38/6,815 (0.6%)	4/254 (1.6%)	0/26 (0%)	0.1559220	1
MI within 72 hours of procedure	16/6,667 (0.2%)	2/251 (0.8%)	0/26 (0%)	0.2028986	1
Major, life threatening or disabling bleeding	70/6,544 (1.1%)	5/246 (2.0%)	0/25 (0%)	0.3958021	1
Major vascular complications	87/6,541 (1.3%)	5/245 (2.0%)	0/26 (0%)	0.5742129	1
Tamponade during or after procedure	52/6,976 (0.7%)	0/258 (0%)	0/27 (0%)	0.3953023	1
Stroke before discharge	107/6,479 (1.7%)	3/245 (1.2%)	1/26 (3.8%)	0.4117941	1
Modified Rankin score of 4 or above	9/707 (1.3%)	1/17 (5.9%)	0/3 (0%)	0.2413793	1
Need for renal replacement therapy	8/6,511 (0.1%)	1/246 (0.4%)	0/26 (0%)	0.3303348	1
Deaths	89/7,065 (1.3%)	3/260 (1.2%)	1/27 (3.7%)	0.3963018	1
Prescribed NOACs	1,791/6,483 (27.6%)	94/242 (38.8%)	8/24 (33.3%)	0.0009995	0.022*
Prescribed other anti-thrombotics	607/6,483 (9.4%)	27/242 (11.2%)	1/24 (4.2%)	0.5252374	1
Prescribed antiplatelets	4,174/6,395 (65.3%)	144/244 (59.0%)	16/23 (69.6%)	0.1264368	1
Technical success (VARC-3)	6,398/6,699 (95.5%)	233/250 (93.2%)	23/26 (88.5%)	0.0459770	0.828

Key: Significance of **adjusted** p-values (using Holm-Bonferroni correction) denoted by: *** < 0.001, ** <0.01, * < 0.05. Abbreviations: MI, Myocardial infarction; NOAC, Non-vitamin-K oral anticoagulant; PCI, Percutaneous coronary intervention; Q1, Quartile 1; Q3, Quartile 3; SAVR, Surgical aortic valve replacement; TAVI, Transcatheter aortic valve implantation; VARC-3, Valve Academic Research Consortium-3

Patient characteristics for TAVI-in-SAVR subgroup by device

Patient and procedural characteristics (TAVI-in-SAVR subgroup) by device manufacturer, unadjusted. [Key: Significant following Holm-Bonferroni correction: *** < 0.001, ** <0.01, * < 0.05]

Patient and procedural characteristics	**All valves (n=263)**	Edwards Sapien 3 (n=24)	Edwards Sapien 3 Ultra (n=101)	Medtronic Evolut R (n=79)	Medtronic Evolut Pro+ (n=51)	Abbott Navitor (n=8)	p-value (comparison between five devices, **unadjusted**)	p-value (comparison between five devices, **adjusted**)
Age, years: median [Q1,Q3]	78.0 [73.5 to 82.0] (n=263)	76.5 [71.8 to 81.2] (n=24)	79.0 [74.0 to 83.0] (n=101)	80.0 [75.0 to 82.0] (n=79)	76.0 [71.0 to 81.0] (n=51)	76.0 [74.0 to 77.0] (n=8)	0.0000000	<0.0001*
Age (90+ years)	3/263 (1.1%)	0/24 (0%)	3/101 (3.0%)	0/79 (0%)	0/51 (0%)	0/8 (0%)	0.4597701	1
Male sex	170/263 (64.6%)	19/24 (79.2%)	71/101 (70.3%)	37/79 (46.8%)	37/51 (72.5%)	6/8 (75.0%)	0.0024988	0.102
Height, m: median [Q1,Q3]	1.7 [1.6 to 1.8] (n=253)	1.7 [1.6 to 1.8] (n=24)	1.7 [1.6 to 1.8] (n=94)	1.6 [1.6 to 1.7] (n=77)	1.7 [1.6 to 1.7] (n=50)	1.8 [1.7 to 1.8] (n=8)	0.0000000	<0.0001*
Weight, kg: median [Q1,Q3]	78.0 [66.0 to 88.0] (n=253)	85.5 [69.8 to 90.5] (n=24)	78.0 [67.3 to 90.4] (n=95)	75.0 [64.0 to 88.0] (n=77)	78.0 [64.4 to 84.0] (n=50)	82.0 [72.5 to 94.8] (n=7)	0.0000000	<0.0001*
BMI, kg/m2: median [Q1,Q3]	27.0 [23.6 to 30.5] (n=251)	28.5 [25.7 to 30.4] (n=24)	26.1 [23.3 to 30.4] (n=93)	27.2 [23.6 to 30.9] (n=77)	26.9 [23.7 to 28.5] (n=50)	25.3 [24.0 to 31.2] (n=7)	0.0076485	0.306
Underweight (BMI under 17.5)	3/251 (1.2%)	1/24 (4.2%)	0/93 (0%)	2/77 (2.6%)	0/50 (0%)	0/7 (0%)	0.1509245	1
Obese (BMI 30 or above)	69/251 (27.5%)	8/24 (33.3%)	25/93 (26.9%)	24/77 (31.2%)	9/50 (18.0%)	3/7 (42.9%)	0.3408296	1
Pulmonary artery systolic pressure, mmHg: median [Q1,Q3]	40.0 [31.2 to 48.0] (n=126)	45.0 [42.0 to 51.0] (n=7)	40.0 [26.0 to 46.0] (n=51)	40.5 [34.2 to 50.0] (n=46)	35.0 [33.0 to 45.0] (n=19)	35.0 [30.5 to 41.5] (n=3)	0.0000000	<0.0001*
Mean pressure gradient, mmHg: median [Q1,Q3]	36.0 [23.0 to 49.0] (n=233)	27.5 [19.0 to 42.5] (n=18)	36.0 [21.0 to 47.0] (n=91)	38.0 [27.2 to 55.8] (n=70)	33.0 [24.5 to 47.2] (n=48)	20.0 [16.0 to 36.0] (n=6)	0.0000000	<0.0001*
Peak pressure gradient, mmHg: median [Q1,Q3]	60.0 [39.0 to 81.0] (n=230)	43.8 [30.2 to 66.8] (n=20)	59.0 [36.8 to 76.2] (n=88)	70.0 [44.5 to 95.5] (n=67)	58.5 [42.8 to 77.0] (n=48)	43.0 [31.5 to 55.0] (n=7)	0.0000000	<0.0001*
Valve area, cm2: median [Q1,Q3]	0.9 [0.7 to 1.2] (n=172)	1.3 [0.9 to 1.7] (n=9)	0.9 [0.6 to 1.3] (n=73)	0.7 [0.6 to 0.9] (n=45)	0.9 [0.7 to 1.2] (n=41)	0.9 [0.9 to 1.1] (n=4)	0.0000000	<0.0001*
Annular diameter, mm: median [Q1,Q3]	22.0 [20.0 to 23.3] (n=197)	25.0 [23.0 to 27.7] (n=21)	21.5 [20.0 to 23.1] (n=76)	21.0 [19.0 to 23.0] (n=53)	22.0 [19.4 to 23.8] (n=42)	25.0 [22.7 to 25.1] (n=5)	0.0000000	<0.0001*
Presence of aortic calcification	12/251 (4.8%)	1/24 (4.2%)	6/93 (6.5%)	5/77 (6.5%)	0/49 (0%)	0/8 (0%)	0.3908046	1
Critical status pre-procedure	21/257 (8.2%)	6/24 (25.0%)	3/98 (3.1%)	8/78 (10.3%)	3/49 (6.1%)	1/8 (12.5%)	0.0119940	0.468
CCS Angina Status (any limitation of physical activity)	48/259 (18.5%)	7/24 (29.2%)	14/99 (14.1%)	13/78 (16.7%)	13/50 (26.0%)	1/8 (12.5%)	0.2518741	1
CCS Angina Status (symptoms at rest)	4/259 (1.5%)	0/24 (0%)	1/99 (1.0%)	2/78 (2.6%)	1/50 (2.0%)	0/8 (0%)	0.9045477	1
NYHA dyspnoea status (marked limitation of physical activity, or symptoms at rest or minimal activity)	219/256 (85.5%)	23/24 (95.8%)	85/98 (86.7%)	63/77 (81.8%)	42/49 (85.7%)	6/8 (75.0%)	0.3803098	1
NYHA dyspnoea status (symptoms at rest)	60/256 (23.4%)	8/24 (33.3%)	21/98 (21.4%)	18/77 (23.4%)	13/49 (26.5%)	0/8 (0%)	0.3958021	1
Severe symptoms (symptoms at rest measured by CCS Angina Status or NYHA dyspnoea status)	62/260 (23.8%)	8/24 (33.3%)	22/100 (22.0%)	19/78 (24.4%)	13/50 (26.0%)	0/8 (0%)	0.4307846	1
CSHA Clinical Frailty Score (moderately or severely frail)	16/256 (6.2%)	3/24 (12.5%)	5/99 (5.1%)	6/76 (7.9%)	2/49 (4.1%)	0/8 (0%)	0.5807096	1
Katz Index less than 3	7/243 (2.9%)	0/24 (0%)	5/93 (5.4%)	0/71 (0%)	2/47 (4.3%)	0/8 (0%)	0.2328836	1
Katz Index less than 6	36/243 (14.8%)	5/24 (20.8%)	17/93 (18.3%)	2/71 (2.8%)	12/47 (25.5%)	0/8 (0%)	0.0009995	0.042*
Frailty composite (moderately or severely frail on CSHA, or Katz Index less than 6)	49/259 (18.9%)	7/24 (29.2%)	22/99 (22.2%)	8/78 (10.3%)	12/50 (24.0%)	0/8 (0%)	0.0639680	1
Poor LV function (LVEF<30%)	27/259 (10.4%)	3/24 (12.5%)	12/100 (12.0%)	5/77 (6.5%)	7/50 (14.0%)	0/8 (0%)	0.5447276	1

Patient and procedural characteristics	**All valves (n=263)**	Edwards Sapien 3 (n=24)	Edwards Sapien 3 Ultra (n=101)	Medtronic Evolut R (n=79)	Medtronic Evolut Pro+ (n=51)	Abbott Navitor (n=8)	p-value (comparison between five devices, **unadjusted**)	p-value (comparison between five devices, **adjusted**)
Diabetes	53/261 (20.3%)	4/24 (16.7%)	19/100 (19.0%)	19/78 (24.4%)	10/51 (19.6%)	1/8 (12.5%)	0.8840580	1
Ever smoked (current and ex smokers)	96/236 (40.7%)	11/21 (52.4%)	37/88 (42.0%)	23/74 (31.1%)	23/47 (48.9%)	2/6 (33.3%)	0.2503748	1
Dialysis	7/262 (2.7%)	0/24 (0%)	4/100 (4.0%)	0/79 (0%)	2/51 (3.9%)	1/8 (12.5%)	0.1014493	1
Presence of left main stem disease	9/245 (3.7%)	1/22 (4.5%)	4/92 (4.3%)	3/76 (3.9%)	1/48 (2.1%)	0/7 (0%)	0.9495252	1
Presence of >50% stenosis in at least one coronary vessel	54/244 (22.1%)	4/22 (18.2%)	22/93 (23.7%)	18/76 (23.7%)	10/48 (20.8%)	0/5 (0%)	0.8930535	1
Valve size, mm: median [Q1,Q3]	23.0 [23.0 to 26.0] (n=263)	26.0 [23.0 to 29.0] (n=24)	23.0 [23.0 to 26.0] (n=101)	23.0 [23.0 to 26.0] (n=79)	26.0 [23.0 to 26.0] (n=51)	25.0 [24.5 to 25.5] (n=8)	0.0000000	<0.0001*
Valve size (categorical: small, medium, large)	S: 155/263 (58.9%); M: 89/263 (33.8%); L: 19/263 (7.2%)	S: 11/24 (45.8%); M: 4/24 (16.7%); L: 9/24 (37.5%)	S: 75/101 (74.3%); M: 26/101 (25.7%); L: 0/101 (0%)	S: 47/79 (59.5%); M: 28/79 (35.4%); L: 4/79 (5.1%)	S: 20/51 (39.2%); M: 26/51 (51.0%); L: 5/51 (9.8%)	S: 2/8 (25.0%); M: 5/8 (62.5%); L: 1/8 (12.5%)	0.0004998	0.021*
Non-elective procedure	118/263 (44.9%)	12/24 (50.0%)	42/101 (41.6%)	38/79 (48.1%)	21/51 (41.2%)	5/8 (62.5%)	0.6731634	1
Procedure urgency (non-elective procedure, or critical status pre-procedure)	120/263 (45.6%)	13/24 (54.2%)	43/101 (42.6%)	38/79 (48.1%)	21/51 (41.2%)	5/8 (62.5%)	0.6131934	1
Planned use of general anaesthesia	13/262 (5.0%)	2/24 (8.3%)	7/101 (6.9%)	3/79 (3.8%)	1/50 (2.0%)	0/8 (0%)	0.5997001	1
Previous balloon aortic valvuloplasty	3/262 (1.1%)	0/24 (0%)	2/100 (2.0%)	0/79 (0%)	1/51 (2.0%)	0/8 (0%)	0.6291854	1
Use of cardiopulmonary bypass	2/257 (0.8%)	0/24 (0%)	0/96 (0%)	2/79 (2.5%)	0/50 (0%)	0/8 (0%)	0.3578211	1
Use of cerebral circulation protection device(s)	37/261 (14.2%)	4/24 (16.7%)	14/99 (14.1%)	16/79 (20.3%)	3/51 (5.9%)	0/8 (0%)	0.1599200	1
Creatinine clearance, mL/min: median [Q1,Q3]	53.2 [39.2 to 69.6] (n=244)	60.8 [44.5 to 86.4] (n=24)	52.2 [40.3 to 67.9] (n=88)	53.1 [38.5 to 68.4] (n=77)	52.9 [35.7 to 68.8] (n=49)	62.8 [50.8 to 76.4] (n=6)	0.0000000	<0.0001*
Creatinine clearance less than 30 mL/min	23/244 (9.4%)	1/24 (4.2%)	7/88 (8.0%)	8/77 (10.4%)	7/49 (14.3%)	0/6 (0%)	0.6496752	1
Previous MI (ever)	35/262 (13.4%)	5/24 (20.8%)	14/100 (14.0%)	8/79 (10.1%)	7/51 (13.7%)	1/8 (12.5%)	0.6731634	1
Previous MI (within previous 90 days)	8/262 (3.1%)	0/24 (0%)	5/100 (5.0%)	1/79 (1.3%)	1/51 (2.0%)	1/8 (12.5%)	0.2263868	1
Previous PCI	29/262 (11.1%)	1/24 (4.2%)	11/100 (11.0%)	9/79 (11.4%)	7/51 (13.7%)	1/8 (12.5%)	0.8065967	1
Previous CABG	75/262 (28.6%)	4/24 (16.7%)	29/100 (29.0%)	23/79 (29.1%)	17/51 (33.3%)	2/8 (25.0%)	0.6766617	1
Previous stroke or TIA	33/261 (12.6%)	1/24 (4.2%)	8/99 (8.1%)	19/79 (24.1%)	5/51 (9.8%)	0/8 (0%)	0.0154923	0.589
Presence of extracardiac arteriopathy	25/262 (9.5%)	3/24 (12.5%)	7/101 (6.9%)	8/79 (10.1%)	7/50 (14.0%)	0/8 (0%)	0.5852074	1
Any cardiac or coronary comorbidity (previous MI, PCI, or CABG, presence of extracardiac arteriopathy or aortic calcification, symptoms at rest on NYHA or CCS, poor LV function, left main stem disease or stenosis of at least 50% in one vessel)	166/263 (63.1%)	18/24 (75.0%)	62/101 (61.4%)	50/79 (63.3%)	33/51 (64.7%)	3/8 (37.5%)	0.4562719	1
Anatomical coronary comorbidity (left main stem disease, or stenosis of at least 50% in one vessel)	55/248 (22.2%)	4/22 (18.2%)	22/95 (23.2%)	19/76 (25.0%)	10/48 (20.8%)	0/7 (0%)	0.7206397	1
Clinical coronary comorbidity (previous MI, PCI or CABG)	93/263 (35.4%)	7/24 (29.2%)	34/101 (33.7%)	30/79 (38.0%)	19/51 (37.3%)	3/8 (37.5%)	0.9285357	1
Any non-cardiac or non-coronary comorbidity (previous stroke or TIA, diabetes, current or former smoker, extracardiac arteriopathy, current dialysis or creatinine clearance less than 30)	156/263 (59.3%)	15/24 (62.5%)	57/101 (56.4%)	46/79 (58.2%)	35/51 (68.6%)	3/8 (37.5%)	0.4217891	1
Non-cardiac non-coronary other comorbidity (previous stroke or extracardiac arteriopathy)	51/263 (19.4%)	4/24 (16.7%)	13/101 (12.9%)	23/79 (29.1%)	11/51 (21.6%)	0/8 (0%)	0.0604698	1
Non-cardiac non-coronary risk factor (current or former smoker, or diabetes)	129/263 (49.0%)	13/24 (54.2%)	47/101 (46.5%)	37/79 (46.8%)	30/51 (58.8%)	2/8 (25.0%)	0.3568216	1

Patient and procedural characteristics	**All valves (n=263)**	Edwards Sapien 3 (n=24)	Edwards Sapien 3 Ultra (n=101)	Medtronic Evolut R (n=79)	Medtronic Evolut Pro+ (n=51)	Abbott Navitor (n=8)	p-value (comparison between five devices, **unadjusted**)	p-value (comparison between five devices, **adjusted**)
Renal comorbidity (current dialysis or creatinine clearance less than 30)	27/262 (10.3%)	1/24 (4.2%)	9/100 (9.0%)	8/79 (10.1%)	8/51 (15.7%)	1/8 (12.5%)	0.5537231	1

Key: Significance of **adjusted** p-values (using Holm-Bonferroni correction) denoted by: *** < 0.001, ** <0.01, * < 0.05. Abbreviations: CABG, Coronary artery bypass grafting; CCS, Canadian Cardiovascular Society; CSHA, Canadian Study of Health and Aging; LV, Left ventricular; MI, Myocardial infarction; NYHA, New York Heart Association; PCI, Percutaneous coronary intervention; Q1, Quartile 1; Q3, Quartile 3; TIA, Transient ischaemic attack

In-hospital outcomes for TAVI-in-SAVR cohort by device, unadjusted

Outcomes	**All valves (n=263)**	Edwards Sapien 3 (n=24)	Edwards Sapien 3 Ultra (n=101)	Medtronic Evolut R (n=79)	Medtronic Evolut Pro+ (n=51)	Abbott Navitor (n=8)	p-value (comparison between five devices, **unadjusted**)	p-value (comparison between five devices, **adjusted**)
Length of procedure, minutes: median [Q1,Q3]	77.5 [60.0 to 97.0] (n=234)	60.0 [43.5 to 82.5] (n=24)	74.0 [60.0 to 89.2] (n=84)	83.0 [65.5 to 105.0] (n=71)	80.0 [70.0 to 98.5] (n=48)	88.0 [70.0 to 106.0] (n=7)	0.0024755	0.062
Length of hospital stay, overnight stays: median [Q1,Q3]	6.0 [2.0 to 19.0] (n=230)	3.5 [2.8 to 12.5] (n=24)	6.0 [2.0 to 15.0] (n=74)	7.0 [3.0 to 20.8] (n=78)	7.0 [3.0 to 24.0] (n=49)	5.0 [2.0 to 31.0] (n=5)	0.2906331	1
Peak pressure gradient, mmHg: median [Q1,Q3]	22.0 [15.0 to 30.0] (n=198)	26.0 [13.5 to 31.8] (n=19)	23.5 [16.0 to 28.2] (n=84)	20.5 [14.2 to 31.8] (n=54)	20.0 [15.0 to 29.0] (n=35)	15.0 [9.0 to 18.8] (n=6)	0.2820281	1
Mean pressure gradient, mmHg: [Q1,Q3]	12.0 [8.0 to 19.0] (n=200)	17.0 [7.5 to 19.0] (n=19)	12.0 [9.0 to 17.0] (n=85)	13.0 [9.0 to 21.5] (n=51)	11.0 [6.5 to 14.5] (n=39)	7.0 [4.5 to 9.5] (n=6)	0.0225785	0.519
Valve area, cm2: median [Q1,Q3]	1.6 [1.4 to 2.0] (n=151)	1.5 [1.3 to 1.8] (n=8)	1.6 [1.3 to 2.0] (n=72)	1.5 [1.3 to 1.8] (n=36)	1.8 [1.5 to 2.0] (n=32)	2.4 [2.3 to 2.5] (n=3)	0.0068906	0.165
Aortic regurgitation	10/258 (3.9%)	0/24 (0%)	6/99 (6.1%)	1/78 (1.3%)	2/50 (4.0%)	1/7 (14.3%)	0.1829085	1
Valve failure	2/263 (0.8%)	0/24 (0%)	2/101 (2.0%)	0/79 (0%)	0/51 (0%)	0/8 (0%)	0.6361819	1
Unsuccessful valve deployment	7/263 (2.7%)	0/24 (0%)	5/101 (5.0%)	0/79 (0%)	2/51 (3.9%)	0/8 (0%)	0.2393803	1
Malposition of valve	6/254 (2.4%)	0/24 (0%)	2/97 (2.1%)	2/79 (2.5%)	2/46 (4.3%)	0/8 (0%)	0.8370815	1
Use of post implantation balloon dilatation	71/251 (28.3%)	0/24 (0%)	33/94 (35.1%)	29/79 (36.7%)	6/46 (13.0%)	3/8 (37.5%)	0.0004998	0.013*
Need for permanent pacing	8/249 (3.2%)	1/24 (4.2%)	0/94 (0%)	4/79 (5.1%)	2/45 (4.4%)	1/7 (14.3%)	0.0509745	1
Conversion to sternotomy for valve surgery	0/260 (0%)	0/24 (0%)	0/99 (0%)	0/79 (0%)	0/50 (0%)	0/8 (0%)	Not calculated	Not calculated
Valve reintervention before discharge	1/260 (0.4%)	0/24 (0%)	1/99 (1.0%)	0/79 (0%)	0/50 (0%)	0/8 (0%)	1.0000000	1
Failure of percutaneous closure device	8/245 (3.3%)	1/24 (4.2%)	0/93 (0%)	3/76 (3.9%)	4/45 (8.9%)	0/7 (0%)	0.0484758	1
Need for bailout PCI	1/259 (0.4%)	0/24 (0%)	0/98 (0%)	0/79 (0%)	1/50 (2.0%)	0/8 (0%)	0.3193403	1
Need for bailout TAVI-in-TAVI	4/254 (1.6%)	0/24 (0%)	2/97 (2.1%)	2/79 (2.5%)	0/46 (0%)	0/8 (0%)	0.9050475	1
MI within 72 hours of procedure	2/251 (0.8%)	0/23 (0%)	1/94 (1.1%)	0/79 (0%)	1/49 (2.0%)	0/6 (0%)	0.7846077	1
Major, life threatening or disabling bleeding	5/246 (2.0%)	0/24 (0%)	1/93 (1.1%)	3/77 (3.9%)	1/45 (2.2%)	0/7 (0%)	0.6851574	1
Major vascular complications	5/245 (2.0%)	0/24 (0%)	0/93 (0%)	2/77 (2.6%)	3/45 (6.7%)	0/6 (0%)	0.1044478	1
Tamponade during or after procedure	0/258 (0%)	0/24 (0%)	0/97 (0%)	0/78 (0%)	0/51 (0%)	0/8 (0%)	Not calculated	Not calculated
Stroke before discharge	3/245 (1.2%)	0/23 (0%)	2/93 (2.2%)	0/77 (0%)	1/45 (2.2%)	0/7 (0%)	0.6126937	1
Modified Rankin score of 4 or above	1/17 (5.9%)	0/2 (0%)	0/11 (0%)	0/1 (0%)	1/1 (100.0%)	0/2 (0%)	0.1109445	1
Need for renal replacement therapy	1/246 (0.4%)	0/24 (0%)	0/95 (0%)	0/76 (0%)	0/44 (0%)	1/7 (14.3%)	0.0234883	0.519
Deaths	3/260 (1.2%)	0/24 (0%)	3/99 (3.0%)	0/79 (0%)	0/51 (0%)	0/7 (0%)	0.4212894	1
Prescribed NOACs	94/242 (38.8%)	7/23 (30.4%)	37/86 (43.0%)	32/76 (42.1%)	13/50 (26.0%)	5/7 (71.4%)	0.0799600	1
Prescribed other anti-thrombotics	27/242 (11.2%)	5/23 (21.7%)	9/86 (10.5%)	7/76 (9.2%)	6/50 (12.0%)	0/7 (0%)	0.4927536	1
Prescribed antiplatelets	144/244 (59.0%)	15/23 (65.2%)	45/87 (51.7%)	50/78 (64.1%)	32/50 (64.0%)	2/6 (33.3%)	0.2618691	1
Technical success (VARC-3)	233/250 (93.2%)	24/24 (100.0%)	85/95 (89.5%)	77/79 (97.5%)	40/45 (88.9%)	7/7 (100.0%)	0.1009495	1

Key: Significance of **adjusted** p-values (using Holm-Bonferroni correction) denoted by: *** < 0.001, ** <0.01, * < 0.05

Abbreviations: CABG, Coronary artery bypass grafting; CCS, Canadian Cardiovascular Society; CSHA, Canadian Study of Health and Aging; GA, General anaesthesia; Left Main Stem disease; LV, Left ventricular; MI, Myocardial infarction; NOAC, non-vitamin-K oral anticoagulant; NYHA, New York Heart Association; PCI, Percutaneous coronary intervention

Appendix D: Hospital Episode Statistics (HES)

Appendix D1: Cohort Definition and Cleaning

Group	Descriptor [Data field]	Procedure (OPCS 4.10) codes	Diagnosis (ICD10) codes	Additional notes
Initial HES APC query	Finished consultant episodes [FCE=1] with a discharge date [DISDATE] between 01 April 2021 and 31 October 2023, including procedure codes within OPERTN01-24 AND diagnosis codes within DIAG01-20, in patients with a start age [STARTAGE_CALC] greater than 16 years	K26.1 Allograft replacement of aortic valve **OR** K26.2 Xenograft replacement of aortic valve **OR** K26.3 Prosthetic replacement of aortic valve **OR** K26.4 Replacement of aortic valve NEC **OR** K26.5 Aortic valve repair NEC **OR** K26.8 Other specified plastic repair of aortic valve **OR** K26.9 Unspecified plastic repair of aortic valve **OR** K30.2 Revision of plastic repair of aortic valve **OR** K35.8 Other specified therapeutic transluminal operations on valve of heart	I35.0 Aortic (valve) stenosis **OR** I35.2 Aortic (valve) stenosis with insufficiency **OR** I06.0 Rheumatic aortic stenosis **OR** I06.2 Rheumatic aortic stenosis with insufficiency **OR** Q23.0 Congenital stenosis of aortic valve **OR** T82.0 Mechanical complication of heart valve prosthesis **OR** T82.2 Mechanical complication of coronary artery bypass and valve grafts **OR** T82.6 Infection and inflammatory reaction due to cardiac valve prosthesis **OR** T82.8 Other specified complications of cardiac and vascular prosthetic devices, implants and grafts **OR** T82.9 Unspecified complication of cardiac and vascular prosthetic device, implant and graft **OR** I08.0 Multiple valve disease	Initial query will identify TAVI and SAVR patients; these are separated in subsequent cleaning. NICE IPG568 (2017) NICE IPG653 (2019)
Cohort refining	TAVI [OPERTN 01-24]	(K26.1 Allograft replacement of aortic valve **OR** K26.2 Xenograft replacement of aortic valve **OR** K26.3 Prosthetic replacement of aortic valve **OR** K26.4 Replacement of aortic valve NEC **OR** K26.5 Aortic valve repair NEC **OR** K26.8 Other specified plastic repair of aortic valve **OR** K26.9 Unspecified plastic repair of aortic valve **OR** K30.2 Revision of plastic repair of aortic valve **OR** (K35.8 Other specified therapeutic transluminal operations on valve of heart **AND** Z32.2 Aortic valve)) **AND** (Y49.4 Revision of plastic repair of aortic valve **OR** Y79 Approach to organ through artery **OR** Y53 Approach to organ under imaging control **OR** Y68 Other approach to organ under image control)	-	-
Cohort refining	SAVR [OPERTN 01-24]	(K26.1 Allograft replacement of aortic valve **OR** K26.2 Xenograft replacement of aortic valve **OR** K26.3 Prosthetic replacement of aortic valve **OR** K26.4 Replacement of aortic valve NEC **OR** K26.5 Aortic valve repair NEC **OR** K26.8 Other specified plastic repair of aortic valve **OR** K26.9 Unspecified plastic repair of aortic valve **OR** K30.2 Revision of plastic repair of aortic valve **OR** (K35.8 Other specified therapeutic transluminal operations on valve of heart **AND** Z32.2 Aortic valve)) **NOT** supplemented by (Y49.4 Revision of plastic repair of aortic valve **OR** Y79 Approach to organ through artery **OR** Y53 Approach to organ under imaging control **OR** Y68 Other approach to organ under image control) **OR** Above K codes supplemented by Y49.1 Median sternotomy approach	-	-
Patient and procedural characteristics	Age on admission, years [ADMIAGE]	-	-	Integer value; mandatory field therefore no missing values
Patient and procedural characteristics	Male sex [SEX=1]	-	-	Valid entries 1=Male, and 2=Female; all other values considered missing/unknown.
Patient and procedural characteristics	Diabetes [DIAG 01-20]	-	E10 Type 1 diabetes mellitus **OR** E11 Type 2 diabetes mellitus **OR** E12 Malnutrition-related diabetes mellitus **OR** E13 Other specified diabetes mellitus **OR** E14 Unspecified diabetes mellitus	Type I and II diabetes combined
Patient and procedural characteristics	Emergency admission [ADMIMETH=21, 22, 23, 24, 28, 2A ,2B **OR** 2D]	-	-	Emergency admission classed as 21=A&E, 22=GP after a request for immediate admission has been made direct to a hospital provider, 23=bed bureau, 24=consultant clinic, 28|2A|2B|2D=other emergency admissions (from another A&E or transferred from other trust). Values of 99=Not known considered missing.
Patient and procedural characteristics	Previous CABG [OPERTN 01-24]	K40 Saphenous vein graft replacement of coronary artery **OR** K41 Other autograft replacement of coronary artery **OR** K42 Allograft replacement of coronary artery **OR** K43 Prosthetic replacement of coronary artery **OR** K44 Other	-	Searched for within historic admissions (prior to index back to 01 April 2007). NICE IPG 377 (2011)

Group	Descriptor [Data field]	Procedure (OPCS 4.10) codes	Diagnosis (ICD10) codes	Additional notes
		replacement of coronary artery **OR** K45 Connection of thoracic artery to coronary artery **OR** K46 Other bypass of coronary artery **OR** Y73.1 Cardiopulmonary bypass **OR** Y73.4 Modified ultrafiltration adjunct to cardiopulmonary bypass		
Patient and procedural characteristics	Previous PCI [OPERTN 01-24]	K49 Transluminal balloon angioplasty of coronary artery **OR** K50 Other therapeutic transluminal operations on coronary artery **OR** K75 Percutaneous transluminal balloon angioplasty and insertion of stent into coronary artery	-	Searched for within historic admissions (prior to index back to 01 April 2007)
Patient and procedural characteristics	Previous Dialysis [OPERTN 01-24]	X40.1 Renal dialysis **OR** X40.2 Peritoneal dialysis NEC **OR** X40.3 Haemodialysis NEC **OR** X40.5 Automated peritoneal dialysis **OR** X40.6 Continuous ambulatory peritoneal dialysis **OR** X40.8 Other specified compensation for renal failure **OR** X40.9 Unspecified compensation for renal failure **OR** X41.1 Insertion of ambulatory peritoneal dialysis catheter **OR** X41.8 Other specified placement of ambulatory apparatus for compensation for renal failure **OR** X41.9 Unspecified placement of ambulatory apparatus for compensation for renal failure **OR** X42.1 Insertion of temporary peritoneal dialysis catheter **OR** X42.8 Other specified placement of other apparatus for compensation for renal failure **OR** X42.9 Unspecified placement of other apparatus for compensation for renal failure	-	Searched for within historic admissions (prior to index back to 01 April 2007)
Patient and procedural characteristics	Prior stroke or TIA [DIAG 01-20]	-	Haemorrhagic (I60 Subarachnoid haemorrhage **OR** I61 Intracerebral haemorrhage **OR** I62 Other nontraumatic intracranial haemorrhage) **OR** Embolic (I63 Cerebral infarction) **OR** Stroke unspecified (I64 Stroke, not specified as haemorrhage or infarction) **OR** TIA (G45 Transient cerebral ischaemic attacks and related syndromes)	Searched for within historic admissions (prior to index back to 01 April 2007)
Patient and procedural characteristics	Prior MI [DIAG 01-20]	-	I21 Acute myocardial infarction **OR** I22 Subsequent myocardial infarction **OR** I23 Certain current complications following acute myocardial infarction	Searched for within historic admissions (prior to index back to 01 April 2007)
Patient and procedural characteristics	Prior conduction abnormalities or In-hospital outcomes (from TAVI admission until discharge) arrhythmias [DIAG 01-20]	-	I44 Atrioventricular and left bundle-branch block **OR** I45 Other conduction disorders **OR** I47 Paroxysmal tachycardia **OR** I48 Atrial fibrillation and flutter **OR** I49 Other cardiac arrhythmias	Searched for within historic admissions (prior to index back to 01 April 2007)
Patient and procedural characteristics	Cerebral protection	L73.1 Mechanical embolic protection Not elsewhere classified L73.2 Mechanical embolic protection of artery	-	As obtained from NICE IPG650 recommended clinical coding
In-hospital outcomes (from TAVI admission until discharge)	Total length of hospital stay [DISDATE-ADMIDATE], in nights	-	-	Calculated field
In-hospital outcomes (from TAVI admission until discharge)	Length of ICU stay [data fields from Critical Care database; CCDISDATE-CCSTARTDATE]	-	-	Calculated field (aggregated per admission, linked to Admitted Patient Care dataset via unique episode SUSRECID)
In-hospital outcomes (from TAVI admission until discharge)	Pacemaker implantation [OPERTN 01-24]	K60.1 Implantation of intravenous cardiac pacemaker system NEC **OR** K60.5 Implantation of intravenous single chamber cardiac pacemaker system **OR** K60.6 Implantation of intravenous dual chamber cardiac pacemaker system **OR** K60.7 Implantation of intravenous biventricular cardiac pacemaker system **OR** K60.8 Other specified cardiac pacemaker system introduced through vein **OR** K60.9 Unspecified cardiac pacemaker system introduced through vein NOT followed by any of the following supplementary codes which would indicate temporary pacing Y70.5: Temporary operations; K60.4: Removal of intravenous cardiac pacemaker system; K61.4: Removal of cardiac pacemaker system NEC	-	-

Group	Descriptor [Data field]	Procedure (OPCS 4.10) codes	Diagnosis (ICD10) codes	Additional notes
In-hospital outcomes (from TAVI admission until discharge)	Vascular complication [DIAG 01-20]	-	I97 Postprocedural disorders of circulatory system, not elsewhere classified **OR** T81.7 Vascular complications following a procedure, not elsewhere classified	Excluding reason for admission (DIAG01) of the first episode within spell (EPIORDER=1)
In-hospital outcomes (from TAVI admission until discharge)	Bleeding [DIAG 01-20]	-	T81.0 Haemorrhage and haematoma complicating a procedure, not elsewhere classified **OR** T82.8 Other specified complications of cardiac and vascular prosthetic devices, implants and grafts	Excluding reason for admission (DIAG01) of the first episode within spell (EPIORDER=1)
In-hospital outcomes (from TAVI admission until discharge)	Stroke [DIAG 01-20]	-	I60 Subarachnoid haemorrhage **OR** I61 Intracerebral haemorrhage **OR** I62 Other nontraumatic intracranial haemorrhage **OR** I63 Cerebral infarction **OR** I64 Stroke, not specified as haemorrhage or infarction	-
In-hospital outcomes (from TAVI admission until discharge)	Occurrence of death [DISMETH]	-	-	DISMETH=4(DISMETH data field codes where patient was discharged to) Cause of death obtained through linkage to Civil Mortality Registration (formerly known as ONS) through tracking of unique patient ID (TOKEN_PERSON_ID).
In-hospital outcomes (from TAVI admission until discharge)	Discharge destination [DISDEST]	-	-	Usual place of residence=19. Another hospital=49,50,51,52,53 Care or nursing home=54,55,56,85,86.
Longitudinal outcomes (discharge to 31 October 2023 or date of death whichever latest)	Aortic reintervention [OPERTN 01-24]	(K26.1 Allograft replacement of aortic valve **OR** K26.2 Xenograft replacement of aortic valve **OR** K26.3 Prosthetic replacement of aortic valve **OR** K26.4 Replacement of aortic valve NEC **OR** K26.5 Aortic valve repair NEC **OR** K26.8 Other specified plastic repair of aortic valve **OR** K26.9 Unspecified plastic repair of aortic valve **OR** K30.2 Revision of plastic repair of aortic valve **OR** (K35.8 Other specified therapeutic transluminal operations on valve of heart **AND** Z32.2 Aortic valve))	-	Occurring after discharge from TAVI procedural admission.
Longitudinal outcomes (discharge to 31 October 2023 or date of death whichever latest)	Stroke [DIAG 01]	-	I60 Subarachnoid haemorrhage **OR** I61 Intracerebral haemorrhage **OR** I62 Other nontraumatic intracranial haemorrhage **OR** I63 Cerebral infarction **OR** I64 Stroke, not specified as haemorrhage or infarction	Occurring after discharge from TAVI procedural admission.
Longitudinal outcomes (discharge to 31 October 2023 or date of death whichever latest)	Stroke or TIA [DIAG 01]	-	I60 Subarachnoid haemorrhage **OR** I61 Intracerebral haemorrhage **OR** I62 Other nontraumatic intracranial haemorrhage **OR** I63 Cerebral infarction **OR** I64 Stroke, not specified as haemorrhage or infarction **OR** G45 Transient cerebral ischaemic attacks and related syndromes	Occurring after discharge from TAVI procedural admission.
Longitudinal outcomes (discharge to 31 October 2023 or date of death whichever latest)	Heart failure [DIAG 01]	-	I50 Heart failure	Occurring after discharge from TAVI procedural admission.
Longitudinal outcomes (discharge to 31 October 2023 or date of death whichever latest)	Pacemaker implantation [OPERTN 01-24]	K60.1 Implantation of intravenous cardiac pacemaker system NEC **OR** K60.5 Implantation of intravenous single chamber cardiac pacemaker system **OR** K60.6 Implantation of intravenous dual chamber cardiac pacemaker system **OR** K60.7 Implantation of intravenous biventricular cardiac pacemaker system **OR** K60.8 Other specified cardiac pacemaker system introduced through vein **OR** K60.9 Unspecified cardiac pacemaker system introduced through vein	-	Occurring after discharge from TAVI procedural admission.
Longitudinal outcomes (discharge to 31 October 2023 or date of death whichever latest)	Death [record and cause of death reported in Civil Mortality Registration dataset]	-	-	Record available in Civil Registration of Mortality, with in-hospital deaths excluded Main cause of death dichotmoised into cardiovascular or non-cardiovascular (Joshy et al. 2015.)

Abbreviations: A&E, Accident and Emergency; AKI, Acute Kidney Injury; CVA, Cerebrovascular accident; KCCQ, Kansas City Cardiomyopathy Questionnaire; TAVI, Transcatheter aortic valve implantation; TIA, Transient ischaemic attack; VARC-3, Valve Academic Research Consortium-3

Appendix D2: VARC-3 endpoints

Summary of alignment of HES data fields to VARC-3 endpoints

VARC-3 outcome [green=full alignment, amber=partial alignment, red=no alignment]	Outcome definition	HES Admitted Patient Care (APC)
Mortality	Causes: • All-cause mortality but should be classified as cardiovascular or non-cardiovascular where possible. Timings: • Periprocedural: if within 30 days (or >30 days if the patient is still hospitalized), • Early: if within 30 days and 1 year, • Late: if beyond 1 year.	APC and linked to ONS (in-hospital, early and late). Main causes of death should be categorised as cardiovascular and non-cardiovascular (with clinical adjudication).
Neurologic events	Categories: • Overt CNS injury (all strokes: ischaemic, haemorrhagic, stroke not otherwise specified), • Covert CNS injury (covert CNS infarction or haemorrhage) • Neurological dysfunction without CNS injury (TIA and delirium without CNS injury). Timings: • Peri-procedural or within 30 days of discharge. • Early: within 30 days and 1 year of discharge. • Late: and after 1 year of discharge	APC and linked to ONS for all causes of death including stroke or TIA (ICD10: I60-64, G45)
Hospitalisation (or re-hospitalisation)	Heart failure related hospitalisations including A&E attendances.	Readmissions with ICD10: I50 Heart Failure (restrict to DIAG01 to avoid double counting prior events)
Bleeding and transfusions	Categories: • Type 1 (minor) • Type 2 (major) • Type 3 (life-threatening) • Type 4 (leading to death) Timings: • Peri-procedural. • Early: within 48 hours of discharge. • Late: and after 48 hours of discharge	ICD10: T81.0 (For events post-discharge restrict to DIAG01 to avoid double counting prior events) Note unable to determine severity.

VARC-3 outcome [green=full alignment, amber=partial alignment, red=no alignment]	Outcome definition	HES Admitted Patient Care (APC)
Vascular and access-related complications	Categories: • Major • Minor	ICD10: I97 Postprocedural disorders of circulatory system, not elsewhere classified **OR** T81.7 Vascular complications following a procedure, not elsewhere classified Note unable to determine severity.
Cardiac structural complications	Categories: • Major • Minor	Not recorded
Other procedural or valve-related complications	Conversion to open surgery OR unplanned use of mechanical circulatory support, OR implantation of multiple TAVI valves during index hospitalisation, OR valve malposition OR paravalvular regurgitation.	Not recorded (could assume multiple TAVI valves from repeated procedure code within hospital admission)
New conduction disturbances and arrhythmias	Conduction disturbances OR permanent pacemaker OR atrial fibrillation Timepoints differ across event	OPCS codes: K60.1, K60.5, K60.6, K60.7, K60.8, K60.9 for pacemaker implantation.
Acute kidney injury	Categories: • Stage 1 • Stage 2 • Stage 3 • Stage 4	Not recorded
Myocardial infarction	Categories: • Type 1 • Type 2 • Type 3 • Type 4A • Type 4B • Type 5	ICD10: I21 Acute myocardial infarction OR I22 Subsequent myocardial infarction OR I23 Certain current complications following acute myocardial infarction (Note: unable to align with Types 1-5 in VARC3)
Bioprosthetic valve dysfunction	Including structural valve deterioration (Stages: 1, 2, 3), non-structural valve dysfunction, thrombosis, endocarditis	Not recorded (Could use ICD10: I38 to recorded

VARC-3 outcome [green=full alignment, amber=partial alignment, red=no alignment]	Outcome definition	HES Admitted Patient Care (APC)
		endocarditis, valve unspecified)
Leaflet thickening and reduced motion	Including hypo-attenuated leaflet thickening, reduced leaflet motion Timing: • Acute: within 24 hours of procedure • Subacute: between 24 hours and 30 days • Late: between 30 days and 1 year • Very late: more than 1 year	Not recorded
Clinically significant valve thrombosis	Timing: • Acute: within 24 hours of procedure • Subacute: between 24 hours and 30 days • Late: between 30 days and 1 year • Very late: more than 1 year	Not recorded (T82.8 Other specified complications of cardiac and vascular prosthetic devices, implants and grafts is not specific to aortic valve, and includes embolism, fibrosis, haemorrhage, pain, stenosis and thrombosis).
Patient reported outcomes and health status	Minnesota Living with Heart Failure Questionnaire (MLHFQ) Kansas City Cardiomyopathy Questionnaire (KCCQ or short version KCCQ-12) 36-item Short-Form Health Survey (SF-36) 12-item Short-Form Health Survey (SF-12) EuroQoL (EQ-5D)	Not recorded
Technical success (at exit from procedure room)	Freedom from mortality AND	In-hospital death captured.
	Successful access, delivery of the device and retrieval of the delivery system AND	Not recorded
	Correct positioning of a single prosthetic heart valve into the proper anatomical location AND	Not recorded
	Freedom of surgery or intervention related to the device or to a major vascular or access-related or cardiac structural complication.	T81.7 Vascular complications following a procedure, not elsewhere classified.
Device success (at 30 days)	Technical success	As above
	Freedom from mortality	As above
	Freedom from surgery or intervention related to the device or to a major vascular or access-related or cardiac structural complication	T81.7 Vascular complications following

VARC-3 outcome [green=full alignment, amber=partial alignment, red=no alignment]	Outcome definition	HES Admitted Patient Care (APC)
		a procedure, not elsewhere classified.
	Intended performance of the valve (mean gradient <20 mmHg, peak velocity <3m/s,)	Not recorded
Early safety (at 30 days)	Freedom from all-cause mortality	As above
	Freedom from all stroke	As above
	Freedom from VARC type 2-4 bleeding	Not recorded
	Freedom from major vascular, access-related or cardiac structural complication	Not recorded
	Freedom from acute kidney injury stage 3 or 4	Not recorded
	Freedom from moderate or severe aortic regurgitation	Not recorded
	Freedom from new permanent pacemaker due to the procedure-related conduction abnormalities	As above
	Freedom from surgery or intervention related to the device	OPCS codes for subsequent valve surgery, or supplementary codes indicating revision.
Clinical efficacy (at 1 year and thereafter)	Freedom from all-cause mortality	As above
	Freedom from all stroke	As above
	Freedom from hospitalisation for procedure- or valve-related causes	As above
	Freedom from KCCQ overall summary score	Not recorded
Valve-related long-term clinical efficacy (at 5 years and thereafter)	Freedom from bioprosthetic valve failure	Not recorded
	Freedom from stroke or peripheral embolism	Not recorded
	Freedom from VARC type 2-4 bleeding	Not recorded

Abbreviations: A&E, Accident and Emergency; AKI, Acute Kidney Injury; APC, Admitted Patient Care; CNS, Central nervous system; CVA, Cerebrovascular accident; KCCQ, Kansas City Cardiomyopathy Questionnaire; ONS, Office for National Statistics; TAVI, Transcatheter aortic valve implantation; TIA, Transient ischaemic attack; VARC-3, Valve Academic Research Consortium-3

Appendix D3: Additional analysis

Comparison of 2021/22 to 2022/23 financial years, unadjusted

Parameter	HES 2021/2022 (n=6,079)	HES 2022/2023 (n=6,879)	p-value, **unadjusted**	p-value, **adjusted**
Age, years; median [Q1,Q3]	82 [77 to 86] (n=6,079)	82 [77 to 86] (n=6,879)	0.2732938	1
Male sex, (%)	3,484/6,079 (57.3%)	3,937/6,879 (57.2%)	0.9291215	1
Diabetes, (%)	1,646/6,079 (27.1%)	1,835/6,879 (26.7%)	0.6196007	1
Emergency admission, (%)	1,136/6,079 (18.7%)	1,394/6,879 (20.3%)	0.0249086	0.199
Previous CABG, % (%)	408/6,079 (6.7%)	447/6,879 (6.5%)	0.6448937	1
Previous PCI, %	764/6,079 (12.6%)	770/6,879 (11.2%)	0.0164899	0.148
Previous dialysis, %	92/6,079 (1.5%)	98/6,879 (1.4%)	0.7144042	1
History of stroke, %	491/6,079 (8.1%)	558/6,879 (8.1%)	0.9485645	1
History of myocardial infarction, %	731/6,079 (12%)	805/6,879 (11.7%)	0.5860558	1
History of conduction abnormalities/arrhythmia, %	3,210/6,079 (52.8%)	3,420/6,879 (49.7%)	0.0004583	0.005*

Key: Significance of **adjusted** p-values (using Holm-Bonferroni correction) denoted by: *** < 0.001, ** <0.01, * < 0.05. Abbreviations: CABG, Coronary artery bypass graft; CI, Confidence Interval; HES, Hospital Episode Statistics; PCI, Percutaneous coronary intervention; Q1, Quartile 1; Q3, Quartile 3

Mortality

There were a total of 249 in-hospital deaths during the TAVI procedural admission. A total of 1,884 deaths occurred at any time after hospital discharge from the index procedure; 229 deaths occurred between discharge and 30 days. Of the 1,655 deaths occurring after 30 days follow-up, 628 (33.3%) were because of major cardiovascular disease.

Main cause of death (in-hospital, within 30 days of discharge); restricted to the top ten causes reported per time period.

ICD10 code (main cause)	Description	Freq (in-hospital)	Freq (between discharge and 30 days)
I35.0	Aortic (valve) stenosis	115	39
I35.9	Aortic valve disorder, unspecified	24	12
I71.8	Aortic aneurysm of unspecified site, ruptured	<10	-
I08.3	Combined disorders of mitral, aortic and tricuspid valves	<10	-
I21.9	Acute myocardial infarction, unspecified	<10	10
I25.1	Atherosclerotic heart disease	<10	<10

ICD10 code (main cause)	Description	Freq (in-hospital)	Freq (between discharge and 30 days)
I25.9	Chronic ischaemic heart disease, unspecified	<10	14
I38	Endocarditis, valve unspecified	<10	-
I64	Stroke, not specified as haemorrhage or infarction	<10	<10
J44.0	Chronic obstructive pulmonary disease with acute lower respiratory infection	-	<10
J44.1	Chronic obstructive pulmonary disease with acute exacerbation, unspecified	-	-
I71.0	Dissection of aorta [any part]	<10	-
J18.0	Bronchopneumonia, unspecified	-	-
J18.9	Pneumonia, unspecified	-	<10
U07.1	Emergency use of U07.1 (COVID-19)	-	<10
W19	Unspecified fall	-	<10

Major cardiovascular causes of death (main cause of death >30 days, with frequency 10 or more)

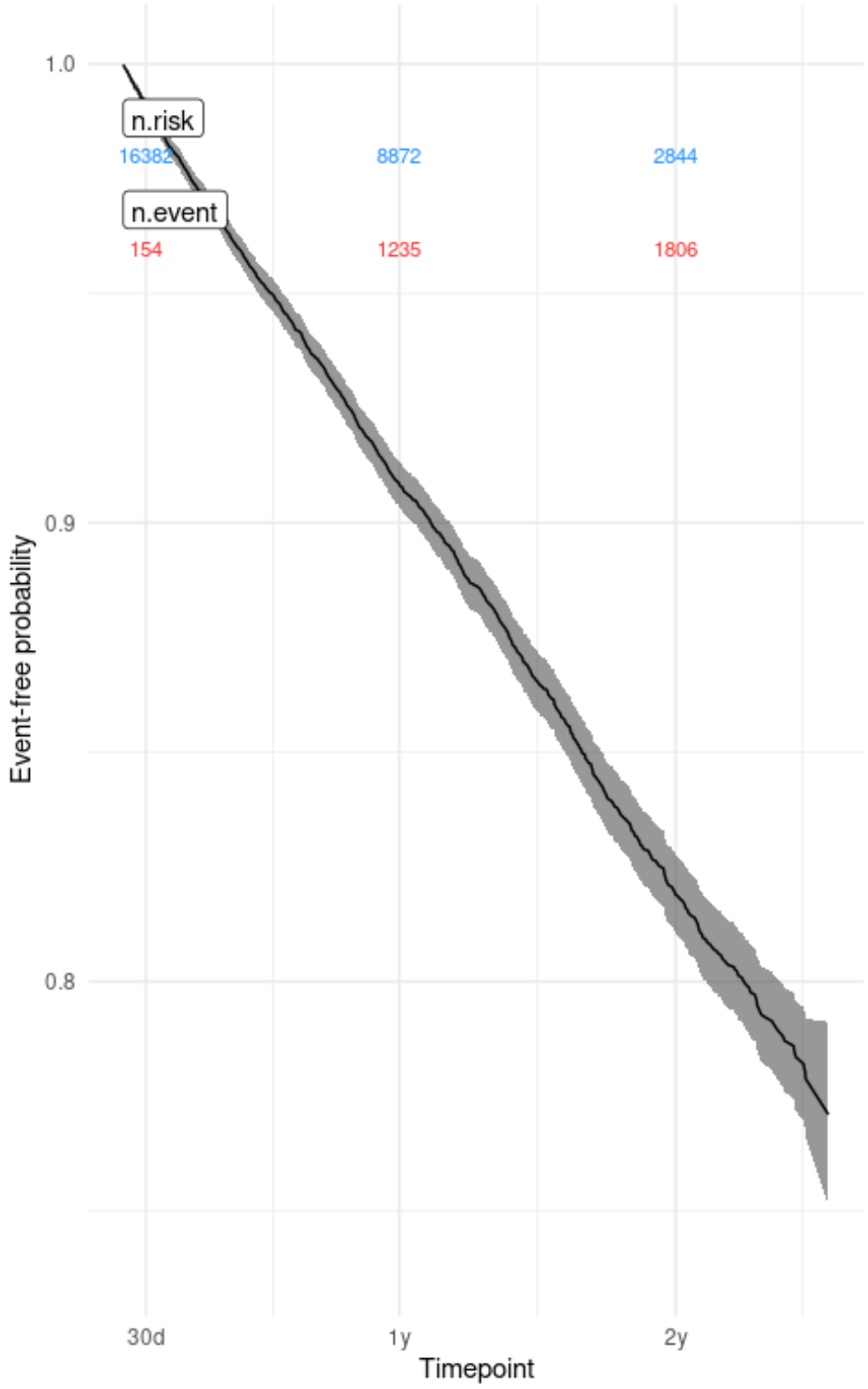
Freq	ICD10 code (main cause)	Description
135	I25.9	Chronic ischaemic heart disease, unspecified
109	I35.0	Aortic (valve) stenosis
53	I21.9	Acute myocardial infarction, unspecified
37	I35.9	Aortic valve disorder, unspecified
34	I50.0	Congestive heart failure
31	I48.9	Atrial fibrillation and atrial flutter, unspecified
29	I25.1	Atherosclerotic heart disease
23	I50.9	Heart failure, unspecified
19	I64	Stroke, not specified as haemorrhage or infarction
17	I67.9	Cerebrovascular disease, unspecified
16	I63.9	Cerebral infarction, unspecified
14	I61.9	Intracerebral haemorrhage, unspecified
14	I73.9	Peripheral vascular disease, unspecified
11	I11.0	Hypertensive heart disease with (congestive) heart failure

Other causes of death, including non-major cardiovascular causes (main cause of death >30 days, with frequency 10 or more).

Freq	ICD10 code (main cause)	Description
75	J18.9	Pneumonia, unspecified

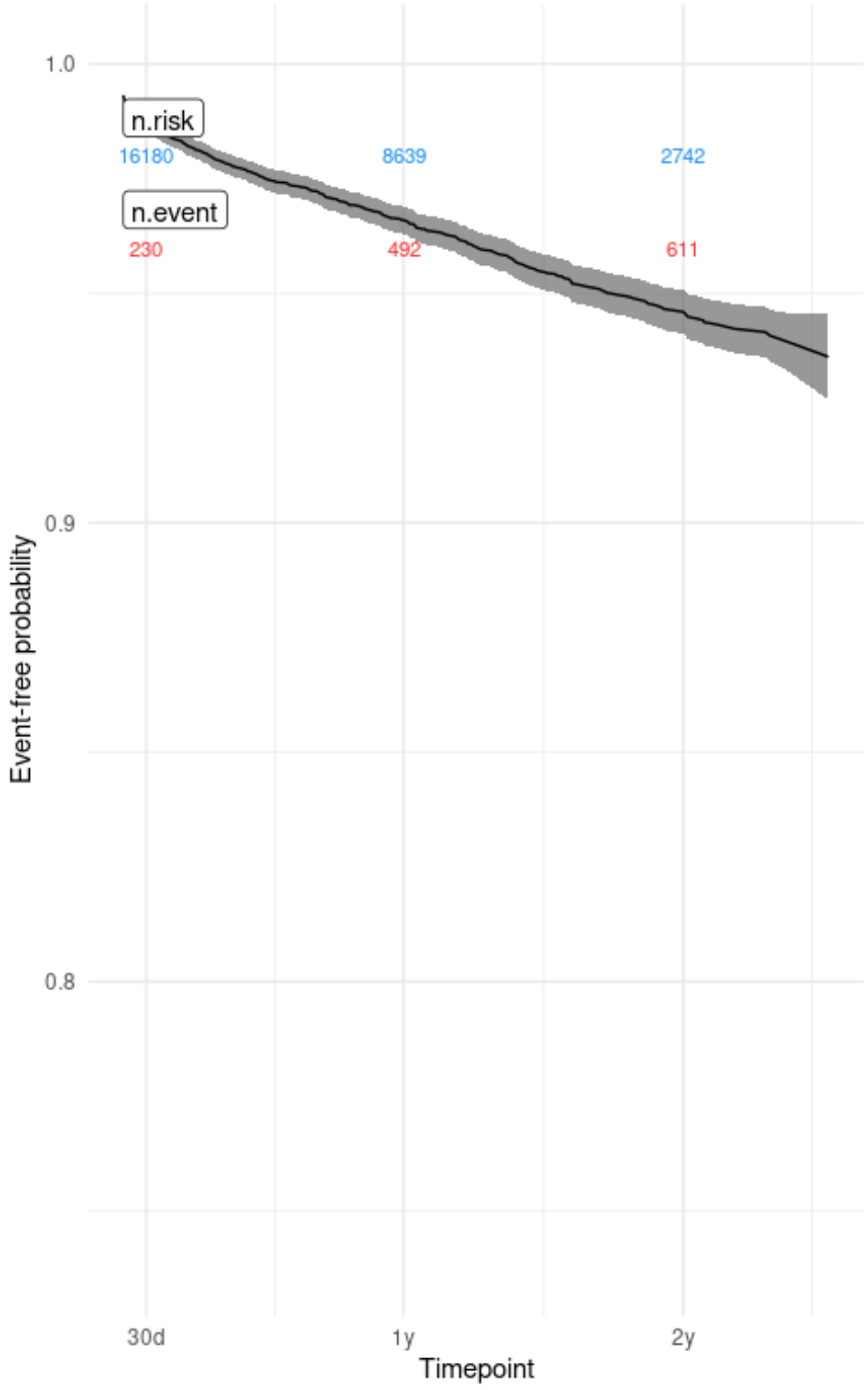
Freq	ICD10 code (main cause)	Description
52	U07.1	Emergency use of U07.1 (COVID-19)
49	C34.9	Malignant neoplasm: Bronchus or lung, unspecified
40	I38	Endocarditis, valve unspecified
39	J44.0	Chronic obstructive pulmonary disease with acute lower respiratory infection
37	C61	Malignant neoplasm of prostate
35	N39.0	Urinary tract infection, site not specified
30	F03	Unspecified dementia
25	A41.9	Sepsis, unspecified
22	W19	Unspecified fall
21	I33.0	Acute and subacute infective endocarditis
20	C25.9	Malignant neoplasm: Pancreas, unspecified
17	C67.9	Malignant neoplasm: Bladder, unspecified
17	J18.0	Bronchopneumonia, unspecified
17	J84.1	Other interstitial pulmonary diseases with fibrosis
15	J44.9	Chronic obstructive pulmonary disease, unspecified
14	C50.9	Malignant neoplasm: Breast, unspecified
13	K55.9	Vascular disorder of intestine, unspecified
12	F01.9	Vascular dementia, unspecified
12	J22	Unspecified acute lower respiratory infection
12	J84.9	Interstitial pulmonary disease, unspecified
12	R68.8	Other specified general symptoms and signs
11	C18.9	Malignant neoplasm: Colon, unspecified
11	C64	Malignant neoplasm of kidney, except renal pelvis
10	C15.9	Malignant neoplasm: Oesophagus, unspecified
10	C80.0	Malignant neoplasm, primary site unknown, so stated
10	J44.1	Chronic obstructive pulmonary disease with acute exacerbation, unspecified
10	R54	Senility

Kaplan-Meier (mortality outcome post-discharge); HES only



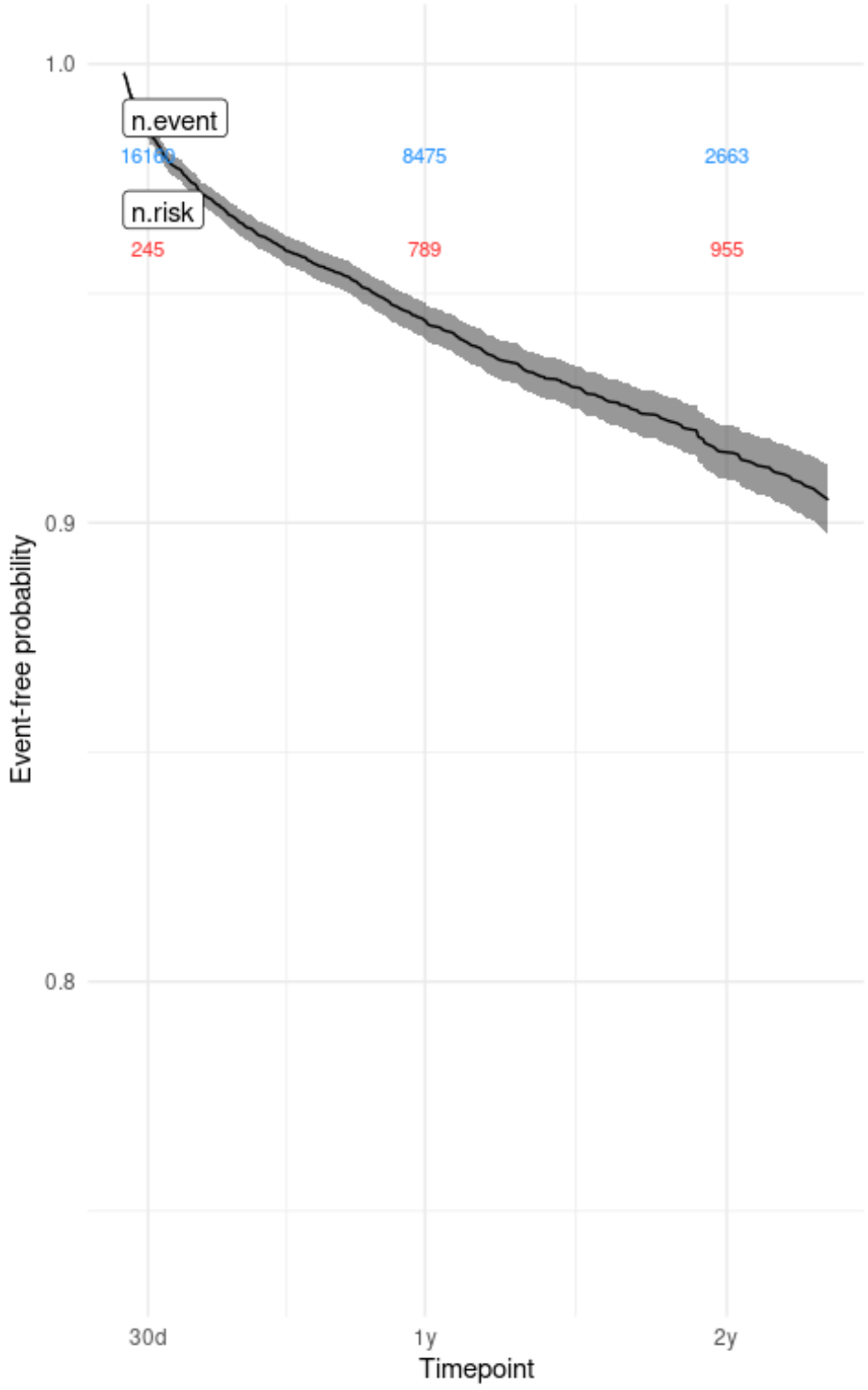
Stroke

Kaplan-Meier (stroke outcome post-discharge) for cohort identified in HES



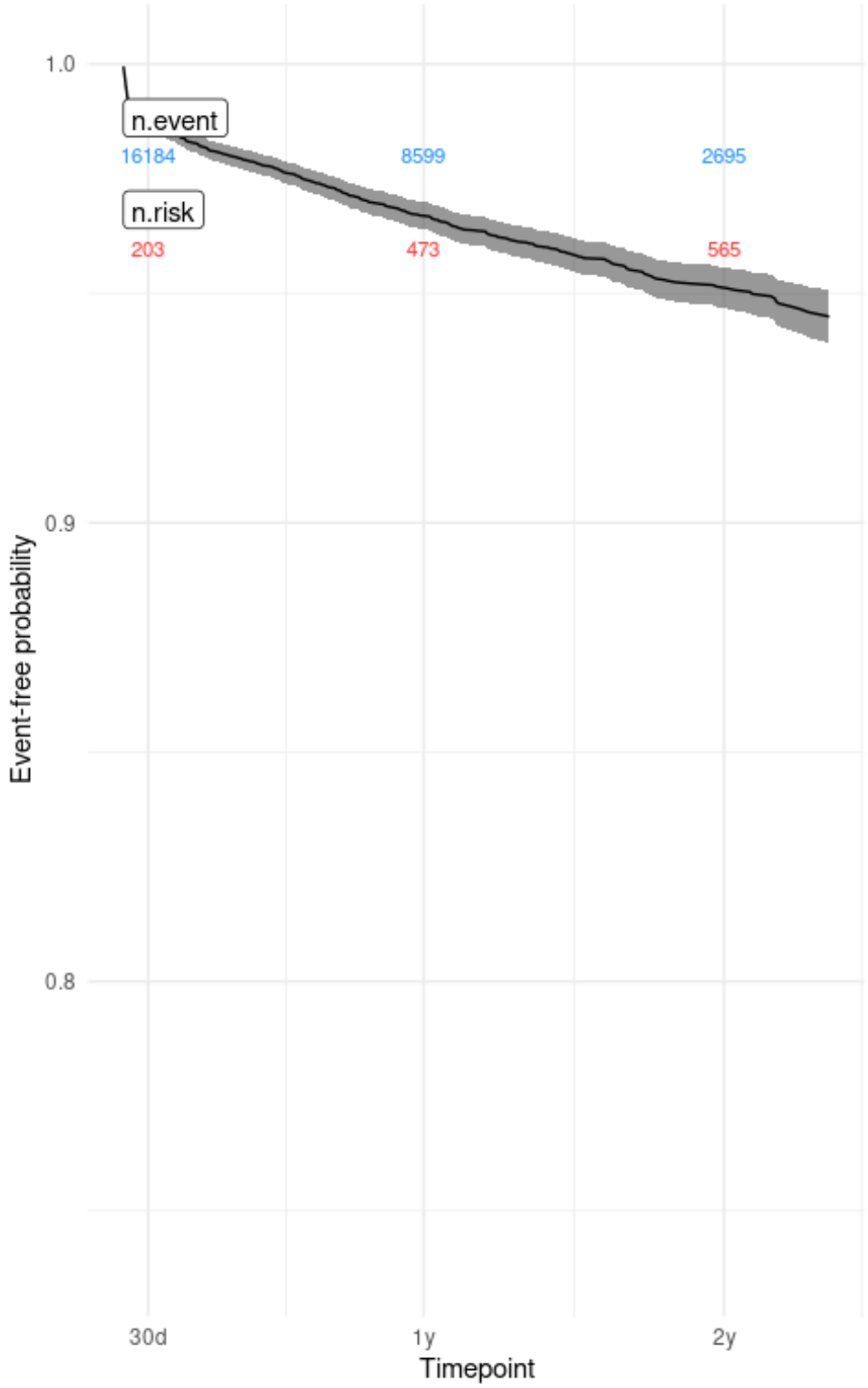
Readmission with heart failure

Kaplan-Meier (readmission for heart failure outcome post-discharge) for cohort identified in HES



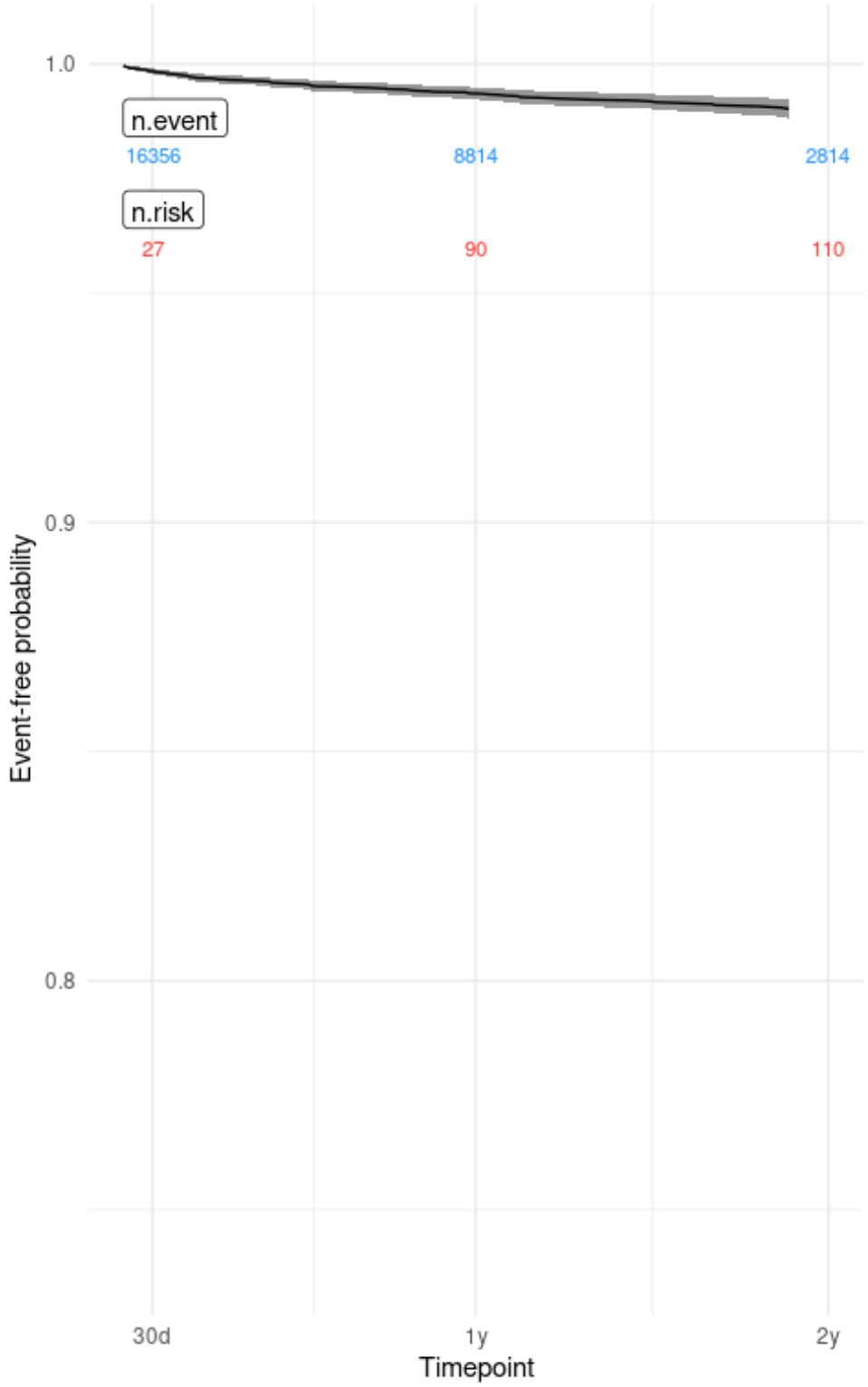
Pacemaker implantation

Kaplan-Meier (pacemaker implantation outcome post-discharge) for cohort identified in HES



Aortic valve reintervention

Kaplan-Meier (aortic valve reintervention, including both SAVR and TAVI, post-discharge) for cohort identified in HES



Appendix D4: Data Suitability Assessment Tool (DataSAT) for HES
Reviewer: KK

Research question: to define the patient and procedural characteristics, and outcomes of a population undergoing TAVI within UK NHS setting.

Data provenance

Item	Response
Data sources	Hospital episode statistics (HES) Admitted Patient Care data.
Data linkage and data pooling	Linked to Civil Registration of Mortality (formerly ONS mortality).
Type of data source	Administrative records.
Purpose of data collection	Hospital Episode Statistics (HES) is derived from the Secondary Uses Service (SUS) data based on information submitted to NHS digital by healthcare providers. Data collection is primarily intended to support the reimbursement of hospitals for the provision of services in England.
Data collection	Diagnoses (ICD-10), procedures (OPCS-4), admission, discharge, type of care, basic demographics. HES data are collected during a patient's time at hospital and may be recorded during their interactions with health and care staff in the hospital and assembled by teams of clinical coders (usually after discharge from patient notes).
Care setting	Secondary care (NHS and private)
Geographical setting	England only
Population coverage	HES data covers all NHS Clinical Commissioning Groups in England.
Time period of data	Discharge date between 01 April 2021 to 31 October 2023
Data preparation	Pseudonymised episode-level data shared by NHS Digital; HES applies centralised processing before the data are released for research. EAG aggregates episodes into spells (or admission).
Data governance	HES data is controlled by the Health and Social Care Information Centre (also known as NHS Digital). HES data collection is mandated and funded by the UK Government. Hospital episode statistics GDPR webpage.
Data specification	Fields in HES are derived from the NHS data model and the NHS data dictionary.
Data management plan and quality assurance methods	HES undertakes processing and data quality checks: The processing cycle and HES data quality.
Other documents	Provisional monthly reports for HES APC

Abbreviations: APC, Admitted patient care; EAG, External Assessment Group; HES, Hospital episode statistics; ONS, Office for National Statistics

Data quality

Study variable	Target concept	Operational definition	Quality dimension	How assessed	Assessment result
Population	Patients undergoing TAVI	OPCS codes: see Appendix D1	Completeness	Compared with NICOR annual report (14,407)	Completeness of HES for same time period (01 April 2021 to 31 March 2023): 89.9% (12,958/14,407)
Population	Age	STARTAGE (age on admission)	Accuracy (mandatory field so implied 100% completeness)	Missingness and range	0 missing STARTAGE (mandatory field); range 34 to 91 years.
Intervention	Emergency admission	ADMIMETH	Accuracy	Compared with NICOR 2024 report	3344/17218 (19.4%) compared with NICOR report 2024 (25%)
Outcome	Length of stay	Calculated from DISDATE-ADMIDATE	Accuracy (mandatory fields so implied 100% completeness)	Compared with NICOR 2024 report	Median [Q1,Q3]; 3 [2 to 8 days] in agreement with NICOR report 2024; median of 3 days.
Outcome	In-hospital stroke	DIAG 01-20 using ICD10 codes (see Appendix D1)	Accuracy (mandatory fields so implied 100% completeness)	Compared with NICOR 2024 report	359/17,218 (2.1%) compared with NICOR report 2024 (1.4%)
Outcome	Bleeding	DIAG 01-20 using ICD10 codes (see Appendix D1)	Accuracy (mandatory fields so implied 100% completeness)	Compared with NICOR 2024 report	1,664/17,218 (9.7%) compared with NICOR report 2024 (1.0%). HES does not capture severity of events hence leading to overestimate.
Outcome	Permanent pacemaker	OPERTN 01-24 using OPCS codes (see Appendix D1)	Accuracy	Compared with NICOR 2024 report	1,568/17,218 (9.1%) compared with NICOR report 2024 (7.4%)

Abbreviations: HES, Hospital episode statistics; NICOR, National Institute for Cardiovascular Outcomes Research; Q1, Quartile 1 Q3, Quartile 3

Data relevance

Item	Response
Population	Cleaning steps aggregate episodes into spells (admissions) and consistency checks applied. Additional exclusions applied to narrow to similar population to UK TAVI Registry analysis.
Care setting	Appropriate. TAVI are conducted in secondary care setting, while relevant events may be observed in primary or secondary care.
Treatment pathway	The data represents routine practice in the NHS.
Availability of key study elements	No physiological measurements, surgical risk group, annular calcification (burden or distribution), coronary height, valve morphology (bicuspid), left ventricular outflow tract or other risk factors which may inform choice of TAVI valve. No information on device (type, manufacturer, model, size) or medication used. No quality of life or mobility measures. No measurement of operator experience.
Study period	Latest 2 years of data, reflective of NHS practice.
Timing of measurements	Longitudinal analysis, capturing both in-hospital and out-of-hospital outcomes.
Follow up	Follow-up to 31st October 2023 (latest quarterly data available to EAG within DARS-NIC-170211-Z1B4J)
Sample size	Sample size represents all TAVI patients within 2 financial years.

Abbreviations: EAG, External Assessment Group; TAVI, transcatheter aortic valve implantation

Appendix E: Linked UK TAVI Registry & HES data

Appendix E1: Matching criteria and matches at each step

Note that data linkage between UK TAVI Registry and HES data is only possible for 7,028 procedures conducted in England (hence 381 procedures have been removed from the main analysis).

Step	Criteria	Available for matching	Unmatched	Unique 1:1 matches using NHS Trust, sex, age, dates of admission, procedure and discharge.	Non-unique matches made unique by adding extra characteristics (consistency between patient comorbidities: diabetes, procedural characteristics: elective procedure, or clinical history: previous MI, previous stroke)	Total matched in step
1	NHS Trust: exact match Sex: exact match Age: exact match Procedure date: exact match Admission date: exact match Discharge date: exact match	7017	3210	3781	26	3807
2	NHS Trust: exact match Sex: exact match Age: exact match Procedure date: exact match Admission date: matched to +/- 1 day Discharge date: matched to +/- 1 day Admission date, discharge date: 1 exact match	3210	2803	406	1	407
3	NHS Trust: exact match Sex: exact match Age: exact match Procedure date: matched to +/- 1 day Admission date: matched to +/- 1 day Discharge date: matched to +/- 1 day Procedure date, admission date, discharge date: 2 exact matches	2803	2650	153	0	153
4	NHS Trust: exact match Sex: exact match Age: exact match Procedure date: matched to +/- 1 day Admission date: matched to +/- 1 day Discharge date: matched to +/- 1 day Procedure date, admission date, discharge date: 1 exact match	2650	2597	52	1	53
5	NHS Trust: exact match Sex: exact match Age: exact match Procedure date: exact match	2597	713	1829	55	1884
6	Separate matching procedure described in flowchart (Figure 3)	-	-	-	-	-
7	NHS Trust: exact match Sex: exact match Age: exact match Procedure date: matched to +/- 1 day	713	639	72	2	74
8	NHS Trust: exact match Sex: exact match Age: matched to +/- 1 year Procedure date: exact match	639	584	53	2	55
9	NHS Trust: exact match Sex: exact match Age: exact match Procedure date: matched to +/- 2 days	584	564	20	0	20
10	NHS Trust: exact match Sex: exact match Age: matched to +/- 2 years Procedure date: exact match	564	552	11	1	12
11	NHS Trust: exact match Sex: exact match Age: matched to +/- 1 year Procedure date: matched to +/- 1 day	552	542	9	1	10
12	NHS Trust: exact match Sex: exact match Age: matched to +/- 2 years Procedure date:+/- 2 days	542	518	21	3	24

Appendix E2: Comparison of UK TAVI Registry procedures matched, and unmatched, to a HES procedure, unadjusted

Cohort 1: TAVI in native aortic valve (n=6,757)

Patient and procedural characteristics	Unmatched (n=487)	Matched (n=6,270)	p-value, **unadjusted**	p-value, **adjusted**
Age, years: median [Q1,Q3]	82.0 [77.0 to 86.0] (n=487)	82.0 [77.0 to 86.0] (n=6,270)	0.9569072	1
Age (90+ years)	37/487 (7.6%)	517/6,270 (8.2%)	0.6685964	1
Male sex	294/483 (60.9%)	3,666/6,261 (58.6%)	0.3375259	1
Height, m: median [Q1,Q3]	1.7 [1.6 to 1.7] (n=461)	1.7 [1.6 to 1.7] (n=5,875)	0.3356724	1
Weight, kg: median [Q1,Q3]	76.0 [65.0 to 89.0] (n=463)	76.0 [65.9 to 88.0] (n=5,894)	0.7674284	1
BMI, kg/m2: median [Q1,Q3]	27.2 [23.8 to 31.6] (n=461)	27.3 [24.1 to 31.1] (n=5,846)	0.9103061	1
Underweight (BMI under 17.5)	8/461 (1.7%)	105/5,846 (1.8%)	1.0000000	1
Obese (BMI 30 or above)	152/461 (33.0%)	1843/5,846 (31.5%)	0.5326016	1
Pulmonary artery systolic pressure, mmHg: median [Q1,Q3]	29.0 [20.0 to 40.0] (n=133)	34.0 [25.0 to 45.0] (n=1,723)	0.0009876	0.052
Mean pressure gradient, mmHg: median [Q1,Q3]	44.0 [37.0 to 55.0] (n=456)	44.0 [35.0 to 55.0] (n=5,887)	0.3765017	1
Peak pressure gradient, mmHg: median [Q1,Q3]	70.0 [56.5 to 83.3] (n=455)	70.0 [58.0 to 86.0] (n=5,776)	0.5433322	1
Valve area, cm2: median [Q1,Q3]	0.7 [0.6 to 0.8] (n=434)	0.7 [0.6 to 0.9] (n=5,547)	0.3346420	1
Annular diameter, mm: median [Q1,Q3]	24.6 [23.0 to 26.0] (n=397)	24.6 [23.0 to 26.0] (n=4,883)	0.8834980	1
Extensive calcification of ascending aorta	16/458 (3.5%)	198/5,826 (3.4%)	0.8933736	1
Critical status pre-procedure	4/478 (0.8%)	71/6,080 (1.2%)	0.6575410	1
CCS Angina Status (any limitation of physical activity)	111/473 (23.5%)	1,386/6,058 (22.9%)	0.7764823	1
CCS Angina Status (symptoms at rest)	4/473 (0.8%)	58/6,058 (1.0%)	1.0000000	1
NYHA dyspnoea status (marked limitation of physical activity, or symptoms at rest or minimal activity)	357/476 (75.0%)	4,522/6,103 (74.1%)	0.7036401	1
NYHA dyspnoea status (symptoms at rest)	67/476 (14.1%)	689/6,103 (11.3%)	0.0730042	1
Severe symptoms (symptoms at rest measured by CCS Angina Status or NYHA dyspnoea status)	71/478 (14.9%)	721/6,144 (11.7%)	0.0479573	1
CSHA Clinical Frailty Score (moderately or severely frail)	32/468 (6.8%)	445/5,851 (7.6%)	0.5864447	1
Katz Index less than 3	16/450 (3.6%)	170/5,624 (3.0%)	0.4787631	1
Katz Index less than 6	63/450 (14.0%)	749/5,624 (13.3%)	0.6661093	1
Frailty composite (moderately or severely frail on CSHA, or Katz Index less than 6)	81/477 (17.0%)	1,060/5,961 (17.8%)	0.7085752	1
Poor LV function (LVEF<30%)	39/481 (8.1%)	495/6,021 (8.2%)	1.0000000	1
Diabetes	100/469 (21.3%)	1,616/6,124 (26.4%)	0.0162120	0.827
Ever smoked (current and ex smokers)	176/361 (48.8%)	2,431/5,017 (48.5%)	0.9133112	1
Dialysis	8/478 (1.7%)	101/6,083 (1.7%)	1.0000000	1
Presence of left main stem disease	13/428 (3.0%)	131/5,340 (2.5%)	0.4212249	1
Presence of >50% stenosis in at least one coronary vessel	97/428 (22.7%)	1,365/5,304 (25.7%)	0.1668559	1
Valve size, mm: median [Q1,Q3]	26.0 [23.0 to 29.0] (n=487)	26.0 [23.0 to 29.0] (n=6,270)	0.7931440	1
Valve size (categorical: small, medium, large)	S: 140/487 (28.7%); M: 194/487 (39.8%); L: 153/487 (31.4%)	S: 1,867/6,270 (29.8%); M: 2,443/6,270 (39%); L: 1,960/6,270 (31.3%)	0.8930535	1
Non-elective procedure	132/486 (27.2%)	1,493/6,253 (23.9%)	0.1103016	1
Procedure urgency (non-elective procedure, or critical status pre-procedure)	132/487 (27.1%)	1,508/6,270 (24.1%)	0.1383966	1
Planned use of general anaesthesia	4/478 (0.8%)	62/6,235 (1.0%)	1.0000000	1
Previous balloon aortic valvuloplasty	18/482 (3.7%)	175/6,185 (2.8%)	0.2575437	1
Use of cardiopulmonary bypass	5/479 (1.0%)	20/6,181 (0.3%)	0.0301449	1
Use of cerebral circulation protection device(s)	34/479 (7.1%)	725/6,227 (11.6%)	0.0020661	0.107
Creatinine clearance, mL/min: median [Q1,Q3]	55.6 [41.9 to 73.9] (n=452)	56.2 [41.2 to 73.3] (n=5,588)	0.6796966	1
Creatinine clearance less than 30 mL/min	42/452 (9.3%)	500/5,588 (8.9%)	0.7973967	1
Previous MI (ever)	52/483 (10.8%)	746/6,185 (12.1%)	0.4240491	1
Previous MI (within previous 90 days)	11/483 (2.3%)	127/6,185 (2.1%)	0.7387076	1
Previous PCI	69/478 (14.4%)	784/6,167 (12.7%)	0.2868038	1
Previous CABG	38/474 (8.0%)	497/6,050 (8.2%)	0.9309120	1
Previous stroke or TIA	63/477 (13.2%)	709/6,146 (11.5%)	0.2670130	1
Presence of extracardiac arteriopathy	37/475 (7.8%)	535/6,081 (8.8%)	0.4997883	1
Any cardiac or coronary comorbidity (previous MI, PCI, or CABG, presence of extracardiac arteriopathy or aortic calcification, symptoms at rest on NYHA or CCS, poor LV function, left main stem disease or stenosis of at least 50% in one vessel)	243/487 (49.9%)	2,895/6,253 (46.3%)	0.1313033	1

Patient and procedural characteristics	Unmatched (n=487)	Matched (n=6,270)	p-value, **unadjusted**	p-value, **adjusted**
Anatomical coronary comorbidity (left main stem disease, or stenosis of at least 50% in one vessel)	98/439 (22.3%)	1,379/5,430 (25.4%)	0.1698943	1
Clinical coronary comorbidity (previous MI, PCI or CABG)	113/484 (23.3%)	1,390/6,221 (22.3%)	0.6107412	1
Any non-cardiac or non-coronary comorbidity (previous stroke or TIA, diabetes, current or former smoker, extracardiac arteriopathy, current dialysis or creatinine clearance less than 30)	291/485 (60.0%)	3,929/6,218 (63.2%)	0.1716516	1
Non-cardiac non-coronary other comorbidity (previous stroke or extracardiac arteriopathy)	92/481 (19.1%)	1,131/6,190 (18.3%)	0.6250127	1
Non-cardiac non-coronary risk factor (current or former smoker, or diabetes)	231/475 (48.6%)	3,340/6,183 (54.0%)	0.0248027	1
Renal comorbidity (current dialysis or creatinine clearance less than 30)	45/479 (9.4%)	534/6,152 (8.7%)	0.6138198	1

Key: Significance of **adjusted** p-values (using Holm-Bonferroni correction) denoted by: *** < 0.001, ** <0.01, * < 0.05. Abbreviations: CABG, Coronary artery bypass grafting; CCS, Canadian Cardiovascular Society; LVEF, Left ventricular ejection fraction; MI, Myocardial infarction; NYHA, New York Heart Association; PCI, Percutaneous coronary intervention; TIA, Transient ischaemic attack; Q1, Quartile 1; Q3, Quartile 3

Cohort 2: TAVI in SAVR (n=245)

Patient and procedural characteristics	Unmatched (n=30)	Matched (n=215)	p-value, **unadjusted**	p-value, **adjusted**
Age, years: median [Q1,Q3]	77.0 [74.0 to 82.0] (n=30)	78.0 [73.0 to 82.0] (n=215)	0.6825829	1
Age (90+ years)	1/30 (3.3%)	2/215 (0.9%)	0.3253638	1
Male sex	19/30 (63.3%)	139/215 (64.7%)	1.0000000	1
Height, m: median [Q1,Q3]	1.7 [1.6 to 1.8] (n=29)	1.7 [1.6 to 1.8] (n=206)	0.6042779	1
Weight, kg: median [Q1,Q3]	77.2 [64.2 to 82.0] (n=29)	78.0 [65.8 to 90.0] (n=206)	0.4231693	1
BMI, kg/m2: median [Q1,Q3]	26.0 [24.2 to 28.4] (n=28)	27.4 [23.6 to 30.9] (n=205)	0.3253919	1
Underweight (BMI under 17.5)	0/28 (0%)	1/205 (0.5%)	1.0000000	1
Obese (BMI 30 or above)	5/28 (17.9%)	62/205 (30.2%)	0.2646629	1
Pulmonary artery systolic pressure, mmHg: median [Q1,Q3]	37.5 [35.0 to 43.0] (n=10)	41.0 [29.5 to 48.0] (n=99)	0.9204987	1
Mean pressure gradient, mmHg: median [Q1,Q3]	41.0 [30.0 to 51.5] (n=23)	34.0 [22.0 to 48.0] (n=192)	0.0875948	1
Peak pressure gradient, mmHg: median [Q1,Q3]	64.0 [50.0 to 89.0] (n=25)	59.0 [38.0 to 77.5] (n=187)	0.2145292	1
Valve area, cm2: median [Q1,Q3]	0.8 [0.6 to 1.0] (n=17)	0.9 [0.7 to 1.2] (n=137)	0.2096571	1
Annular diameter, mm: median [Q1,Q3]	23.0 [20.6 to 23.0] (n=23)	22.0 [20.0 to 24.0] (n=156)	0.6584836	1
Extensive calcification of ascending aorta	2/29 (6.9%)	6/204 (2.9%)	0.2610912	1
Critical status pre-procedure	0/30 (0%)	20/209 (9.6%)	0.0862126	1
CCS Angina Status (any limitation of physical activity)	7/30 (23.3%)	37/211 (17.5%)	0.4514089	1
CCS Angina Status (symptoms at rest)	0/30 (0%)	4/211 (1.9%)	1.0000000	1
NYHA dyspnoea status (marked limitation of physical activity, or symptoms at rest or minimal activity)	21/29 (72.4%)	181/209 (86.6%)	0.0552168	1
NYHA dyspnoea status (symptoms at rest)	8/29 (27.6%)	46/209 (22.0%)	0.4849958	1
Severe symptoms (symptoms at rest measured by CCS Angina Status or NYHA dyspnoea status)	8/30 (26.7%)	48/212 (22.6%)	0.6456690	1
CSHA Clinical Frailty Score (moderately or severely frail)	3/30 (10.0%)	13/208 (6.2%)	0.4338912	1
Katz Index less than 3	1/28 (3.6%)	6/197 (3.0%)	1.0000000	1
Katz Index less than 6	7/28 (25.0%)	29/197 (14.7%)	0.1726610	1
Frailty composite (moderately or severely frail on CSHA, or Katz Index less than 6)	10/30 (33.3%)	39/211 (18.5%)	0.0862586	1
Poor LV function (LVEF<30%)	4/29 (13.8%)	22/212 (10.4%)	0.5300993	1
Diabetes	6/30 (20.0%)	42/213 (19.7%)	1.0000000	1
Ever smoked (current and ex smokers)	11/28 (39.3%)	74/190 (38.9%)	1.0000000	1
Dialysis	1/30 (3.3%)	6/214 (2.8%)	1.0000000	1
Presence of left main stem disease	1/27 (3.7%)	7/200 (3.5%)	1.0000000	1
Presence of >50% stenosis in at least one coronary vessel	4/28 (14.3%)	45/198 (22.7%)	0.4619995	1
Valve size, mm: median [Q1,Q3]	23.0 [23.0 to 26.0] (n=30)	23.0 [23.0 to 26.0] (n=215)	0.6928077	1
Valve size (categorical: small, medium, large)	S: 16/30 (53.3%); M: 14/30 (46.7%); L: 0/30 (0%)	S: 128/215 (59.5%); M: 70/215 (32.6%); L: 17/215 (7.9%)	0.1219390	1
Non-elective procedure	8/30 (26.7%)	100/215 (46.5%)	0.0494420	1
Procedure urgency (non-elective procedure, or critical status pre-procedure)	8/30 (26.7%)	102/215 (47.4%)	0.0486425	1
Planned use of general anaesthesia	1/30 (3.3%)	12/214 (5.6%)	1.0000000	1
Previous balloon aortic valvuloplasty	1/30 (3.3%)	2/214 (0.9%)	0.3265307	1
Use of cardiopulmonary bypass	1/29 (3.4%)	1/210 (0.5%)	0.2284027	1
Use of cerebral circulation protection device(s)	3/29 (10.3%)	32/214 (15.0%)	0.7776054	1
Creatinine clearance, mL/min: median [Q1,Q3]	56.1 [39.8 to 65.3] (n=27)	53.3 [39.1 to 72.5] (n=199)	0.8753750	1
Creatinine clearance less than 30 mL/min	2/27 (7.4%)	19/199 (9.5%)	1.0000000	1
Previous MI (ever)	3/30 (10.0%)	29/214 (13.6%)	0.7760331	1
Previous MI (within previous 90 days)	1/30 (3.3%)	7/214 (3.3%)	1.0000000	1
Previous PCI	4/30 (13.3%)	20/214 (9.3%)	0.5109425	1
Previous CABG	11/30 (36.7%)	58/214 (27.1%)	0.2845417	1
Previous stroke or TIA	5/30 (16.7%)	23/213 (10.8%)	0.3592767	1
Presence of extracardiac arteriopathy	3/30 (10.0%)	16/214 (7.5%)	0.7128411	1

Patient and procedural characteristics	Unmatched (n=30)	Matched (n=215)	p-value, **unadjusted**	p-value, **adjusted**
Any cardiac or coronary comorbidity (previous MI, PCI, or CABG, presence of extracardiac arteriopathy or aortic calcification, symptoms at rest on NYHA or CCS, poor LV function, left main stem disease or stenosis of at least 50% in one vessel)	22/30 (73.3%)	128/215 (59.5%)	0.1657907	1
Anatomical coronary comorbidity (left main stem disease, or stenosis of at least 50% in one vessel)	4/28 (14.3%)	46/202 (22.8%)	0.4628054	1
Clinical coronary comorbidity (previous MI, PCI or CABG)	13/30 (43.3%)	72/215 (33.5%)	0.3100047	1
Any non-cardiac or non-coronary comorbidity (previous stroke or TIA, diabetes, current or former smoker, extracardiac arteriopathy, current dialysis or creatinine clearance less than 30)	19/30 (63.3%)	124/215 (57.7%)	0.6931997	1
Non-cardiac non-coronary other comorbidity (previous stroke or extracardiac arteriopathy)	8/30 (26.7%)	35/215 (16.3%)	0.1975623	1
Non-cardiac non-coronary risk factor (current or former smoker, or diabetes)	15/30 (50.0%)	103/215 (47.9%)	0.8478468	1
Renal comorbidity (current dialysis or creatinine clearance less than 30)	3/30 (10.0%)	22/214 (10.3%)	1.0000000	1

Key: Significance of **adjusted** p-values (using Holm-Bonferroni correction) denoted by: *** < 0.001, ** <0.01, * < 0.05. Abbreviations: CABG, Coronary artery bypass grafting; CCS, Canadian Cardiovascular Society; LVEF, Left ventricular ejection fraction; MI, Myocardial infarction; NYHA, New York Heart Association; PCI, Percutaneous coronary intervention; TIA, Transient ischaemic attack; Q1, Quartile 1; Q3, Quartile 3

Cohort 3: TAVI in TAVI (n=26)

Patient and procedural characteristics	Unmatched (n=3)	Matched (n=23)	p-value, **unadjusted**	p-value, **adjusted**
Age, years: median [Q1,Q3]	77.0 [72.5 to 80.0] (n=3)	78.0 [73.0 to 82.5] (n=23)	0.7783436	1
Age (90+ years)	0/3 (0%)	0/23 (0%)	1.0000000	1
Male sex	2/3 (66.7%)	14/23 (60.9%)	1.0000000	1
Height, m: median [Q1,Q3]	1.8 [1.6 to 1.8] (n=3)	1.7 [1.6 to 1.8] (n=22)	0.8670479	1
Weight, kg: median [Q1,Q3]	89.0 [75.0 to 106.0] (n=3)	79.6 [70 to 89] (n=22)	0.5579205	1
BMI, kg/m2: median [Q1,Q3]	28.4 [28.3 to 33.0] (n=3)	28.6 [24.8 to 30.7] (n=22)	0.5033353	1
Underweight (BMI under 17.5)	0/3 (0%)	1/22 (4.5%)	1.0000000	1
Obese (BMI 30 or above)	1/3 (33.3%)	8/22 (36.4%)	1.0000000	1
Pulmonary artery systolic pressure, mmHg: median [Q1,Q3]	51.0 [43.0 to 73.5] (n=3)	42.5 [30.2 to 51.5] (n=10)	0.3525421	1
Mean pressure gradient, mmHg: median [Q1,Q3]	41.0 [32.0 to 41.5] (n=3)	36.0 [20.0 to 49.5] (n=19)	1.0000000	1
Peak pressure gradient, mmHg: median [Q1,Q3]	62.0 [54.0 to 64.0] (n=3)	68.5 [43.8 to 85.5] (n=18)	0.6151878	1
Valve area, cm2: median [Q1,Q3]	1.3 [0.9 to 1.8] (n=3)	0.8 [0.6 to 1.0] (n=14)	0.3757661	1
Annular diameter, mm: median [Q1,Q3]	23.3 [17.1 to 24.6] (n=3)	23.0 [22.0 to 24.0] (n=13)	1.0000000	1
Extensive calcification of ascending aorta	0/3 (0%)	2/21 (9.5%)	1.0000000	1
Critical status pre-procedure	0/3 (0%)	1/23 (4.3%)	1.0000000	1
CCS Angina Status (any limitation of physical activity)	1/3 (33.3%)	7/23 (30.4%)	1.0000000	1
CCS Angina Status (symptoms at rest)	0/3 (0%)	1/23 (4.3%)	1.0000000	1
NYHA dyspnoea status (marked limitation of physical activity, or symptoms at rest or minimal activity)	3/3 (100.0%)	18/23 (78.3%)	1.0000000	1
NYHA dyspnoea status (symptoms at rest)	1/3 (33.3%)	6/23 (26.1%)	1.0000000	1
Severe symptoms (symptoms at rest measured by CCS Angina Status or NYHA dyspnoea status)	1/3 (33.3%)	7/23 (30.4%)	1.0000000	1
CSHA Clinical Frailty Score (moderately or severely frail)	1/3 (33.3%)	2/19 (10.5%)	0.3707792	1
Katz Index less than 3	0/3 (0%)	0/18 (0%)	1.0000000	1
Katz Index less than 6	1/3 (33.3%)	3/18 (16.7%)	0.4887218	1
Frailty composite (moderately or severely frail on CSHA, or Katz Index less than 6)	1/3 (33.3%)	3/20 (15.0%)	0.4528515	1
Poor LV function (LVEF<30%)	1/3 (33.3%)	2/23 (8.7%)	0.3188462	1
Diabetes	1/3 (33.3%)	8/22 (36.4%)	1.0000000	1
Ever smoked (current and ex smokers)	1/3 (33.3%)	11/20 (55.0%)	0.5900621	1
Dialysis	0/3 (0%)	2/22 (9.1%)	1.0000000	1
Presence of left main stem disease	0/3 (0%)	2/19 (10.5%)	1.0000000	1
Presence of >50% stenosis in at least one coronary vessel	1/3 (33.3%)	5/20 (25.0%)	1.0000000	1
Valve size, mm: median [Q1,Q3]	26.0 [24.5 to 26.0] (n=3)	26.0 [23.0 to 27.5] (n=23)	0.9663144	1
Valve size (categorical: small, medium, large)	S: 1/3 (33.3%); M: 2/3 (66.7%); L: 0/3 (0%)	S: 10/23 (43.5%); M: 7/23 (30.4%); L: 6/23 (26.1%)	0.4612694	1
Non-elective procedure	2/3 (66.7%)	9/23 (39.1%)	0.5557692	1
Procedure urgency (non-elective procedure, or critical status pre-procedure)	2/3 (66.7%)	9/23 (39.1%)	0.5557692	1
Planned use of general anaesthesia	1/3 (33.3%)	1/22 (4.5%)	0.2300000	1
Previous balloon aortic valvuloplasty	0/3 (0%)	1/23 (4.3%)	1.0000000	1
Use of cardiopulmonary bypass	0/3 (0%)	0/22 (0%)	1.0000000	1
Use of cerebral circulation protection device(s)	0/3 (0%)	6/22 (27.3%)	0.5539130	1
Creatinine clearance, mL/min: median [Q1,Q3]	67.1 [63.1 to 67.2] (n=3)	64.0 [45.7 to 75.6] (n=20)	0.8194770	1
Creatinine clearance less than 30 mL/min	0/3 (0%)	3/20 (15.0%)	1.0000000	1
Previous MI (ever)	0/3 (0%)	6/22 (27.3%)	0.5539130	1
Previous MI (within previous 90 days)	0/3 (0%)	2/22 (9.1%)	1.0000000	1
Previous PCI	0/3 (0%)	6/23 (26.1%)	1.0000000	1
Previous CABG	2/3 (66.7%)	4/22 (18.2%)	0.1326087	1
Previous stroke or TIA	0/2 (0%)	3/22 (13.6%)	1.0000000	1
Presence of extracardiac arteriopathy	0/3 (0%)	3/22 (13.6%)	1.0000000	1
Any cardiac or coronary comorbidity (previous MI, PCI, or CABG, presence of extracardiac arteriopathy or aortic calcification, symptoms at rest on NYHA or CCS, poor LV function, left	2/3 (66.7%)	17/23 (73.9%)	1.0000000	1

Patient and procedural characteristics	Unmatched (n=3)	Matched (n=23)	p-value, **unadjusted**	p-value, **adjusted**
main stem disease or stenosis of at least 50% in one vessel)				
Anatomical coronary comorbidity (left main stem disease, or stenosis of at least 50% in one vessel)	1/3 (33.3%)	5/20 (25.0%)	1.0000000	1
Clinical coronary comorbidity (previous MI, PCI or CABG)	2/3 (66.7%)	10/23 (43.5%)	0.5800000	1
Any non-cardiac or non-coronary comorbidity (previous stroke or TIA, diabetes, current or former smoker, extracardiac arteriopathy, current dialysis or creatinine clearance less than 30)	2/3 (66.7%)	16/23 (69.6%)	1.0000000	1
Non-cardiac non-coronary other comorbidity (previous stroke or extracardiac arteriopathy)	0/3 (0%)	5/22 (22.7%)	1.0000000	1
Non-cardiac non-coronary risk factor (current or former smoker, or diabetes)	2/3 (66.7%)	14/22 (63.6%)	1.0000000	1
Renal comorbidity (current dialysis or creatinine clearance less than 30)	0/3 (0%)	3/22 (13.6%)	1.0000000	1

Key: Significance of **adjusted** p-values (using Holm-Bonferroni correction) denoted by: *** < 0.001, ** <0.01, * < 0.05. Abbreviations: CABG, Coronary artery bypass grafting; CCS, Canadian Cardiovascular Society; LVEF, Left ventricular ejection fraction; MI, Myocardial infarction; NYHA, New York Heart Association; PCI, Percutaneous coronary intervention; TIA, Transient ischaemic attack; Q1, Quartile; Q3, Quartile 3

Appendix E3: Additional analysis

Comparison of demographics and outcomes across matched cohorts, unadjusted

Patient and procedural characteristics between TAVI in native aortic valve (n=6,270), TAVI-in-SAVR (n=215), TAVI-in-TAVI (n=23) cohorts, for UK TAVI Registry procedures successfully matched to a procedure in HES.

Patient and procedural characteristics	TAVI in native aortic valve (n=6,270)	TAVI in SAVR (n=215)	TAVI in TAVI (n=23)	p-value (comparison between three cohorts; **unadjusted**)	p-value (comparison between three cohorts; **adjusted**)
Age, years: median [Q1,Q3]	82.0 [77.0 to 86.0] (n=6,270)	78.0 [73.0 to 82.0] (n=215)	78.0 [73.0 to 82.5] (n=23)	0.0000000	<0.0001*
Age (90+ years)	517/6,270 (8.2%)	2/215 (0.9%)	0/23 (0%)	0.0004998	0.024*
Male sex	3,666/6,261 (58.6%)	139/215 (64.7%)	14/23 (60.9%)	0.1949025	1
Height, m: median [Q1,Q3]	1.7 [1.6 to 1.7] (n=5,875)	1.7 [1.6 to 1.8] (n=206)	1.7 [1.6 to 1.8] (n=22)	0.1987149	1
Weight, kg: median [Q1,Q3]	76.0 [65.9 to 88.0] (n=5,894)	78.0 [65.8 to 90.0] (n=206)	79.6 [70.0 to 89.0] (n=22)	0.4220604	1
BMI, kg/m2: median [Q1,Q3]	27.3 [24.1 to 31.1] (n=5,846)	27.4 [23.6 to 30.9] (n=205)	28.6 [24.8 to 30.7] (n=22)	0.4806449	1
Underweight (BMI under 17.5)	105/5,846 (1.8%)	1/205 (0.5%)	1/22 (4.5%)	0.1769115	1
Obese (BMI 30 or above)	1,843/5,846 (31.5%)	62/205 (30.2%)	8/22 (36.4%)	0.7901049	1
Pulmonary artery systolic pressure, mmHg: median [Q1,Q3]	34.0 [25.0 to 45.0] (n=1,723)	41.0 [29.5 to 48.0] (n=99)	42.5 [30.2 to 51.5] (n=10)	0.8216741	1
Aortic valve mean pressure gradient, mmHg: median [Q1,Q3]	44.0 [35.0 to 55.0] (n=5,887)	34.0 [22.0 to 48.0] (n=192)	36.0 [20.0 to 49.5] (n=19)	0.0052502	0.194
Aortic valve peak pressure gradient, mmHg: median [Q1,Q3]	70.0 [58.0 to 86.0] (n=5,776)	59.0 [38.0 to 77.5] (n=187)	68.5 [43.8 to 85.5] (n=18)	0.0000000	<0.0001*
Valve area, cm2: median [Q1,Q3]	0.7 [0.6 to 0.9] (n=5,547)	0.9 [0.7 to 1.2] (n=137)	0.8 [0.6 to 1.0] (n=14)	0.0000000	<0.0001*
Annular diameter, mm: median [Q1,Q3]	24.6 [23.0 to 26.0] (n=4,883)	22.0 [20.0 to 24.0] (n=156)	23.0 [22.0 to 24.0] (n=13)	0.0000000	<0.0001*
Extensive calcification of ascending aorta	198/5,826 (3.4%)	6/204 (2.9%)	2/21 (9.5%)	0.2673663	1
Critical status pre-procedure	71/6,080 (1.2%)	20/209 (9.6%)	1/23 (4.3%)	0.0004998	0.024*
CCS Angina Status (any limitation of physical activity)	1,386/6,058 (22.9%)	37/211 (17.5%)	7/23 (30.4%)	0.1204398	1
CCS Angina Status (symptoms at rest)	58/6,058 (1.0%)	4/211 (1.9%)	1/23 (4.3%)	0.0599700	1
NYHA dyspnoea status (marked limitation of physical activity, or symptoms at rest or minimal activity)	4,522/6,103 (74.1%)	181/209 (86.6%)	18/23 (78.3%)	0.0004998	0.024*
NYHA dyspnoea status (symptoms at rest)	689/6,103 (11.3%)	46/209 (22.0%)	6/23 (26.1%)	0.0004998	0.024*
Severe symptoms (symptoms at rest measured by CCS Angina Status or NYHA dyspnoea status)	721/6,144 (11.7%)	48/212 (22.6%)	7/23 (30.4%)	0.0004998	0.024*
CSHA Clinical Frailty Score (moderately or severely frail)	445/5,851 (7.6%)	13/208 (6.2%)	2/19 (10.5%)	0.6091954	1
Katz Index less than 3	170/5,624 (3.0%)	6/197 (3.0%)	0/18 (0%)	1.0000000	1
Katz Index less than 6	749/5,624 (13.3%)	29/197 (14.7%)	3/18 (16.7%)	0.6516742	1
Frailty composite (moderately or severely frail on CSHA, or Katz Index less than 6)	1,060/5,961 (17.8%)	39/211 (18.5%)	3/20 (15.0%)	0.9565217	1
Poor LV function (LVEF<30%)	495/6,021 (8.2%)	22/212 (10.4%)	2/23 (8.7%)	0.4827586	1
Diabetes	1,616/6,124 (26.4%)	42/213 (19.7%)	8/22 (36.4%)	0.0534733	1
Ever smoked (current and ex smokers)	2,431/5,017 (48.5%)	74/190 (38.9%)	11/20 (55%)	0.0254873	0.892
Dialysis	101/6,083 (1.7%)	6/214 (2.8%)	2/22 (9.1%)	0.0159920	0.576
Presence of left main stem disease	131/5,340 (2.5%)	7/200 (3.5%)	2/19 (10.5%)	0.0559720	1
Presence of >50% stenosis in at least one coronary vessel	1,365/5,304 (25.7%)	45/198 (22.7%)	5/20 (25.0%)	0.6751624	1
Valve size, mm: median [Q1,Q3]	26.0 [23.0 to 29.0] (n=6,270)	23.0 [23.0 to 26.0] (n=215)	26.0 [23.0 to 27.5] (n=23)	0.6344032	1
Valve size (categorical: small, medium, large)	S: 1,867/6,270 (29.8%); M: 2,443/6,270 (39.0%); L: 1,960/6,270 (31.3%)	S: 128/215 (59.5%); M: 70/215 (32.6%); L: 17/215 (7.9%)	S: 10/23 (43.5%); M: 7/23 (30.4%); L: 6/23 (26.1%)	0.0004998	0.024*
Non-elective procedure	1,493/6,253 (23.9%)	100/215 (46.5%)	9/23 (39.1%)	0.0004998	0.024*
Procedure urgency (non-elective procedure, or critical status pre-procedure)	1,508/6,270 (24.1%)	102/215 (47.4%)	9/23 (39.1%)	0.0004998	0.024*

Patient and procedural characteristics	TAVI in native aortic valve (n=6,270)	TAVI in SAVR (n=215)	TAVI in TAVI (n=23)	p-value (comparison between three cohorts; **unadjusted**)	p-value (comparison between three cohorts; **adjusted**)
Planned use of general anaesthesia	62/6,235 (1.0%)	12/214 (5.6%)	1/22 (4.5%)	0.0004998	0.024*
Previous balloon aortic valvuloplasty	175/6,185 (2.8%)	2/214 (0.9%)	1/23 (4.3%)	0.1714143	1
Use of cardiopulmonary bypass	20/6,181 (0.3%)	1/210 (0.5%)	0/22 (0%)	0.5297351	1
Use of cerebral circulation protection device(s)	725/6,227 (11.6%)	32/214 (15.0%)	6/22 (27.3%)	0.0284858	0.94
Creatinine clearance, mL/min: median [Q1,Q3]	56.2 [41.2 to 73.3] (n=5,588)	53.3 [39.1 to 72.5] (n=199)	64.0 [45.7 to 75.6] (n=20)	0.0266681	0.907
Creatinine clearance less than 30 mL/min	500/5,588 (8.9%)	19/199 (9.5%)	3/20 (15.0%)	0.5342329	1
Previous MI (ever)	746/6,185 (12.1%)	29/214 (13.6%)	6/22 (27.3%)	0.0669665	1
Previous MI (within previous 90 days)	127/6,185 (2.1%)	7/214 (3.3%)	2/22 (9.1%)	0.0359820	1
Previous PCI	784/6,167 (12.7%)	20/214 (9.3%)	6/23 (26.1%)	0.0569715	1
Previous CABG	497/6,050 (8.2%)	58/214 (27.1%)	4/22 (18.2%)	0.0004998	0.024*
Previous stroke or TIA	709/6,146 (11.5%)	23/213 (10.8%)	3/22 (13.6%)	0.8435782	1
Presence of extracardiac arteriopathy	535/6,081 (8.8%)	16/214 (7.5%)	3/22 (13.6%)	0.5247376	1
Any cardiac or coronary comorbidity (previous MI, PCI, or CABG, presence of extracardiac arteriopathy or aortic calcification, symptoms at rest on NYHA or CCS, poor LV function, left main stem disease or stenosis of at least 50% in one vessel)	2,895/6,253 (46.3%)	128/215 (59.5%)	17/23 (73.9%)	0.0004998	0.024*
Anatomical coronary comorbidity (left main stem disease, or stenosis of at least 50% in one vessel)	1,379/5,430 (25.4%)	46/202 (22.8%)	5/20 (25.0%)	0.7066467	1
Clinical coronary comorbidity (previous MI, PCI or CABG)	1,390/6,221 (22.3%)	72/215 (33.5%)	10/23 (43.5%)	0.0004998	0.024*
Any non-cardiac or non-coronary comorbidity (previous stroke or TIA, diabetes, current or former smoker, extracardiac arteriopathy, current dialysis or creatinine clearance less than 30)	3,929/6,218 (63.2%)	124/215 (57.7%)	16/23 (69.6%)	0.2158921	1
Non-cardiac non-coronary other comorbidity (previous stroke or extracardiac arteriopathy)	1,131/6,190 (18.3%)	35/215 (16.3%)	5/22 (22.7%)	0.6181909	1
Non-cardiac non-coronary risk factor (current or former smoker, or diabetes)	3,340/6,183 (54.0%)	103/215 (47.9%)	14/22 (63.6%)	0.1424288	1
Renal comorbidity (current dialysis or creatinine clearance less than 30)	534/6,152 (8.7%)	22/214 (10.3%)	3/22 (13.6%)	0.4042979	1

Key: Significance of **adjusted** p-values (using Holm-Bonferroni correction) denoted by: *** < 0.001, ** <0.01, * < 0.05

Abbreviations: CABG, Coronary artery bypass grafting; CCS, Canadian Cardiovascular Society; CSHA, Canadian Study of Health and Aging; LV, Left ventricular; LVEF, Left ventricular ejection fraction; MI, Myocardial infarction; NYHA, New York Heart Association; PCI, Percutaneous coronary intervention; Q1, Quartile; Q3, Quartile 3; SAVR, Surgical aortic valve replacement; TAVI, Transcatheter aortic valve implantation

In-hospital outcomes between TAVI in native aortic valve (n=6,270), TAVI-in-SAVR (n=215), TAVI-in-TAVI (n=23) cohorts, except death (taken from HES instead) for UK TAVI Registry procedures successfully matched to a procedure in HES, unadjusted.

In-hospital outcome	TAVI in native aortic valve (n=6,270)	TAVI in SAVR (n=215)	TAVI in TAVI (n=23)	p-value (comparison of three cohorts; **unadjusted**)	p-value (comparison of three cohorts; **adjusted**)
Length of procedure, minutes: median [Q1,Q3]	62.0 [56.0 to 83.0] (n=5,326)	80.0 [60.0 to 100.0] (n=191)	80.0 [60.0 to 98.0] (n=19)	0.0000000	<0.0001*
Length of hospital stay, overnight stays: median [Q1,Q3]	3.0 [2.0 to 9.0] (n=5,134)	6.0 [2.0 to 18.0] (n=191)	17.5 [3.2 to 34.5] (n=18)	0.0000003	<0.0001*
Peak pressure gradient, mmHg: median [Q1,Q3]	14.0 [10.0 to 20.0] (n=4,212)	23.0 [15.0 to 30.5] (n=163)	20.0 [13.0 to 27.0] (n=17)	0.0000000	<0.0001*
Mean pressure gradient, mmHg: [Q1,Q3]	7.0 [5.0 to 11.0] (n=4,471)	12.0 [8.0 to 19.0] (n=165)	10.5 [6.5 to 15.2] (n=18)	0.0000000	<0.0001*
Valve area, cm2: median [Q1,Q3]	1.8 [1.5 to 2.1] (n=2,862)	1.6 [1.4 to 2.0] (n=118)	1.6 [1.4 to 2.0] (n=8)	0.0005897	0.014*
Aortic regurgitation	108/6,006 (1.8%)	6/210 (2.9%)	1/23 (4.3%)	0.1944028	1
Valve failure	12/6,227 (0.2%)	0/215 (0%)	0/22 (0%)	1.0000000	1
Unsuccessful valve deployment	112/6,270 (1.8%)	3/215 (1.4%)	2/23 (8.7%)	0.0999500	1
Malposition of valve	39/5,980 (0.7%)	4/206 (1.9%)	0/22 (0%)	0.1454273	1
Use of post implantation balloon dilatation	491/5,947 (8.3%)	62/204 (30.4%)	1/22 (4.5%)	0.0004998	0.012*
Need for permanent pacing	442/5,834 (7.6%)	7/203 (3.4%)	0/22 (0%)	0.0439780	0.924
Conversion to sternotomy for valve surgery	6/6,215 (0.1%)	0/214 (0%)	0/23 (0%)	1.0000000	1
Valve reintervention before discharge	23/6,187 (0.4%)	0/212 (0%)	0/23 (0%)	1.0000000	1
Failure of percutaneous closure device	78/5780 (1.3%)	7/199 (3.5%)	0/22 (0%)	0.0669665	1
Need for bailout PCI	17/6,197 (0.3%)	1/212 (0.5%)	0/23 (0%)	0.4957521	1
Need for bailout TAVI-in-TAVI	33/6,001 (0.5%)	4/206 (1.9%)	0/22 (0%)	0.0534733	1
MI within 72 hours of procedure	14/5,861 (0.2%)	2/205 (1.0%)	0/22 (0%)	0.1474263	1
Major, life threatening or disabling bleeding	63/5,761 (1.1%)	4/201 (2.0%)	0/21 (0%)	0.4407796	1
Major vascular complications	78/5,753 (1.4%)	4/199 (2.0%)	0/22 (0%)	0.5062469	1
Tamponade during or after procedure	46/6,141 (0.7%)	0/211 (0%)	0/23 (0%)	0.4842579	1
Stroke before discharge	91/5,702 (1.6%)	3/199 (1.5%)	1/22 (4.5%)	0.4072964	1
Modified Rankin score of 4 or above	8/654 (1.2%)	1/16 (6.2%)	0/2 (0%)	0.2028986	1
Need for renal replacement therapy	7/5,739 (0.1%)	1/200 (0.5%)	0/22 (0%)	0.2708646	1
Deaths	85/6,270 (1.4%)	3/215 (1.4%)	1/23 (4.3%)	0.3178411	1
Prescribed NOACs	1,566/5,740 (27.3%)	75/201 (37.3%)	7/21 (33.3%)	0.0064968	0.143
Prescribed other anti-thrombotics	564/5,740 (9.8%)	21/201 (10.4%)	1/21 (4.8%)	0.8170915	1
Prescribed antiplatelets	3,678/5,657 (65.0%)	123/201 (61.2%)	13/20 (65.0%)	0.4932534	1
Technical success (VARC-3)	5,652/5,910 (95.6%)	193/204 (94.6%)	19/22 (86.4%)	0.0839580	1

Key: Significance of **adjusted** p-values (using Holm-Bonferroni correction) denoted by: *** < 0.001, ** <0.01, * < 0.05
Abbreviations: MI, Myocardial infarction; NOAC, Non-vitamin-K oral anticoagulant; PCI, Percutaneous coronary intervention; Q1, Quartile 1; Q3, Quartile 3; SAVR, Surgical aortic valve replacement; TAVI, Transcatheter aortic valve implantation; VARC-3, Valve Academic Research Consortium-3

TAVI-in-SAVR by device

Patient and procedural characteristics (TAVI-in-SAVR subgroup) by device model, for UK TAVI Registry procedures successfully matched to procedure in HES, unadjusted. [Key: Significant following Holm-Bonferroni correction: *** < 0.001, ** <0.01, * < 0.05]

Patient and procedural characteristics	**All valves (n=215)**	Edwards Sapien 3 (n=20)	Edwards Sapien 3 Ultra (n=87)	Medtronic Evolut R (n=59)	Medtronic Evolut Pro+ (n=44)	Abbott Navitor (n=5)	p-value (comparison between five devices; **unadjusted**)	p-value (comparison between five devices; **adjusted**)
Age, years: median [Q1,Q3]	78.0 [73.0 to 82.0] (n=215)	76.5 [72.0 to 82.2] (n=20)	79.0 [74.5 to 83] (n=87)	79.0 [74.0 to 82.0] (n=59)	76.0 [71.0 to 80.2] (n=44)	76.0 [74.0 to 76.0] (n=5)	0.0000015	<0.0001*
Age (90+ years)	2/215 (0.9%)	0/20 (0%)	2/87 (2.3%)	0/59 (0%)	0/44 (0%)	0/5 (0%)	0.6306847	1
Male sex	139/215 (64.7%)	17/20 (85.0%)	59/87 (67.8%)	28/59 (47.5%)	32/44 (72.7%)	3/5 (60.0%)	0.0109945	0.429
Height, m: median [Q1,Q3]	1.7 [1.6 to 1.8] (n=206)	1.7 [1.7 to 1.8] (n=20)	1.7 [1.6 to 1.8] (n=81)	1.6 [1.6 to 1.7] (n=57)	1.7 [1.6 to 1.7] (n=43)	1.7 [1.6 to 1.8] (n=5)	0.0000000	<0.0001*
Weight, kg: median [Q1,Q3]	78.0 [65.8 to 90.0] (n=206)	87.2 [69.8 to 93.0] (n=20)	78.5 [66.0 to 90.7] (n=82)	75.0 [63.5 to 88.5] (n=57)	79.0 [64.9 to 84.0] (n=43)	90.0 [73.4 to 103.8] (n=4)	0.0000000	<0.0001*
BMI, kg/m2: median [Q1,Q3]	27.4 [23.6 to 30.9] (n=205)	28.7 [25.0 to 31.0] (n=20)	26.8 [23.2 to 30.5] (n=81)	27.6 [23.7 to 31.6] (n=57)	26.9 [23.7 to 29.0] (n=43)	27.9 [24.0 to 32.7] (n=4)	0.0020147	0.084
Underweight (BMI under 17.5)	1/205 (0.5%)	1/20 (5.0%)	0/81 (0%)	0/57 (0%)	0/43 (0%)	0/4 (0%)	0.1194403	1
Obese (BMI 30 or above)	62/205 (30.2%)	8/20 (40.0%)	23/81 (28.4%)	20/57 (35.1%)	9/43 (20.9%)	2/4 (50.0%)	0.3393303	1
Pulmonary artery systolic pressure, mmHg: median [Q1,Q3]	41.0 [29.5 to 48.0] (n=99)	45.0 [42.0 to 51.0] (n=7)	40.0 [25.0 to 45.0] (n=45)	44.0 [32.2 to 55.0] (n=30)	36.0 [31.5 to 45.0] (n=15)	41.5 [38.2 to 44.8] (n=2)	0.0000000	<0.0001*
Mean pressure gradient, mmHg: median [Q1,Q3]	34.0 [22.0 to 48.0] (n=192)	20.0 [16.0 to 37.5] (n=15)	36.0 [22.0 to 47.0] (n=81)	36.0 [23.5 to 57.5] (n=50)	34.5 [23.0 to 46.5] (n=42)	20.0 [16.0 to 28.0] (n=4)	0.0000000	<0.0001*
Peak pressure gradient, mmHg: median [Q1,Q3]	59.0 [38.0 to 77.5] (n=187)	38.0 [24.0 to 59.2] (n=16)	59.5 [37.2 to 76] (n=78)	61.0 [40.0 to 95.5] (n=47)	60.5 [42.0 to 75.8] (n=42)	43.0 [35.2 to 51.0] (n=4)	0.0000000	<0.0001*
Valve area, cm2: median [Q1,Q3]	0.9 [0.7 to 1.2] (n=137)	1.3 [0.9 to 1.7] (n=9)	0.9 [0.7 to 1.3] (n=65)	0.8 [0.6 to 1.0] (n=26)	0.9 [0.7 to 1.0] (n=36)	0.9 [0.9 to 0.9] (n=1)	0.0000000	<0.0001*
Annular diameter, mm: median [Q1,Q3]	22.0 [20.0 to 24.0] (n=156)	26.0 [23.0 to 28.0] (n=17)	21.0 [20.0 to 23.1] (n=68)	21.1 [19.1 to 22.8] (n=34)	22.0 [19.5 to 24.5] (n=35)	23.9 [23.3 to 24.5] (n=2)	0.0000000	<0.0001*
Presence of aortic calcification	6/204 (2.9%)	1/20 (5.0%)	4/80 (5.0%)	1/57 (1.8%)	0/42 (0%)	0/5 (0%)	0.4637681	1
Critical status pre-procedure	20/209 (9.6%)	6/20 (30.0%)	3/84 (3.6%)	8/58 (13.8%)	2/42 (4.8%)	1/5 (20.0%)	0.0019990	0.084
CCS Angina Status (any limitation of physical activity)	37/211 (17.5%)	6/20 (30.0%)	11/85 (12.9%)	8/58 (13.8%)	11/43 (25.6%)	1/5 (20.0%)	0.1854073	1
CCS Angina Status (symptoms at rest)	4/211 (1.9%)	0/20 (0%)	1/85 (1.2%)	2/58 (3.4%)	1/43 (2.3%)	0/5 (0%)	0.9030485	1
NYHA dyspnoea status (marked limitation of physical activity, or symptoms at rest or minimal activity)	181/209 (86.6%)	19/20 (95.0%)	74/85 (87.1%)	49/57 (86.0%)	36/42 (85.7%)	3/5 (60.0%)	0.3803098	1
NYHA dyspnoea status (symptoms at rest)	46/209 (22.0%)	5/20 (25.0%)	19/85 (22.4%)	13/57 (22.8%)	9/42 (21.4%)	0/5 (0%)	0.9235382	1
Severe symptoms (symptoms at rest measured by CCS Angina Status or NYHA dyspnoea status)	48/212 (22.6%)	5/20 (25.0%)	20/86 (23.3%)	14/58 (24.1%)	9/43 (20.9%)	0/5 (0%)	0.9175412	1
CSHA Clinical Frailty Score (moderately or severely frail)	13/208 (6.2%)	2/20 (10.0%)	5/85 (5.9%)	4/56 (7.1%)	2/42 (4.8%)	0/5 (0%)	0.8785607	1
Katz Index less than 3	6/197 (3.0%)	0/20 (0%)	4/80 (5.0%)	0/52 (0%)	2/40 (5.0%)	0/5 (0%)	0.3863068	1
Katz Index less than 6	29/197 (14.7%)	4/20 (20.0%)	11/80 (13.8%)	2/52 (3.8%)	12/40 (30.0%)	0/5 (0%)	0.0094953	0.38
Frailty composite (moderately or severely frail on CSHA, or Katz Index less than 6)	39/211 (18.5%)	5/20 (25.0%)	16/85 (18.8%)	6/58 (10.3%)	12/43 (27.9%)	0/5 (0%)	0.1539230	1

Patient and procedural characteristics	**All valves (n=215)**	Edwards Sapien 3 (n=20)	Edwards Sapien 3 Ultra (n=87)	Medtronic Evolut R (n=59)	Medtronic Evolut Pro+ (n=44)	Abbott Navitor (n=5)	p-value (comparison between five devices; **unadjusted**)	p-value (comparison between five devices; **adjusted**)
Poor LV function (LVEF<30%)	22/212 (10.4%)	1/20 (5.0%)	11/87 (12.6%)	5/57 (8.8%)	5/43 (11.6%)	0/5 (0%)	0.8790605	1
Diabetes	42/213 (19.7%)	3/20 (15.0%)	16/86 (18.6%)	15/58 (25.9%)	8/44 (18.2%)	0/5 (0%)	0.6926537	1
Ever smoked (current and ex smokers)	74/190 (38.9%)	9/19 (47.4%)	29/74 (39.2%)	14/54 (25.9%)	21/40 (52.5%)	1/3 (33.3%)	0.0889555	1
Dialysis	6/214 (2.8%)	0/20 (0%)	3/86 (3.5%)	0/59 (0%)	2/44 (4.5%)	1/5 (20.0%)	0.0979510	1
Presence of left main stem disease	7/200 (3.5%)	1/19 (5.3%)	4/80 (5.0%)	2/56 (3.6%)	0/41 (0%)	0/4 (0%)	0.5407296	1
Presence of >50% stenosis in at least one coronary vessel	45/198 (22.7%)	4/19 (21.1%)	19/80 (23.8%)	13/56 (23.2%)	9/41 (22.0%)	0/2 (0%)	1.0000000	1
Valve size, mm: median [Q1,Q3]	23.0 [23.0 to 26.0] (n=215)	26.0 [23.0 to 29.0] (n=20)	23.0 [23.0 to 23.0] (n=87)	23.0 [23.0 to 26.0] (n=59)	26.0 [23.0 to 26.0] (n=44)	25.0 [25.0 to 25.0] (n=5)	0.0000000	<0.0001*
Valve size (categorical: small, medium, large)	S: 128/215 (59.5%); M: 70/215 (32.6%); L: 17/215 (7.9%)	S: 8/20 (40.0%); M: 3/20 (15.0%); L: 9/20 (45.0%)	S: 66/87 (75.9%); M: 21/87 (24.1%); L: 0/87 (0%)	S: 36/59 (61.0%); M: 20/59 (33.9%); L: 3/59 (5.1%)	S: 17/44 (38.6%); M: 23/44 (52.3%); L: 4/44 (9.1%)	S: 1/5 (20.0%); M: 3/5 (60.0%); L: 1/5 (20.0%)	0.0004998	0.021*
Non-elective procedure	100/215 (46.5%)	9/20 (45.0%)	40/87 (46.0%)	29/59 (49.2%)	19/44 (43.2%)	3/5 (60.0%)	0.9490255	1
Procedure urgency (non-elective procedure, or critical status pre-procedure)	102/215 (47.4%)	10/20 (50.0%)	41/87 (47.1%)	29/59 (49.2%)	19/44 (43.2%)	3/5 (60.0%)	0.9485257	1
Planned use of general anaesthesia	12/214 (5.6%)	2/20 (10.0%)	6/87 (6.9%)	3/59 (5.1%)	1/43 (2.3%)	0/5 (0%)	0.6291854	1
Previous balloon aortic valvuloplasty	2/214 (0.9%)	0/20 (0%)	1/86 (1.2%)	0/59 (0%)	1/44 (2.3%)	0/5 (0%)	0.7681159	1
Use of cardiopulmonary bypass	1/210 (0.5%)	0/20 (0%)	0/83 (0%)	1/59 (1.7%)	0/43 (0%)	0/5 (0%)	0.6061969	1
Use of cerebral circulation protection device(s)	32/214 (15.0%)	3/20 (15.0%)	14/86 (16.3%)	12/59 (20.3%)	3/44 (6.8%)	0/5 (0%)	0.3623188	1
Creatinine clearance, mL/min: median [Q1,Q3]	53.3 [39.1 to 72.5] (n=199)	60.8 [50.7 to 88.1] (n=20)	52.3 [38.6 to 67.8] (n=77)	51.0 [38.5 to 70.6] (n=57)	54.4 [40.8 to 69.3] (n=42)	80.4 [63.9 to 100.7] (n=3)	0.0000000	<0.0001*
Creatinine clearance less than 30 mL/min	19/199 (9.5%)	0/20 (0%)	7/77 (9.1%)	6/57 (10.5%)	6/42 (14.3%)	0/3 (0%)	0.4872564	1
Previous MI (ever)	29/214 (13.6%)	5/20 (25.0%)	13/86 (15.1%)	5/59 (8.5%)	6/44 (13.6%)	0/5 (0%)	0.3733133	1
Previous MI (within previous 90 days)	7/214 (3.3%)	0/20 (0%)	5/86 (5.8%)	1/59 (1.7%)	1/44 (2.3%)	0/5 (0%)	0.6471764	1
Previous PCI	20/214 (9.3%)	1/20 (5.0%)	7/86 (8.1%)	5/59 (8.5%)	6/44 (13.6%)	1/5 (20.0%)	0.5797101	1
Previous CABG	58/214 (27.1%)	4/20 (20.0%)	23/86 (26.7%)	16/59 (27.1%)	14/44 (31.8%)	1/5 (20.0%)	0.9215392	1
Previous stroke or TIA	23/213 (10.8%)	1/20 (5.0%)	7/85 (8.2%)	12/59 (20.3%)	3/44 (6.8%)	0/5 (0%)	0.1554223	1
Presence of extracardiac arteriopathy	16/214 (7.5%)	3/20 (15.0%)	5/87 (5.7%)	3/59 (5.1%)	5/43 (11.6%)	0/5 (0%)	0.3998001	1
Any cardiac or coronary comorbidity (previous MI, PCI, or CABG, presence of extracardiac arteriopathy or aortic calcification, symptoms at rest on NYHA or CCS, poor LV function, left main stem disease or stenosis of at least 50% in one vessel)	128/215 (59.5%)	15/20 (75.0%)	52/87 (59.8%)	34/59 (57.6%)	26/44 (59.1%)	1/5 (20.0%)	0.2868566	1
Anatomical coronary comorbidity (left main stem disease,	46/202 (22.8%)	4/19 (21.1%)	19/82 (23.2%)	14/56 (25.0%)	9/41 (22.0%)	0/4 (0%)	0.9545227	1

Patient and procedural characteristics	**All valves (n=215)**	Edwards Sapien 3 (n=20)	Edwards Sapien 3 Ultra (n=87)	Medtronic Evolut R (n=59)	Medtronic Evolut Pro+ (n=44)	Abbott Navitor (n=5)	p-value (comparison between five devices; **unadjusted**)	p-value (comparison between five devices; **adjusted**)
or stenosis of at least 50% in one vessel)								
Clinical coronary comorbidity (previous MI, PCI or CABG)	72/215 (33.5%)	7/20 (35.0%)	28/87 (32.2%)	20/59 (33.9%)	16/44 (36.4%)	1/5 (20.0%)	0.9735132	1
Any non-cardiac or non-coronary comorbidity (previous stroke or TIA, diabetes, current or former smoker, extracardiac arteriopathy, current dialysis or creatinine clearance less than 30)	124/215 (57.7%)	12/20 (60.0%)	46/87 (52.9%)	34/59 (57.6%)	30/44 (68.2%)	2/5 (40.0%)	0.4792604	1
Non-cardiac non-coronary other comorbidity (previous stroke or extracardiac arteriopathy)	35/215 (16.3%)	4/20 (20.0%)	10/87 (11.5%)	14/59 (23.7%)	7/44 (15.9%)	0/5 (0%)	0.3103448	1
Non-cardiac non-coronary risk factor (current or former smoker, or diabetes)	103/215 (47.9%)	10/20 (50.0%)	37/87 (42.5%)	28/59 (47.5%)	27/44 (61.4%)	1/5 (20.0%)	0.2098951	1
Renal comorbidity (current dialysis or creatinine clearance less than 30)	22/214 (10.3%)	0/20 (0%)	8/86 (9.3%)	6/59 (10.2%)	7/44 (15.9%)	1/5 (20.0%)	0.2808596	1

Key: Significance of **adjusted** p-values (using Holm-Bonferroni correction) denoted by: *** < 0.001, ** <0.01, * < 0.05. Abbreviations: CABG, Coronary artery bypass grafting; CCS, Canadian Cardiovascular Society; CSHA, Canadian Study of Health and Aging; LV, Left ventricular; LVEF, Left ventricular ejection fraction; MI, Myocardial infarction; NYHA, New York Heart Association; PCI, Percutaneous coronary intervention; Q1, Quartile 1; Q3, Quartile 3; TIA, Transient ischaemic attack

In hospital outcomes (TAVI-in-SAVR subgroup), except death (taken from HES instead) for UK TAVI Registry procedures successfully matched to a procedure in HES, unadjusted

Outcomes	**All valves (n=215)**	**Edwards Sapien 3** (n=20)	Edwards Sapien 3 Ultra (n=87)	Medtronic Evolut R (n=59)	Medtronic Evolut Pro+ (n=44)	Abbott Navitor (n=5)	p-value (comparison between five devices; **unadjusted**)	p-value (comparison between five devices; **adjusted**)
Length of procedure, minutes: median [Q1,Q3]	80.0 [60.0 to 100.0] (n=191)	60.5 [48.0 to 82.5] (n=20)	75.0 [60.0 to 89.8] (n=74)	89.5 [65.0 to 120.0] (n=52)	80.0 [70.0 to 100.0] (n=41)	101.5 [73.8 to 129.8] (n=4)	0.0000000	<0.0001*
Length of hospital stay, overnight stays: median [Q1,Q3]	6.0 [2.0 to 18.0] (n=191)	3.0 [2.0 to 12.5] (n=20)	6.5 [2.0 to 15.0] (n=66)	6.0 [2.2 to 19.5] (n=58)	6.0 [3.0 to 22.0] (n=43)	3.5 [1.5 to 11.5] (n=4)	0.0000004	<0.0001*
Peak pressure gradient, mmHg: median [Q1,Q3]	23.0 [15.0 to 30.5] (n=163)	25.0 [13.0 to 29.0] (n=17)	25.0 [17.0 to 29.0] (n=73)	21.0 [16.0 to 32.0] (n=37)	22.0 [15.0 to 30.0] (n=31)	12.0 [8.0 to 18.0] (n=5)	0.0000000	<0.0001*
Mean pressure gradient, mmHg: [Q1,Q3]	12.0 [8.0 to 19.0] (n=165)	16.0 [7.0 to 19.0] (n=17)	13.0 [9.2 to 17.0] (n=74)	12.0 [9.5 to 21.5] (n=35)	11.0 [7.0 to 16.5] (n=34)	6.0 [4.0 to 8.0] (n=5)	0.0000000	<0.0001*
Valve area, cm2: median [Q1,Q3]	1.6 [1.4 to 2.0] (n=118)	1.6 [1.5 to 1.9] (n=6)	1.6 [1.3 to 2.0] (n=62)	1.5 [1.3 to 1.7] (n=20)	1.8 [1.5 to 2.0] (n=28)	2.5 [2.4 to 2.5] (n=2)	0.0000000	<0.0001*
Aortic regurgitation	6/210 (2.9%)	0/20 (0%)	4/85 (4.7%)	1/58 (1.7%)	1/43 (2.3%)	0/4 (0%)	0.7866067	1
Valve failure	0/215 (0%)	0/20 (0%)	0/87 (0%)	0/59 (0%)	0/44 (0%)	0/5 (0%)	NA	NA
Unsuccessful valve deployment	3/215 (1.4%)	0/20 (0%)	2/87 (2.3%)	0/59 (0%)	1/44 (2.3%)	0/5 (0%)	0.7166417	1
Malposition of valve	4/206 (1.9%)	0/20 (0%)	1/83 (1.2%)	2/59 (3.4%)	1/39 (2.6%)	0/5 (0%)	0.8140930	1
Use of post implantation balloon dilatation	62/204 (30.4%)	0/20 (0%)	31/81 (38.3%)	24/59 (40.7%)	5/39 (12.8%)	2/5 (40.0%)	0.0004998	0.009*
Need for permanent pacing	7/203 (3.4%)	0/20 (0%)	0/80 (0%)	4/59 (6.8%)	2/39 (5.1%)	1/5 (20.0%)	0.0259870	0.468
Conversion to sternotomy for valve surgery	0/214 (0%)	0/20 (0%)	0/86 (0%)	0/59 (0%)	0/44 (0%)	0/5 (0%)	NA	NA
Valve reintervention before discharge	0/212 (0%)	0/20 (0%)	0/85 (0%)	0/59 (0%)	0/43 (0%)	0/5 (0%)	NA	NA
Failure of percutaneous closure device	7/199 (3.5%)	1/20 (5.0%)	0/79 (0%)	2/56 (3.6%)	4/39 (10.3%)	0/5 (0%)	0.0374813	0.6
Need for bailout PCI	1/212 (0.5%)	0/20 (0%)	0/84 (0%)	0/59 (0%)	1/44 (2.3%)	0/5 (0%)	0.3293353	1
Need for bailout TAVI-in-TAVI	4/206 (1.9%)	0/20 (0%)	2/83 (2.4%)	2/59 (3.4%)	0/39 (0%)	0/5 (0%)	0.9025487	1
MI within 72 hours of procedure	2/205 (1.0%)	0/19 (0%)	1/80 (1.2%)	0/59 (0%)	1/43 (2.3%)	0/4 (0%)	0.7801099	1
Major, life threatening or disabling bleeding	4/201 (2.0%)	0/20 (0%)	1/80 (1.2%)	2/57 (3.5%)	1/39 (2.6%)	0/5 (0%)	0.8135932	1
Major vascular complications	4/199 (2.0%)	0/20 (0%)	0/79 (0%)	1/57 (1.8%)	3/39 (7.7%)	0/4 (0%)	0.0894553	1
Tamponade during or after procedure	0/211 (0%)	0/20 (0%)	0/84 (0%)	0/58 (0%)	0/44 (0%)	0/5 (0%)	NA	NA
Stroke before discharge	3/199 (1.5%)	0/19 (0%)	2/79 (2.5%)	0/57 (0%)	1/39 (2.6%)	0/5 (0%)	0.6111944	1
Modified Rankin score of 4 or above	1/16 (6.2%)	0/2 (0%)	0/10 (0%)	0/1 (0%)	1/1 (100.0%)	0/2 (0%)	0.1254373	1
Need for renal replacement therapy	1/200 (0.5%)	0/20 (0%)	0/81 (0%)	0/56 (0%)	0/38 (0%)	1/5 (20.0%)	0.0329835	0.561
Deaths	3/215 (1.4%)	0/20 (0%)	3/87 (3.4%)	0/59 (0%)	0/44 (0%)	0/5 (0%)	0.5267366	1
Prescribed NOACs	75/201 (37.3%)	6/19 (31.6%)	32/77 (41.6%)	23/57 (40.4%)	10/43 (23.3%)	4/5 (80.0%)	0.0649675	0.975
Prescribed other anti-thrombotics	21/201 (10.4%)	3/19 (15.8%)	7/77 (9.1%)	5/57 (8.8%)	6/43 (14.0%)	0/5 (0%)	0.7506247	1
Prescribed antiplatelets	123/201 (61.2%)	13/19 (68.4%)	41/77 (53.2%)	39/58 (67.2%)	29/43 (67.4%)	1/4 (25.0%)	0.1879060	1
Technical success (VARC-3)	193/204 (94.6%)	20/20 (100.0%)	75/81 (92.6%)	57/59 (96.6%)	36/39 (92.3%)	5/5 (100.0%)	0.6621689	1

Key: Significance of **adjusted** p-values (using Holm-Bonferroni correction) denoted by: *** < 0.001, ** <0.01, * < 0.05
Abbreviations: MI, Myocardial infarction; NA, Not applicable; NOAC, non-vitamin-K oral anticoagulant; NYHA, New York Heart Association; PCI, Percutaneous coronary intervention; TAVI, transcatheter aortic valve implantation; Q1, Quartile 1; Q3, Quartile 3; VARC-3, Valve Academic Research Consortium-3

Complete case analysis (univariate)

Results of univariate statistical tests (that is, unadjusted by multivariate analysis) of UK TAVI Registry data (TAVI in native aortic valve) for **in-hospital death** pre- and post-exclusion of missing data. [Key: Significant following Holm-Bonferroni correction: *** < 0.001, ** <0.01, * < 0.05]

Characteristics	No Death (pre-exclusion)	Death (pre-exclusion)	p-value (pre-exclusion)	No Death (post-exclusion)	Death (post-exclusion)	p-value (post-exclusion)
Total no. of procedures	6976	89	-	4769	52	-
Age median adjusted, years; mean (SD)	-0.82 (6.75)	-0.54 (6.82)	1	-0.97 (6.82)	-0.79 (6.85)	1
Sex, %	58%	59%	1	58%	51%	1
Height median adjusted, m; mean (SD)	-0.05 (1)	-0.08 (1.09)	1	-0.04 (0.99)	-0.08 (1.06)	1
Frailty, %	17%	25%	0.78	17%	34%	0.04*
Severe symptoms, %	12%	21%	0.14	13%	19%	1
Aortic valve mean gradient median adjusted, mmHg; mean (SD)	2.11 (16.72)	2.64 (18.27)	1	1.69 (16.25)	0.35 (15.89)	1
Annular diameter median adjusted, mm; mean (SD)	0.07 (2.69)	0.38 (2.68)	1	0.04 (2.67)	0.4 (2.69)	1
Valve size (small, medium, large), %	S = 29, M = 39, L = 39	S = 25, M = 35, L = 35	1	S = 29, M = 38, L = 38	S = 27, M = 37, L = 37	1
Urgency, %	24%	35%	0.22	25%	32%	1
Anaesthesia, %	1%	4%	0.14	1%	5%	0.18
LVEF Poor, %	8%	10%	1	8.%	9%	1
Coronary anatomical comorbidities, %	25%	27%	1	24%	26%	1
Coronary clinical comorbidities, %	22%	25%	1	23%	23%	1
Non-coronary clinical comorbidities, %	18%	25%	1	19%	23%	1
Non-coronary risk factors, %	53%	50%	1	54%	50%	1

Non-coronary renal, %	8%	17%	0.055	9%	15%	1

Abbreviations: LVEF, Left ventricular ejection fraction; SD, Standard deviation

Results of univariate statistical tests (that is, unadjusted by multivariate analysis) of UK TAVI Registry data (TAVI in native aortic valve) for **in-hospital stroke**. [Key: Significant following Holm-Bonferroni correction: *** < 0.001, ** <0.01, * < 0.05]

Characteristics	No Stroke (pre-exclusion)	Stroke (pre-exclusion)	p-value (pre-exclusion)	No Stroke (post-exclusion)	Stroke (post-exclusion)	p-value (post-exclusion)
Total no. of procedures	6372	107	-	4555	78	-
Age median adjusted, years; mean (SD)	-0.86 (6.78)	1.42 (5.88)	0.002**	-0.97 (6.81)	1.23 (6.28)	0.0048*
Sex, %	59	52	1	58	47	1
Height median adjusted, m; mean (SD)	-0.05 (1)	-0.15 (0.99)	1	-0.04 (0.99)	-0.18 (1)	1
Frailty, %	17	17	1	18	18	1
Severe symptoms, %	12	14	1	13	14	1
Aortic valve mean gradient median adjusted, mmHg; mean (SD)	1.72 (16.42)	0.02 (13.86)	1	1.57 (16.15)	0.32 (13.39)	1
Annular diameter median adjusted, mm; mean (SD)	0.08 (2.7)	0.15 (2.73)	1	0.05 (2.68)	0.15 (2.76)	1
Valve size (small, medium, large), %	S = 29, M = 39, L = 39	S = 28, M = 30, L = 30	0.72	S = 30, M = 39, L = 39	S = 29, M = 29, L = 29	1
Urgency, %	24	30	1	25	31	1
Anaesthesia, %	1	1	1	1	0	1
LVEF Poor, %	8	11	1	8	12	1
Coronary anatomical comorbidities, %	25	30	1	25	31	1
Coronary clinical comorbidities, %	23	24	1	24	27	1
Non-coronary clinical comorbidities, %	18	27	0.33	NA	NA	1
Non-coronary risk factors, %	54	47	1	54	49	1
Non-coronary renal, %	9	18	0.03*	9	19	0.07

Abbreviations: LVEF, Left ventricular ejection fraction; SD, Standard deviation

Results of univariate statistical tests (that is, unadjusted by multivariate analysis) of UK TAVI Registry data (TAVI in native aortic valve) for **in-hospital aortic regurgitation (AR)**. [Key: Significant following Holm-Bonferroni correction: *** < 0.001, ** <0.01, * < 0.05]

Characteristics	No AR (pre-exclusion)	AR (pre-exclusion)	p-value (pre-exclusion)	No AR (post-exclusion)	AR (post-exclusion)	p-value (post-exclusion)
Total no. of procedures	6713	122	-	4742	60	-
Age median adjusted, years; mean (SD)	-0.83 (6.78)	-1.84 (6.93)	1	-0.94 (6.81)	-2.63 (7.31)	1
Sex, %	59	59	1	58	62	1
Height median adjusted, m; mean (SD)	-0.05 (1)	-0.03 (0.94)	1	-0.05 (0.99)	0.12 (0.86)	1
Frailty, %	18	21	1	18	20	1
Severe symptoms, %	12	14	1	14	15	1
Aortic valve mean gradient median adjusted, mmHg; mean (SD)	1.99 (16.61)	9.42 (20.55)	0.003**	1.65 (16.28)	6.98 (15.06)	0.13
Annular diameter median adjusted, mm; mean (SD)	0.08 (2.69)	0.32 (2.79)	1	0.04 (2.67)	0.16 (2.82)	1
Valve size (small, medium, large), %	S = 29, M = 39, L = 39	S = 20, M = 32, L = 32	0.02*	S = 29, M = 39, L = 39	S = 20, M = 27, L = 27	0.04*
Urgency, %	25	32	1	25	25	1
Anaesthesia, %	1	3	1	1	3	1
LVEF Poor, %	8	8	1	8	10	1
Coronary anatomical comorbidities, %	25	28	1	24	25	1
Coronary clinical comorbidities, %	23	27	1	24	25	1
Non-coronary clinical comorbidities, %	19	21	1	20	13	1
Non-coronary risk factors, %	53	61	1	54	62	1
Non-coronary renal, %	9	8	1	9	8	1

Abbreviations: AR, Aortic regurgitation; LVEF, Left ventricular ejection fraction; SD, Standard deviation

Results of univariate statistical tests (that is, unadjusted by multivariate analysis) of UK TAVI Registry data (TAVI in native aortic valve) for **in-hospital permanent pacemaker implantation (PPI)**. [Key: Significant following Holm-Bonferroni correction: *** < 0.001, ** <0.01, * < 0.05]

Characteristics	No PPI (pre-exclusion)	PPI (pre-exclusion)	p-value (pre-exclusion)	No PPI (post-exclusion)	PPI (post-exclusion)	p-value (post-exclusion)
Total no. of procedures	6124	512	-	4374	344	-
Age median adjusted, years; mean (SD)	-0.86 (6.79)	-0.27 (6.28)	0.58	-0.98 (6.82)	-0.38 (6.47)	0.23
Sex, %	58	65	0.02*	57	64	1
Height median adjusted, m; mean (SD)	-0.05 (1)	0.01 (1)	1	-0.05 (0.99)	-0.01 (1)	1
Frailty, %	17	20	1	18	20	1
Severe symptoms, %	12	14	1	13	16	1
Aortic valve mean gradient median adjusted, mmHg; mean (SD)	1.72 (16.37)	1.82 (16.81)	1	1.58 (16.11)	1.12 (15.57)	1
Annular diameter median adjusted, mm; mean (SD)	0.06 (2.71)	0.3 (2.51)	0.84	0.03 (2.69)	0.31 (2.51)	063
Valve size (small, medium, large), %	S = 30, M = 39, L = 39	S = 22, M = 38, L = 38	<0.001***	S = 30, M = 39, L = 39	S = 21, M = 35, L = 35	<0.001 ***
Urgency, %	25	25	1	25	23	1
Anaesthesia, %	1	1	1	1	1	1
LVEF Poor, %	8	8	1	8	8	1
Coronary anatomical comorbidities, %	25	28	1	24	27	1
Coronary clinical comorbidities, %	23	27	0.82	23	28	0.48
Non-coronary clinical comorbidities, %	19	19	1	20	19	1
Non-coronary risk factors, %	53	56	1	54	56	1

Non-coronary renal, %	9	11	1	9	11	1

Abbreviations: LVEF, Left ventricular ejection fraction; SD, Standard deviation

Results of univariate statistical tests (that is, unadjusted by multivariate analysis) of UK TAVI Registry data (TAVI in native aortic valve) for **in-hospital major or life threatening bleed**. [Key: Significant following Holm-Bonferroni correction: *** < 0.001, ** <0.01, * < 0.05]

Characteristics	No bleed (pre-exclusion)	Bleed (pre-exclusion)	p-value (pre-exclusion)	No bleed (post-exclusion)	Bleed (post-exclusion)	p-value (post-exclusion)
Total no. of procedures	6474	70	1	4598	57	1
Age median adjusted, years; mean (SD)	-0.82 (6.74)	-0.47 (9.41)	1	-0.94 (6.8)	-0.04 (7.92)	1
Sex, %	59	53	1	58	53	1
Height median adjusted, m; mean (SD)	-0.05 (1)	-0.13 (1.18)	0.70	-0.05 (0.99)	-0.07 (1.15)	0.43
Frailty, %	17	27	1	18	30	1
Severe symptoms, %	11	9	1	13	9	1
Aortic valve mean gradient median adjusted, mmHg; mean (SD)	1.67 (16.41)	3.84 (13.74)	1	1.51 (16.11)	3.7 (13.97)	1
Annular diameter median adjusted, mm; mean (SD)	0.08 (2.69)	0.13 (2.95)	0.67	0.05 (2.67)	0.18 (2.96)	0.14
Valve size (small, medium, large), %	S = 29, M = 39, L = 39	S = 17, M = 40, L = 40	1	S = 30, M = 38, L = 38	S = 12, M = 42, L = 42	1
Urgency, %	25	23	1	25	26	1
Anaesthesia, %	1	0	0.98	1	0	1
LVEF Poor, %	8	1	1	8	2	1
Coronary anatomical comorbidities, %	26	27	1	25	25	1
Coronary clinical comorbidities, %	23	21	1	24	23	1
Non-coronary clinical comorbidities, %	18	24	1	20	21	1
Non-coronary risk factors, %	53	51	1	54	53	1
Non-coronary renal, %	9	10	1	9	11	1

Abbreviations: LVEF, Left ventricular ejection fraction; SD, Standard deviation

Results of univariate statistical tests (that is, unadjusted by multivariate analysis) of UK TAVI Registry data (TAVI in native aortic valve) for **in-hospital major vascular complications**. [Key: Significant following Holm-Bonferroni correction: *** < 0.001, ** <0.01, * < 0.05]

Characteristics	No vascular complication (pre-exclusion)	Vascular complication (pre-exclusion)	p-value (pre-exclusion)	No vascular complication (post-exclusion)	Vascular complication (post-exclusion)	p-value (post-exclusion)
Total no. of procedures	6454	87	1	4608	61	1
Age median adjusted, years; mean (SD)	-0.82 (6.75)	-0.43 (7.89)	1	-0.94 (6.81)	-0.13 (7.14)	1
Sex, %	59	53	1	58	52	1
Height median adjusted, m; mean (SD)	-0.05 (1)	-0.15 (0.93)	1	-0.05 (0.99)	-0.11 (0.9)	1
Frailty, %	17	23	1	18	23	1
Severe symptoms, %	12	13	1	13	13	1
Aortic valve mean gradient median adjusted, mmHg; mean (SD)	1.65 (16.4)	4.24 (15.34)	1	1.49 (16.09)	4.93 (16.01)	1
Annular diameter median adjusted, mm; mean (SD)	0.09 (2.7)	-0.08 (2.63)	1	0.06 (2.68)	-0.04 (2.63)	1
Valve size (small, medium, large), %	S = 29, M = 39, L = 39	S = 26, M = 31, L = 31	1	S = 30, M = 38, L = 38	S = 26, M = 30, L = 30	1
Urgency, %	25	24	1	25	31	1
Anaesthesia, %	1	1	1	1	2	1
LVEF Poor, %	8	7	1	8	7	1
Coronary anatomical comorbidities, %	26	27	1	25	26	1
Coronary clinical comorbidities, %	23	25	1	24	30	1
Non-coronary clinical comorbidities, %	18	27	1	20	25	1
Non-coronary risk factors, %	53	59	1	54	59	1
Non-coronary renal, %	9	11	1	9	15	1

Abbreviations: LVEF, Left ventricular ejection fraction; SD, Standard deviation

Results of univariate statistical tests (that is, unadjusted by multivariate analysis) of UK TAVI Registry data (TAVI in native aortic valve) for **in-hospital bailout TAVI-in-TAVI**. [Key: Significant following Holm-Bonferroni correction: *** < 0.001, ** <0.01, * < 0.05]

Characteristics	No bailout TAVI-in-TAVI (pre-exclusion)	TAVI-in-TAVI (pre-exclusion)	p-value (pre-exclusion)	No TAVI-in-TAVI (post-exclusion)	TAVI-in-TAVI (post-exclusion)	p-value (post-exclusion)
Total no. of procedures	6992	30	1	4786	21	1
Age median adjusted, years; mean (SD)	-0.82 (6.77)	-2.3 (5.7)	1	-0.96 (6.84)	-1.67 (6.07)	1
Sex, %	59	43	1	58	38	1
Height median adjusted, m; mean (SD)	-0.05 (1)	-0.19 (1.13)	1	-0.04 (0.99)	-0.25 (1.22)	1
Frailty, %	18	21	1	18	19	1
Severe symptoms, %	12	3	1	14	0	1
Aortic valve mean gradient median adjusted, mmHg; mean (SD)	2.11 (16.76)	4.1 (16.76)	1	1.66 (16.27)	3.33 (12.87)	1
Annular diameter median adjusted, mm; mean (SD)	0.07 (2.69)	0.41 (3.1)	1	0.04 (2.67)	0.35 (3.29)	1
Valve size (small, medium, large), %	S = 29, M = 39, L = 39	S = 23, M = 33, L = 33	1	S = 29, M = 39, L = 39	S = 29, M = 33, L = 33	1
Urgency, %	25	23	1	25	29	1
Anaesthesia, %	1	3	1	1	5	1
LVEF Poor, %	8	3	1	8	5	1
Coronary anatomical comorbidities, %	25	15	1	25	19	1
Coronary clinical comorbidities, %	23	27	1	24	29	1
Non-coronary clinical comorbidities, %	19	17	1	20	14	1
Non-coronary risk factors, %	53	67	1	54	57	1
Non-coronary renal, %	9	3	1	9	5	1

Abbreviations: LVEF, Left ventricular ejection fraction; SD, Standard deviation

Results of univariate statistical tests (that is, unadjusted by multivariate analysis) of UK TAVI Registry data (TAVI in native aortic valve) for **in-hospital conversion to SAVR**. [Key: Significant following Holm-Bonferroni correction: *** < 0.001, ** <0.01, * < 0.05]

Characteristics	No conversion to SAVR (pre-exclusion)	Conversion to SAVR (pre-exclusion)	p-value (pre-exclusion)	No conversion to SAVR (post-exclusion)	Conversion to SAVR (post-exclusion)	p-value (post-exclusion)
Total no. of procedures	7045	8	1	4810	7	1
Age median adjusted, years; mean (SD)	-0.82 (6.75)	-0.12 (5.06)	1	-0.96 (6.83)	0.57 (5.03)	1
Sex, %	58	75	1	58	71	1
Height median adjusted, m; mean (SD)	-0.05 (1)	0.15 (1.16)	1	-0.04 (0.99)	0 (1.17)	1
Frailty, %	18	0	1	18	0	1
Severe symptoms, %	12	13	1	14	0	1
Aortic valve mean gradient median adjusted, mmHg; mean (SD)	2.11 (16.77)	9.25 (10.87)	1	1.66 (16.26)	7.86 (10.95)	1
Annular diameter median adjusted, mm; mean (SD)	0.07 (2.69)	0.7 (2.61)	1	0.04 (2.67)	0.87 (2.77)	1
Valve size (small, medium, large), %	S = 29, M = 39, L = 39	S = 0, M = 50, L = 50	1	S = 29, M = 39, L = 39	S = 0, M = 57, L = 57	1
Urgency, %	25	38	1	25	29	1
Anaesthesia, %	1	0	1	1	0	1
LVEF Poor, %	8	0	1	8	0	1
Coronary anatomical comorbidities, %	25	43	1	24	43	1
Coronary clinical comorbidities, %	23	38	1	24	43	1
Non-coronary clinical comorbidities, %	19	25	1	20	14	1
Non-coronary risk factors, %	53	50	1	54	43	1
Non-coronary renal, %	9	0	1	9	0	1

Abbreviations: LVEF, Left ventricular ejection fraction; SAVR, Surgical Aortic Valve Replacement SD, Standard deviation

Appendix F: Economic model

Appendix F1: Critical appraisal of the NG208 economic model

CHEERS checklist for the NG208 economic model

Item	NG208 economic analysis report	Additional EAG comments
Title	**Page 8**	**-**
Title	Cost-utility analysis: Transcatheter intervention for patients who have operable aortic stenosis	The type of economic evaluation is identified, and the interventions is specified in the title.
Abstract	**-**	**-**
Abstract	No abstract/summary	The report is not a peer-reviewed paper, but a structured abstract could have been useful.
Introduction	**Page 7**	**-**
Background and objectives	Background is provided but the objective of the economic evaluation is not clearly stated.	The study objective and its relevance to policy and practice is not clearly stated
Methods	**Pages 8-13**	**-**
Health economic analysis plan	There is no reference to an existing Health Economics Assessment Plan or protocol	-
Study population	Adults with operable aortic stenosis (non-bicuspid) requiring intervention in three risk groups	-
Setting and location	UK	-
Comparators	Standard (surgical) aortic valve replacement (SAVR) with biological valves Transcatheter aortic valve implantation (TAVI)	-
Perspective	UK NHS and personal social services perspective	-
Time horizon	15 years	-
Discount rate	3.5%	-
Selection of outcomes	9 post-procedural outcomes were considered.	Refer to Final Scope for outcomes of interest to this late-stage assessment
Measurement of outcomes	Page 14-29: clinical outcomes Page 30: utility values	-
Valuation of outcomes	Not applicable	-
Measurement and valuation of resources and costs	Page 32-36	-
Currency, price date, and conversion	Page 32 - price year and inflation application is not mentioned	-
Rationale and description of model	Page 9 :procedural decision tree model nested within long term Markov models.	-
Analytics and assumptions	Page 10-11	-
Characterising heterogeneity	Not provided	-

Item	NG208 economic analysis report	Additional EAG comments
Characterising distributional effects	Not provided	-
Characterising uncertainty	Page 12	They produced probabilistic and deterministic sensitivity analysis and various scenario analysis to address uncertainties
Approach to engagement with patients and others affected by the study	Not provided	-
Results	**Page 54 -59**	**-**
Study parameters	It is mentioned earlier in method section page 32	-
Summary of main results	It is provided in the discussion section	-
Effect of uncertainty	Page 56	-
Effect of engagement with patients and others affected by the study	Not provided	-
Discussion	**Page 60 -63**	**-**
Study findings, limitations, generalisability, and current knowledge	A summary of finding is provided, limitations are mentioned, generalisability is discussed, and results are compared with current literature.	-
Other relevant information	**-**	**-**
Source of funding	NICE	-
Conflict of interest	Not mentioned	-

Abbreviations: EAG, External Assessment Group; NICE, National Institute for Health and Care Excellence; SAVR, Surgical aortic valve replacement; TAVI, Transcatheter aortic valve implantation

Summary of additional assumptions incorporated within the economic model used within NG208

Assumption within economic model used within NG208	EAG comment	Summary of feedback gained from 5 Clinical Experts (Appendix G)
Economic model does not account for general or local anaesthesia	The EAG assumed that type of anaesthesia used is captured within the average cost of procedure and length of stay (obtained from the Healthcare Resource Group, HRG). The EAG note that Getting It Right First Time (GIRFT)	• General or local anaesthesia not considered to differ between TAVI devices • Local anaesthesia considered as the

Assumption within economic model used within NG208	EAG comment	Summary of feedback gained from 5 Clinical Experts (Appendix G)
	have recommended conducting TAVI under local anaesthesia and have developed a delivery guide to support heart teams to increase the volume of TAVI procedures, based on the experience of James Cook University hospital (GIRFT, 2023). Between 2022 and 2023, 93.9% of all TAVI procedures were undertaken under conscious sedation (NICOR, 2024). Clinical Experts previously advised that this related to the general health of the patient and not associated with particularly TAVI devices.	default (general anaesthesia used in specific cases dependent upon patient characteristics, which occurs in minority of cases).
Economic model does not account for day-case procedures	Related to the above. The EAG assumed that this is captured within the average cost of the procedure and length of stay (from HRG). The EAG considered length of stay from the UK TAVI Registry separately for each device to determine impact on economic modelling.	• All 5 Clinical Experts responding to this question considered this an appropriate approach. • One Clinical Expert stated that length of stay was unlikely to differ between TAVI devices.
Economic model does not account for different delivery approach (for example transfemoral, subclavian, transapical)	Most TAVI procedures are undertaken via percutaneous transfemoral delivery approach (93.3% as stated in BCIS 2021-22 report); and recommended as default position by GIRFT in its 2021 cardiology report. The EAG assumed that the delivery approach and associated complications was captured within the average cost of the procedure (from HRG) and clinical outcomes. For simplicity only transfemoral TAVI were modelled by the EAG, which represents most of the TAVI procedures in the NHS.	• 3 of 5 Clinical Experts felt that this approach was appropriate. • 2 Clinical Experts stated that the outcomes and costs of non-transfemoral would be significantly different.
Economic model does not account for different staffing	The EAG assumed that staffing is captured within the average cost of the procedure (within HRG) which are updated annually. Current BCIS guidance recommends that TAVI should be done by 2 appropriately trained TAVI operators (MacCarthy et al. 2021) and noted that thoracic approaches (such as transapical or direct aortic) procedures are led by cardiac surgeons. The EAG assumed no difference in staffing between delivery of different TAVI	• All 5 Clinical Experts responding to this question considered this an appropriate approach. • One Clinical Expert noted that the Royal College of Physicians (RCP) TAVI reviews demonstrated that staffing can be variable

Assumption within economic model used within NG208	EAG comment	Summary of feedback gained from 5 Clinical Experts (Appendix G)
	valves. However, did incorporate procedure duration within the economic model which does vary by device and therefore sought Clinical Expert opinion on the staffing that would be used for a typical TAVI procedure. The EAG also considered a proportion of procedures had an anaesthetist and Operating Department Practitioner (ODP), this proportion will be varied in sensitivity analysis to demonstrate impact on economic results.	within TAVI units (Appendix G).
Economic modelling subgroups the cohort by surgical risk.	The Clinical Experts have previously advised that they would not routinely categorise patients by surgical risk when performing TAVI. Surgical risk (low, intermediate, high) is not routinely captured in the UK TAVI Registry, nor routinely calculated by the interventional cardiologists conducting the procedure as this risk does not capture other features relevant to TAVI (for example vascular anatomy or frailty). Surgical risk is poorly reported and varied in its definition and thresholds used across published literature also. The only parameter which appeared to vary by surgical risk group was mortality. For reasons outlined (see EAG protocol), surgical risk was not modelled by the EAG.	• 4 of 5 Clinical Experts considered this an appropriate approach. • 1 Clinical Expert raised concerns that comparing with SAVR would be biased if risk groups were not used.
Base case assumption: Time horizon of 10 years	The EAG acknowledge that most of the published literature reports short-term outcomes (in-hospital, 30 days) and that long-term evidence is only available for older generations of TAVI devices no longer available within the NHS (Ali et al. 2023). The EAG also note that technological developments, such as the addition or lengthening of a pericardial skirt, have been shown to impact outcomes, such as haemodynamic outcomes including PVL (see Section 5.2.6) Therefore, use of data relating to older devices may overestimate adverse events or provide poorer clinical outcomes. The EAG used data from 01 April 2021 onwards, focusing on evidence related to currently available TAVI devices, and used data from	• 3 of 5 Clinical Experts considered this an appropriate approach. • 1 Clinical Expert stated that extrapolation to 10 years should be supported by published 5- and 10-year data to define medium to long term outcomes. • 1 Clinical Expert stated concern that newer implantable devices are not necessarily safer, reporting that extrapolation to 10 years was inappropriate.

Assumption within economic model used within NG208	EAG comment	Summary of feedback gained from 5 Clinical Experts (Appendix G)
	Hospital Episode Statistics (HES) to determine 30 day, 1 year and 2 year outcomes, which were extrapolated over the model lifetime (limitation because of data availability). Additional time horizons were explored in sensitivity analysis.	
Base case assumption: Treatment effects calculated using only second and third generation TAVI valves	Treatment effects applied in economic modelling was restricted to specific devices and versions listed in the NICE Final Scope.	• All 5 Clinical Experts responding to this question considered this an appropriate approach.
Base case assumption: only moderate and severe paravalvular leak affects mortality	The EAG considered only moderate and severe paravalvular leaks within the economic model.	• All 4 Clinical Experts responding to this question considered this an appropriate approach. • 1 Clinical Expert stated that there was no need to consider mild paravalvular leak impact on mortality.

Abbreviations: BCIS, British Cardiovascular Intervention Society; EAG, External Assessment Group; GIRFT, Getting It Right First Time; HES, Hospital Episode Statistics; HRG, Healthcare resource group; ICU, Intensive care unit; NICE, National Institute for Health and Care Excellence; PVL, Paravalvular leak; SSDP, Specialised Services Devices Programme; TAVI, Transcatheter aortic valve implantation

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Appendix F2: Validation of the EAG economic model

For model verification, the *rdecision* package, which includes the Markov model engine and the methods for probabilistic sensitivity analysis includes approximately 1300 self tests which must pass before the package is released. It also includes replications of published economic models.

The EAG used the model structure developed for this late-stage assessment, and applied parameters taken from the NG208 economic model report for the TAVI arm. Although the structures differed, the accumulated QALYs agreed; there were differences in costs due to some (for example dialysis costs) not being included in the late-stage assessment model.

In NG208 the mean per patient cost in a high-risk population was £28,052 and mean QALYs were 3.02. The EAG mean cost per patient across the 6 devices ranged between £23,764 and £29,011; and mean QALYs ranged between 1.52 and 3.15. These broadly agree. The EAG note that the updated economic model did not include costs or utilities for dialysis but did include additional utility decrements (not considered in NG208) such as pacemaker implantation, heart failure and paravalvular leak.

Number of simulated patients

The EAG modelled 1000, 500 and 100 patients in the base case to investigate model stability and to advise simulation size for pragmatic purposes. Due to the below results the EAG selected 500 simulated patients for the economic modelling.

a) Mean cost per patient

Number of simulated patients	Sapien 3 (Male)	Sapien 3 Ultra (Male)	ACURATE neo2 (Male)	Evolut R (Male)	Evolut Pro+ (Male)	Navitor (Male)
1000	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
500	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of simulated patients	Sapien 3 (Female)	Sapien 3 Ultra (Female)	ACURATE neo2 (Female)	Evolut R (Female)	Evolut Pro+ (Female)	Navitor (Female)
1000	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
500	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

b) Mean QALY per patient

Number of simulated patients	Sapien 3 (Male)	Sapien 3 Ultra (Male)	ACURATE neo2 (Male)	Evolut R (Male)	Evolut Pro+ (Male)	Navitor (Male)
1000	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
500	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of simulated patients	Sapien 3 (Female)	Sapien 3 Ultra (Female)	ACURATE neo2 (Female)	Evolut R (Female)	Evolut Pro+ (Female)	Navitor (Female)
1000	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
500	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

c) Mean net monetary benefit (NMB), per patient

Number of simulated patients	Sapien 3 (Male)	Sapien 3 Ultra (Male)	ACURATE neo2 (Male)	Evolut R (Male)	Evolut Pro+ (Male)	Navitor (Male)
1000	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
500	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of simulated patients	Sapien 3 (Female)	Sapien 3 Ultra (Female)	ACURATE neo2 (Female)	Evolut R (Female)	Evolut Pro+ (Female)	Navitor (Female)
1000	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
500	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

d) Probability of highest NMB

Number of simulated patients	Sapien 3 (Male)	Sapien 3 Ultra (Male)	ACURATE neo2 (Male)	Evolut R (Male)	Evolut Pro+ (Male)	Navitor (Male)
1000	75 [66 to 83] %	3 [1 to 7] %	0 [0 to 0] %	17 [10 to 25] %	5 [2 to 10] %	0 [0 to 0] %
500	76 [67 to 84] %	4 [1 to 9] %	0 [0 to 0] %	16 [10 to 24] %	4 [1 to 9] %	0 [0 to 0] %
100	75 [66 to 83] %	4 [1 to 9] %	0 [0 to 0] %	15 [9 to 23] %	6 [2 to 11] %	0 [0 to 0] %
Number of simulated patients	Sapien 3 (Female)	Sapien 3 Ultra (Female)	ACURATE neo2 (Female)	Evolut R (Female)	Evolut Pro+ (Female)	Navitor (Female)
1000	70 [61 to 79] %	10 [5 to 16] %	0 [0 to 0] %	13 [7 to 20] %	7 [3 to 13] %	0 [0 to 0] %
500	74 [65 to 82] %	9 [4 to 16] %	0 [0 to 0] %	11 [6 to 18] %	6 [2 to 12] %	0 [0 to 0] %
100	70 [61 to 79] %	16 [10 to 24] %	0 [0 to 0] %	12 [6 to 19] %	2 [0 to 5] %	0 [0 to 0] %

Appendix F3: EAG estimated breakdown of the TAVI HRG (EY21A, EY21B)

Parameter	Value	Source	Unit cost	Cost source	Per admission cost
Median length of stay (elective)	[redacted]	HES analysis 01/04/2021 to 31/10/2023	[redacted]	NHS Reference Costs 2017-2018 weighted average of bed days applied. The costs used in the original model are inflated to 2021/22 using NHS Cost Inflation Index	[redacted]
Median length of stay (non-elective)	[redacted]	HES analysis 01/04/2021 to 31/10/2023	[redacted]	NHS Reference Costs 2017-2018 weighted average of bed days applied. The costs used in the original model are inflated to 2021/22 using NHS Cost Inflation Index	[redacted]
Proportion non-elective	[redacted]	UK TAVI Registry (01/04/2021 to 31/03/2023)	[redacted]	-	[redacted]
Proportion with ICU stay	[redacted]	HES analysis 01/04/2021 to 31/10/2023 (1595/10906)	[redacted]	-	[redacted]
Length of ICU	[redacted]	HES analysis 01/04/2021 to 31/10/2023	[redacted]	Updated value from NHS Reference Costs 2021-2022 Weighted average of XC01Z-XC07Z within CC: “Non-specific, general adult critical care”	[redacted]
Additional ICU stay if bailout SAVR	[redacted]	NG208, 2021	[redacted]	-	[redacted]
Additional ICU stay if bailout TAVI	[redacted]	NG208, 2021	[redacted]	-	[redacted]
Median procedure time (mins)	[redacted]	UK TAVI Registry. EAG note that the median procedure duration was 70 minutes in 2021/22 and 69 minutes in 2022/23 (little difference in procedure times nationally). However, within sensitivity analysis will apply a procedure duration of 45 minutes in line with suggestion from Clinical Experts.	[redacted]	Public Health Scotland 2023. R040 table adding cardiology (not cardiac surgery) other direct care, labs only (not included staff to avoid double counting). This equates to [redacted] per minute assuming median 70-minute procedure.	[redacted]
Additional minutes for bailout TAVI-in-TAVI	[redacted]	Clinical Experts	[redacted]	-	[redacted]
Staff - consultants (operator)	[redacted]	Clinical Experts	[redacted]	Unit costs of health and social care 2023. Consultant (medical) with qual (table 11.3.2)	[redacted]
Proportion with anaesthetist, ODP	[redacted]	Clinical Experts	[redacted]	-	[redacted]
Staff - consultants (anaesthetist)	[redacted]	Clinical Experts	[redacted]	Unit costs of health and social care 2023. Consultant (medical) with qual (table 11.3.2)	[redacted]
ODP (when anaesthetist present) (B5)	[redacted]	Clinical Experts	[redacted]	Unit costs of health and social care 2023. Hospital based nurse (B5) with qual (table 11.2.2)	[redacted]
Nurse-led sedation (if no anaesthetist) (B7)	[redacted]	Clinical Experts (only if no anaesthetist)	[redacted]	Unit costs of health and social care 2023. Hospital based nurse (B7) with qual (table 11.2.2)	[redacted]
Nurse - scrub (B5)	[redacted]	Clinical Experts	[redacted]	Unit costs of health and social care 2023. Hospital based nurse (B5) with qual (table 11.2.2)	[redacted]
Nurse - runner (B5)	[redacted]	Clinical Experts	[redacted]	Unit costs of health and social care 2023. Hospital based nurse (B5) with qual (table 11.2.2)	[redacted]
Radiographer (B6)	[redacted]	Clinical Experts	[redacted]	Unit costs of health and social care 2023. Hospital based scientific and professional staff with qual B6 (table 11.1.2)	[redacted]
Cardiac physiologist (B7)	[redacted]	Clinical Experts	[redacted]	Unit costs of health and social care 2023. Hospital based scientific and professional staff with qual (table 11.1.2)	[redacted]
Nurse - preparing valve (B6)	[redacted]	Clinical Experts	[redacted]	Unit costs of health and social care 2023. Hospital based nurse (B6) with qual (table 11.2.2)	[redacted]
CT imaging	[redacted]	Clinical Experts	[redacted]	NHS 21/22 reference costs: RD60Z IMAG worksheet	[redacted]
% with pacemaker	[redacted]	UK TAVI Registry	[redacted]	Updated from NG208	[redacted]
% with major vascular complication	[redacted]	UK TAVI Registry	[redacted]	Updated from NG208	[redacted]
% with major bleeding	[redacted]	UK TAVI Registry	[redacted]	Updated from NG208	[redacted]
% with in-hospital stroke	[redacted]	HES	[redacted]	Updated from NG208	[redacted]
% kidney damage (dialysis)	[redacted]	UK TAVI Registry	[redacted]	Updated from NG208	[redacted]
% bailout SAVR	[redacted]	UK TAVI Registry	[redacted]	Nonelective SAVR (NHS Ref 2021/22) ED24ABC, ED25ABC	[redacted]
% bailout TAVI-in-TAVI	[redacted]	UK TAVI Registry	[redacted]	Additional time (additional valve captured separately)	[redacted]
Echo for PVL before discharge	[redacted]	Clinical Experts	[redacted]	APC guide price: RD51A IMAG worksheet (NHS Ref 2021/22)	[redacted]
-	-	-	-	*Sub-total*	[redacted]
-	-	-	-	*Other non-accounted for overhead/management costs*	[redacted]
-	-	-	-	**TOTAL HRG Costs**	[redacted]
-	-	-	-	**TOTAL HRG + ICU cost**	[redacted]
-	-	-	-	**TOTAL HRG + ICU cost + TAVI valve**	[redacted]

Abbreviations: EAG, External Assessment Group; HES, Hospital Episode Statistics; ICU, Intensive care unit; ODP; Operating department practitioner; PVL, Paravalvular leak, SAVR, Surgical Aortic Valve Replacement; TAVI, transcatheter aortic valve implantation

Appendix F4: EAG base case

Health state occupancy (for 1,000 patients)

Male, median age, Edwards Sapien 3

Years	Implantation	Reimplantation	NoComp	Paced	PVL	Paced+PVL	Stroke	Post-stroke	HF	SAVR	Dead
0	1000	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0	0.00
1	0	0	703.47	82.53	33.18	2.35	19.05	12.25	14.65	0	132.51
2	0	0	557.29	90.38	22.47	1.51	18.27	25.98	25.95	0	258.16
3	0	0	434.26	90.05	14.62	0.92	15.00	34.32	32.84	0	377.99
4	0	0	332.33	83.94	9.10	0.53	11.65	37.10	36.01	0	489.34
5	0	0	248.98	74.04	5.38	0.29	8.72	35.54	36.13	0	590.91
6	0	0	181.82	62.04	2.98	0.15	6.31	31.06	33.88	0	681.77
7	0	0	129.40	49.65	1.56	0.07	4.44	25.23	30.08	0	759.57
8	0	0	89.54	37.98	0.76	0.03	3.03	19.19	25.43	0	824.05
9	0	0	59.89	27.67	0.34	0.01	1.98	13.63	20.44	0	876.04
10	0	0	38.72	19.23	0.14	0.00	1.25	9.09	15.69	0	915.88
11	0	0	24.10	12.71	0.05	0.00	0.76	5.68	11.47	0	945.23
12	0	0	14.33	7.93	0.02	0.00	0.43	3.29	7.95	0	966.05
13	0	0	8.19	4.71	0.01	0.00	0.24	1.79	5.25	0	979.81
14	0	0	4.45	2.63	0.00	0.00	0.12	0.90	3.28	0	988.61
15	0	0	2.32	1.40	0.00	0.00	0.06	0.43	1.96	0	993.84

Female, median age, Edwards Sapien 3

Years	Implantation	Reimplantation	NoComp	Paced	PVL	Paced+PVL	Stroke	Post-stroke	HF	SAVR	Dead
0	1000	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0	0.00
1	0	0	705.04	71.98	44.28	2.70	17.23	13.37	10.64	0	134.75
2	0	0	570.20	80.84	30.65	1.77	15.04	24.64	19.00	0	257.85
3	0	0	452.74	82.19	20.28	1.10	12.14	30.75	24.22	0	376.58
4	0	0	351.88	77.78	12.73	0.64	9.40	32.20	26.65	0	488.71
5	0	0	266.65	69.29	7.52	0.35	7.02	30.08	26.72	0	592.37
6	0	0	196.64	58.51	4.15	0.18	5.08	25.77	25.00	0	684.67
7	0	0	140.23	46.75	2.11	0.08	3.53	20.35	21.97	0	764.97
8	0	0	96.41	35.37	0.98	0.03	2.35	14.89	18.23	0	831.73
9	0	0	63.79	25.35	0.42	0.01	1.51	10.14	14.32	0	884.47

10	0	0	40.26	17.07	0.16	0.00	0.91	6.36	10.59	0	924.64
11	0	0	24.18	10.79	0.05	0.00	0.52	3.68	7.38	0	953.40
12	0	0	13.68	6.34	0.02	0.00	0.28	1.94	4.81	0	972.93
13	0	0	7.39	3.52	0.00	0.00	0.15	0.95	2.97	0	985.02
14	0	0	3.75	1.81	0.00	0.00	0.07	0.43	1.70	0	992.24
15	0	0	1.77	0.86	0.00	0.00	0.03	0.17	0.91	0	996.26

Male, median age, Edwards Sapien 3 Ultra

Years	Implantation	Reimplantation	NoComp	Paced	PVL	Paced+PVL	Stroke	Post-stroke	HF	SAVR	Dead
0	1000	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0	0.00
1	0	0	707.59	80.60	20.13	1.59	14.48	8.11	11.14	0	156.36
2	0	0	553.79	80.17	12.70	0.93	14.11	18.26	19.19	0	300.85
3	0	0	424.65	74.36	7.62	0.52	11.30	23.81	23.52	0	434.21
4	0	0	318.42	65.17	4.33	0.27	8.47	24.82	24.88	0	553.63
5	0	0	232.57	54.21	2.31	0.13	6.09	22.61	23.96	0	658.12
6	0	0	164.55	42.77	1.14	0.06	4.20	18.57	21.43	0	747.29
7	0	0	112.78	32.13	0.52	0.02	2.80	14.05	18.03	0	819.67
8	0	0	74.64	22.96	0.22	0.01	1.80	9.85	14.34	0	876.19
9	0	0	47.37	15.51	0.08	0.00	1.10	6.38	10.77	0	918.80
10	0	0	28.82	9.92	0.03	0.00	0.64	3.84	7.65	0	949.10
11	0	0	16.73	5.98	0.01	0.00	0.36	2.14	5.13	0	969.66
12	0	0	9.18	3.37	0.00	0.00	0.19	1.09	3.22	0	982.95
13	0	0	4.79	1.79	0.00	0.00	0.09	0.52	1.92	0	990.89
14	0	0	2.35	0.88	0.00	0.00	0.04	0.22	1.06	0	995.44
15	0	0	1.10	0.41	0.00	0.00	0.02	0.09	0.56	0	997.83

Female, median age, Edwards Sapien 3 Ultra

Years	Implantation	Reimplantation	NoComp	Paced	PVL	Paced+PVL	Stroke	Post-stroke	HF	SAVR	Dead
0	1000	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0	0.00
1	0	0	715.29	70.67	27.17	1.85	12.05	7.48	8.12	0	157.39
2	0	0	570.07	71.91	17.52	1.11	11.38	15.62	14.10	0	298.29
3	0	0	444.08	67.92	10.68	0.63	9.10	19.90	17.40	0	430.28
4	0	0	336.91	60.26	6.10	0.33	6.82	20.45	18.45	0	550.68

5	0	0	247.70	50.41	3.23	0.16	4.88	18.32	17.72	0	657.57
6	0	0	176.09	39.91	1.58	0.07	3.36	14.82	15.78	0	748.41
7	0	0	120.08	29.73	0.69	0.03	2.20	10.89	13.09	0	823.29
8	0	0	78.26	20.82	0.27	0.01	1.37	7.31	10.16	0	881.80
9	0	0	48.63	13.70	0.10	0.00	0.81	4.51	7.39	0	924.86
10	0	0	28.51	8.38	0.03	0.00	0.45	2.52	5.01	0	955.10
11	0	0	15.71	4.75	0.01	0.00	0.23	1.28	3.16	0	974.85
12	0	0	8.05	2.47	0.00	0.00	0.11	0.58	1.84	0	986.95
13	0	0	3.89	1.20	0.00	0.00	0.05	0.24	1.00	0	993.61
14	0	0	1.74	0.53	0.00	0.00	0.02	0.09	0.50	0	997.12
15	0	0	0.71	0.21	0.00	0.00	0.01	0.03	0.23	0	998.81

Male, median age, ACURATE neo2

Years	Implantation	Reimplantation	NoComp	Paced	PVL	Paced+PVL	Stroke	Post-stroke	HF	SAVR	Dead
0	1000	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0	0.00
1	0	0	587.57	72.11	93.08	5.74	10.51	6.08	14.55	0	210.36
2	0	0	438.72	79.69	55.49	3.16	9.57	12.76	24.16	0	376.45
3	0	0	320.04	77.15	31.25	1.63	7.22	15.69	28.51	0	518.51
4	0	0	227.60	68.38	16.53	0.78	5.11	15.43	28.96	0	637.20
5	0	0	157.09	56.39	8.13	0.34	3.47	13.23	26.72	0	734.62
6	0	0	104.57	43.46	3.66	0.14	2.26	10.19	22.82	0	812.90
7	0	0	67.14	31.54	1.51	0.05	1.42	7.19	18.27	0	872.88
8	0	0	41.43	21.56	0.56	0.02	0.85	4.68	13.77	0	917.13
9	0	0	24.37	13.79	0.19	0.00	0.49	2.79	9.75	0	948.62
10	0	0	13.66	8.28	0.06	0.00	0.26	1.54	6.49	0	969.70
11	0	0	7.26	4.65	0.01	0.00	0.14	0.78	4.06	0	983.11
12	0	0	3.62	2.41	0.00	0.00	0.06	0.36	2.36	0	991.19
13	0	0	1.71	1.17	0.00	0.00	0.03	0.15	1.29	0	995.66
14	0	0	0.75	0.52	0.00	0.00	0.01	0.06	0.65	0	998.01
15	0	0	0.31	0.22	0.00	0.00	0.00	0.02	0.31	0	999.14

Female, median age, ACURATE neo2

Years	Implantation	Reimplantation	NoComp	Paced	PVL	Paced+PVL	Stroke	Post-stroke	HF	SAVR	Dead

0	1000	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0	0.00
1	0	0	566.45	60.81	119.68	6.36	8.78	5.77	10.50	0	221.66
2	0	0	432.05	68.90	73.01	3.59	7.63	11.03	17.55	0	386.23
3	0	0	321.11	67.98	41.80	1.88	5.70	13.13	20.78	0	527.62
4	0	0	231.57	61.00	22.23	0.91	4.01	12.63	21.09	0	646.56
5	0	0	161.15	50.56	10.84	0.39	2.69	10.58	19.33	0	744.45
6	0	0	107.93	39.08	4.81	0.15	1.73	7.97	16.37	0	821.96
7	0	0	68.95	28.06	1.90	0.05	1.06	5.42	12.86	0	881.70
8	0	0	41.83	18.73	0.66	0.02	0.61	3.34	9.40	0	925.41
9	0	0	24.04	11.62	0.20	0.00	0.34	1.88	6.41	0	955.50
10	0	0	12.93	6.62	0.05	0.00	0.17	0.95	4.04	0	975.23
11	0	0	6.48	3.46	0.01	0.00	0.08	0.43	2.35	0	987.18
12	0	0	2.99	1.64	0.00	0.00	0.04	0.17	1.25	0	993.91
13	0	0	1.29	0.72	0.00	0.00	0.01	0.06	0.62	0	997.30
14	0	0	0.51	0.28	0.00	0.00	0.01	0.02	0.28	0	998.91
15	0	0	0.18	0.10	0.00	0.00	0.00	0.01	0.11	0	999.60

Male, median age, Evolut R

Years	Implantation	Reimplantation	NoComp	Paced	PVL	Paced+PVL	Stroke	Post-stroke	HF	SAVR	Dead
0	1000	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0	0.00
1	0	0	507.51	117.20	129.99	21.56	10.56	9.58	18.91	0	184.70
2	0	0	402.39	116.75	88.67	13.90	8.01	15.50	33.12	0	321.66
3	0	0	313.74	109.85	58.05	8.54	6.08	17.96	41.46	0	444.32
4	0	0	240.17	98.58	36.33	4.98	4.55	17.97	44.99	0	552.42
5	0	0	179.93	84.66	21.57	2.73	3.33	16.34	44.69	0	646.74
6	0	0	131.33	69.53	12.02	1.39	2.37	13.73	41.51	0	728.12
7	0	0	93.39	54.79	6.28	0.66	1.64	10.81	36.52	0	795.91
8	0	0	64.53	41.40	3.06	0.29	1.11	8.00	30.59	0	851.03
9	0	0	43.08	29.84	1.37	0.11	0.72	5.55	24.38	0	894.94
10	0	0	27.78	20.55	0.56	0.04	0.45	3.62	18.55	0	928.44
11	0	0	17.24	13.47	0.21	0.01	0.27	2.21	13.45	0	953.13
12	0	0	10.21	8.33	0.07	0.00	0.15	1.26	9.24	0	970.73
13	0	0	5.81	4.91	0.02	0.00	0.09	0.67	6.06	0	982.44
14	0	0	3.14	2.72	0.01	0.00	0.04	0.33	3.75	0	990.01
15	0	0	1.63	1.43	0.00	0.00	0.02	0.15	2.21	0	994.55

Female, median age, Evolut R

Years	Implantation	Reimplantation	NoComp	Paced	PVL	Paced+PVL	Stroke	Post-stroke	HF	SAVR	Dead
0	1000	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0	0.00
1	0	0	477.61	95.46	162.77	23.23	11.93	13.66	13.45	0	201.90
2	0	0	386.06	97.16	113.20	15.29	7.08	18.83	23.67	0	338.71
3	0	0	306.27	93.05	75.20	9.53	4.89	19.68	29.71	0	461.66
4	0	0	237.76	84.59	47.38	5.59	3.53	18.32	32.21	0	570.61
5	0	0	179.88	73.20	28.02	3.05	2.54	15.73	31.85	0	665.73
6	0	0	132.39	60.46	15.49	1.53	1.79	12.63	29.39	0	746.32
7	0	0	94.17	47.46	7.88	0.70	1.21	9.45	25.48	0	813.64
8	0	0	64.54	35.37	3.66	0.29	0.79	6.61	20.87	0	867.87
9	0	0	42.54	25.02	1.54	0.11	0.50	4.31	16.19	0	909.79
10	0	0	26.72	16.65	0.58	0.03	0.30	2.61	11.84	0	941.28
11	0	0	15.96	10.40	0.19	0.01	0.17	1.45	8.15	0	963.66
12	0	0	8.98	6.04	0.06	0.00	0.09	0.74	5.24	0	978.85
13	0	0	4.82	3.31	0.01	0.00	0.05	0.35	3.19	0	988.26
14	0	0	2.42	1.68	0.00	0.00	0.02	0.15	1.81	0	993.91
15	0	0	1.13	0.79	0.00	0.00	0.01	0.06	0.95	0	997.06

Male, median age, Evolut Pro+

Years	Implantation	Reimplantation	NoComp	Paced	PVL	Paced+PVL	Stroke	Post-stroke	HF	SAVR	Dead
0	1000	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0	0.00
1	0	0	511.40	101.48	148.84	22.50	19.37	13.97	17.57	0	164.87
2	0	0	405.04	96.83	100.13	14.30	17.02	26.84	30.51	0	309.31
3	0	0	315.51	88.19	64.68	8.67	13.30	33.67	37.88	0	438.10
4	0	0	241.32	77.10	39.95	4.99	9.91	35.10	40.80	0	550.83
5	0	0	180.66	64.78	23.42	2.70	7.16	32.64	40.25	0	648.39
6	0	0	131.80	52.21	12.89	1.36	5.01	27.79	37.14	0	731.81
7	0	0	93.69	40.46	6.66	0.63	3.43	22.04	32.48	0	800.62
8	0	0	64.72	30.11	3.21	0.27	2.28	16.39	27.07	0	855.95
9	0	0	43.21	21.41	1.42	0.11	1.46	11.40	21.48	0	899.51
10	0	0	27.87	14.56	0.58	0.04	0.90	7.45	16.28	0	932.31
11	0	0	17.30	9.44	0.21	0.01	0.54	4.56	11.77	0	956.17
12	0	0	10.26	5.78	0.07	0.00	0.30	2.59	8.06	0	972.93
13	0	0	5.84	3.37	0.02	0.00	0.17	1.38	5.28	0	983.94

14	0	0	3.16	1.85	0.01	0.00	0.09	0.68	3.26	0	990.95
15	0	0	1.64	0.97	0.00	0.00	0.04	0.32	1.93	0	995.10

Female, median age, Evolut Pro+

Years	Implantation	Reimplantation	NoComp	Paced	PVL	Paced+PVL	Stroke	Post-stroke	HF	SAVR	Dead
0	1000	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0	0.00
1	0	0	483.88	83.06	187.61	24.41	18.72	16.86	12.67	0	172.79
2	0	0	391.48	81.16	129.12	15.90	14.22	27.56	22.14	0	318.43
3	0	0	310.88	75.44	84.92	9.82	10.67	31.98	27.60	0	448.70
4	0	0	241.62	67.01	52.98	5.70	7.83	31.80	29.73	0	563.34
5	0	0	183.04	56.90	31.05	3.08	5.59	28.50	29.22	0	662.63
6	0	0	134.91	46.25	17.02	1.54	3.89	23.56	26.82	0	746.02
7	0	0	96.13	35.81	8.58	0.70	2.60	18.01	23.15	0	815.01
8	0	0	66.01	26.38	3.96	0.28	1.68	12.79	18.88	0	870.02
9	0	0	43.60	18.46	1.66	0.10	1.05	8.46	14.60	0	912.06
10	0	0	27.46	12.17	0.62	0.03	0.62	5.16	10.64	0	943.29
11	0	0	16.45	7.55	0.20	0.01	0.35	2.91	7.31	0	965.22
12	0	0	9.28	4.35	0.06	0.00	0.19	1.49	4.70	0	979.93
13	0	0	5.00	2.37	0.01	0.00	0.10	0.71	2.86	0	988.94
14	0	0	2.52	1.20	0.00	0.00	0.04	0.31	1.63	0	994.30
15	0	0	1.19	0.56	0.00	0.00	0.02	0.12	0.86	0	997.26

Male, median age, Navitor

Years	Implantation	Reimplantation	NoComp	Paced	PVL	Paced+PVL	Stroke	Post-stroke	HF	SAVR	Dead
0	1000	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0	0.00
1	0	0	315.57	76.37	191.86	36.90	15.09	11.13	13.51	0	339.58
2	0	0	216.84	58.44	90.06	15.41	9.84	16.31	19.25	0	573.86
3	0	0	143.97	42.46	38.87	5.83	5.75	15.33	19.44	0	728.35
4	0	0	92.06	29.26	15.31	1.98	3.23	11.76	16.83	0	829.57
5	0	0	56.33	19.02	5.41	0.60	1.77	7.86	13.14	0	895.88
6	0	0	32.68	11.56	1.68	0.15	0.93	4.66	9.39	0	938.95
7	0	0	17.97	6.57	0.46	0.03	0.47	2.50	6.22	0	965.78
8	0	0	9.32	3.48	0.11	0.01	0.23	1.21	3.82	0	981.82
9	0	0	4.50	1.70	0.02	0.00	0.10	0.53	2.16	0	990.99

10	0	0	2.03	0.76	0.00	0.00	0.04	0.21	1.13	0	995.83
11	0	0	0.84	0.31	0.00	0.00	0.02	0.07	0.54	0	998.22
12	0	0	0.32	0.11	0.00	0.00	0.01	0.02	0.23	0	999.30
13	0	0	0.11	0.04	0.00	0.00	0.00	0.01	0.09	0	999.75
14	0	0	0.03	0.01	0.00	0.00	0.00	0.00	0.03	0	999.92
15	0	0	0.01	0.00	0.00	0.00	0.00	0.00	0.01	0	999.98

Female, median age, Navitor

Years	Implantation	Reimplantation	NoComp	Paced	PVL	Paced+PVL	Stroke	Post-stroke	HF	SAVR	Dead
0	1000	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0	0.00
1	0	0	284.18	59.47	231.97	38.47	14.31	13.30	9.74	0	348.56
2	0	0	200.12	46.74	112.45	16.64	8.09	16.70	13.95	0	585.30
3	0	0	135.64	34.70	49.65	6.45	4.51	14.55	14.08	0	740.43
4	0	0	87.94	24.23	19.67	2.20	2.46	10.57	12.10	0	840.83
5	0	0	54.09	15.80	6.85	0.65	1.30	6.70	9.30	0	905.30
6	0	0	31.45	9.60	2.08	0.16	0.67	3.79	6.53	0	945.73
7	0	0	17.05	5.36	0.53	0.03	0.33	1.90	4.19	0	970.62
8	0	0	8.57	2.73	0.11	0.01	0.15	0.84	2.45	0	985.15
9	0	0	3.97	1.27	0.02	0.00	0.06	0.33	1.31	0	993.04
10	0	0	1.67	0.52	0.00	0.00	0.02	0.11	0.63	0	997.04
11	0	0	0.63	0.19	0.00	0.00	0.01	0.03	0.27	0	998.86
12	0	0	0.21	0.06	0.00	0.00	0.00	0.01	0.10	0	999.61
13	0	0	0.06	0.02	0.00	0.00	0.00	0.00	0.03	0	999.88
14	0	0	0.02	0.00	0.00	0.00	0.00	0.00	0.01	0	999.97
15	0	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0	999.99

Accumulated costs and QALYs (for 1,000 patients)

Sapien 3

Year	Costs, £ Base case (male)	QALY Base case (male)	Costs, £ Base case (female)	QALY Base case (female)
0	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]
TOTAL	[redacted]	[redacted]	[redacted]	[redacted]

Sapien 3 Ultra

Year	Costs, £ Base case (male)	QALY Base case (male)	Costs, £ Base case (female)	QALY Base case (female)
0	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]
TOTAL	[redacted]	[redacted]	[redacted]	[redacted]

ACURATE neo2

Year	Costs, £ Base case (male)	QALY Base case (male)	Costs, £ Base case (female)	QALY Base case (female)
0	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]
TOTAL	[redacted]	[redacted]	[redacted]	[redacted]

Evolut R

Year	Costs, £ Base case (male)	QALY Base case (male)	Costs, £ Base case (female)	QALY Base case (female)
0	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]
TOTAL	[redacted]	[redacted]	[redacted]	[redacted]

Evolut Pro+

Year	Costs, £ Base case (male)	QALY Base case (male)	Costs, £ Base case (female)	QALY Base case (female)
0	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]
TOTAL	[redacted]	[redacted]	[redacted]	[redacted]

Navitor

Year	Costs, £ Base case (male)	QALY Base case (male)	Costs, £ Base case (female)	QALY Base case (female)
0	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]
TOTAL	[redacted]	[redacted]	[redacted]	[redacted]

Appendix F5: Scenario analysis undertaken by the EAG

The EAG base case was updated using the following data from comparative studies to determine impact on total costs, quality-adjusted life years (QALYs) and net monetary benefit (NMB).

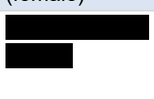
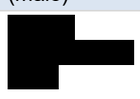
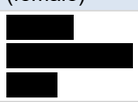
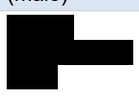
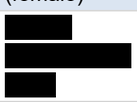
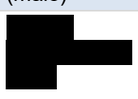
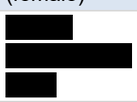
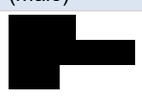
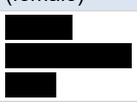
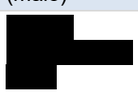
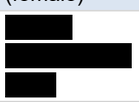
Scenario 1: Coronary obstruction

Settings:

Predicted outcome	Sapien 3 (male)	Sapien 3 (female)	Sapien 3 Ultra (male)	Sapien 3 Ultra (female)	ACURATE neo2 (male)	ACURATE neo2 (female)	Evolut R (male)	Evolut R (female)	Evolut Pro+ (male)	Evolut Pro+ (female)	Navitor (male)	Navitor (female)
In-hospital death	1.25 (0.13, 10.57)	1.78 (0.17, 15.92)	1.45 (0.21, 9.27)	2.07 (0.26, 14.58)	3.35 (0.35, 25.66)	4.73 (0.48, 33.91)	4.38 (0.44, 32.13)	6.17 (0.61, 41.18)	1.61 (0.17, 13.6)	2.3 (0.25, 18.34)	1.41 (0.09, 18.8)	2.01 (0.13, 24.84)
In-hospital stroke	1.22 (0.16, 8.44)	2.19 (0.27, 15.54)	0.38 (0.06, 2.47)	0.68 (0.09, 4.87)	0.37 (0.02, 5.32)	0.66 (0.04, 9.46)	2.02 (0.23, 15.55)	3.6 (0.41, 25.43)	1.93 (0.26, 12.89)	3.46 (0.48, 21.07)	1.94 (0.24, 14.14)	3.46 (0.42, 23.22)
In-hospital AR	5.07 (0.45, 38.66)	6.62 (0.56, 47.09)	3.28 (0.34, 24.97)	4.3 (0.41, 33.01)	15.95 (1.28, 73.53)	20.12 (1.67, 78.86)	22.37 (2.21, 78.62)	27.67 (2.87, 83.23)	24.89 (2.92, 78.5)	30.55 (3.92, 82.57)	45.41 (6.81, 90.45)	52.48 (8.68, 92.77)
In-hospital PPI	8.01 (3.12, 19.06)	6.96 (2.58, 17.45)	8.93 (3.96, 18.93)	7.77 (3.18, 17.79)	7.16 (2.21, 20.82)	6.22 (1.89, 18.61)	16.92 (6.42, 37.68)	14.9 (5.5, 34.47)	15.67 (6.43, 33.45)	13.77 (5.6, 30.07)	19.92 (7.71, 42.55)	17.61 (6.62, 39.19)
In-hospital major bleeding	0.74 (0.07, 7.08)	3.5 (0.34, 28.02)	0.76 (0.1, 5.8)	3.61 (0.44, 24.17)	1.34 (0.12, 13.52)	6.2 (0.6, 42.01)	0.59 (0.04, 8.08)	2.79 (0.22, 27.46)	0.31 (0.03, 3.5)	1.5 (0.15, 13.46)	0.81 (0.06, 9.94)	3.84 (0.31, 33.64)
In-hospital vascular comp	1.46 (0.13, 14.41)	3.61 (0.3, 31.47)	2.42 (0.29, 17.33)	5.87 (0.66, 36.82)	7.12 (0.66, 47.01)	16.19 (1.66, 68.82)	1.6 (0.1, 21.03)	3.94 (0.26, 39.03)	1.78 (0.15, 17.8)	4.35 (0.41, 33.73)	5.92 (0.54, 42.4)	13.68 (1.35, 64.69)
One-year death	12.39 (3.75, 20.25)	11.92 (3.17, 19.87)	15.11 (6.2, 23.18)	14.55 (5.21, 22.96)	17 (3.78, 28.41)	16.37 (3.52, 27.51)	12.58 (2.4, 21.69)	12.1 (2.18, 21.01)	12.5 (3.44, 20.71)	12.02 (3.34, 19.93)	24.03 (3.78, 40.03)	23.18 (3.55, 38.82)
One-year stroke	3.16 (0, 7.23)	2.46 (0, 5.84)	2.71 (0, 5.8)	2.11 (0, 4.76)	2.09 (0, 5.46)	1.63 (0, 4.32)	1.36 (0, 3.67)	1.06 (0, 2.91)	3.07 (0, 7.12)	2.4 (0, 5.61)	3.33 (0, 8.61)	2.6 (0, 6.79)
One-year PPI	2.85 (0, 6.61)	2.55 (0, 6.07)	2.06 (0, 4.48)	1.85 (0, 4.18)	3.75 (0, 9.18)	3.36 (0, 8.26)	3.51 (0, 8.62)	3.14 (0, 7.81)	2.53 (0, 6.02)	2.27 (0, 5.39)	2.14 (0, 5.98)	1.92 (0, 5.37)
One-year heart failure	2.22 (0.19, 4.2)	1.61 (0.05, 3.15)	1.72 (0.34, 3.08)	1.25 (0.14, 2.34)	2.37 (0, 4.8)	1.72 (0, 3.54)	3 (0, 6.03)	2.19 (0, 4.45)	2.74 (0.16, 5.25)	1.99 (0.11, 3.84)	2.52 (0, 5.46)	1.84 (0, 4.01)

Abbreviations: AR, aortic regurgitation; PPI, permanent pacemaker implantation

Results:

Economic modelling results	Sapien 3 (male)	Sapien 3 (female)	Sapien 3 Ultra (male)	Sapien 3 Ultra (female)	ACURATE neo2 (male)	ACURATE neo2 (female)	Evolut R (male)	Evolut R (female)	Evolut Pro+ (male)	Evolut Pro+ (female)	Navitor (male)	Navitor (female)
Total Costs												
Total QALYs												
NMB at £20,000												
Highest NMB, P	78 [70 to 86] %	70 [61 to 78] %	3 [1 to 7] %	11 [6 to 18] %	0 [0 to 0] %	0 [0 to 0] %	15 [9 to 22] %	12 [7 to 19] %	4 [1 to 9] %	7 [3 to 13] %	0 [0 to 0] %	0 [0 to 0] %

Abbreviations: NMB, Net monetary benefit; QALY, Quality Adjusted Life Year

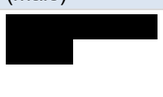
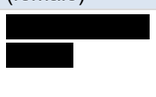
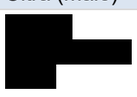
Scenario 2: Younger (preservation of coronary access)

Settings:

Predicted outcome	Sapien 3 (male)	Sapien 3 (female)	Sapien 3 Ultra (male)	Sapien 3 Ultra (female)	ACURATE neo2 (male)	ACURATE neo2 (female)	Evolut R (male)	Evolut R (female)	Evolut Pro+ (male)	Evolut Pro+ (female)	Navitor (male)	Navitor (female)
In-hospital death	1.31 (0.13, 12.29)	1.87 (0.16, 18.14)	1.53 (0.2, 10.71)	2.18 (0.25, 16.48)	3.52 (0.32, 29.11)	4.97 (0.45, 37.67)	4.61 (0.42, 35.58)	6.48 (0.59, 44.75)	1.7 (0.16, 15.41)	2.42 (0.24, 20.51)	1.49 (0.09, 21.12)	2.12 (0.12, 27.52)
In-hospital stroke	0.44 (0.05, 3.73)	0.79 (0.08, 7.1)	0.13 (0.02, 1.07)	0.24 (0.03, 2.11)	0.13 (0.01, 2.24)	0.24 (0.01, 4.06)	0.73 (0.07, 7.09)	1.31 (0.13, 12.32)	0.7 (0.08, 5.78)	1.26 (0.15, 9.92)	0.7 (0.07, 6.56)	1.26 (0.13, 11.37)
In-hospital AR	6.95 (0.6, 47.83)	9.02 (0.76, 56.34)	4.52 (0.47, 32.24)	5.91 (0.56, 41.24)	20.97 (1.71, 80.17)	26.05 (2.24, 84.42)	28.72 (2.94, 84.29)	34.85 (3.81, 87.83)	31.66 (3.98, 83.8)	38.08 (5.35, 87)	53.77 (8.82, 93.32)	60.69 (11.21, 94.97)
In-hospital PPI	5.95 (2.15, 15.41)	5.16 (1.78, 14.02)	6.66 (2.74, 15.33)	5.78 (2.2, 14.3)	5.31 (1.54, 16.8)	4.6 (1.31, 14.92)	12.91 (4.52, 31.7)	11.29 (3.86, 28.74)	11.91 (4.52, 27.86)	10.41 (3.92, 24.84)	15.33 (5.42, 36.36)	13.46 (4.65, 33.18)
In-hospital major bleeding	0.73 (0.06, 7.88)	3.48 (0.3, 30.33)	0.76 (0.08, 6.56)	3.59 (0.38, 26.55)	1.33 (0.1, 14.98)	6.17 (0.53, 44.96)	0.58 (0.04, 8.75)	2.78 (0.2, 29.27)	0.31 (0.02, 3.89)	1.49 (0.13, 14.88)	0.81 (0.05, 11.31)	3.82 (0.27, 36.97)
In-hospital vascular comp	1.42 (0.12, 15.02)	3.49 (0.27, 32.4)	2.34 (0.26, 18.03)	5.69 (0.6, 37.78)	6.9 (0.59, 48.27)	15.73 (1.48, 69.84)	1.55 (0.09, 21.29)	3.81 (0.24, 39.35)	1.72 (0.14, 18.39)	4.21 (0.36, 34.59)	5.73 (0.47, 44.18)	13.28 (1.18, 66.26)
One-year death	8.61 (2.16, 14.64)	8.28 (1.82, 14.32)	10.56 (3.74, 16.9)	10.15 (3.13, 16.67)	11.92 (2.06, 20.79)	11.47 (1.93, 20.08)	8.75 (1.29, 15.64)	8.41 (1.18, 15.11)	8.7 (2.01, 14.93)	8.36 (1.97, 14.33)	17.08 (1.87, 29.93)	16.45 (1.79, 28.92)
One-year stroke	2.26 (0, 5.37)	1.76 (0, 4.32)	1.94 (0, 4.33)	1.51 (0, 3.53)	1.49 (0, 4.02)	1.16 (0, 3.17)	0.97 (0, 2.69)	0.76 (0, 2.12)	2.2 (0, 5.27)	1.71 (0, 4.14)	2.38 (0, 6.34)	1.86 (0, 4.99)
One-year PPI	3.33 (0, 7.91)	2.98 (0, 7.26)	2.41 (0, 5.39)	2.16 (0, 5)	4.38 (0, 10.93)	3.92 (0, 9.85)	4.09 (0, 10.23)	3.67 (0, 9.26)	2.96 (0, 7.17)	2.65 (0, 6.42)	2.5 (0, 7.08)	2.24 (0, 6.36)
One-year heart failure	1.55 (0.03, 3.05)	1.13 (0, 2.28)	1.2 (0.15, 2.24)	0.87 (0.05, 1.7)	1.66 (0, 3.47)	1.2 (0, 2.55)	2.1 (0, 4.36)	1.53 (0, 3.21)	1.92 (0.01, 3.79)	1.39 (0, 2.76)	1.77 (0, 3.93)	1.28 (0, 2.88)

Abbreviations: AR, aortic regurgitation; PPI, permanent pacemaker implantation;

Results

Economic modelling results	Sapien 3 (male)	Sapien 3 (female)	Sapien 3 Ultra (male)	Sapien 3 Ultra (female)	ACURATE neo2 (male)	ACURATE neo2 (female)	Evolut R (male)	Evolut R (female)	Evolut Pro+ (male)	Evolut Pro+ (female)	Navitor (male)	Navitor (female)
Total Costs												
Total QALYs												
NMB at £20,000												
Highest NMB, P	69 [60 to 78] %	72 [62 to 80] %	8 [4 to 14] %	12 [6 to 19] %	0 [0 to 0] %	0 [0 to 0] %	17 [10 to 25] %	9 [4 to 15] %	6 [2 to 11] %	7 [3 to 13] %	0 [0 to 0] %	0 [0 to 0] %

Abbreviations: NMB, Net monetary benefit; QALY, Quality Adjusted Life Year

Scenario 3: Small annular diameter size (<22mm)

Settings:

Predicted outcome	Sapien 3 (male)	Sapien 3 (female)	Sapien 3 Ultra (male)	Sapien 3 Ultra (female)	ACURATE neo2 (male)	ACURATE neo2 (female)	Evolut R (male)	Evolut R (female)	Evolut Pro+ (male)	Evolut Pro+ (female)	Navitor (male)	Navitor (female)
In-hospital death	1.04 (0.1, 9.83)	1.67 (0.17, 14.7)	1.21 (0.17, 8.15)	1.95 (0.27, 12.56)	2.79 (0.27, 23.6)	4.45 (0.46, 32.06)	3.66 (0.33, 30.31)	5.81 (0.58, 39.58)	1.34 (0.13, 12.6)	2.16 (0.23, 17.65)	1.17 (0.06, 18.14)	1.89 (0.11, 24.68)
In-hospital stroke	0.87 (0.11, 6.58)	1.95 (0.25, 13.6)	0.27 (0.04, 1.77)	0.61 (0.09, 3.89)	0.26 (0.02, 3.91)	0.59 (0.04, 8.15)	1.44 (0.15, 12.26)	3.21 (0.37, 23)	1.38 (0.17, 10.17)	3.08 (0.42, 19.18)	1.38 (0.15, 11.77)	3.08 (0.36, 21.86)
In-hospital AR	7.56 (0.67, 49.82)	10.29 (0.96, 57.63)	4.93 (0.57, 31.82)	6.79 (0.79, 40.03)	22.52 (2, 80.53)	28.97 (2.88, 84.85)	30.62 (3.31, 85.07)	38.25 (4.77, 88.46)	33.66 (4.4, 84.83)	41.6 (6.41, 88.1)	56.03 (9.42, 93.98)	64.13 (13.3, 95.42)
In-hospital PPI	5.53 (2, 14.36)	4.8 (1.75, 12.46)	6.19 (2.65, 13.78)	5.38 (2.27, 12.21)	4.93 (1.46, 15.33)	4.28 (1.29, 13.29)	12.04 (4.23, 29.79)	10.55 (3.76, 26.26)	11.1 (4.25, 26.03)	9.72 (3.8, 22.69)	14.33 (5, 34.7)	12.6 (4.47, 30.74)
In-hospital major bleeding	0.37 (0.03, 4.15)	0.95 (0.08, 9.75)	0.38 (0.05, 3.11)	0.98 (0.12, 7.51)	0.68 (0.05, 7.78)	1.71 (0.15, 16.79)	0.29 (0.02, 4.4)	0.75 (0.05, 9.74)	0.16 (0.01, 1.94)	0.4 (0.04, 4.36)	0.41 (0.03, 6.02)	1.04 (0.07, 13.15)
In-hospital vascular comp	1.67 (0.14, 17.3)	3.38 (0.29, 29.34)	2.76 (0.34, 19.09)	5.51 (0.7, 32.44)	8.07 (0.75, 50.64)	15.29 (1.61, 66.49)	1.83 (0.11, 23.63)	3.69 (0.25, 37.1)	2.03 (0.17, 20.19)	4.08 (0.38, 32.28)	6.72 (0.55, 48.51)	12.9 (1.21, 64.1)
One-year death	10.42 (2.71, 17.52)	10.35 (2.79, 17.32)	12.74 (4.97, 19.88)	12.65 (4.89, 19.78)	14.37 (2.93, 24.45)	14.27 (3.18, 24.08)	10.58 (1.7, 18.66)	10.5 (1.88, 18.37)	10.52 (2.62, 17.77)	10.44 (2.83, 17.45)	20.45 (2.25, 35.25)	20.31 (2.78, 34.68)
One-year stroke	4.47 (0, 10.34)	3.77 (0, 8.72)	3.84 (0, 8.14)	3.24 (0, 6.94)	2.97 (0, 7.69)	2.5 (0, 6.46)	1.94 (0, 5.23)	1.63 (0, 4.39)	4.35 (0, 10.14)	3.67 (0, 8.46)	4.71 (0, 12.33)	3.98 (0, 10.31)
One-year PPI	3.52 (0, 8.29)	3.84 (0, 8.93)	2.55 (0, 5.53)	2.79 (0, 6.03)	4.64 (0, 11.35)	5.06 (0, 12.11)	4.33 (0, 10.7)	4.73 (0, 11.46)	3.13 (0, 7.52)	3.42 (0, 8.01)	2.65 (0, 7.49)	2.89 (0, 8.03)
One-year heart failure	2.42 (0.08, 4.71)	1.95 (0.08, 3.78)	1.88 (0.34, 3.4)	1.51 (0.25, 2.76)	2.59 (0, 5.27)	2.08 (0, 4.23)	3.28 (0, 6.69)	2.64 (0, 5.35)	2.99 (0.08, 5.81)	2.41 (0.14, 4.63)	2.76 (0, 6.1)	2.22 (0, 4.86)

Abbreviations: AR, aortic regurgitation; PPI, permanent pacemaker implantation

Results

Economic modelling results	Sapien 3 (male)	Sapien 3 (female)	Sapien 3 Ultra (male)	Sapien 3 Ultra (female)	ACURATE neo2 (male)	ACURATE neo2 (female)	Evolut R (male)	Evolut R (female)	Evolut Pro+ (male)	Evolut Pro+ (female)	Navitor (male)	Navitor (female)
Total Costs												
Total QALYs												
NMB at £20,000												
Highest NMB, P	63 [54 to 73] %	66 [57 to 75] %	8 [4 to 14] %	14 [8 to 21] %	0 [0 to 0] %	1 [0 to 4] %	24 [16 to 32] %	11 [6 to 18] %	5 [2 to 10] %	8 [4 to 14] %	0 [0 to 0] %	0 [0 to 0] %

Abbreviations: NMB, Net monetary benefit; QALY, Quality Adjusted Life Year

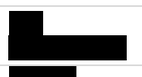
Scenario 4: Large annular diameter size (>32mm)

Settings:

Predicted outcome	Sapien 3 (male)	Sapien 3 (female)	Sapien 3 Ultra (male)	Sapien 3 Ultra (female)	ACURATE neo2 (male)	ACURATE neo2 (female)	Evolut R (male)	Evolut R (female)	Evolut Pro+ (male)	Evolut Pro+ (female)	Navitor (male)	Navitor (female)
In-hospital death	1.97 (0.24, 14.42)	3.17 (0.32, 25.15)	2.3 (0.25, 18.32)	3.68 (0.32, 31.17)	5.23 (0.47, 39.2)	8.22 (0.66, 54.85)	6.8 (0.75, 41.3)	10.6 (1.05, 56.91)	2.54 (0.27, 20.21)	4.07 (0.38, 31.99)	2.23 (0.13, 29.27)	3.58 (0.19, 42.25)
In-hospital stroke	1.15 (0.16, 7.65)	2.58 (0.3, 18.66)	0.36 (0.04, 2.8)	0.8 (0.08, 7.35)	0.35 (0.02, 5.57)	0.78 (0.04, 13.06)	1.91 (0.22, 14.64)	4.23 (0.43, 30.87)	1.83 (0.24, 12.64)	4.06 (0.48, 27.25)	1.83 (0.19, 15.43)	4.07 (0.39, 31.7)
In-hospital AR	7.51 (0.64, 50.4)	10.22 (0.72, 64.17)	4.9 (0.39, 40.58)	6.74 (0.42, 55.39)	22.39 (1.55, 84.13)	28.82 (1.79, 89.98)	30.46 (3, 86.11)	38.07 (3.43, 91.42)	33.49 (3.75, 86.68)	41.41 (4.3, 91.75)	55.84 (8.07, 94.79)	63.96 (9.21, 96.88)
In-hospital PPI	10.07 (4.01, 23.11)	8.8 (3.14, 22.35)	11.21 (4.15, 26.91)	9.81 (3.21, 26.32)	9.03 (2.58, 27.15)	7.88 (2.07, 25.72)	20.77 (7.97, 44.26)	18.43 (6.42, 42.65)	19.3 (7.71, 40.65)	17.09 (6.21, 39.1)	24.26 (8.77, 51.61)	21.63 (7.16, 49.71)
In-hospital major bleeding	0.41 (0.04, 4.47)	1.05 (0.08, 12.46)	0.43 (0.03, 5.47)	1.09 (0.07, 15.03)	0.75 (0.05, 10.5)	1.9 (0.11, 25.22)	0.33 (0.02, 5.78)	0.83 (0.04, 14.61)	0.17 (0.01, 2.56)	0.45 (0.03, 6.85)	0.45 (0.02, 8.21)	1.16 (0.05, 20.08)
In-hospital vascular comp	2.81 (0.24, 25.52)	5.62 (0.41, 46.09)	4.61 (0.35, 39.95)	9.03 (0.58, 62.7)	13 (0.94, 70.08)	23.51 (1.65, 84.89)	3.08 (0.17, 37.77)	6.12 (0.3, 58.56)	3.4 (0.23, 34.65)	6.75 (0.42, 55.45)	10.92 (0.75, 66.44)	20.14 (1.35, 82.29)
One-year death	15.62 (4.93, 25.11)	15.51 (3.8, 25.79)	18.97 (4.68, 31.13)	18.85 (3.19, 31.97)	21.29 (2.86, 36.22)	21.14 (1.76, 36.71)	15.85 (2.92, 27.06)	15.74 (2.09, 27.49)	15.76 (3.66, 26.34)	15.65 (2.81, 26.79)	29.74 (2.31, 49.47)	29.56 (1.04, 49.85)
One-year stroke	4.34 (0, 9.71)	3.66 (0, 8.69)	3.73 (0, 8.89)	3.14 (0, 7.97)	2.87 (0, 7.85)	2.42 (0, 6.86)	1.88 (0, 5.06)	1.58 (0, 4.42)	4.22 (0, 9.93)	3.56 (0, 8.75)	4.57 (0, 12.34)	3.86 (0, 10.73)
One-year PPI	6.77 (0, 14.78)	7.38 (0, 16.88)	4.93 (0, 11.48)	5.38 (0, 13.16)	8.86 (0, 21.54)	9.64 (0, 23.95)	8.29 (0, 19.24)	9.03 (0, 21.58)	6.03 (0, 13.9)	6.57 (0, 15.62)	5.11 (0, 14.1)	5.57 (0, 15.61)
One-year heart failure	2.29 (0.19, 4.36)	1.85 (0, 3.7)	1.78 (0, 3.53)	1.43 (0, 3)	2.45 (0, 5.24)	1.97 (0, 4.37)	3.11 (0, 6.31)	2.5 (0, 5.28)	2.83 (0, 5.63)	2.28 (0, 4.71)	2.61 (0, 5.89)	2.1 (0, 4.87)

Abbreviations: AR, aortic regurgitation; PPI, permanent pacemaker implantation

Results

Economic modelling results	Sapien 3 (male)	Sapien 3 (female)	Sapien 3 Ultra (male)	Sapien 3 Ultra (female)	ACURATE neo2 (male)	ACURATE neo2 (female)	Evolut R (male)	Evolut R (female)	Evolut Pro+ (male)	Evolut Pro+ (female)	Navitor (male)	Navitor (female)
Total Costs												
Total QALYs												
NMB at £20,000												
Highest NMB, P	70 [61 to 78] %	59 [50 to 69] %	11 [6 to 18] %	21 [13 to 29] %	1 [0 to 4] %	2 [0 to 5] %	13 [7 to 20] %	11 [6 to 18] %	5 [2 to 10] %	7 [3 to 13] %	0 [0 to 0] %	0 [0 to 0] %

Abbreviations: NMB, Net monetary benefit; QALY, Quality Adjusted Life Year

Scenario 5: No severe symptoms

Settings:

Predicted outcome	Sapien 3 (male)	Sapien 3 (female)	Sapien 3 Ultra (male)	Sapien 3 Ultra (female)	ACURATE neo2 (male)	ACURATE neo2 (female)	Evolut R (male)	Evolut R (female)	Evolut Pro+ (male)	Evolut Pro+ (female)	Navitor (male)	Navitor (female)
In-hospital death	0.89 (0.12, 6.29)	1.27 (0.15, 9.72)	1.04 (0.19, 5.39)	1.48 (0.24, 8.76)	2.4 (0.3, 16.98)	3.41 (0.41, 23.18)	3.16 (0.39, 21.5)	4.47 (0.54, 28.68)	1.15 (0.15, 8.18)	1.65 (0.22, 11.17)	1.01 (0.07, 12.56)	1.44 (0.11, 16.9)
In-hospital stroke	0.95 (0.16, 5.4)	1.71 (0.27, 10.22)	0.29 (0.06, 1.52)	0.53 (0.09, 3.03)	0.29 (0.02, 3.61)	0.52 (0.04, 6.47)	1.58 (0.22, 10.52)	2.82 (0.39, 17.76)	1.51 (0.26, 8.29)	2.71 (0.48, 13.87)	1.51 (0.22, 9.5)	2.71 (0.41, 16.03)
In-hospital AR	7.09 (0.86, 40.27)	9.2 (1.05, 49.14)	4.62 (0.67, 25.93)	6.04 (0.77, 34.65)	21.34 (2.33, 75.56)	26.48 (3.01, 80.71)	29.18 (4.11, 79.82)	35.36 (5.27, 84.33)	32.14 (5.53, 79.31)	38.61 (7.34, 83.31)	54.32 (12.07, 91.16)	61.22 (15.02, 93.38)
In-hospital PPI	5.64 (2.38, 12.79)	4.88 (1.95, 11.69)	6.31 (3.08, 12.5)	5.47 (2.44, 11.8)	5.03 (1.64, 14.39)	4.35 (1.4, 12.76)	12.27 (4.89, 27.58)	10.73 (4.17, 24.91)	11.32 (4.97, 23.75)	9.88 (4.32, 21.04)	14.59 (5.89, 31.83)	12.8 (5.03, 28.91)
In-hospital major bleeding	0.81 (0.11, 5.7)	3.83 (0.5, 23.94)	0.84 (0.15, 4.59)	3.95 (0.66, 20.32)	1.47 (0.18, 11.26)	6.77 (0.89, 37.11)	0.64 (0.06, 6.72)	3.06 (0.32, 23.59)	0.34 (0.04, 2.83)	1.65 (0.23, 11.05)	0.89 (0.09, 8.71)	4.2 (0.44, 30.54)
In-hospital vascular comp	1.98 (0.24, 14.41)	4.83 (0.55, 31.93)	3.25 (0.54, 17.14)	7.8 (1.2, 37.18)	9.42 (1.18, 47.54)	20.76 (2.93, 69.48)	2.16 (0.18, 21.36)	5.27 (0.47, 39.6)	2.39 (0.28, 17.74)	5.81 (0.75, 33.66)	7.86 (0.92, 43.88)	17.69 (2.3, 66.26)
One-year death	8.53 (3.04, 13.71)	8.2 (2.6, 13.48)	10.46 (4.95, 15.65)	10.06 (4.18, 15.58)	11.81 (3.17, 19.68)	11.36 (2.96, 19.03)	8.66 (2.07, 14.82)	8.33 (1.89, 14.34)	8.61 (2.87, 14.01)	8.28 (2.77, 13.47)	16.92 (3.41, 28.55)	16.29 (3.21, 27.61)
One-year stroke	3.81 (0, 8.06)	2.97 (0, 6.56)	3.27 (0.06, 6.38)	2.55 (0, 5.3)	2.52 (0, 6.27)	1.97 (0, 4.97)	1.65 (0, 4.23)	1.28 (0, 3.35)	3.71 (0, 7.97)	2.89 (0, 6.28)	4.01 (0, 9.83)	3.14 (0, 7.77)
One-year PPI	3.35 (0, 7.24)	3 (0, 6.69)	2.43 (0, 4.83)	2.17 (0, 4.55)	4.41 (0, 10.18)	3.95 (0, 9.17)	4.12 (0, 9.53)	3.7 (0, 8.65)	2.98 (0, 6.6)	2.67 (0, 5.92)	2.52 (0, 6.73)	2.26 (0, 6.05)
One-year heart failure	1.63 (0.28, 2.96)	1.19 (0.13, 2.23)	1.26 (0.37, 2.15)	0.92 (0.19, 1.65)	1.74 (0.03, 3.42)	1.27 (0, 2.52)	2.21 (0.08, 4.3)	1.61 (0.02, 3.17)	2.01 (0.31, 3.69)	1.47 (0.22, 2.7)	1.86 (0, 3.92)	1.35 (0, 2.87)

Abbreviations: AR, aortic regurgitation; PPI, permanent pacemaker implantation

Results

Economic modelling results	Sapien 3 (male)	Sapien 3 (female)	Sapien 3 Ultra (male)	Sapien 3 Ultra (female)	ACURATE neo2 (male)	ACURATE neo2 (female)	Evolut R (male)	Evolut R (female)	Evolut Pro+ (male)	Evolut Pro+ (female)	Navitor (male)	Navitor (female)
Total Costs												
Total QALYs												
NMB at £20,000												
Highest NMB, P	76 [67 to 84] %	74 [65 to 82] %	5 [2 to 10] %	14 [8 to 21] %	0 [0 to 0] %	0 [0 to 0] %	16 [9 to 24] %	8 [4 to 14] %	3 [1 to 7] %	4 [1 to 9] %	0 [0 to 0] %	0 [0 to 0] %

Abbreviations: NMB, Net monetary benefit; QALY, Quality Adjusted Life Year

Scenario 6: LVEF<30

Settings:

Predicted outcome	Sapien 3 (male)	Sapien 3 (female)	Sapien 3 Ultra (male)	Sapien 3 Ultra (female)	ACURATE neo2 (male)	ACURATE neo2 (female)	Evolut R (male)	Evolut R (female)	Evolut Pro+ (male)	Evolut Pro+ (female)	Navitor (male)	Navitor (female)
In-hospital death	1.19 (0.13, 10.35)	1.7 (0.16, 15.57)	1.38 (0.19, 9.22)	1.97 (0.24, 14.45)	3.19 (0.32, 24.98)	4.51 (0.45, 33.07)	4.18 (0.41, 31.8)	5.89 (0.57, 40.77)	1.54 (0.15, 13.57)	2.19 (0.22, 18.29)	1.35 (0.08, 19.45)	1.92 (0.11, 25.62)
In-hospital stroke	1.04 (0.14, 7.49)	1.87 (0.23, 13.87)	0.32 (0.05, 2.21)	0.58 (0.08, 4.34)	0.31 (0.02, 4.66)	0.57 (0.04, 8.32)	1.72 (0.19, 13.62)	3.08 (0.35, 22.57)	1.65 (0.21, 11.59)	2.96 (0.39, 19.11)	1.66 (0.18, 13.35)	2.96 (0.33, 22.03)
In-hospital AR	5.65 (0.5, 41.7)	7.37 (0.63, 49.91)	3.66 (0.38, 27.32)	4.81 (0.46, 35.42)	17.56 (1.43, 75.72)	22.05 (1.9, 80.53)	24.45 (2.54, 80.09)	30.05 (3.33, 84.26)	27.11 (3.19, 80.78)	33.06 (4.34, 84.31)	48.29 (7.09, 91.95)	55.36 (9.15, 93.85)
In-hospital PPI	6 (2.21, 15.27)	5.2 (1.82, 13.92)	6.71 (2.79, 15.26)	5.82 (2.24, 14.27)	5.35 (1.58, 16.61)	4.64 (1.34, 14.77)	12.99 (4.65, 31.36)	11.37 (3.97, 28.46)	11.99 (4.58, 27.89)	10.48 (3.97, 24.9)	15.43 (5.45, 36.61)	13.55 (4.66, 33.46)
In-hospital major bleeding	0.14 (0.01, 2.51)	0.68 (0.04, 11.63)	0.15 (0.01, 2.15)	0.7 (0.04, 10.19)	0.26 (0.01, 4.78)	1.23 (0.07, 19.14)	0.11 (0, 2.67)	0.54 (0.02, 10.85)	0.06 (0, 1.2)	0.29 (0.02, 5.12)	0.15 (0.01, 3.62)	0.75 (0.03, 14.96)
In-hospital vascular comp	0.72 (0.05, 9.13)	1.79 (0.12, 21.54)	1.19 (0.11, 11.5)	2.96 (0.26, 26.51)	3.61 (0.27, 34.06)	8.62 (0.68, 56.46)	0.79 (0.04, 13.21)	1.96 (0.11, 26.98)	0.87 (0.06, 11.58)	2.17 (0.16, 23.77)	2.98 (0.2, 32.13)	7.18 (0.5, 54.31)
One-year death	12.81 (3.76, 21)	12.32 (3.16, 20.62)	15.62 (6.27, 24.03)	15.03 (5.24, 23.81)	17.57 (3.85, 29.32)	16.92 (3.57, 28.41)	13 (2.51, 22.36)	12.51 (2.28, 21.67)	12.92 (3.41, 21.5)	12.43 (3.29, 20.71)	24.79 (3.34, 41.48)	23.92 (3.11, 40.26)
One-year stroke	4.91 (0, 11.09)	3.84 (0, 8.97)	4.22 (0, 8.96)	3.3 (0, 7.34)	3.26 (0, 8.42)	2.54 (0, 6.67)	2.13 (0, 5.67)	1.66 (0, 4.48)	4.78 (0, 11.03)	3.74 (0, 8.7)	5.17 (0, 13.32)	4.05 (0, 10.54)
One-year PPI	5.87 (0, 13.22)	5.26 (0, 12.2)	4.27 (0, 9.02)	3.82 (0, 8.44)	7.69 (0, 18.07)	6.9 (0, 16.37)	7.19 (0, 16.99)	6.46 (0, 15.47)	5.22 (0, 12.08)	4.68 (0, 10.88)	4.42 (0, 12.07)	3.97 (0, 10.89)
One-year heart failure	2.43 (0.2, 4.61)	1.77 (0.04, 3.47)	1.88 (0.37, 3.37)	1.37 (0.15, 2.57)	2.59 (0, 5.25)	1.89 (0, 3.88)	3.29 (0, 6.58)	2.4 (0, 4.87)	3 (0.15, 5.76)	2.18 (0.1, 4.22)	2.76 (0, 6.02)	2.01 (0, 4.43)

Abbreviations: AR, aortic regurgitation; PPI, permanent pacemaker implantation

Results

Economic modelling results	Sapien 3 (male)	Sapien 3 (female)	Sapien 3 Ultra (male)	Sapien 3 Ultra (female)	ACURATE neo2 (male)	ACURATE neo2 (female)	Evolut R (male)	Evolut R (female)	Evolut Pro+ (male)	Evolut Pro+ (female)	Navitor (male)	Navitor (female)
Total Costs												
Total QALYs												
NMB at £20,000												
Highest NMB, P	72 [63 to 80] %	71 [61 to 79] %	6 [2 to 11] %	10 [5 to 17] %	0 [0 to 0] %	0 [0 to 0] %	18 [11 to 26] %	13 [7 to 20] %	4 [1 to 9] %	6 [2 to 11] %	0 [0 to 0] %	0 [0 to 0] %

Abbreviations: NMB, Net monetary benefit; QALY, Quality Adjusted Life Year

Scenario 7: Frail

Settings:

Predicted outcome	Sapien 3 (male)	Sapien 3 (female)	Sapien 3 Ultra (male)	Sapien 3 Ultra (female)	ACURATE neo2 (male)	ACURATE neo2 (female)	Evolut R (male)	Evolut R (female)	Evolut Pro+ (male)	Evolut Pro+ (female)	Navitor (male)	Navitor (female)
In-hospital death	2.5 (0.28, 19.03)	3.55 (0.37, 26.88)	2.91 (0.44, 16.87)	4.12 (0.56, 24.82)	6.56 (0.72, 40.45)	9.16 (1.02, 49.61)	8.51 (0.91, 48.59)	11.77 (1.29, 57.69)	3.22 (0.36, 23.58)	4.56 (0.53, 30.02)	2.83 (0.18, 31.87)	4.01 (0.27, 39.54)
In-hospital stroke	0.47 (0.06, 3.56)	0.85 (0.1, 6.64)	0.14 (0.02, 1.03)	0.26 (0.03, 1.98)	0.14 (0.01, 2.18)	0.25 (0.02, 3.88)	0.78 (0.08, 6.87)	1.4 (0.15, 11.68)	0.75 (0.1, 5.54)	1.35 (0.18, 9.26)	0.75 (0.08, 6.38)	1.35 (0.15, 10.8)
In-hospital AR	4.93 (0.44, 38.01)	6.44 (0.57, 45.32)	3.19 (0.33, 24.47)	4.19 (0.42, 31.4)	15.57 (1.26, 72.67)	19.67 (1.72, 77.41)	21.87 (2.1, 78.52)	27.1 (2.84, 82.52)	24.35 (2.87, 77.81)	29.94 (4.04, 81.27)	44.7 (6.51, 90.37)	51.76 (8.65, 92.4)
In-hospital PPI	7.62 (2.92, 18.47)	6.62 (2.44, 16.71)	8.51 (3.69, 18.41)	7.4 (3.01, 17.07)	6.81 (2.08, 20.07)	5.91 (1.8, 17.75)	16.18 (6.02, 36.79)	14.23 (5.21, 33.34)	14.97 (6.05, 32.5)	13.14 (5.33, 28.9)	19.08 (7.2, 41.75)	16.85 (6.25, 38.11)
In-hospital major bleeding	1.15 (0.11, 10.6)	5.36 (0.54, 37.34)	1.19 (0.15, 8.9)	5.53 (0.69, 33.17)	2.08 (0.19, 19.38)	9.37 (0.97, 52.26)	0.91 (0.06, 12.02)	4.3 (0.35, 36.68)	0.49 (0.04, 5.31)	2.33 (0.24, 19.14)	1.27 (0.09, 14.96)	5.88 (0.49, 44.33)
In-hospital vascular comp	1.74 (0.16, 16.53)	4.26 (0.37, 34.61)	2.86 (0.35, 19.82)	6.91 (0.81, 40.19)	8.36 (0.8, 50.62)	18.68 (2.07, 71.4)	1.9 (0.12, 23.86)	4.65 (0.32, 42.5)	2.1 (0.18, 20.12)	5.13 (0.5, 36.67)	6.96 (0.63, 46.86)	15.86 (1.63, 68.24)
One-year death	15.27 (4.65, 24.71)	14.7 (4.03, 24.19)	18.56 (7.58, 28.24)	17.88 (6.5, 27.88)	20.83 (4.78, 34.18)	20.08 (4.58, 33.05)	15.5 (2.97, 26.41)	14.92 (2.79, 25.54)	15.41 (4.33, 25.21)	14.83 (4.29, 24.21)	29.14 (4.51, 47.42)	28.15 (4.41, 45.99)
One-year stroke	4.49 (0, 10.11)	3.51 (0, 8.15)	3.86 (0, 8.22)	3.01 (0, 6.7)	2.98 (0, 7.68)	2.32 (0, 6.06)	1.94 (0, 5.2)	1.52 (0, 4.1)	4.37 (0, 9.99)	3.41 (0, 7.84)	4.73 (0, 12.1)	3.7 (0, 9.54)
One-year PPI	3.06 (0, 7.13)	2.74 (0, 6.51)	2.22 (0, 4.87)	1.99 (0, 4.5)	4.03 (0, 9.88)	3.61 (0, 8.85)	3.77 (0, 9.28)	3.38 (0, 8.36)	2.72 (0, 6.47)	2.44 (0, 5.76)	2.3 (0, 6.45)	2.06 (0, 5.78)
One-year heart failure	2.77 (0.22, 5.26)	2.02 (0.07, 3.94)	2.15 (0.39, 3.88)	1.57 (0.18, 2.94)	2.96 (0, 5.99)	2.16 (0, 4.4)	3.75 (0, 7.53)	2.74 (0, 5.54)	3.42 (0.19, 6.54)	2.49 (0.17, 4.77)	3.16 (0, 6.84)	2.3 (0, 5.02)

Abbreviations: AR, aortic regurgitation; PPI, permanent pacemaker implantation

Results

Economic modelling results	Sapien 3 (male)	Sapien 3 (female)	Sapien 3 Ultra (male)	Sapien 3 Ultra (female)	ACURATE neo2 (male)	ACURATE neo2 (female)	Evolut R (male)	Evolut R (female)	Evolut Pro+ (male)	Evolut Pro+ (female)	Navitor (male)	Navitor (female)
Total Costs												
Total QALYs												
NMB at £20,000												
Highest NMB, P	73 [64 to 81] %	71 [61 to 79] %	7 [3 to 13] %	13 [7 to 20] %	0 [0 to 0] %	0 [0 to 0] %	15 [9 to 23] %	7 [3 to 13] %	5 [2 to 10] %	9 [4 to 15] %	0 [0 to 0] %	0 [0 to 0] %

Abbreviations: NMB, Net monetary benefit; QALY, Quality Adjusted Life Year

Scenario 8: Urgent

Settings:

Predicted outcome	Sapien 3 (male)	Sapien 3 (female)	Sapien 3 Ultra (male)	Sapien 3 Ultra (female)	ACURATE neo2 (male)	ACURATE neo2 (female)	Evolut R (male)	Evolut R (female)	Evolut Pro+ (male)	Evolut Pro+ (female)	Navitor (male)	Navitor (female)
In-hospital death	1.69 (0.19, 13.14)	2.41 (0.25, 19.46)	1.97 (0.31, 11.51)	2.8 (0.38, 17.82)	4.5 (0.47, 31.78)	6.33 (0.66, 40.77)	5.87 (0.64, 37.71)	8.21 (0.89, 47.11)	2.18 (0.25, 16.77)	3.1 (0.36, 22.22)	1.91 (0.13, 23.06)	2.72 (0.18, 29.86)
In-hospital stroke	1.26 (0.18, 8.21)	2.26 (0.3, 15.04)	0.39 (0.06, 2.39)	0.7 (0.1, 4.67)	0.38 (0.03, 5.38)	0.68 (0.05, 9.49)	2.08 (0.25, 15.22)	3.71 (0.45, 24.77)	1.99 (0.29, 12.48)	3.56 (0.53, 20.27)	2 (0.26, 13.6)	3.56 (0.48, 22.24)
In-hospital AR	5.46 (0.51, 39.29)	7.13 (0.64, 47.85)	3.54 (0.39, 25.42)	4.64 (0.46, 33.66)	17.04 (1.42, 74.61)	21.43 (1.85, 79.82)	23.78 (2.55, 78.81)	29.29 (3.3, 83.42)	26.4 (3.38, 78.63)	32.26 (4.53, 82.71)	47.38 (7.76, 90.6)	54.46 (9.83, 92.91)
In-hospital PPI	5.73 (2.23, 13.95)	4.97 (1.84, 12.7)	6.42 (2.85, 13.81)	5.56 (2.28, 12.93)	5.12 (1.56, 15.49)	4.43 (1.33, 13.74)	12.46 (4.66, 29.32)	10.9 (3.98, 26.5)	11.49 (4.67, 25.62)	10.04 (4.06, 22.74)	14.81 (5.62, 33.68)	13 (4.81, 30.63)
In-hospital major bleeding	0.82 (0.09, 7.36)	3.86 (0.39, 29.03)	0.85 (0.11, 6.02)	3.99 (0.51, 25.06)	1.49 (0.14, 14.22)	6.84 (0.69, 43.57)	0.65 (0.05, 8.19)	3.09 (0.26, 27.77)	0.35 (0.03, 3.64)	1.67 (0.18, 13.98)	0.9 (0.07, 10.41)	4.24 (0.37, 34.9)
In-hospital vascular comp	1.76 (0.17, 15.89)	4.31 (0.39, 34.11)	2.9 (0.38, 18.92)	6.99 (0.86, 39.5)	8.45 (0.83, 50.41)	18.87 (2.09, 71.71)	1.92 (0.13, 22.59)	4.7 (0.35, 41.23)	2.13 (0.2, 19.45)	5.19 (0.53, 36.21)	7.04 (0.69, 45.38)	16.02 (1.73, 67.45)
One-year death	13.84 (4.35, 22.38)	13.31 (3.71, 21.96)	16.85 (7.23, 25.47)	16.22 (6.12, 25.23)	18.93 (4.28, 31.34)	18.24 (4.02, 30.35)	14.05 (2.81, 23.98)	13.52 (2.58, 23.22)	13.96 (4.06, 22.84)	13.43 (3.96, 21.97)	26.62 (4.71, 43.5)	25.7 (4.49, 42.2)
One-year stroke	3.21 (0, 7.24)	2.51 (0, 5.85)	2.76 (0, 5.79)	2.15 (0, 4.76)	2.13 (0, 5.52)	1.66 (0, 4.36)	1.39 (0, 3.7)	1.08 (0, 2.93)	3.13 (0, 7.12)	2.44 (0, 5.6)	3.39 (0, 8.61)	2.65 (0, 6.79)
One-year PPI	6.19 (0, 13.78)	5.56 (0, 12.7)	4.51 (0, 9.4)	4.04 (0, 8.79)	8.11 (0, 19.02)	7.29 (0, 17.21)	7.59 (0, 17.77)	6.82 (0, 16.17)	5.52 (0, 12.56)	4.95 (0, 11.29)	4.67 (0, 12.55)	4.19 (0, 11.32)
One-year heart failure	3.33 (0.35, 6.21)	2.42 (0.12, 4.67)	2.58 (0.57, 4.55)	1.88 (0.26, 3.47)	3.55 (0, 7.15)	2.59 (0, 5.28)	4.49 (0, 8.9)	3.28 (0, 6.59)	4.1 (0.33, 7.72)	2.99 (0.25, 5.66)	3.78 (0, 8.03)	2.76 (0, 5.92)

Abbreviations: AR, aortic regurgitation; PPI, permanent pacemaker implantation

Results

Economic modelling results	Sapien 3 (male)	Sapien 3 (female)	Sapien 3 Ultra (male)	Sapien 3 Ultra (female)	ACURATE neo2 (male)	ACURATE neo2 (female)	Evolut R (male)	Evolut R (female)	Evolut Pro+ (male)	Evolut Pro+ (female)	Navitor (male)	Navitor (female)
Total Costs												
Total QALYs												
NMB at £20,000												
Highest NMB, P	77 [68 to 85] %	72 [63 to 80] %	6 [2 to 12] %	14 [8 to 22] %	0 [0 to 0] %	0 [0 to 0] %	12 [6 to 19] %	8 [4 to 14] %	5 [2 to 10] %	6 [2 to 11] %	0 [0 to 0] %	0 [0 to 0] %

Abbreviations: NMB, Net monetary benefit; QALY, Quality Adjusted Life Year

Scenario 9: Calcification

Notes:

- *using extensive calcification of the ascending aorta as a surrogate marker of aortic valve calcification*
- *No patient with calcification experiences vascular or bleeding complications in the observed data, therefore the predicted values are 0 for all devices.*

Settings:

Predicted outcome	Sapien 3 (male)	Sapien 3 (female)	Sapien 3 Ultra (male)	Sapien 3 Ultra (female)	ACURATE neo2 (male)	ACURATE neo2 (female)	Evolut R (male)	Evolut R (female)	Evolut Pro+ (male)	Evolut Pro+ (female)	Navitor (male)	Navitor (female)
In-hospital death	0.65 (0.03, 12.21)	0.93 (0.04, 17.55)	0.75 (0.05, 11.36)	1.08 (0.06, 16.72)	1.75 (0.08, 28.52)	2.5 (0.11, 36.62)	2.31 (0.11, 32.95)	3.28 (0.16, 41.5)	0.84 (0.04, 15.19)	1.2 (0.06, 20.1)	0.73 (0.02, 19.49)	1.05 (0.03, 25.42)
In-hospital stroke	0.78 (0.06, 8.65)	1.4 (0.11, 15.48)	0.24 (0.02, 2.57)	0.43 (0.04, 4.89)	0.23 (0.01, 4.89)	0.42 (0.02, 8.63)	1.29 (0.1, 14.83)	2.32 (0.18, 24.09)	1.24 (0.1, 13.05)	2.23 (0.19, 21.11)	1.24 (0.09, 14.3)	2.23 (0.17, 23.19)
In-hospital AR	17.85 (1.52, 75.34)	22.4 (1.92, 80.98)	12.12 (1.17, 61.56)	15.47 (1.42, 69.97)	43.59 (4.39, 92.85)	50.64 (5.74, 94.53)	53.99 (7.52, 94.43)	60.9 (9.69, 95.77)	57.43 (9.48, 94.56)	64.17 (12.56, 95.71)	77.2 (19.36, 97.95)	81.81 (24, 98.46)
In-hospital PPI	5.75 (1.7, 17.7)	4.98 (1.42, 15.97)	6.43 (2.11, 17.94)	5.58 (1.73, 16.5)	5.13 (1.25, 18.7)	4.44 (1.08, 16.56)	12.49 (3.73, 34.45)	10.92 (3.21, 31.19)	11.52 (3.59, 31.26)	10.06 (3.13, 27.89)	14.84 (4.35, 40.04)	13.03 (3.75, 36.55)
In-hospital major bleeding	0 (0, NaN)	0 (0, NaN)	0 (0, NaN)	0 (0, NaN)	0 (0, NaN)	0 (0, NaN)	0 (0, NaN)	0 (0, NaN)	0 (0, NaN)	0 (0, NaN)	0 (0, NaN)	0 (0, NaN)
In-hospital vascular comp	0 (0, NaN)	0 (0, NaN)	0 (0, NaN)	0 (0, NaN)	0 (0, NaN)	0 (0, NaN)	0 (0, NaN)	0 (0, NaN)	0 (0, NaN)	0 (0, NaN)	0 (0, NaN)	0 (0, NaN)
One-year death	8.79 (0.55, 16.34)	8.45 (0.35, 15.89)	10.77 (1.61, 19.08)	10.36 (1.22, 18.65)	12.16 (0.06, 22.79)	11.69 (0.06, 21.97)	8.92 (0.03, 17.03)	8.58 (0, 16.42)	8.87 (0.48, 16.55)	8.52 (0.53, 15.88)	17.4 (0, 32.48)	16.76 (0, 31.36)
One-year stroke	3.82 (0, 9.79)	2.98 (0, 7.82)	3.28 (0, 8.03)	2.56 (0, 6.46)	2.53 (0, 7.2)	1.97 (0, 5.66)	1.65 (0, 4.79)	1.29 (0, 3.76)	3.72 (0, 9.59)	2.9 (0, 7.52)	4.03 (0, 11.3)	3.14 (0, 8.9)
One-year PPI	5.59 (0, 14.25)	5.01 (0, 13.01)	4.06 (0, 9.94)	3.64 (0, 9.14)	7.33 (0, 19.13)	6.58 (0, 17.25)	6.86 (0, 17.81)	6.15 (0, 16.14)	4.98 (0, 12.84)	4.46 (0, 11.52)	4.21 (0, 12.43)	3.78 (0, 11.17)
One-year heart failure	1.91 (0, 4.08)	1.39 (0, 3.03)	1.48 (0, 3.04)	1.07 (0, 2.27)	2.03 (0, 4.56)	1.48 (0, 3.35)	2.58 (0, 5.71)	1.88 (0, 4.19)	2.35 (0, 5.04)	1.71 (0, 3.68)	2.17 (0, 5.11)	1.58 (0, 3.74)

Abbreviations: AR, aortic regurgitation; PPI, permanent pacemaker implantation

Results

Economic modelling results	Sapien 3 (male)	Sapien 3 (female)	Sapien 3 Ultra (male)	Sapien 3 Ultra (female)	ACURATE neo2 (male)	ACURATE neo2 (female)	Evolut R (male)	Evolut R (female)	Evolut Pro+ (male)	Evolut Pro+ (female)	Navitor (male)	Navitor (female)
Total Costs												
Total QALYs												
NMB at £20,000												
Highest NMB, P	61 [51 to 70] %	57 [47 to 66] %	19 [12 to 27] %	28 [20 to 37] %	1 [0 to 4] %	1 [0 to 4] %	15 [9 to 23] %	9 [4 to 15] %	4 [1 to 9] %	5 [2 to 10] %	0 [0 to 0] %	0 [0 to 0] %

Abbreviations: NMB, Net monetary benefit; QALY, Quality Adjusted Life Year

Appendix G: Correspondence log with Clinical Experts

Questions sent 05 February 2024

#	Date responses received	Name, Affiliation
[redacted]	[redacted]	[redacted]

Question 1	What patient characteristics influence the choice of TAVI valve?
Expert 1:	Most of these are determined by the factors seen in the work up, especially the CT but also including LV function, presence of coronary artery disease (CAD), pre-existing conduction disturbance, peripheral vascular disease (PVD) etc Examples include: 1. Access characteristics 2. Annulus size 3. Risk of coronary occlusion 4. Risk of conduction disturbance / permanent pacemaker (PPM) Risk of PVL.
Expert 2:	High surgical risk, age >75, patient choice.
Expert 3:	Known coronary artery disease and/or previous PCI. Age / Life expectancy. Previous surgical aortic valve replacement. Other determinants are anatomical rather than clinical
Expert 4:	In the main it will be anatomical features of the patient, and then the valve choice they have in their centres.
Question 2	**The EAG note that patient characteristics and anatomy may differ between selection of a balloon- or self-expanding device. Therefore the EAG is suggesting comparing balloon-expanding TAVI valves with each other, and separately comparing self-expanding TAVI valves with each other (separate analysis and the populations characteristics are likely different by expansion type). Do you agree with this approach?**
Expert 1:	Not justified. There is only one balloon expandable valve widely used and with any data. Head to head datasets are very few and far between so any comparisons are very challenging.
Expert 2:	Approach justified.
Expert 3:	Not justified.
Expert 4:	Although this seems attractive as a concept, the truth is many patients can be treated with either valve type. There are certain sub groups that suit self expanding better for example small annulus and those that suit balloon expandable. Other features of the device are

	important for example intra-annular vs supravalvular leaflets. Self expanding can be supra or intra annular. Another issue is that until Myval was launched, the only balloon expandable was Edwards so (was) a monopoly. Medtronic dominates self expanding though there are other well established for example Boston.
Question 3	**Do NHS hospitals routinely have access to at least one balloon-expanding and one self-expanding TAVI valve?**
Expert 1:	Yes
Expert 2:	I can only speak for our centre – yes.
Expert 3:	Yes
Expert 4:	The majority do.
Question 4	**Some of the TAVI valves contain a nickel frame. In clinical practice do you screen for Nickel allergy?**
Expert 1:	No. Quantities are miniscule.
Expert 2:	No – allergy is on contact with skin rather than vascular endothelium.
Expert 3:	No.
Expert 4:	No.
Question 5	**Does presence of Nickel allergy inform choice of TAVI valve, or whether SAVR is clinically suitable?**
Expert 1:	Choice of TAVI/Choice of SAVR no.
Expert 2:	No.
Expert 3:	Neither.
Expert 4:	No.
Question 6	**The EAG is considering analysing frame material (predominantly nickel and predominantly non-nickel) in subgroup analysis. Is this appropriate?**
Expert 1:	No. Quantities are miniscule.
Expert 2:	No evidence to suggest it is.
Expert 3:	No.
Expert 4:	No – unless you can show outcome data and I'm not aware of any? Though this might evolve over time.
Question 7	**The EAG is considering analysing pericardium tissue material (bovine and porcine) in subgroup analysis. Is this appropriate?**
Expert 1:	Yes. May be relevant to longevity, so need longer term data.
Expert 2:	Yes – durability data is clinically useful.
Expert 3:	No.
Expert 4:	There are differences but again, I'm not sure of outcome data.

Question 8	**Does the waiting list for TAVI differ between TAVI valve?**
Expert 1:	No – waiting list applies across all devices approximately equally.
Expert 2:	No – waiting list applies across all devices approximately equally.
Expert 3:	No – waiting list applies across all devices approximately equally,
Expert 4:	No – waiting list applies across all devices approximately equally,
Question 9	**Does your centre ever refer to a different Trust due to TAVI valve accessibility?**
Expert 1:	No.
Expert 2:	No.
Expert 3:	No.
Expert 4:	We used to but not now.
Question 10	**This Late-stage assessment is focused on patients with aortic stenosis. Should the EAG include patients with rheumatic aortic stenosis?**
Expert 1:	Yes.
Expert 2:	Not yet – as no evidence and numbers of patients is too small to develop evidence base.
Expert 3:	No. They should be treated as part of the same group.
Expert 4:	Yes.
Question 11	**This Late-stage assessment is focused on patients with aortic stenosis. Should the EAG include patients with congenital aortic stenosis?**
Expert 1:	Yes
Expert 2:	Not yet – no evidence.
Expert 3:	It is the same thing. It doesn't matter what is the cause of the aortic stenosis for this work.
Expert 4:	Yes – if you mean bicuspid.
Question 12	**This Late-stage assessment is for adults with aortic stenosis, is an age threshold of 16 years appropriate?**
Expert 1:	Yes
Expert 2:	No – should be >55yo
Expert 3:	Yes.
Expert 4:	Yes.
Question 13	**In the 12 months prior to the NHS England position statement (January 2023) can you estimate the proportion of all TAVI procedures that were conducted in low, intermediate and high surgical risk populations?**

Expert 1:	No. We do not use these arbitrary thresholds much in heart team discussions.
Expert 2:	Low risk: 0%, Intermediate risk: 20%, High risk: 80%
Expert 3:	Low risk: 20%, Intermediate risk: 40%, High risk: 40%.
Expert 4:	Low risk: 5%, Intermediate risk: 15%, High risk: 80%. National databases for example NICOR will demonstrate that the mean age is 82 in the UK.
Question 14	**In the 12 months after to the NHS England position statement (January 2023) can you estimate the proportion of all TAVI procedures that were conducted in low, intermediate and high surgical risk populations?**
Expert 1:	No. We do not use these arbitrary thresholds much in heart team discussions.
Expert 2:	Low risk: 10%, Intermediate risk: 20%, High risk: 70%
Expert 3:	Low risk: 20%, Intermediate risk: 40%, High risk: 40%.
Expert 4:	Low risk: 5%, Intermediate risk: 15%, High risk: 80%.
Question 15	**Are there any specific populations where only one TAVI valve may be considered appropriate?**
Expert 1:	Yes. Device selection needs to be individualised according to patient characteristics. Some TAVI valves have lower gradients and are best choice for small anatomy. Some have quicker implants which is relevant for unstable patients. Some have better coronary access. TAVI teams need to weigh up these factors in valve selection.
Expert 2:	Yes – above 80 yo
Expert 3:	Yes – no calcium on valve – JenaValve Trilogy
Expert 4:	No – though there are preferences.
Question 16	**Several devices are indicated for TAVI-in-SAVR. In this population what informs the choice of TAVI valve (when there is a previous SAVR in place)?**
Expert 1:	Self expandable valves have lower gradients and may be best suited to small surgical valves. Balloon expandable better for coronary access / protection. Detailed review of the planning CT scan is the key to individualising the valve choice.
Expert 2:	Good haemodynamics.
Expert 3:	Size of SAVR. Centre experience with TAVI valve for TAV-in-SAV.
Expert 4:	Size of annulus – if small generally prefer a supra-annular device. Coronary heights relative to the skirt and frame height – short frame preferable if risk of obstruction.
Question 17	**Within the equalities section the EAG have considered the use of animal-derived tissue (bovine or porcine), nickel allergy (which disproportionately affects females). Are there any other equality considerations for TAVI valves?**
Expert 1:	Yes. Several datasets show disproportionately lower implant rates in females. This is probably related to referral patterns and diagnostic tests rather than related to one device over another.
Expert 2:	No.
Expert 3:	No.

Expert 4:	Women have smaller annuli which might affect valve choice. Women are under investigated, under diagnosed and under treated compared to male counter.
Question 18	**The final scope includes a subgroup for "people with a failed previous bioprosthetic valve". The EAG propose to treat these patients as a completely different group (that is the EAG do not plan on aggregating with first line TAVI patients due to different patient characteristics). Is this an appropriate approach?**
Expert 1:	Appropriate assumption. Although valve in valve is very well established and the treatment of choice in a large proportion of patients.
Expert 2:	Appropriate assumption.
Expert 3:	Appropriate assumption.
Expert 4:	Appropriate assumption.
Question 19	**In terms of hospital resources (staff time, band) is TAVI in prior failed bioprosthesis (TAVI or SAVR) the same as the placement of TAVI in the native aortic valve?**
Expert 1:	Yes. With very few exceptions – for example very complex procedures requiring leaflet modification techniques.
Expert 2:	No – higher risk of coronary occlusion, higher risk of embolisation of debris
Expert 3:	Yes.
Expert 4:	Yes.
Question 20	**Where a secondary procedure (after the initial TAVI) is required, what proportion of patients would undergo TAVI or SAVR as a reintervention?**
Expert 1:	TAVI: 95%, SAVR: 5%
Expert 2:	TAVI: 99%, SAVR: 1%
Expert 3:	TAVI: 97%, SAVR: 3%
Expert 4:	TAVI: 99%, SAVR: 1%
Question 21	**NG208 modelling assumed that vascular complications would impact quality of life for 30 days, is this assumption and duration still appropriate?**
Expert 1:	Appropriate assumption. Major vascular complications may impact for longer than 30d.
Expert 2:	Inappropriate assumption due to improved delivery sheaths, smaller delivery devices and better experience with closure devices.
Expert 3:	Appropriate assumption.
Expert 4:	Appropriate assumption.
Question 22	**Treatment for heart failure (which could include medication) has been assumed to be the same across TAVI valves and therefore omitted from the economic model. Is this approach appropriate?**
Expert 1:	Appropriate assumption.
Expert 2:	Inappropriate assumption.

Expert 3:	Appropriate assumption.
Expert 4:	Appropriate assumption
Question 23	**Is it appropriate to assume that the median length of hospital stay is the same across all TAVI devices?**
Expert 1:	No. Definitely not. Self-expandable devices have higher risk of early or late permanent pacemaker (PPM) / conduction disease. Patients are often monitored for much longer before discharge.
Expert 2:	Yes.
Expert 3:	No. Risk of conduction disturbance and/or pacemaker rate, which varies between TAVI valves, will influence length of stay.
Expert 4:	Yes – broadly, though there is a clear relationship with Medtronic valves have a higher PPM rate, and need to monitor which could potentially prolong LOS.
Question 24	**Is it anticipated that the length of critical care stay will vary significantly between TAVI valves?**
Expert 1:	No. Critical care need is now very low and usually only needed for extremely unstable patients or post major complication.
Expert 2:	No.
Expert 3:	No.
Expert 4:	There is no critical care stay with TAVI.
Question 25	**Are there any outcomes anticipated to differ between TAVI valves that you would recommend considering in an economic evaluation?**
Expert 1:	Yes. PPM would be the main one.
Expert 2:	Yes, bicuspid aortic valves may have different outcomes. Data, in my opinion, needs to be more extensive before judgement can be made.
Expert 3:	Yes. Risk of pacemaker.
Expert 4:	Yes – PPM rates and need for post op monitoring as this increases LOS.
Question 26	**After events such as pacemaker or stroke, is it appropriate to assume that the risk of hospitalisation (for example due to heart failure) or ongoing rehabilitation/treatment costs is the same regardless of which TAVI valve is used?**
Expert 1:	Yes – if the complication has occurred.
Expert 2:	Yes.
Expert 3:	Yes.
Expert 4:	Yes.
Question 27	**In terms of clinical coding of TAVI procedures using data from Hospital Episode Statistic (HES) from 1st April 2021 onwards, the EAG has applied the following rules to procedure (OPCS 4.10) codes:** **First line TAVI: (K26.2 OR K26.3 OR K26.4) AND (Y49.4 OR Y79 OR Y53 OR Y68)**

	Second line TAVI: K26.8 AND (Y49.4 OR Y79 OR Y53 OR Y68) K30.2 **Repeated first line TAVI codes** **Conversion from TAVI to SAVR: (K26.1 OR K26.2 OR K26.3 OR K26.4) AND (Y71.4 OR Y71.5)** **Prior SAVR: K26.1 OR K26.2 OR K26.3 OR K26.4 (but not supplemented by Y49.4 OR Y79 OR Y53 OR Y68)** **Note K26.1 allograft has been excluded from TAVI analysis (not relevant to the 11 devices in scope).** **Do these procedure codes seem appropriate?**
Expert 1:	I have no expertise in coding and cannot see the codes in the link to determine whether these are correct and whether others should also be included.
Expert 2:	Yes.
Expert 3:	I don't know.
Expert 4:	No idea – I assume that NICE would know the correct codes for TAVI.
Question 28	**In terms of clinical coding of TAVI procedures using data from Hospital Episode Statistic (HES) from 1st April 2021 onwards, the EAG has applied the following rules to diagnosis (ICD10) codes:** **First line TAVI: I35.0 OR I35.2 OR I06.0 OR I06.2 OR Q23.0** **Second line TAVI:** **T82.0 OR T82.2 OR T82.6 OR T82.9** **Repeated first line TAVI codes beyond 30 days** **Do these diagnosis codes seem appropriate?**
Expert 1:	I have no expertise in coding and cannot see the codes in the link to determine whether these are correct and whether others should also be included.
Expert 2:	Yes.
Expert 3:	Don't know.
Expert 4:	No response.
Question 29	**In terms of pacemaker implantation during TAVI admissions, the EAG is monitoring the use of the following to procedure (OPCS 4.10) codes:** **K60.1 OR K60.5 OR K60.6 OR K60.7 OR K60.8 OR K60.9**

	Do these procedure codes seem appropriate?
Expert 1:	I have no expertise in coding and cannot see the codes in the link to determine whether these are correct and whether others should also be included.
Expert 2:	Yes.
Expert 3:	Don't know.
Expert 4:	No response.
Question 30	**In terms of prior CABG within historical hospital admissions, the EAG is monitoring the following procedure (OPCS 4.10) code within HES between 2007 and 2021:** **K44** **Is this approach seem appropriate?**
Expert 1:	Expert 1: I have no expertise in coding and cannot see the codes in the link to determine whether these are correct and whether others should also be included.
Expert 2:	Expert 2: Appropriate.
Expert 3:	Expert 3: Don't know.
Expert 4:	Expert 4: No response.

Questions sent 12 March 2024

#	Date responses received	Name, Affiliation
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Question 1	The EAG notes that in January 2023, that NHS England (NHSE) published a position statement broadening access to TAVI for eligible patients with intermediate or low SAVR risk to alleviate pressures on local systems in supporting elective performance. The EAG previously considered analysing data from 21/22 and 22/23 financial years separately in order to account for potential differences in patient case mix over time. The EAG has reviewed the data fields which contribute to EuroSCORE II that are available in the UK TAVI Registry. After accounting for multiple hypothesis testing only extracardiac arteriopathy was found to be statistically different between 21/22 and 22/23 financial years. Can you confirm that it is appropriate for the EAG to assume that the TAVI population has broadly remained the same during 1st April 2021 and 31st March 2023, and that it is reasonable that all the data be pooled together (rather than separated by financial year)?
Expert 1:	Appropriate
Expert 2:	Yes
Expert 3:	Yes – the populations are similar and there is no evidence of major change.
Expert 4:	Yes
Expert 5:	Yes
Question 2	The EAG has identified 3 separate cohorts of patients from UK TAVI Registry real-world data sources: a.TAVI in native aortic valve (95.4%) b.TAVI in failed prior TAVI valve (0.6%) c.TAVI in failed prior SAVR valve (4.0%)

	Due to limited time within the TAVI Late-stage assessment the EAG has focused on detailed reporting of the real-world data and published evidence from the native aortic valve subgroup as this represents the majority of TAVI cases. Is this approach appropriate?
Expert 1:	Appropriate
Expert 2:	TAVI in a failed SAVR still represents a significant number of patients and this number will rise in the future. I would like to see this subgroup analysed as it is a very good indication for TAVI.
Expert 3:	Yes – these are the majority of TAVI population
Expert 4:	Yes
Expert 5:	Yes
Question 3	Several assumptions were made in the original economic model which was developed for NG208. The EAG has made comments on why some assumptions remain valid and made suggested changes for others. Please can you go through each (in the table below) and indicate whether you think the EAG approach is considered appropriate or not appropriate?
Assumption 1	Assumption within the economic model used with NG208: Economic model does not account for general or local anaesthesia EAG comment: The EAG assume that type of anaesthesia used is captured within the average cost of procedure and length of stay (obtained from the Healthcare Resource Group, HRG). The EAG note that Getting It Right First Time (GIRFT) have recommended conducting TAVI under local anaesthesia and have developed a delivery guide to support heart teams to increase the volume of TAVI procedures, based on the experience of James Cook University Hospital (GIRFT, 2023). The EAG will consider type of anaesthesia from the UK TAVI Registry to determine whether there are differences between devices.
Expert 1:	I don't think GA vs LA rate will differ between devices but GA vs LA will impact on outcomes (not device specific)
Expert 2:	Appropriate
Expert 3:	Not appropriate, I think that it should only be local anaesthetic population. This is the default strategy and GA is used in specific cases only
Expert 4:	Not appropriate – over 94% of TAVI procedures in England are done under conscious sedation. Need for GA is not dependent on device choice but rather patient characteristics including need for non femoral access.
Expert 5:	Not appropriate Whether a unit uses GA or LA is not an innate feature of the device. It is a reflection of the working practices of the unit. However – the economic model does need to be updated to reflect that TAVI requires LA only, no GA, in the majority of cases – see NICOR data>93.4% - occurs in a cath lab not a theatre, and the patient returns to a level 1 or 2 bed (not critical care stay.)
Assumption 2	Assumption within the economic model used with NG208: Economic model does not account for day-case procedures EAG Comment: Related to the above; assumed captured within the average cost of the procedure and length of stay (from HRG). The EAG will consider length of stay from the UK TAVI Registry to determine whether there are differences between devices.

Expert 1:	Expert 1: Appropriate, Day case procedures are likely to be a small minority of cases in most centres though some will do more (around 20% at [redacted])
Expert 2:	Expert 2: Appropriate
Expert 3:	Expert 3: Appropriate, Yes this is reasonable
Expert 4:	Expert 4: Appropriate – LOS may be affected by different complication rates (for example pacemaker rates, vascular complications)
Expert 5:	Appropriate but unlikely to demonstrate major differences at the device level. Usually more to do with the unit's practice. Self expanding valves (SEVs) have the potential to develop late pacing issues so patients may have an increased LOS but there are mechanisms to mitigate Day case discharge is the minority and limited to those who already have a Pacemaker in situ, or ballon expanding valves (BEV), with good social support. It has limited applicability to the whole cohort; the current elderly UK TAVI cohort, and so is not a device specific feature per se
Assumption 3	Assumption within the economic model used with NG208: Economic model does not account for different delivery approach (for example transfemoral, subclavian, transapical) EAG Comment: The majority of TAVI procedures are conducted via percutaneous transfemoral delivery approach (93.3% as stated in British Cardiovascular Intervention Society (BCIS) 2021-22 report); and recommended as default position by GIRFT in its 2021 cardiology report. The EAG assume that delivery approach and associated complications will be captured within the average cost of the procedure (from HRG) and clinical outcomes.
Expert 1:	Expert 1: Not appropriate, Non vascular access (apical and aortic) are associated with higher risk, higher morbidity and longer LoS. I think that should be considered separately from TF
Expert 2:	Expert 2: Appropriate – alternative delivery routes will be more expensive (GA, vascular surgery presence, longer LoS)
Expert 3:	Expert 3: Appropriate
Expert 4:	Expert 4: Appropriate
Expert 5:	Expert 5: Not appropriate my understanding is that the current HRG tariff includes a critical care stay, and theatre time which is only relevant to surgical approaches. A percutaneous TF approach will be associated with a shorter LOS, and reduced costs as the procedure is done in cath lab – but I don't think this is currently reflected in the tariff? Complications should be captured in outcomes
Assumption 4	Assumption within the economic model used with NG208: Economic model does not account for different staffing EAG Comment: The EAG assume that staffing is captured within the average cost of the procedure (within HRG) which are updated annually. Current BCIS guidance recommends that TAVI should be performed by 2 appropriately trained TAVI operators (MacCarthy et al. 2021) and noted that thoracic approaches (such as transapical or direct aortic) procedures are led by cardiac surgeons. The EAG

	assume that there will be no difference in staffing between delivery of different TAVI valves. To explore potential impact of staffing changes over time (for example, reduction in the number of cardiac surgeons in the delivery of TAVI), the HRG costs will be adjusted by +/-10% in the scenario analysis.
Expert 1:	Appropriate
Expert 2:	Appropriate, Royal College of Physicians (RCP) TAVI reviews have demonstrated that staffing can be variable within TAVI units.
Expert 3:	Appropriate
Expert 4:	Appropriate
Expert 5:	Appropriate
Assumption 5	Assumption within the economic model used with NG208: Economic modelling subgroups the cohort by surgical risk. EAG Comment: Surgical risk subgroups will not be modelled separately. The Clinical Experts have previously advised that they would not routinely categorise patients by surgical risk when performing TAVI. Surgical risk (low, intermediate, high) is not routinely captured in the UK TAVI Registry. Surgical risk is poorly reported and varied in its definition across published literature. The EAG will model an average TAVI arm (which is a combination of all surgical risk) using data from the UK TAVI Registry to ensure generalisability to the NHS UK setting.
Expert 1:	Appropriate, Surgical risks scores are modelled for surgery and not for TAVI. They are of limited use
Expert 2:	Not appropriate, There will be inevitable comparisons with SAVR and any comparisons will inevitably be biased if risk groups are not used.
Expert 3:	Appropriate
Expert 4:	Appropriate
Expert 5:	Appropriate
Assumption 6	Assumption within the economic model used with NG208: Base case assumption: Time horizon of 15 years EAG Comment: The EAG acknowledge that the majority of the published literature reports short-term outcomes (in-hospital, 30 days) and that long-term evidence is only available for older generations of TAVI devices no longer available within the NHS (Ali et al. 2023). The EAG also note that technological developments, such as the addition or lengthening of a pericardial skirt, have been shown to impact outcomes, such as vascular outcomes including PVL (Chatfield et al. 2021; Forrest et al. 2020). Therefore, use of data relating to older devices may overestimate adverse events or poorer clinical outcomes. The EAG will use data from 1st April 2021 onwards, focusing on evidence related to currently available TAVI devices, and will use data from Hospital Episode Statistics (HES) to

	determine 30 day, 1 year and 2 year outcomes, which will then be extrapolated to 10 years, to represent an average TAVI valve lifetime. Additional time horizons will be explored in sensitivity analysis.
Expert 1:	Appropriate
Expert 2:	Not appropriate, The MHRA (Medicines and Healthcare products Regulatory Agency) have evidence that, for any implanted devices, newer is not necessarily better or safer. Technology often advances more rapidly than data availability and it is a fundamental mistake to extrapolate up to 10 years. Again – there will be inevitable comparisons with sAVR where actual 10 year data exists.
Expert 3:	Appropriate
Expert 4:	Not appropriate – the extrapolation to 10 years should be supported by published 5 year and 10 year data from randomised trials. In addition 5 year outcome HES data (using older TAVI device iterations) would be be useful in defining medium to longer term outcomes in this patient group.
Expert 5:	Appropriate
Assumption 7	Assumption within the economic model used with NG208: Base case assumption: Treatment effects calculated using only 2nd and 3rd generation TAVI valves EAG Comment: Treatment effects applied in economic modelling will be restricted to specific devices and versions listed in the NICE Final Scope.
Expert 1:	Appropriate
Expert 2:	Appropriate
Expert 3:	Appropriate
Expert 4:	Appropriate
Expert 5:	Appropriate
Assumption 8	Assumption within the economic model used with NG208: Only moderate and severe paravalvular leak affects mortality EAG Comment: The EAG assume that only moderate and severe paravalvular leak will affect the mortality. This assumption will be tested within the sensitivity analysis by allowing mild paravalvular leaks to increase mortality. In addition, the effect of no paravalvular leak on mortality will also be considered in the sensitivity analysis.
Expert 1:	Appropriate
Expert 2:	Appropriate
Expert 3:	Not appropriate, Only moderate and severe PVL need to be considered
Expert 4:	Appropriate
Expert 5:	No Response

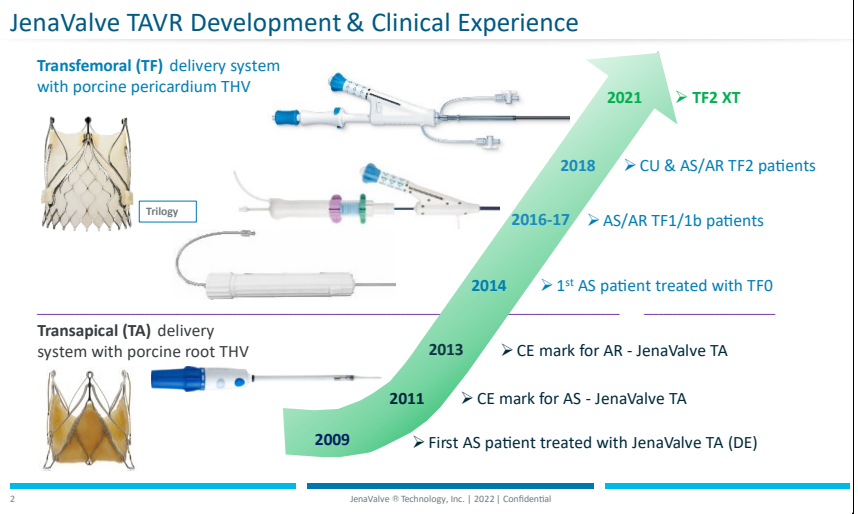
Assumption 9	Assumption within the economic model used with NG208: Base case assumption: Costs of short-term complications assumed within HRG costs EAG Comment: The EAG assume costs associated with acute complications, including major bleeding, vascular complications, and pacemaker implantation are captured in the average costs of the procedure (within HRG). The costs of major bleeding, vascular complication and pacemaker will be considered in addition to the HRG costs in the model in the sensitivity analysis.
Expert 1:	Appropriate
Expert 2:	Appropriate
Expert 3:	Sorry I don't understand this approach proposed?
Expert 4:	Appropriate
Expert 5:	Appropriate

HealthTech Programme

Transcatheter heart valves for transcatheter aortic valve implantation in people with aortic stenosis: Late Stage

External Assessment Report, User Preference Report and economic model – Collated comments

Section A: Comments on the External Assessment Report

Comment no.	Name	Page no.	Section no.	Comment	EAG/NICE response
1	JenaValve Technology, Inc	111	5.4.1	In JenaValve's single product history from 2009 through present day, there have been two iterations of that single product. The first was the Porcine Root THV from 2009 through 2013, and the second is the Trilogy which is a Porcine Pericardial THV from 2014 to present. Please see the embedded slide for a visual of Trilogy's history, as well as the delivery catheter. 	Thank you for this clarification. We have also added some additional text to Table 3 to describe the differences between iterations.

HealthTech Programme

Transcatheter heart valves for transcatheter aortic valve implantation in people with aortic stenosis: Late Stage

External Assessment Report, User Preference Report and economic model – Collated comments

2	Cook Medical	11	Executive summary	(page 11 the EAG state) *Data were analysable for the following 6 TAVI devices in scope for this assessment: ACURATE neo2, Evolut R, Evolut Pro+, Navitor, Sapien 3, Sapien 3 Ultra (Evolut FX was not included in analysis comparing different TAVI devices, because it was used in fewer than 5 procedures). Four TAVI devices were added to the NHS Supply Chain after the collection period and so there was no information on them in the Registry (Allegra, Hydra, Myval Octacor, Trilogy).* Then on page 13 the EAG summarise that ". *Because of a lack of patient-level data enabling adjustment for population differences, multivariate analysis and subsequent economic modelling were not possible for TAVI devices with no data, or minimal data, in the Registry. This limitation affected those TAVI devices recently added to the NHS Supply Chain (Allegra, Hydra, Myval Octacor, Trilogy), or used in only a few cases (Evolut FX); therefore, their incremental value remains uncertain."* And Given that economic modelling was not possible and EAG do not estimate a NMB for Allegra, Hydra, Myval Octacor, Trilogy, to say the value is "uncertain" is only partly true as with the current methods the value has been unable to be estimated. The use of "uncertain" for these 5 devices implies a base case estimate of value has been calculated which is not the case and the use of "unbale to be estimated" is more accurate representation and should be used.	The EAG has summarised technical differences between valves, and summarised published literature with clinical outcomes for all valves. Some valves were not recorded in extract from the UK TAVI Registry and therefore were omitted from the economic analysis. Therefore "uncertain" remains appropriate.
3	Cook Medical	28	Tavi-in Tavi indications	The EAG reports states "*When considering the separate TAVI-in-TAVI cohort, the EAG will only include devices where this is not explicitly contraindicated (as stated in the device Instructions for Use). Recommendation 6.2.4 of the NICE Health Technology Evaluations Manual (PMG36) enables consideration of evidence for comparator technologies outside regulatory approval, the EAG note this is only where use is considered as part of established clinical practice. The*	The EAG has summarised the published evidence available and summarised the use of devices in the UK TAVI Registry reflecting current use. The EAG has explicitly tabulated the indications of each device, and the number of devices used within each cohort (native aortic, TAVI-in-TAVI, and TAVI-in-SAVR) to make this clear to committee.

				extent and quality of evidence, particularly for safety and efficacy, in this specific emerging subgroup is lacking.". Section 6.2.4 of the manual states "*The committee can consider as comparators technologies that do not have regulatory approval for the population defined in the scope when they* ***are considered to be part of established clinical practice for the population in the NHS****. Long-standing treatments often do not have a company to support the regulatory process. Specifically, when considering an 'off-label', 'unlicensed' or 'unregulated' comparator technology, the committee will take into account the extent and quality of evidence, particularly for safety and efficacy, for the unregulated use*." How can the EAG justify the use of these TAVI devices outside of their marketing authorisation to be both part of established practice while the evidence is lacking? These comments contract one another. Can the EAG provide robust evidence of TAVI use being established practice for Tavi-in Tavi indications?	NICE comment: clinical advice to the EAG was that devices that are not explicitly indicated for valve-in-valve use are being used as such in clinical practice. However, as the evidence was lacking, the EAG has not provided an assessment of the comparative clinical or cost effectiveness of any valve in the valve-in-valve population. As stated in the manual, when considering an 'off-label', 'unlicensed' or 'unregulated' comparator technology, the committee will take into account the extent and quality of evidence, particularly for safety and efficacy, for the unregulated use.
4	Cook Medical	20	Table 2	Building on comment 3 above table 2 highlights in amber where devices are *not explicitly contraindicated,* as above in order to comply with section 6.2.4 established practice needs to be firmly ascertained for each of these parameters.	Please see response to comment 3
5	Cook Medical	Various	Table 18 Table 20 Table 29	The in hospital mortality data reported in various sections of the EAR appear, not to align. In-hospital death in Table 18 for Sapien 3 ultra is 1% and for Sapien 3 it is 1.3%, it seems implausible that the OR in Table 20 for Sapien 3 (compared with Sapien 3 Ultra) is 0.8 (lower odds of death) when more deaths were recorded for Sapien 3 compared with Sapien 3 ultra. Could the EAG please check this data.	Thank you for your comment. Table 18 (now Table 21 in the updated report) reports the unadjusted number of in-hospital deaths in patients available in the UK TAVI Registry with data linked to HES. Table 20 (now Table 23 in the updated report) shows the odds ratios (effect sizes on the response variable) for each covariate, after adjusting

				These inconsistencies link through to table 29 (predicted event proportions), where there are higher predictive proportions of deaths for Sapien 3 Ultra than Sapien 3 – this does not appear to align with data in Table 18 In addition, Navitor had 3.5% in-hospital deaths reported in Table 18, but an OR (compared with Sapien 3 Ultra) of 0.97 – this seems implausible -the risk of death from Table 18 data seems higher for Navitor. Similarly, in-hospital deaths for Navitor in Table 18 is 3.5% but the predictive proportions of deaths in Table 29 is lower than all other devices except sapient 3, despite Navitor having the highest in-hospital death in Table 18. Could the EAG kindly double-check the interplay between tables 18, 20 and 29 for all in-hospital death, as these variances may impact the outcomes of the economic model.?	for other covariates. using binary logistic regression. For example, the population having Sapien 3 included a higher proportion of people with frailty and having planned GA compared with those having Sapien 3 Ultra, both factors found independently to be significantly associated with increased risk of in-hospital death. In addition, the population having Sapien 3 were on average younger and had a greater proportion of male patients than the Sapien 3 Ultra population, both factors found to have a (non-significant) negative association with in-hospital death. Similarly, the Navitor patient group has more female patients than the Sapien 3 Ultra group, a higher proportion with critical status pre-procedure, and higher proportion with presence of 50% or greater stenosis in at least one coronary vessel. Table 29 (now Table 27 in the updated report) shows the predicted proportions of each outcome for each scenario, from multivariate modelling (that is, after adjusting for known differences in population).
6	Cook Medical	Various	Table 18 Table 21 Table 29 Figure 5	Table 21 reports a HR of death (post discharge) for Sapien 3 as 0.8 as compared with Sapien 3 Ultra, whereas the data in Table 19 indicates that deaths were higher for Sapein 3 compared with Sapien 3 Ultra at 6 and 12 months with only the 30 day death being higher for Sapien 3 Ultra than Sapien 3– this is also backed up visually by the KM in Figure 5. The HR in Table 21 do not appear to align with Table 19 and KM Figure 5.	Please see the EAG's response to comment 5.

				This then translates into Table 29 where the one-year death predicted event proportions are lower for Sapien 3 than Sapien 3 Ultra. Could the EAG kindly check as these numbers do not appear to align with the data presented in Table 19 and may impact the outcomes of the economic model. Similarly, the Evolut R have higher deaths reported at 6,12, 18 and 24 months (not at 30 days) than Sapien 3 Ultra but a HR of 0.82 in Table 21, and corresponding lower predicted event proportions in Table 29 which may impact the model. There may be a similar issue with Evolut Pro+plus but the data is not clear. Could the EAG kindly double-check the data in Tables 19, 21 and in 29 for longer-term mortality across the devices as these numbers are pivotal for the model outcomes.	
7	Edwards Lifesciences	10, 31	Executive Summary Clinical context	"***TAVI is now considered standard of care in patients where open surgery is considered high risk***". This statement is outdated as the 2017 ESC/EACTS guidelines recommended TAVI for Intermediate Risk patients and the latest 2021 ESC/EACTS guidelines recommend TAVI with a class IA all elective, transfemoral eligible patients of 75 years of age or older. British Cardiovascular Intervention Society refer to ESC/EACTS guidelines in their own recommendations (bcis.org.uk): MacCarthy et al. Extended Statement by the British Cardiovascular Intervention Society President Regarding Transcatheter Aortic Valve Implantation. Interventional Cardiology Review 2021;16:e03.	Not factual inaccuracy, TAVI does remain standard of care in high risk as confirmed by Clinical Experts. Clinical Experts have also advised that the majority of cases would be considered surgical high risk, however that surgical risk is not routinely captured in TAVI patients in the NHS. EAG have referred to NHS position statement, but also to the response to this policy change by the Society of Cardiothoracic Surgery in Great Britain & Ireland, The Royal College of Surgeons, which acknowledged the concern for long waiting times following the pandemic and ongoing staffing shortages but stated the policy change was contrary to NICE guidance, not clinically appropriate

				Also, there should also be consideration to adding a statement in the executive summary about intermediate and low risk patients, following interim guidance issued by NHSE in February 2023 in order to add relevance to the populations being considered in the LSA.	and may increase patient risks if subsequent surgery was required. No change to Executive Summary.
8	Edwards Lifesciences	10, 190	Executive summary	The stated aim in the EAG report is "***to evaluate the evidence available for these devices to support procurement and commissioning decisions.***" This is different from that contained within the final TAVI LSA scope "***To assess the incremental clinical, economic and non-clinical benefits of transcatheter aortic valve implantation devices for people with severe aortic stenosis to justify price variation and inform procurement decisions.***" This difference is welcomed as there is no current methodology or criteria for determining price variation as acknowledged by NICE in their responses to comments on latest LSA methods and process interim document p12, section 45, which states "***Insights from the first 8 topics will inform the final process for topic selection, including the development of detailed criteria for defining price variation.***" The report acknowledges that it has many limitations or uncertainties and should not be the sole determination of whether a price variation is justified. Please also see comment 5.	
9	Edwards Lifesciences	14, 57, 113, 209	EAG Key Issues, Table 6, 5.4.1, Appendix B	Key issue 7 states. "***Poor quality of published literature comparing TAVI devices. Only 15 identified studies attempted to control for different population characteristics between devices.***" The EAG report states repeatedly that the timeframe constraints restricted their literature search (see comment 9), so it would be in the interests of creating a more robust evidence base for the EAG to be enabled to conduct a more thorough and appropriate investigation to better inform this assessment.	Pragmatic searches are permitted within LSA Process and methods guide, and the EAG transparently reported the literature searches conducted. The EAG has restructured the report to highlight the limitations of published network meta-analyses that have compared multiple TAVI devices. Given these limitations additional studies comparing 2 devices or studies comparing TAVI to SAVR, are unlikely to change the overall summary of the EAG report. The EAG has also removed the count of the number of papers and number of patients included in them, as to

				Some key clinical studies (meta-analysis from RCTs, other comparative RCTs or large RWD from other countries with healthcare systems similar to the NHS) were not captured (c.f. list below) or referenced. - Senguttuvan et.al. 2023 - The safety and efficacy of balloon-expandable versus self-expanding transcatheter aortic valve replacement in high-risk patients with severe symptomatic aortic stenosis. Front Cardiovasc Med. 2023 May 25;10:1130354 - Gozdek, et.al. 2020 - Transcatheter Aortic Valve Replacement with Self-Expandable ACURATE neo as Compared to Balloon-Expandable SAPIEN 3™ in Patients with Severe Aortic Stenosis: Meta-Analysis of Randomized and Propensity-Matched Studies. J Clin Med- 2020 Mar 0;9(3):861. doi: 10.3390/jcm9030861.Li, et.al. 2020 - Comparison of third generation balloon-expandable Edwards SAPIEN 3™ versus self-expandable Evolut R in transcatheter aortic valve implantation: a meta-analysis. Ann Palliat Med. 2020 May;9(3):700-708. - Takagi, et.al. 2019. Network meta-analysis of new-generation valves for transcatheter aortic valve implantation. Heart Vessels. 2019 Dec;34(12):1984-1992. - Van Belle, et.al. 2020 - Balloon-Expandable Versus Self-Expanding Transcatheter Aortic Valve Replacement: A Propensity-Matched Comparison From the FRANCE-TAVI Registry. Circulation. 2020 Jan 28;141(4):243-259. - Beyersdorf, et.al. 2021 - Five-year outcome in 18 010 patients from the German Aortic Valve Registry. Eur J Cardiothorac Surg. 2021 Nov 2;60(5):1139-1146. - Attinger-Toller, et.al. 2021 - Age-Related Outcomes After Transcatheter Aortic Valve Replacement: Insights From the SwissTAVI Registry. JACC Cardiovasc Interv. 2021 May 10;14(9):952-960. - Deharo, et.al. 2020 - Impact of SAPIEN 3™ Balloon-Expandable Versus Evolut R Self-Expandable Transcatheter Aortic Valve	not cause confusion as it is acknowledged that the evidence included in the report is not the entirety of the evidence available for each device. The EAG has added the paper by Cassata to the report (which represents a longer follow-up of propensity matched Sapien 3 and Sapien 3 Ultra patients than was previously in the report).

				Implantation in Patients With Aortic Stenosis: Data From a Nationwide Analysis. Circulation. 2020 Jan 28;141(4):260-268.Guerreiro, et.al. 2020. Short and long-term clinical impact of transcatheter aortic valve implantation in Portugal according to different access routes: Data from the Portuguese National Registry of TAVI. Rev Port Cardiol (Engl Ed). 2020 Dec;39(12):705-717. - Durand, et.al. 2020 - Analysis of length of stay after transfemoral transcatheter aortic valve replacement: results from the FRANCE TAVI registry. Clin Res Cardiol. 2021 Jan;110(1):40-49 - Okuno et. al. 2023 - 5-Year Outcomes with Self-Expanding vs Balloon-Expandable Transcatheter Aortic Valve Replacement in Patients with Small Annuli. JACC Cardiovasc Interv. 2023 Feb 27;16(4):429-440 - Schofer, et.al. 2022 - Risk-related short-term clinical outcomes after transcatheter aortic valve implantation and their impact on early mortality: an analysis of claims-based data from Germany. Clin Res Cardiol 2022 Aug;111(8):934-943. - Jørgensen, et.al. 2021- Eight-year outcomes for patients with aortic valve stenosis at low surgical risk randomized to transcatheter vs. surgical aortic valve replacement. Eur Heart J. 2021 Aug 7;42(30):2912-2919 - Tarantini, et.al 2021 - Four-year mortality in women and men after transfemoral transcatheter aortic valve implantation using the SAPIEN 3™. Catheter Cardiovasc Interv. 2021 Apr 1;97(5):876-884. - Costa, et.al. 2021 - Long-term outcomes of self-expanding versus balloon-expandable transcatheter aortic valves: Insights from the OBSERVANT study. Catheter Cardiovasc Interv. 2021 Nov 15;98(6):1167-1176. - Welle, G.A., et al. Effect of a fourth-generation transcatheter valve enhanced skirt on paravalvular leak. Catheter Cardiovasc Interv 97, 895-902 (2021).	

HealthTech Programme

Transcatheter heart valves for transcatheter aortic valve implantation in people with aortic stenosis: Late Stage

External Assessment Report, User Preference Report and economic model – Collated comments

10	Edwards Lifesciences	13, 14, 183	Executive summary, Key issues point 5 and 6.4 Strengths and limitations	The executive summary highlights an issue of lack of data for certain technologies and states that as a result, "***their incremental value remains uncertain.***" The Key issues table, point 5 also states that "***the incremental clinical and economic value of these devices in an NHS setting remain uncertain***." On page 183, there is clearer explanation stating that "***As the EAG was unable to adjust for patient characteristics from the published literature to enable fair comparison; the relative cost, QALY, NMB differences using those 5 devices in the UK remain unknown***." Given the inability to perform an analysis, the term "uncertain" on p13 and p14 should be changed to "unknown" as a reader who relies on the executive summary alone may be misled in thinking that some comparative analysis was possible. Unknown is a more accurate description.	The EAG has summarised technical differences between valves, and published clinical evidence. No change required
11	Edwards Lifesciences	19	Technologies	The EAG states that it has not verified manufacturer claims. How can the report accurately determine "***if the value added by incremental innovation justifies the price variation***" as stated in the interim methods and process update, or accurately assess if technologies have "***incremental innovation and performance claims that may have led to incremental price increases***" (https://www.nice.org.uk/about/what-we-do/late-stage-assessment-for-medtech) if any such claims have not been verified? Please also see comment 2.	The EAG report has been reviewed by SCMs, no challenges to technology sections have been received.

12	Edwards Lifesciences	20, 30	Table 2	Categorising technologies with "***Not explicitly contraindicated***" status presents significant safety risks based on a high degree of evidential uncertainty and the amber category should be removed. The EAG cites section 6.2.4 of the NICE manual as the rationale for including technologies where certain indications are not explicitly contra-indicated. 6.2.4 states that this is possible "***when they are considered to be part of established clinical practice***" and "***when considering an 'off-label', 'unlicensed' or 'unregulated' comparator technology, the committee will take into account the extent and quality of evidence, particularly for safety and efficacy, for the unregulated use***." Many of the technologies in the LSA have no data upon which any judgement can be made for unregulated use in specific indications. The data presented (or the absence of data) shows that there cannot be a conclusion of being part of "established clinical practice" in many cases. There have been repeated written and verbal assurances from the LSA team that there will be no deviation from section 2.2.5 of the manual – "***A technology is only evaluated if it has or is expected to have regulatory approval (or appropriate regulatory signal) by the planned draft or final guidance publication date.***" There is a potential for patient safety to be compromised if there is any inference that a technology has the indication for use without specific approval. It is very concerning that the EAG has assumed technologies are approved for use based on an absence of information in the instructions for use.	See response to Comment 2.
13	Edwards	22	Table 3	SAPIEN 3 Ultra RESILIA is now CE Marked is listed in the NHSSC catalogue. CE mark was received in January 2024. Please update this in the report.	The text in the report reflected the information provided to the EAG in the RFI. We have adjusted

	Lifesciences				Table 3 based on the new information provided, thank you.
14	Edwards Lifesciences	38, 142, 143, 187	Cohort Identification	Edwards supports the findings of the EAG that it is not possible to show equivalence between devices in this LSA. It is surprising that the report says that it is not possible to show differences as that is exactly what it concludes. The decision to conduct separate analyses by device type and by indication is supported by multiple publications in high-ranking journals, previously supplied to the LSA team, which show that assuming equivalence between technologies in terms of device type and indication is not possible.	
15	Edwards Lifesciences	54,55, 56, 170, 371	Completeness of analysis	The EAG notes repeatedly that time constraint in conducting the LSA has resulted in a lack of completeness of data and an introduction of bias. Please see comments 3, 10, 12 and 13 for examples of data that have not been captured in the EAG report. Why was the EAG not permitted time to conduct a thorough search for evidence to ensure that this, the first LSA topic, was conducted to give the greatest evidential certainty?	NICE comment: As per section 4 in the LSA interim methods and processes, the EAG has prioritised the evidence it believes to be most relevant to the decision question, in this case real-world evidence from the UK TAVI registry. Pragmatic reviews of the literature are permitted and were used to address uncertainties in the evidence. Prioritisation will always be necessary to complete an assessment regardless of the process being used. The EAG was given longer than originally planned (more than double the time of an average HealthTech assessment report), as per section 3 in the interim methods and processes, to ensure that it had enough time to complete all relevant analyses.
16	Edwards Lifesciences	147	6.1 Quality appraisal of	*"**To enable comparison with the economic model used within NG208, the EAG reviewed and summarised the 11 studies with associated economic models which were published after 2020 (identified from 6 systematic reviews), which included 7 peer-***	Pragmatic search conducted and transparently reported which can be reproduced. The EAG has reviewed the title and abstract of the references, all compare TAVI and SAVR, none in a UK setting; therefore unlikely to change the summary of the EAG

			economic evidence	***reviewed papers and 4 health technology assessment reports, 2 of which were in the French language) (Appendix B6).”*** This systematic review of the literature was not comprehensive, as additional economic evaluations that were published after 2020, such as those below, could have been taken into consideration. - Mennini et al. 2022 (Italy) - Vázquez Rodríguez et al. 2023 (Spain) - Kuck et al. 2023 (Germany) - Galper et al. 2023 (USA) - Tchétché et al. 2023 (France) - Dubois et al. 2023 (Belgium) - Eerdekens et al. 2024 (Netherlands) - Kobayashi et al. 2024 (Japan)	report. Individual economic evaluations of individual TAVI devices has the same limitations as the clinical evidence – see response to comment 9.
17	Edwards Lifesciences	72, 87	Table 13 / 17	The SAPIEN 3 data indicates that 92% of patients are male, which could be explained by the fact that SAPIEN 3 Ultra is available in 20mm, 23mm and 26mm valve sizes; and SAPIEN 3 is available in the additional 29mm valve size. The extract from the UK TAVI registry is from 1st of April 2021 to 31 March 2023. SAPIEN 3 Ultra was introduced in 2018, so most likely the SAPIEN 3 patients included are the ones with a 29mm, as all other sizes would be covered using SAPIEN 3 Ultra, which could explain the unbalanced incidence of Sex (92% male) in the SAPIEN 3 cohort.	
18	Edwards Lifesciences	75, 90, 91, and 161	Table 14, 18, 19 and 29	It seems there are discrepancies among various in-hospital mortality and PPI estimates between Table 14 (Raw data of TAVI UK registry), Table 18 (TAVI UK registry linked with HES), Table 19 (Longitudinal Outcomes for patients linked dataset) and Table 29 (Predicted event proportions for base case). We will focus on SAPIEN 3 and SAPIEN 3 Ultra for in-hospital mortality as an example – see table below:	Not a factual inaccuracy. Regarding the claimed discrepancies in in-hospital mortality, please see the EAG’s response to comment 5 in relation to population differences. Note that the 30-day mortality is exclusive of in-hospital deaths.

				<table><tr><th>UK TAVI Registry (T14)</th><th>S3 (n=1 229)</th><th>S3U (n=3 919)</th></tr><tr><td>In-hospital Mortality (T14)</td><td>1.1%</td><td>1.0%</td></tr><tr><th>UK TAVI Registry / HES Linked</th><th>S3 (n=1 121)</th><th>S3U (n=3 589)</th></tr><tr><td>% linked</td><td>91.2%</td><td>91.6%</td></tr><tr><td>In-hospital Mortality (T18)</td><td>1.3%</td><td>1.0%</td></tr><tr><td>30d Mortality (T19)</td><td>0.4%</td><td>0.7%</td></tr><tr><td>Pred. Mortality (T29, Male/Female)</td><td>1.22% / 1.74%</td><td>1.42% / 2.03%</td></tr></table> • The HES Linkage looks very good for SAPIEN 3 and SAPIEN 3 Ultra – as 90%+ of patients being linked – which is not the case with other TAVI devices. • The in-hospital mortality incidence of SAPIEN 3 and SAPIEN 3 Ultra between Table 14 and Table 18 are consistent and could be explained by the high percentage of linked patients. • The estimates at 30 days from the longitudinal outcomes (Table 19) seem too low and don't reflect what would be expected; also, the incidence is much higher with SAPIEN 3 Ultra, which is not consistent with what was found in Tables 14 and 18 (or the literature). • The corresponding predicted mortality (Table 29), which seems to be the input for the economic evaluation, conflicts with the other tables. We would expect a lower incidence with SAPIEN 3 Ultra (vs. SAPIEN 3) reflecting the outcomes presented in Table 14 and 18, which are consistent also with the results from the literature.	Nazif et al. 2021 was included in the EAG report, which conducted propensity matched analysis to compare Sapien 3 (n=1324) and Sapien 3 Ultra (n=1324). The adjusted analysis reported by Nazif et al. 2021 excluded 24% of patients who received 29mm Sapien 3 device (as this size is not available for Sapien 3 Ultra). The proportion of male patients treated with Sapien 3 is lower in Nazif et al. 2021 (58.1% in unadjusted analysis, 44% in propensity adjusted analysis) when compared with the UK TAVI Registry (92%). The EAG has reviewed the titles and abstracts of the remaining studies highlighted by the company: • Welle et al. 2021 (setting: US); prospective registry comparing Sapien 3 Ultra (n=101), and Sapien 3 (n=159). Follow-up 30 days. • Saia et al. 2020 (setting: Italy); observational single arm registry of Sapien 3 Ultra (n=139). Follow-up 30 days. • Costa et al. 2022 (setting: international); reported propensity matched analysis of Sapien 3 Ultra (n=683) and Evolut Pro/Pro+ (n=683; not reported exclusively). Follow-up 30 days. The EAG did include the study by Costa et al. 2024 which reported data from the OPERA registry up to 1 year (longer follow-up). • Rheude et al. 2020 (setting: Germany); reported propensity matched analysis of Sapien 3 Ultra (n=155) and Sapien 3 (n=155). Follow-up 30 days.

				There are extensive publications showing the benefits of SAPIEN 3 Ultra (vs. SAPIEN 3) – mostly on reduced PVL (or AR) – due to the "augmented" outer skirt feature. Studies specific to SAPIEN 3 ULTRA™ - Nazif et al 2021 - Real-World Experience With the SAPIEN 3 Ultra Transcatheter Heart Valve: A Propensity-Matched Analysis From the United States. Circ Cardiovasc Interv. 2021;14(9):e010543. - Welle et al 2021 - Effect of a fourth-generation transcatheter valve enhanced skirt on paravalvular leak. Catheter Cardiovasc Interv Off J Soc Card Angiogr Interv. 2021;97(5):895-902. - Saia et al 2020 - In-hospital and thirty-day outcomes of the SAPIEN 3 Ultra balloon-expandable transcatheter aortic valve: the S3U registry. EuroIntervention. 2020;15(14):1240-7. - Costa et al 2022 - Transcatheter aortic valve replacement with the latest-iteration self-expanding or balloon-expandable valves: the multicenter OPERA-TAVI registry. J Am Coll Cardiol Intv 2022 – In Press - DOI: 10.1016/j.jcin.2022.08.057 - Rheude et al 2020 - Transcatheter Aortic Valve Replacement With Balloon-Expandable Valves: Comparison of SAPIEN 3 Ultra Versus SAPIEN 3, JACC: Cardiovascular Interventions 2020; 13(22):2631-2638. - Cannata et. al, 2023 - One-year outcomes after transcatheter aortic valve implantation with the latest-generation SAPIEN balloon expandable valve: the S3U registry. EuroIntervention. 2023 Apr 24;18(17):1418-1427 Moreover, the predicted in-hospital mortality estimates for female are consistently higher than the ones for male, which was unexpected, as it is not aligned with the findings from the literature. Indeed, in the PARTNER 1A (Smith et al., 2011), PARTNER 3 trial (Mack et al., 2019),	• Cannata et al. 2023 (setting: 12 European sites); reported propensity matched analysis of Sapien 3 Ultra (n=496) and Sapien 3 (n=496). Follow-up 1 year. Due to its longer follow-up of propensity matched analysis of Sapien 2 and Sapien 3 Ultra devices, the EAG has added Cannata to the EAG report. However, the EAG consider that none of the remaining publications are of higher quality, or more relevant, evidence than that already summarised in the EAG report. The EAG found no significant difference in the odds ratio for in-hospital death between males and females (Table 23 in the updated report), with a point estimate OR of 0.57, after adjusting for the effect of other covariates in n = 3917 patients. The unadjusted rates across all records were 1.4% for males and 1.3% for females (n = 3819), which were not significantly different. Care is required in interpreting results of post-hoc subgroup analysis of trials. For example, in the PARTNER 1A trial, although the TAVI and SAVR arms were balanced across patient characteristics (including m/f), the risk factors between male and female participants in the TAVI arm were not necessarily balanced and were not accounted for in the sub-group analysis. The EAG's multivariate analysis includes much larger numbers of patients (approximately 4000 patients) and has accounted for the effect of known covariates.

				Denegri 2021 or Kuneman 2022 studies, female seem to have better clinical outcomes (survival) than male. As these and other parameters have a major bearing on the model and hence the outcome of the report, the EAG needs to account for the unexplained discrepancies and apparent reversal of results seen in the registry population and literature. These inputs have a major bearing on informing the model, so the EAG findings need to be properly validated.	
19	Edwards Lifesciences	85	5.3.1 Univariate Analysis	"***Differences in short-term hospital outcomes were identified between devices but should be interpreted with caution because they may be influenced by differences in the characteristics of patients receiving different TAVI devices, and not directly link to the TAVI device itself***." This conclusion is surprising as there is extensive literature that confirms the UK TAVI registry findings in term of lowest procedure duration with SAPIEN 3, lower incidence of Aortic regurgitation, need of permanent pacemaker and use of post implantation balloon dilatation – which are directly linked to the TAVI device used. These differences are important as they have been correlated to long-term mortality (AR, PPI). Evidence identifying differentiation of clinical outcomes among TAVI devices: - Senguttuvan et.al. 2023 - The safety and efficacy of balloon-expandable versus self-expanding transcatheter aortic valve replacement in high-risk patients with severe symptomatic aortic stenosis. Front Cardiovasc Med. 2023 May 25;10:1130354 - Durand E et al 2021 - Analysis of length of stay after transfemoral transcatheter aortic valve replacement: results from the FRANCE TAVI registry. H. Clin Res Cardiol. 2021 Jan;110(1):40-49.	See response to comment 9.

				- Tarantini G et al 2021 - Four-year mortality in women and men after transfemoral transcatheter aortic valve implantation using the SAPIEN 3™. Catheter Cardiovasc Interv. 2021 Apr 1;97(5):876-884. - Binder R.K.et al 2012 - Edwards SAPIEN 3 valve. EuroIntervention 2012, 8, Q83–Q87 - Chatfield A et al 2021 - Next-generation balloon-expandable transcatheter heart valve: the SAPIEN 3 Ultra valve. Future Cardiol. 2021 Aug;17(5):811-816Attinger-Toller, et.al. 2021 - Age-Related Outcomes After Transcatheter Aortic Valve Replacement: Insights From the SwissTAVI Registry. JACC Cardiovasc Interv. 2021 May 10;14(9):952-960. - Deharo, et.al. 2020 - Impact of SAPIEN 3™ Balloon-Expandable Versus Evolut R Self-Expandable Transcatheter Aortic Valve Implantation in Patients With Aortic Stenosis: Data From a Nationwide Analysis. Circulation. 2020 Jan 28;141(4):260-268.Guerreiro, et.al. 2020. Short and long-term clinical impact of transcatheter aortic valve implantation in Portugal according to different access routes: Data from the Portuguese National Registry of TAVI. Rev Port Cardiol (Engl Ed). 2020 Dec;39(12):705-717. - Okuno et. al. 2023 - 5-Year Outcomes with Self-Expanding vs Balloon-Expandable Transcatheter Aortic Valve Replacement in Patients with Small Annuli. JACC Cardiovasc Interv. 2023 Feb 27;16(4):429-440 - Schofer, et.al. 2022 - Risk-related short-term clinical outcomes after transcatheter aortic valve implantation and their impact on early mortality: an analysis of claims-based data from Germany. Clin Res Cardiol 2022 Aug;111(8):934-943. - Jørgensen, et.al. 2021- Eight-year outcomes for patients with aortic valve stenosis at low surgical risk randomized to transcatheter vs. surgical aortic valve replacement. Eur Heart J. 2021 Aug 7;42(30):2912-2919	

				- Costa, et.al. 2021 - Long-term outcomes of self-expanding versus balloon-expandable transcatheter aortic valves: Insights from the OBSERVANT study. Catheter Cardiovasc Interv. 2021 Nov 15;98(6):1167-1176. Welle, G.A., et al. Effect of a fourth-generation transcatheter valve enhanced skirt on paravalvular leak. Catheter Cardiovasc Interv 97, 895-902 (2021). Evidence demonstrating the link between PVL (AR) or PPI on long-term mortality: - Schofer et al. 2022. Risk-related short-term clinical outcomes after transcatheter aortic valve implantation and their impact on early mortality: an analysis of claims-based data from Germany. Clin Res Cardiol. 2022 Aug;111(8):934-943. - Takagi et al. 2016. Impact of paravalvular aortic regurgitation after transcatheter aortic valve implantation on survival. Int J Cardiol 2016 Oct 15:221:46-51. - Van belle et al. Postprocedural aortic regurgitation in balloon-expandable and self-expandable transcatheter aortic valve replacement procedures: analysis of predictors and impact on long-term mortality: insights from the FRANCE2 Registry. Circulation. 2014 Apr 1;129(13):1415-27.	
20	Edwards Lifesciences	91	Table 19	Summary of the longitudinal outcomes for patients from linked dataset (UK TAVI registry linked to HES). Please will the EAG provide the number of patients at risk at the different timepoints (30d, 6m, 12m, 18m, and 24m)?	Number at risk are reported in Kaplan-Meier figure 5-9.
21	Edwards Lifesciences	115	5.4.2.1 Balloon-	LANDMARK trial. To ensure the quality of studies are fully understood, it's important for the EAG to know that the protocol for this study was changed twice during the enrollment period and that the last trial protocol was published as a *Letter to the Editor* (Tobe et al. 2024) in	Protocol changes were published after EAG literature search, the EAG has critically appraised the LANDMARK study publication using the information available to them at the time of developing the report.

			Expanding	April 2024, immediately prior to the presentation of the results at EuroPCR 2024 (16 May, Paris, France). According to the initial protocol that was published in Am Heart J. 2021 (Kawashima et al. 2021), it was originally planned to have a 1:1 randomisation to Myval THV and contemporary THV series (including a stratification and equal allocation for each valve within the contemporary THV series, i.e., 50% SAPIEN THV series and 50% Evolut THV series). This means that the original study design allowed testing of the secondary hypothesis of the respective non-inferiority of Myval to SAPIEN THV series and Myval to Evolut THV series (i.e., direct comparison). In the updated protocol, the randomisation scheme remained the same. However, the equal allocation within the contemporary THV series (50% Sapien THV series and 50% Evolut THV series) was reported to have been removed. Accordingly, the direct comparison of Myval vs. SAPIEN/SAPIEN 3 Ultra and Myval vs. Evolut THV series was also removed. As a result, the non-inferiority of Myval was tested against a unique "pooled" group defined as contemporary THV series (SAPIEN and Evolut) – mixing balloon and self-expandable TAVI devices. Despite the updated protocol, the final allocation within the contemporary THV series was equal (384 contemporary THV: 189 SAPIEN/SAPIEN 3 Ultra and 188 Evolut). However, the full analysis comparing Myval vs. SAPIEN 3 / SAPIEN 3 Ultra only, has never been presented. The changes made to the protocol immediately before the release of the data and the clear inconsistency between what was reported and the actual allocation within the comparator group make it possible to question the transparency of results. It becomes clear that no conclusions can be derived from this study about the individual performance of Myval vs. SAPIEN or Evolut. Paradoxically non-inferiority can be achieved even if the test is superior to one control and inferior to the other.	

HealthTech Programme

Transcatheter heart valves for transcatheter aortic valve implantation in people with aortic stenosis: Late Stage

External Assessment Report, User Preference Report and economic model – Collated comments

22	Edwards Lifesciences	160	6.2.2 Clinical Parameters	Is “SAPIEN 3” a typographical error, or has this been used as the reference case, whereas every other reference case is SAPIEN 3 Ultra?	Thank you for highlighting this, this has been amended.
23	Edwards Lifesciences	208	Pubmed search	There appears to be no search for SAPIEN 3 or SAPIEN 3 Ultra which would have revealed data highlighted in comments 3,10, 11, 12 and 13	Both Sapien 3 and Sapien 3 Ultra were included in the UK TAVI Registry dataset which the EAG considered the most generalisable, therefore additional targeted searching was not conducted. See Final Protocol.
24	Edwards Lifesciences	277	VARC-3 endpoints	It is acknowledged that several of the VARC-3 criteria which could impact costs and resource usage are not captured and perhaps most importantly, Quality of Life improvements are also not recorded. QoL improvements should be one of the most important factors in considering technologies. Exclusion of data which informs these criteria from all data considered will not help to deliver technologies that matter most to patients	EAG has acknowledged lack of quality of life information in modelling.
25	Edwards Lifesciences	284	Patient characteristics	Data from HES and NICOR suggest that the ratio of non-elective cases is above 30%, considerably more than the number stated, and growing. This has a number of implications – patients who present as non-elective are associated with higher rates of co-morbidities and their care is made consequently more difficult; length of stay increases with non-elective cases and costs dramatically increase. For this report, it could mean that costs are understated in the model, but on a broader accessibility and equality basis, it could inform the importance of capacity enhancing innovations, such as TAVI, to commissioners so that resources can be maximised	Elective cases were reported in both the UK TAVI Registry and HES. For analysis of the linked dataset the “elective/non-elective” status was taken from the UK TAVI Registry. This clarification has been added to the methods section of the report (section 4.1.4).
26	Boston Scientific	N/A	N/A	Thank you for undertaking this work to trial your new approach to Late Stage Assessment. Having reviewed the documentation sent to us, we wish to raise a number of points which are detailed below.	

				Overall significant limitations within the analysis In the first instance we are concerned that the facts/data used in the assessment have highlighted some limitations in the approach used thereby creating uncertainties that we feel suggests the need to exercise caution in the interpretation of the results. We appreciate that these limitations have been described multiple times throughout the report by the ERG. Given this, and the fact this is a new methodology, we feel it appropriate to highlight our similar concerns. The limitations in the use of data/facts/evidence that we find to be the most significant include: • Potential confounders: These are not captured within the UK TAVI Registry, and therefore could not be adjusted for in the analysis, most notably, patient anatomy characteristics informing device choice. For baseline characteristics which were captured, some significant differences were observed between valves, such as sex and annular diameter. As confirmed by clinical experts and discussed in the scientific community, different valves are used for different patient characteristics. We feel that the absence of key factual patient specific information introduces a significant degree of bias into the assessment, and the clinical significance of any differences is uncertain. • Limitations of the registry itself: We welcome the use of real-world linked data. However, its analysis from the UK NHS is limited by data availability and completeness. The registry is self-reported and unvalidated and therefore we strongly believe that the absence of robust data limits the strength of conclusion which can be drawn.	

				• Statistical uncertainty: We agree with the EAG who advise caution in over interpreting results due to the fact that devices with a small number of patients in the UK TAVI Registry (including ACURATE neo2) automatically had a large degree of statistical uncertainty in the economic analysis caused by large variation in the Confidence Intervals, which therefore led to them having the lowest NMB. This is a major limitation of the model for decision making. We are concerned that this data is therefore insufficiently robust to be applied in this way and that it is factually incorrect to do so. • Published evidence: Evidence for the devices was not identified from systematic searching across all manufacturers and is therefore subject to bias. Given the importance of demonstrating clinical effectiveness in a range of clinical scenarios we are concerned this approach lacks the robustness required to make informed conclusions. As a result of these issues, and to reiterate the findings of the ERG, despite the quality of the analysis performed, it remains unclear whether specific TAVI device design features drive differences in clinical outcomes between TAVI devices.	
27	Boston Scientific	N/A	N/A	**Clinical choice** The data from the registry and feedback from the clinical experts underlines the important of clinical choice when it comes to TAVI device selection. This is emphasised several times in the EAR, and we wish to reiterate these points due to their importance. The report demonstrates that clinical characteristics are influencing device choice beyond what is currently concluded in the User Preference Report, and that choice remains essential: the UK TAVI Registry has shown that patient characteristics are significantly different (statistically and clinically)	

				between devices, meaning that clinical features are contributing to device choice. We feel that the fact the Registry was not able to capture all the factors that influence device choice is a critical issue that requires further consideration and should be taken into account by NICE when developing its recommendations. In particular, given the variety and potential applications between different devices, it is critical to recognise the importance of clinical choice.	
28	Boston Scientific	N/A	N/A	**Data volume and uncertainty in economic analysis** We note that, possibly due to time on the market, there are significant differences in uptake of the different valves included in the decision problem. For the valves which had no/minimal UK TAVI registry data, these valves were automatically excluded due to uncertainty. For valves that have slightly more registry data available, though are still used in much lower numbers (i.e. ACURATE neo2 and Navitor), the economic analysis was performed despite the lower sample numbers leading to uncertainty and therefore low possibility of NMB. We are very concerned that this method has resulted in an assessment that has not taken a consistent approach towards the different products being assessed. We are also alarmed that unlike Allegra, MyVal, Hydra and Trilogy, a NMB analysis has been performed on these valves despite the low chances of positive NMB. We appreciate that the EAG documents this issue multiple times in its report but feel this does not remove this important variation in approach. At the very least we would ask that the significance of this issue is flagged to the committee, and that any impact upon NMB does not result in penalisation of the use of these valves.	
29		106	N/A	**Associations between anatomies and complications**	See response to comment 9.

	Boston Scientific			We are very concerned that key information related to use of specific products has not been taken into consideration. This is primarily related to context and is illustrated in the following ways. As described several times by the clinical experts and ERG, clinicians may be more likely to use certain valves in particular patient types. In the case of ACURATE neo2, as observed in Table 17, the valve is used much more in females and in lower annular diameters. The benefits of ACURATE neo2 in smaller annuli has been confirmed with published evidence (Eckel et al, 2022 and Voigtländer et al, 2021). What is important to note here is how these characteristics may lead to higher complications such as the higher major vascular complications observed in the data: it is known that patients with severe aortic stenosis and smaller aortic annuli are at higher risk of adverse cardiovascular clinical outcomes after TAVI (Herrmann et al, 2024 and Leone et al, 2023). Indeed, this is explored further in the EAR, where the higher major vascular complications observed are thought to be a consequence of higher proportion of female patients being treated with ACURATE neo2, with smaller vessels and therefore increased risk of vascular complications. ACURATE neo2 has the lowest new permanent pacemaker rate after TAVI for self-expanding TAVI devices, as demonstrated in multiple clinical studies provided to NICE. As a result, ACURATE neo2 is often consciously selected for patients with known conduction disorders to prevent new permanent pacemaker implantations (Pellegrini et al, 2022 and Husser et al, 2019) (see comment 6 for further information). ACURATE may also be more frequently used in other more complex patient groups not captured by the UK TAVI Registry and therefore not discussed in the report. For example, in horizontal aorta, where high degree of aortic angulation does not lead to lower rates of device success, unlike with other self-expanding valves (Gallo et al, 2021). More broadly speaking, the clinical experts advised that statistical differences in in-hospital outcomes are likely related to unmeasured	The EAG has added the comparison of multiple TAVI devices to the EAG report (Voigtländer et al. 2021).

				confounders, where often the Sapien devices are the first line choice for straightforward anatomies, and other devices may be used for more complex cases. We are concerned that without this context being taken into account, incorrect assumptions may have been made about the risks associated with a particular valve. As a result, we feel greater caution should have been used in the interpretation of the results and request that this point is made much more clearly particularly in the executive summary and discussion. **References** Eckel C et al. Procedural Outcomes of a Self-Expanding Transcatheter Heart Valve in Small Annuli. J Clin Med. 2022 Sep 9;11(18):5313. doi: 10.3390/jcm11185313. PMID: 36142960; PMCID: PMC9502952. Gallo F et al. Horizontal Aorta in Transcatheter Self-Expanding Valves: Insights From the HORSE International Multicentre Registry. Circulation: Cardiovascular Interventions 2021; 14(9). https://doi.org/10.1161/CIRCINTERVENTIONS.121.010641 Herrmann HC, Mehran R, Blackman DJ, et al. Self-Expanding or Balloon-Expandable TAVR in Patients with a Small Aortic Annulus. N Engl J Med. 2024;390(21):1959-1971. doi:10.1056/NEJMoa2312573 Husser O. et al. Transcatheter Valve SELECTion in Patients With Right Bundle Branch Block and Impact on Pacemaker Implantations, JACC Cardiovascular Interventions VOL. 12, NO. 18, 2019	

				Leone et al. Clinical outcomes in women and men with small aortic annuli undergoing transcatheter aortic valve implantation: A multicenter, retrospective, propensity score-matched comparison. Int J Cardiol. 2023 May 15:379:16-23 Pellegrini C, Garot P, Morice MC, et al. Permanent pacemaker implantation and left bundle branch block with self-expanding valves - a SCOPE 2 subanalysis. EuroIntervention. 2023;18(13):e1077-e1087. Published 2023 Feb 6. doi:10.4244/EIJ-D-22-00558 Voigtländer L et al. Transcatheter aortic valve implantation in patients with a small aortic annulus: performance of supra-, intra- and infra-annular transcatheter heart valves. Clin Res Cardiol. 2021 Dec;110(12):1957-1966. doi: 10.1007/s00392-021-01918-8.	
30	Boston Scientific	168 and 171		**Uncertainties in economic modelling** Despite utilising the most appropriate source of data for the decision problem, the biases and data sparsity in some instances means that meaningful conclusions and decisions cannot be drawn from the economic model alone. The limitations linked to data sparsity are recognised by the ERG, for example: Page 168: *"The EAG note that Navitor and ACURATE neo2 have the lowest probability of having the highest NMB across all scenarios. However, the EAG would advise caution in overinterpreting these numbers, as this finding is likely a consequence of those two devices having the least amount of data entered into the registry (used to power the economic model) and therefore both have the largest uncertainty which translates in the model of having low probability of net monetary benefit, or negative NMB in some scenarios."*	

				And also on page 171: "*The EAG would consider that for ACURATE neo2 and Navitor the 0% probability of having the highest NMB… are likely a result of these two devices having a small number of patients in the UK TAVI Registry (compared to the other 4 devices) and therefore in economic modelling ACURATE neo2 and Navitor incorporates the greatest statistical uncertainty*." There are also limitations discussed in comment 4 around the selection of devices for specific anatomies. Multivariate regression was conducted to adjust for this, and it is unlikely that more could have been done to adjust for this variation, however as stated on page 101, this multivariate analysis accounted for patient characteristics that are known and measured risk factors, and is limited by the availability and quality of the data, and by the presence of unmeasured potential confounders. This reiterates the challenges associated with inherent selection bias when utilising the UK TAVI Registry. We therefore ask that where NMB is discussed, this is always done so in the context of these strong limitations associated with the modelling.	
32a	Boston Scientific	99	N/A	**Risk of PPI** We note that according to Table 20, ACURATE neo2 is the only self-expanding valve analysed which is not associated with a significantly higher risk of pacemaker implantation compared to balloon-expanding valves. This is supported by clinical expert experience (page 85) and the published evidence which shows PPI rates to be lower than other self-expanding valves (Baggio et al, 2023). As a result, ACURATE neo2 is selected by some physicians who are more at risk of conduction disturbances (Pellegrini et al, 2022 and Husser et al,2019), which may introduce a selection bias. This may explain why, when comparing self-expanding devices only, the difference in PPI between ACURATE neo2	

				and Evolut Pro+ is not statistically significant, whilst published trial data has shown statistically lower rates for ACURATE neo2 (Baggio et al, 2023). Despite these results, we feel that there are critical facts missing that would strengthen the EAR report if they were included. For example, page 99 notes that Evolut R, Evolut Pro+, and Navitor were all found to have increased odds relative to Sapien 3 Ultra. The fact that ACURATE neo2 is the only self-expanding valve analysed that is not associated with increased odds relative to Sapien 3 Ultra is not mentioned either in the text or executive summary is an important omission that we suggest should be included. Given patient preferences, and the additional healthcare cost associated with pacemakers, we request that a more accurate picture is presented. **References** Baggio S. et al. Comparison of Transcatheter Aortic Valve Replacement with the ACURATE neo2 versus Evolut PRO/PRO+ Devices. EuroIntervention 2023;18:977-986. DOI: 10.4244/EIJ-D-22-00498 Pellegrini C, Garot P, Morice MC, et al. Permanent pacemaker implantation and left bundle branch block with self-expanding valves - a SCOPE 2 subanalysis. EuroIntervention. 2023;18(13):e1077-e1087. Published 2023 Feb 6. doi:10.4244/EIJ-D-22-00558 Husser O. et al. Transcatheter Valve SELECTion in Patients With Right Bundle Branch Block and Impact on Pacemaker Implantations, JACC Cardiovascular Interventions VOL. 12, NO. 18, 2019	
32b		98	N/A	**Stroke**	

	Boston Scientific			We note that according to Table 20, ACURATE neo2 is the only valve not to be associated with a significantly higher risk of in-hospital stroke compared to the reference valve. This is of particular importance as Table 17 demonstrates that two thirds of ACURATE neo2 patients are female, yet page 98 correctly states that the published literature reports women undergoing TAVI have increased risk of stroke when compared with men. Due to the social and economic significance of stroke, we feel that the report has failed on page 98 to accurately document the lack of negative outcome compared to the reference valve for ACURATE neo2. We ask that this important fact should also be highlighted in the executive summary.	
33	Boston Scientific	17	Table 1	**Comments on and suggested changes to Table 1** <u>Mitigating coronary obstruction</u> We agree that mitigating coronary obstruction is a key consideration in subgroups. With regards to the theoretical consideration for valve design, the valve design can have an impact on coronary occlusion rates after TAVI and are increasingly a consideration alongside patient anatomy. The ACURATE neo2 device has an upper crown which moves down the native leaflets and prevents coronary occlusion (CO). CO rates after ACURATE implant have been observed to be rare (below 1%). <u>Preservation of coronary access</u> We would like to underline the fact that the designs of different supra-annular devices have different implications on coronary access after TAVI and redo-TAVI. ACURATE has a split-level design allowing coronary access based on the open upper cell design making coronary access easier and faster (Costa et al, 2024) Additionally ACURATE	Not factual inaccuracy, source of this table provided.

				neo2 allows preserving coronary access even after redo TAVI with an intra-annular TAVI device (Beneduce et al, 2024) <u>Young patients</u> As mentioned, it is paramount to select a first valve with good valve durability to avoid redo-procedures which may be complicated in the future. Proper initial valve selection may help to plan the patient journey regarding lifetime management. Especially for younger more active patients, a supra-annular platform with better haemodynamics may be more beneficial for the patient. Using for example the ACURATE neo2 in younger patients would provide easy revalving options with an intra-annular device (SAPIEN or MyVal) by still preserving coronary access after redo procedure (de Backer et al, 2023 and Vanhaverbeke et al, 2023). **References** Beneduce A, Khokhar AA, Curio J, et al. Impact of leaflet splitting on coronary access after redo-TAVI for degenerated supra-annular self-expanding platforms. EuroIntervention. 2024;20(12):e770-e780. Published 2024 Jun 17. doi:10.4244/EIJ-D-24-00107 Costa G, Sammartino S, Strazzieri O, et al. Coronary Cannulation Following TAVR Using Self-Expanding Devices With Commissural Alignment: The RE-ACCESS 2 Study. JACC Cardiovasc Interv. 2024;17(6):727-737. doi:10.1016/j.jcin.2023.12.015 De Backer O, Sathananthan J, Landes U, Danenberg HD, Webb J, Sondergaard L. Redo-TAVI with a balloon-expandable valve and the impact of index transcatheter aortic valve design. EuroIntervention. 2023;19(9):714-716. doi:10.4244/EIJ-D-23-00363 Vanhaverbeke M, Kim WK, Mylotte D, et al. Procedural considerations for transcatheter aortic valve-in-valve implantation in a degenerated	

				ACURATE neo prosthesis. EuroIntervention. 2023;18(17):1436-1438. doi:10.4244/EIJ-D-22-00740	
34	Boston Scientific	59	Table 7	**Additional recent evidence for inclusion** We suggest adding the following studies to the analysis on ACURATE neo2, all of which have only recently becoming available: 1. PRECISA registry Reference: Tébar D, Carrillo X, García Del Blanco B, et al. Experience with the ACURATE neo and neo2 transcatheter aortic valves in Spain. The PRECISA (PRospective Evaluation Complementing Investigation with ACURATE devices) registry. Catheter Cardiovasc Interv. 2024;103(6):1015-1022. doi:10.1002/ccd.31032 2. [redacted] (available to ERG/NICE if required) 3. Midterm durability of the ACURATE transcatheter aortic valve implantation system based on VARC-3 definitions Reference: Rück A, Shahim B, Manouras A, et al. Midterm durability of the ACURATE transcatheter aortic valve implantation system based on VARC-3 definitions. EuroIntervention. 2024;20(12):e781-e782. Published 2024 Jun 17. doi:10.4244/EIJ-D-23-01018	These studies have all been published after the EAGs literature search.
35		126	Table 26	**Suggested additional study**	These studies have all been published after the EAGs literature search.

	Boston Scientific			We suggest adding the PRECISA registry: this prospective comparative study was only recently published (April 2024) and therefore omitted until now. Reference: Tébar D, Carrillo X, García Del Blanco B, et al. Experience with the ACURATE neo and neo2 transcatheter aortic valves in Spain. The PRECISA (PRospective Evaluation Complementing Investigation with ACURATE devices) registry. Catheter Cardiovasc Interv. 2024;103(6):1015-1022. doi:10.1002/ccd.31032	
36	Boston Scientific	93-95	Figures 6-9	**Inaccuracies identified in the Kaplan Meier curves, Figures 6-9** • Figure 6: mislabelling of y axis, should read 'freedom from stroke' • Figure 7: mislabelling of title, remove 'mortality' • Figure 7, 8 and 9: mislabelling of y axis, should not be mortality and instead should be linked to the metric in question in respective figure titles	Thank you for highlighting this, these plots have been updated.
37	Boston Scientific	173		**Inclusion of strokes after discharge** We question whether it is appropriate for the model to include strokes observed after discharge as there is no way of knowing if these events are associated with the selected TAVI, and as the EAG recognises, late stroke rates could be influenced by an unmeasured confounder associated with valve choice.	Stroke after discharge is incorporated in modelling, as strokes increase the risk of mortality and have a utility decrement which influence accrued costs and QALYs. However, the impact is low - no difference in late stroke outcome was observed across 6 valves in multivariate analysis (see Table 24 of the updated report). Including late stroke in the model structure will also allow for future comparisons between valves, when more long-term data or data for other devices, may be available.
38	Meril Life Scienc	22 of 375	2 Technologies	In **Table 3: Differences between and within TAVI manufacturers based on Company data**, Company description of unique technology elements from their Request for Information (RFI) and company website is mentioned as "No difference with other technologies stated".	Added points 2-7 have been incorporated into Table 3 of the EAG report.

	es Pvt. Ltd			Please add the following details in this column- • Myval Octacor THV is recommended to be directly crimped on Navigator balloon delivery system prior to its introduction within the 14Fr Python Introducer Sheath • The size matrix of Myval Octacor THV includes conventional (20, 23, 26 and 29 mm), intermediate (21.5, 24.5 and 27.5 mm) and extra-large (30.5 and 32 mm) diameters • All sizes of Myval Octacor THV ranging from 20 mm to 32 mm are compatible with 14F Python introducer sheath • All diameters of an undeployed Myval Octacor THV may be fully retrieved from the 14Fr Python Introducer Sheath in case there is a difficulty in crossing the annulus. • The Myval Octacor THV retains the similar short, expanded frame height as that of its predecessor technology • Myval Octacor THV is manufactured from the same cobalt alloy (MP35N) as before for optimal radial strength and radiopacity. • Myval Octacor THV is a tri-leaflet valve manufactured using bovine pericardium tissue that is decellularized using Meril's proprietary AntiCa treatment. • Myval Octacor THV, has internal and external polyethylene terephthalate PET fabric skirt. The Navigator Balloon delivery system is the OTW system compatible to 0.035" TAVI guide wire and utilizes similar volume of saline:contrast solution for nominal expansion of an individual diameter Myval Octacor THV.	Point 1 has not been added as is a recommendation of use and not a unique technology element. Point 8 has not been added as all devices have a skirt or buff of either PET or animal tissue.
39	Meril Life Scienc	57 of 375	4.1.5 Included and	In **Table 5. Key studies for Myval Octacor (N=8 studies)**, Baumbach et al. (2024) reported 762 patients (ITT) at 30 days: 1. 381 in Myval THV Series (Myval THV: 336 and Myval Octacor: 32)	Thank you for your comment. This is not a factual inaccuracy, because the EAG used the device breakdown from the published Supplementary Material and did not state that this was ITT. We have added the

	es Pvt. Ltd		exclu ded studie s	2. Sapien 3: 108 3. Sapien 3 Ultra: 87 4. Evolut R: 71 5. Evolut Pro+: 116 (including Evolut Pro:106) 6. Evolut FX: 5 Please change the values as per 30 days ITT 1. 381 in Myval THV Series 2. 381 in Contemporary THV Series However, there were six subjects who were randomised but did not undergo randomisation due to death and one subject was implanted with non-study device. This accounts to 755 patients, including 15 cross-overs in the Myval arm and 5 cross-overs in the contemporary arm, who were treated with different generations of study devices summarised below: 1. Myval THV: 336 2. Myval Octacor THV: 32 3. Sapien 3: 108 4. Sapien 3 Ultra: 87 5. Evolut R: 71 6. Evolut Pro+: 116 (including Evolut Pro:106) 7. Evolut FX: 5	cross over detail to Appendix B1 but note that the supplementary material states 16 cross over in Myval arm and 5 in contemporary arm which includes the participant receiving the Portico device.
40	Meril Life Scienc es Pvt. Ltd	111 of 375	5.4.1 Qualit y appra isal	Myval Octacor (Meril) was used in 4 studies and a total of 576 patients (predecessor Myval was used in 5 studies including 419 patients) There is a discrepancy in the number of Myval Octacor THV and Myval THV used in the 5.4.1. section as compared to Table 5: Key studies for Myval Octacor (N=8 studies). The total number of valves as these 8 studies are as mentioned below:	The table of 10 publications was provided separately to the EAG on 12/07/2024: - Kilic et al. 2024, Moscarella et al. 2024, Ubben et al. 2024 were not published when the EAG did their literature search. Not factual inaccuracy. - Amat-Santos et al. 2023 is in Table Appendix B3.

				Myval Octacor THV was used in the three studies, total number of valves used was 156 Myval THV used was 826 However, there are 10 publications available which have not been included in this assessment, we have included these publications and updated table 5 accordingly and attached the same, we request you to consider the updated table and publications in this assessment report.	- Blasco-Turrión et al. 2022 reported on 11 patients with mitral valve-in-valve; which is out of scope for this LSA. - Moscarella et al. 2023 the majority (64/97; 66%) included mitral valve-in-valve; which is out of scope of this LSA. - Duplicate reference to Elkoumy et al. J Clin Med 2022. - Sanchez-Luna et al. 2023 included 113 patients with non-calcified aortic regurgitation; which is out of scope of this LSA. - Halim et al. 2023; Neth Heart J includes 120 patients with 30 day and 6 month follow-up. The EAG had included Halim et al. 2023; J Clin Med in the EAG report (same recruitment period, same hospital, assume same 120 complete data set but reports 91 propensity score matched patients comparing Myval and Evolut R with 12 month follow-up). The EAG has added the following papers to the report: - Elkoumy et al. 2022 which describes Myval in 68 patients with bicuspid valve, demonstrating an incremental benefit of this technology. To avoid confusion (as the EAG did not conduct a systematic search for evidence) the EAG has removed study and patient numbers from the report. The summary of the quality of evidence remains unchanged.
41	Meril Life Scienc	115 of 375	5.4.2.1 Balloon-	**Myval Octacor (Meril):** The non-inferiority RCT by Baumbach et al. (2024) compared Myval (n=379; combination of Myval n=336, Myval Octacor n=32, with the remainder crossover contemporary valve implanted, and 1 Portico device) with a contemporary TAVI group (n=	Thank you for your comment. We understand that the total number of devices in Supplementary Material is across both arms. Due to this we have removed “n” from Table 6 to improve clarity.

	es Pvt. Ltd		expanding	377; Sapien 3 n=108, Sapien 3 Ultra n=87, Evolut R n=71, Evolut Pro n=106, Evolut Pro+ n=10, Evolut FX n=5, with 5 patients having Myval implanted). Please change the values as per 30 days ITT 1. 381 in Myval THV Series 2. 381 in Contemporary THV Series However, there were six subjects who were randomised but did not undergo randomisation due to death and one subject was implanted with non-study device. This accounts to 755 patients, including 15 cross-overs in the Myval arm and 5 cross-overs in the contemporary arm, who were treated with different generations of study devices summarised below: 1. Myval THV: 336 2. Myval Octacor THV: 32 3. Sapien 3: 108 4. Sapien 3 Ultra: 87 5. Evolut R: 71 6. Evolut Pro+: 116 (including Evolut Pro:106) 7. Evolut FX: 5	
42	Meril Life Sciences Pvt. Ltd	117 of 375	5.4.2.1 Balloon-expanding	In **Table 24: Key comparative evidence for Myval Octacor or Myval (Meril) compared with other devices in Scope**, Baumbach et al. (2024) reported Myval or Myval Octacor (n=379) and Contemporary group; Evolut or Sapien series (n=377). Please update the above mentioned n counts Myval or Myval Octacor (n=384) and Contemporary group; Evolut or Sapien series (n=384).	Thank you for highlighting this, this has been amended to reflect the “n” reported in Table 1 baseline demographic of the Baumbach et al. 2024 study.

43	Meril Life Sciences Pvt. Ltd	118 of 375	5.4.2.1 Balloon-expanding	In **Table 24: Key comparative evidence for Myval Octacor or Myval (Meril) compared with other devices in Scope**, Moscarella et al. (2024) reported only few secondary outcomes at 2 years from the publications such as All-cause mortality, cardiovascular mortality, neurological events. Please add the remaining secondary outcomes at 2 years from the publications Major bleeding, structural valve deterioration, prosthetic valve thrombosis, prosthetic valve thrombosis endocarditis and redo procedure.	Tables have been simplified to restrict to those studies which compare more than 2 TAVI devices, and adjusted for confounding. Therefore, Moscarella et al. (2024) has been moved to Appendix B3.
44	Meril Life Sciences Pvt. Ltd	209 of 375	Appendix B1: Key evidence (N=42 studies)	The limitation was observed by the authors in the Baumbach et al. (2024) publication: 1. Inconsistencies in number of valves reported. 2. Comparator arm combined balloon- and self-expanding TAVI devices. 3. Both intervention and comparator arms included different generation TAVI devices. 4. Differences in NYHA, 6- minute walk test and SF-12 appear to compare each arm with baseline (not compared between arms). The number of valves at 30 days as per ITT are mentioned below: 1. 381 in Myval THV Series 2. 381 in Contemporary THV Series Please note that there was no inconsistency in the number of valves reported and equal allocation was performed between Myval and Contemporary THV Series and the generation of valves implanted in the randomised patients was purely based in the investigator's discretion Further, there were six subjects who were randomised but did not undergo randomisation due to death and one subject was implanted with non-study device. This accounts to 755 patients, including 15	Thank you for confirming that the generation of device was at the investigators discretion. The EAG has added this detail to the Appendix B1 table and amended the text.

				cross-overs in the Myval arm and 5 cross-overs in the contemporary arm, who were treated with different generations of study devices summarised below: 1. Myval THV: 336 2. Myval Octacor THV: 32 3. Sapien 3: 108 4. Sapien 3 Ultra: 87 5. Evolut R: 71 6. Evolut Pro+: 116 (including Evolut Pro:106) 7. Evolut FX: 5 In the LANDMARK Trial, the primary combined safety and effectiveness endpoint was assessed between Myval and Contemporary THV Series. The trial only compared the QOL and Functional improvement outcomes of the two arms at baseline and 30 days. The improvement in QOL and Functional improvement outcomes between the Myval THV Series and Contemporary valves group were similar in both the groups.	
45	Meril Life Sciences Pvt. Ltd	215 of 375	Appendix B1: Key evidence (N=42 studies)	Delgado-Arana et al. (2022) study setting was reported as European multicentre with not reported as number of centres. Please add the Nine European centres for number of centres in the Delgado-Arana et al. (2022) study setting	Tables have been simplified to restrict to those studies which compare more than 2 TAVI devices, and adjusted for confounding (see Section 5.2). Therefore, this change has been made to Delgado-Arana et al. (2022) in the table in Appendix B3.
46	Meril Life Scienc	218 of 375	Appendix B1: Key evide	Halim et al. (2023) study reported relevant secondary outcomes Please add the moderate or severe paravalvular leakage at 30 days in the Halim et al. (2023) study's secondary outcomes	Tables have been simplified to restrict to those studies which compare more than 2 TAVI devices, and adjusted for confounding (see Section 5.2). Therefore, this change has been made to Halim et al. 2023a has

	es Pvt. Ltd		nce (N=42 studies)		been moved to the table in Appendix B3 (secondary outcomes are not listed in this table).
47	Meril Life Sciences Pvt. Ltd	222 of 375	Appendix B1: Key evidence (N=42 studies)	Moscarella et al. (2024) study reported relevant secondary outcomes Please add the clinical efficacy at 1 and 2 years in the Moscarella et al. (2024) study's 1 and 2 years outcomes	Tables have been simplified to restrict to those studies which compare more than 2 TAVI devices, and adjusted for confounding (see Section 5.2). Therefore, Moscarella et al. (2024) has been moved to Appendix B3 (secondary outcomes are not listed in this table).
48	Meril Life Sciences Pvt. Ltd	231 of 375	Appendix B2: Critical appraisal of comparative studies that accounted for study population differences	In the appendix it is reported that the **Blinding of outcome assessment** was none with the authors' review judgement as High bias for the Baumbach et al. (2024) study. The clinical event committee (CEC) was masked to the treatment group in order to minimise potential bias as clearly stated in the discussion section page no.12 of the Baumbach et al. (2024) publication of the LANDMARK Trial. The independent statistician was also masked to treatment allocation until unmasking, performed the data analysis.	Thank you for this comment. We have added masking of clinical event committee and statistician to the risk of bias tool. The EAG note that the patients were not blinding, and whilst not possible to blind the TAVI operator (for obvious reasons) a number of patients received a non-protocol device (in both arms). Therefore the EAG has kept the assessment of performance as high.

			(N=14)		
49	Meril Life Sciences Pvt. Ltd	231 of 375	Appendix B2: Critical appraisal of comparative studies that accounted for study population differences (N=14)	In the appendix it is reported here that the **attrition bias** was none with the authors' review judgement as High bias for the Baumbach et al. (2024) study. We would like to bring to your notice that the attrition rate of 10% per arm was already assumed while calculating the sample size for the LANDMARK Trial. The actual drop-out rate was only 0.8% and the number of subjects with primary endpoint assessment was 381 in both arms. Therefore, it can be reported that there was no attrition bias for the Baumbach et al. (2024) study.	Thank you for this comment, the EAG has amended risk of attrition to low.
50	Meril Life Sciences Pvt. Ltd	231 of 375	Appendix B2: Critical appraisal of comparativ	In the appendix comment on the Baumbach et al. (2024) study was that there was Statistical differences for each arm with baseline (not between arms). In the LANDMARK Trial, the primary combined safety and effectiveness endpoint was assessed between Myval and Contemporary THV Series. The trial only compared the QOL and Functional improvement outcomes of the two arms at baseline and 30 days. The improvement in QOL and	Thank you for this comment, we have qualified this sentences to list the variables where analysis was restricted to comparisons with baseline (rather than between arms).

<table>
<tr><td></td><td></td><td></td><td>e studies that accounted for study population differences (N=14)</td><td>Functional improvement outcomes between the Myval THV Series and Contemporary valves group were similar in both the groups.</td><td></td></tr>
<tr><td>51</td><td>Meril Life Sciences Pvt. Ltd</td><td>249 of 375</td><td>Appendix B4: Excluded studies (N=59)</td><td>In the appendix the table on excluded study tabulated Myval Octacor’s study design as protocol

The report has rejected five studies as per Appendix B4: Excluded studies (N=59), we agree the rejection of three studies, however, please reconsider the two studies:
1. Revaiah et al. (2023)- study outcomes related to commissural alignment are mentioned in the paper
2. Santos-Martínez et al. (2020)- publication reported two patients’ in-hospital haemodynamic data.

Key studies for Myval THV/Myval Octacor Not included in the NICE Late-stage assessment report

<table>
<tr><th>Sr. No.</th><th>Author (Year)</th><th>Country (N Centres)</th><th>Study Design</th><th>Duration of follow-up</th><th>Total no of patients</th></tr>
<tr><td>1</td><td>Ignacio J. Amat-Santos,</td><td>India, Spain, Italy, Germany,</td><td>Multicenter registry</td><td>At 30-day follow-up</td><td>122</td></tr>
</table>
</td><td>Abstract only and limited information reported. Commissural alignment is stated as being collected, but not results reported. Additionally commissural alignment is not an outcome listed in the scope.

Santos-Martinez et al (2020) is a letter to an editor, and reports 2 case reports. Studies with larger sample size have been included in the EAG report (see Final Protcol). Study remains excluded, reason for exclusion expanded.</td></tr>
</table>

					et al. 2023[1]	Portugal, Denmark, The Netherlands, Poland (N=12)						
				2	Halim J, et al. 2022 [2]	The Netherlands (N=1)	Prospective, single-center study	At 6-month follow-up	120		Myval THV	
				3	Elkoumy A, et al. 2022[3]	India, Denmark, Italy, Croatia (N=12)	Retrospective study	At 30-day follow-up	68		Myval THV	
				4	Moscarella E, et al. 2023[4]	International sites (N=17)	Prospective, multi-center, international registry	At 1 year follow-up	97 [Aortic ViV (n=33), Mitral ViV (n=64)]		Myval THV	
				5	Blasco-Turrión S, et al. 2022[5]	Multicentre (N=5)	Retrospective, multi-center registry	At 6-month follow-up	11		Myval THV	
				6	Kilic T, et al. 2024[6]	Turkey, Italy, Greece, (N=4)	Multi-centre, registry-based, observational study	At 2-year	207		Myval THV	
				7	Sánchez-Luna JP,	Europe, USA and	International, multicentre,	At 1-year	113		Myval THV	

<table>
<tr><td></td><td></td><td></td><td></td><td>
<table>
<tr><td></td><td>et. al, 2023[7]</td><td>Asia Pacific (N=17)</td><td>observational study</td><td></td><td></td><td></td><td></td></tr>
<tr><td>8</td><td>UbbenT et. al 2024 [8]</td><td>Germany (N=6)</td><td>Investigator-initiated, multicenter, retrospective, observational study</td><td>30-day</td><td>134</td><td></td><td>Myval THV</td></tr>
<tr><td>9</td><td>Elkoumy A et. al., 2022[9]</td><td>India, Denmark, Italy, Croatia (N=12)</td><td>Retrospective</td><td>30-day</td><td>68</td><td></td><td>Myval THV</td></tr>
<tr><td>10</td><td>Moscarella E, et al. 2023 [10]</td><td>Italy (N=1)</td><td>Retrospective, single-center study</td><td>At 2-year</td><td>166 (Evolut R=108, Myval=58)</td><td></td><td>Myval THV</td></tr>
</table>
</td><td></td></tr>
<tr><td>52</td><td>Abbott Medical</td><td>27</td><td>2</td><td>“Beaver et al.(2023) reported 99.3% freedom from structural valve deterioration at 7 years
with a Resilia tissue surgical bioprosthesis (Edwards Lifesciences) from the
COMMENCE trial (NCT01757665).”

We do not believe that this study should be considered and request it is removed as a large cohort (28%) of population dropped out at 5 years.</td><td>Not factual inaccuracy.</td></tr>
</table>

53	Abbott Medical	30	2	*"The EAG note that 3 of the 11 TAVI devices included in the late-stage assessment are also currently indicated where mitral valves have also been replaced (Sapien 3, Sapien 3 Ultra, Allegra). While non-aortic valve replacements are out of Scope of this late-stage assessment (and therefore have not been explored further by the EAG), the EAG acknowledge that this may influence TAVI device choice, as an incremental benefit of a technology and may impact costs. For example, there may be fewer adverse events associated with valve interaction between the valve prostheses (Rogers and Thourani 2018; Salaun and Pibarot 2019)."* We do not believe the referenced literature supports the fewer adverse events statement and we request that it is removed. This reference states that "No significant difference in TAVR procedural success rates was found according to the type of THV (ie, balloon-expandable vs self-expanding). Thus, the choice of THV type should be made according to anatomical features and the experience of operators."	Thank you for your comment. The EAG acknowledges your observation and have removed the sentence and moved these references earlier.
54	Abbott Medical	35, 98	3	*"One Clinical Expert noted that several datasets show disproportionately lower implant rates in females and speculated that this is likely related to referral patterns and diagnostic tests (Appendix G)."* We believe this statement is true overall but is not proportional for all devices. Navitor's data shows that 54% of implants were in female patients and "One Clinical Expert advised that … women undergoing TAVI have increased risk of stroke when compared with men."	Not factual inaccuracy, summary of Clinical Expert opinion.
55	Abbott Medical	102	5	Earlier in the analysis there is mention of the difference in anticoagulation therapy across different valves. As anticoagulation therapy can impact stroke / major bleeding rates, we would recommend including medical therapy in Table 20 to see the correlation between anticoagulation therapy and stroke / major bleeding rates.	Thank you for this suggestion, additional confounders can be considered in future analyses.

HealthTech Programme

Transcatheter heart valves for transcatheter aortic valve implantation in people with aortic stenosis: Late Stage

External Assessment Report, User Preference Report and economic model – Collated comments

56	Abbott Medical	10	Executive summary	TAVI is also considered the standard of care for inoperable patients ("unsuitable for surgery" as per guidelines) not only high-risk patients for open surgery. It is also mentioned further in the text in Chapter 2 "Technologies"	
57	Abbott Medical	20	2	Due to the importance of access, we request you to consider adding the following columns to table 2: - "Indicated for transfemoral delivery" – yes/no - "Indicated for subclavian/axillary delivery" – yes/no	Added details from IFUs to table 3.
58	Abbott Medical	20	2	As Navitor size 35 is now approved, we request you to consider adding this to table 2 In line with comment 7 above and because Navitor size 35 is now available, we request you to change the "treatable annulus diameter range" to 19 to 30 in table 2	Not factual inaccuracy (this size is not available in the UK TAVI registry data analysed). However the EAG has added a comment to acknowledge the new size available.
59	Abbott Medical	143, 161	5, 6	*"This analysis demonstrated statistically significant differences in in-hospital outcomes (stroke, moderate or severe aortic regurgitation, pacemaker implantation) between 6 TAVI devices, but no statistical difference in out-of-hospital outcomes, at 1 year."* The comment above from page 143, is not reflected in 'predicted event proportions' data in Table 29. We are not clear how there can be *"no statistical difference in out-of-hospital outcomes, at 1 year.",* yet the predicated events proportions for one-year death are quoted at a much higher level for Navitor.	Please see the EAG's response to comment 5. There is no *statistical* significance since the hazard ratio crosses the boundary of 1; however the estimated risk of death for Sapien Ultra (reference) is 0.1373 or probability of survival is 1-0.1373 = 0.8627. From the model we know that the hazard ratio of death for Navitor compared to Sapien 3 Ultra is 1.68 so we need to take the exponent of the probability of survival i.e. 0.8627^1.68=0.7802, then to find the probability of survival 1-0.7802 = 0.219 or 21.9% as found in Table 27 in the updated report.

HealthTech Programme

Transcatheter heart valves for transcatheter aortic valve implantation in people with aortic stenosis: Late Stage

External Assessment Report, User Preference Report and economic model – Collated comments

<table>
<tr>
<td>60</td>
<td>Abbott Medical</td>
<td>161</td>
<td>6</td>
<td>In addition to comment number 8 above, the ‘predicted event proportions’ data in Table 29 does not show correlation with real-world Navitor specific outcome data extracted from the UK TAVI Registry, that was subsequently published (shown below). We would request that these data points are considered as they are a lot more consistent with what has been seen in UK clinical practice.

The Real-World United Kingdom Experience (UK TAVI Registry. Apurva H. Bharucha et al, Am J Cardiol 2024;222:23−28) and the OCEAN registry (Shinichi Shirai et al, JACC: Asia. 2024 Jul, 4 (7) 536–544), which represent real-world TAVI experience in UK and Japan respectively, offer insights beyond controlled clinical trials. These are non-sponsored real-world TAVI registries that demonstrated the following outcomes, that differ from those observed in the UK TAVI Registry:

<table>
<tr><th>Outcome</th><th>Real World UK TAVI registry (n = 574)</th><th>Ocean registry (n = 463)</th></tr>
<tr><td>Mortality</td><td>1.6% (30 day)</td><td>1.9% (in hospital)</td></tr>
<tr><td>Stroke</td><td>1.2%</td><td>1.3%</td></tr>
<tr><td>Vascular complication</td><td>1.6%</td><td>2.6%</td></tr>
<tr><td>Pacemaker post TAVI</td><td>11%</td><td>9.7%</td></tr>
<tr><td>≥Moderate PVL</td><td>5.1%</td><td>2.4%</td></tr>
<tr><td>Mean gradient post TAVI</td><td>7.7mmHg</td><td>8.3mmHg</td></tr>
</table>
</td>
<td>Please see the EAG’s response to comment 5.

The two papers cited were published after the EAG literature searches:
- Bharucha et al. 2024 reported a retrospective single arm cohort of 574 patients treated with Navitor across 6 high-volume UK centres between January 2020 and May 2023. The EAG’s analysis of data from the UK TAVI Registry (for procedures between 01 April 2021 and 31 March 2023) prior to data linkage included 260 Navitor patients (see Table 3 of EAG report) and found higher proportions than that reported by Bharucha et al. 2024 for in-hospital death (2.7%), stroke (3.5%), major vascular complication (2.5%), permanent pacemaker (15.8%).

- Shinichi Shirai et al. 2024 reported a prospective registry of 463 patients in Japan treated with Navitor between April 2022 and May 2023. The EAG note that the population treated had a lower proportion of male patients (30.3% compared with the linked UK TAVI Registry data 42.6%), older (median [Q1,Q3] of 86 [82,89] compared with 83 [78 to 86] years), and had lower proportion with NYHA class III or higher (28.7% compared with 73.9%). The EAG would consider that results from this single arm study are not generalisable to the UK NHS.</td>
</tr>
<tr>
<td>61</td>
<td></td>
<td>186, 189, 188</td>
<td>7, 8</td>
<td>In the ‘Summary of economics (using Real World Evidence from UK)’ column for Navitor it says “0% probability of highest NMB at £20,000WTP (likely related to lack of data in registry with available data</td>
<td>Sentence removed.</td>
</tr>
</table>

	Abbott Medical			*reporting less favourable results (possibly purely by chance). Hence, even with the wide confidence interval on event probabilities which might allow some chance of the device having the highest NMB, the device has not performed well."* The text in page 189 goes on to acknowledge the limitations of this analysis by stating *"The results were influenced by the prevalence of use of each TAVI device in the NHS, with those used less frequently rarely achieving the highest probability of net monetary benefit. This may be an artifact of the sparser data or reflective of the relatively poorer performance of these devices".* Considering the acknowledgement of these limitations, it could be that Navitor performs poorly (which would contradict the available evidence for the valve) or most likely it is due to the limitations of the data and the analysis which has been performed on this data. Due to this point and with this uncertainty, we do not think it is justified to say that *"the device has not performed well"* and we request that this wording is removed.	
62	Abbott Medical	10 – 13	Executive Summary	*"The EAG considered that there was a high risk of bias across the included published evidence, which casts further uncertainty on the robustness of the conclusions that can be drawn from them."* *"The analysis may be influenced by unmeasured confounders that cannot be adjusted for."* *"Some patient characteristics (such as surgical risk group, calcium burden and distribution, aortic valve and left ventricular outflow tract) that influence device selection could not be adjusted for because they are not currently recorded in the Registry."* *"The published evidence comparing TAVI devices is subject to bias and limited by short term follow up, whereas the analysis of real-world linked*	

				data from the UK NHS is limited by data availability and completeness and subject to different biases, but is still the best available data for the decision problem." *"As the Registry does not capture sufficient detail of the clinical characteristics that contribute to device choice, the EAG analysis needs to be interpreted carefully and draw upon other evidence such as that generated by a multi-criteria decision analysis exercise to determine whether pricing variations between devices is justified."* *"The aim of this late-stage assessment is to evaluate the evidence available for these devices to support procurement and commissioning decisions."* We strongly agree with all the above comments and although we see the value and importance of this exercise and the need for value-based commissioning within the NHS, due to the number of significant limitations, gaps and uncertainties, we do not believe that the outputs of this document are suitable to support procurement and commissioning decisions. Procurement and commissioning professionals tend to work across a broad spectrum of product portfolios and may look for the headline information without taking time to understand these limitations and ensure that it is "interpreted carefully". For this reason, we would encourage careful consideration on the value of the report in its current form and propose careful consideration be given to the impact it might have on critical topics such as patient access in the context of the many limitations.	
63	Abbott Medical	98	5	*"in-hospital aortic regurgitation: Evolut R, Evolut Pro+, ACURATE neo2, and Navitor were all found to have increased odds relative to Sapien 3 Ultra. Extensive calcification of ascending aorta (which may be considered as a surrogate marker of aortic valve calcification), patient*	This was chosen as a surrogate marker, as advised by the Clinical Lead of the UK TAVI Registry. The draft report was reviewed by several clinical SCMs who did not challenge this assumption. No change required.

				height, and mean valve gradient were associated with increased odds. Weight was associated with decreased odds." We do not believe that using 'extensive calcification of the ascending aorta' as a surrogate measure for aortic valve calcification is accurate and believe that this should be reconsidered.	
64	Abbott Medical	13, 99, 144, 188	Executive Summary, 5	*"Although Clinical Experts have suggested that centres may have one preferred TAVI device they use wherever possible, the UK TAVI Registry has shown that patient characteristics are significantly different (statistically and clinically) between devices, meaning that clinical features are contributing to device choice."* *"Two Clinical Experts advised that statistical differences in in-hospital outcomes are likely related to unmeasured confounders. One explained that in their centre, the Sapien devices are the first line choice for straightforward anatomies, and that Evolut devices would be used for more complex cases; which may explain the higher stroke and AR rates. The other confirmed that major confounders, mostly anatomical or patient characteristics, that affect decision making, are not captured in the Registry."* *"As indicated by the exploratory analyses conducted by the EAG, there is evidence to suggest that differences in outcomes between TAVI devices may be a consequence of different patient populations or being treated with different manufacturer TAVI devices. Therefore, the clinical evidence, including the analysis of short-term (in-hospital only) and medium-term (up to 31 month) outcomes from this real-world data which can only adjust for recorded confounders, and review of published evidence which does not adjust for population differences, should be interpreted with caution during the decision-making process."* *"The clinical significance of the these differences remains uncertain. Clinical Experts advised that differences seen may be related to device*	

				selection in patients with certain characteristics which are not recorded in the UK TAVI Registry." We believe that device choice based on clinical features leads to an unfair comparison in devices. Some patient characteristics will inherently lead to greater rates of complications and therefore devices used for patients with these characteristics have a disadvantage in a head-to-head comparison if results are not adjusted to account for this.	
65	Abbott Medical	14, 104	Executive summary, 5	*"Data entry to the UK TAVI Registry is mandatory for all TAVI procedures conducted in England, Wales and Northern Ireland but it does not collect all clinical information that may inform decision to proceed to TAVI, or choice of TAVI device (for example surgical risk, anatomy, valve morphology). This means that use of real-world evidence incorporates confounding by indication which cannot be adjusted for in either the clinical effectiveness or health economic analysis (see also Key Issue 8)."* *"The EAG adapted the economic model from NG208 to permit multi-way comparisons between TAVI devices, however requires extrapolation of short-term data and the parameter values in the economic model do not account for all potential differences in clinical effectiveness (for example, quality of life), between TAVI devices that were not available from real-world data (see also Key Issue 3)."* *"Data entered into the UK TAVI Registry is self-reported and unvalidated. The data quality of TAVI device model recording was poor within the registry. This required each manufacturer to verify serial numbers to confirm which device model was used. Outcomes captured in the registry post-discharge are restricted to quality of life measures which were almost entirely incomplete in the registry data received by the EAG."*	

				"However, the death model has the lowest concordance (0.663), which suggests that whilst the model has some predictive capability, it is lacking. Further modelling would look to include more patients and include a richer dataset which may include variables that the EAG was unable to obtain from the UK TAVI Registry." We strongly agree with all the above comments regarding the TAVI registry and believe that these highlighted "key issues" could be a major cause of inaccurate outcomes from the review.	
66	Abbott Medical	185	7	As the aim of the exercise is to *"support procurement and commissioning decisions."* we do not believe that the tables should be colour coded as they are. This traffic light system could cause confusion and lead to individuals who do not have time or interest in reviewing the documents in more detail to choose and/or see incremental value in a device purely based on the section(s) highlighted in green.	
67	Abbott Medical	168, 171		*"The EAG note that Navitor and ACURATE neo2 have the lowest probability of having the highest NMB across all scenarios. However, the EAG would advise caution in overinterpreting these numbers, as this finding is likely a consequence of those two devices having the least amount of data entered into the registry (used to power the economic model) and therefore both have the largest uncertainty which translates in the model of having low probability of net monetary benefit, or negative NMB in some scenarios."* *"The EAG would consider that for ACURATE neo2 and Navitor the 0% probability of having the highest NMB (consequence of both having the lowest NMB which in turn was driven by having the lowest QALYs per patient) are likely a result of these two devices having a small number of patients in the UK TAVI Registry (compared to the other 4 devices) and*	The EAG has reported its analyses and stated the limitations of its approach. The interpretation of the report and its translation into advice for clinicians and commissioners is a matter for the committee and for NICE. No change required.

				therefore in economic modelling ACURATE neo2 and Navitor incorporates the greatest statistical uncertainty." This is a very important point, and it is not clear in the results section. It is highly unlikely that procurement and commissioners are going to have the time or appetite to read all 375 pages of the document and will likely focus on the results. Due to this, we suggest that this "*caution in overinterpreting these numbers"* is made clearer in the results section. We wish for you to consider what potential implications could be caused by putting information that requires "caution in overinterpreting" into the public domain, to be used by individuals who may not understand the therapy and/or complexities of the clinical data and analytical models applied.	
68	Medtronic UK Ltd	Summary		Thank you for the opportunity to comment. Given the volume of published data for TAVI, we acknowledge the complexity of the task assigned to the EAG in this pilot late-stage assessment. Regrettably though, the EAG report as it stands does not consider the hierarchy of evidence appropriately due to sole reliance on UK registry data and is therefore not reliable for committee decision making. If procurement decisions by NHSC were to be based on it, we would have significant concern for the adverse impact on patients with Aortic Stenosis in the NHS In summary of our comments, please see below some suggestions for alternative assessment methodology that we feel would better align with NICE Process and Methods; ultimately allowing the EAG to present the body of evidence and economic models in a more suitable manner, enabling the NICE committee to make well-informed recommendations and ultimately driving evidence-based national procurement decisions:	

				1. Perform systematic literature review of the evidence and identify all RCTs comparing TAVI valves, both versus SAVR and versus other TAVI valves. Do not exclude studies based on patient risk group (low, intermediate or high) as this should be a decision made by the committee, not the EAG. 2. Perform independent and in-depth assessment regarding the evolution of TAVI valve platforms in terms of the design features; both what has changed and what has remained the same. Use experts to define which outcomes are likely to have improved as a result of these design changes, and which are not. 3. Assess the feasibility to perform network meta-analysis with careful consideration regarding the different inclusion/exclusion criteria and patient populations between trials. 4. Perform cost-effectiveness analysis (CEA) for each of the trials. Use NHS data to account for changes in implant technique or changes in NHS practice (e.g. length of stay). 5. Where available follow-up periods are limited (some RCTs have 10-year follow up where others only have 30-day follow-up), account for this uncertainty within the economic modelling. 6. In scenario and sensitivity analyses, use the published data on newer generations of TAVI valve to explore the outcomes that are likely to have changed or improved over time. 7. Use the UK TAVI registry analysis for complementary/ validation purposes only and ensure two separate models are developed: one comparing BEVs versus BEVs and one comparing SEVs versus SEVs. In light of the above significant concerns and additional analysis needed, we suggest that an updated EAR should be produced to better inform committee decision making and development of draft guidance.	

				We look forward to receiving the draft NICE guidance taking into account our comments and those of other stakeholders, and making recommendations in compliance with competition law.	
69	Medtronic UK Ltd	General		**The sole reliance on linked registry data in preference to published RCTs (which were excluded by the EAG based on risk of bias) is a significant deviation from NICE Process and Methods, and the NICE real world evidence framework which state RCTs as the preferred study design. We ask the Committee to consider that the outcomes from this registry analysis are not reliable for model input or Committee decision making due to potentially critical bias as outlined below.** The EAG acknowledges the limitations of their analysis: *"…the analysis of real-world linked data from the UK NHS is limited by data availability and completeness and subject to different biases but is still the best available data for the decision problem" [EAG report p13]. "**The EAG advise caution in interpreting the economic analyses in isolation".*** **NICE Process and Methods [PMG36)** states: *to ensure that the guidance issued by NICE is appropriate and robust, the evidence and analysis, and their interpretation, must be of the highest standard possible and transparent" and "for relative treatment effects there is a **strong preference for high-quality randomised controlled trials (RCTs)**. Non-randomised studies may complement RCTs when evidence is limited or form the primary source of evidence **when there is no RCT evidence**".* **NICE real-world evidence framework** state*s: randomised controlled trials are the preferred study design for estimating the causal effects of interventions. This is because randomisation ensures that any differences in known and unknown baseline characteristics between groups are because of chance.*	The comment is directed at the Committee, not the EAG. Within the report, the EAG has explained its reasons for using real-world evidence to address the decision problem of this late-stage assessment.

				*The framework also states that real-world data can be used to **contextualise randomised trials**, to **estimate effects of interventions in the absence of trials**, or to **complement trials** to answer a broader range of questions about the impacts of interventions in routine settings.* It would be expected, in accordance with the NICE Methods, for a network meta-analysis to have been considered by the EAG if appropriate matching methods are identified for the indirect treatment comparison of TAVI vs SAVR and/or TAVI vs. other TAVI: *Section 3.4.11 "Indirect comparisons and network meta-analyses. When technologies are being compared that have not been evaluated within a single RCT, data from a series of pairwise head-to-head RCTs should be presented together with a network meta-analysis if appropriate"* however the EAG has determined that retrospective, unvalidated and incomplete TAVI registry data, combined with HES and ONS, is the best available data for the decision problem because the published evidence comparing TAVI devices is "subject to bias and limited by short term follow up". The EAG multivariate analysis of retrospective registry data is also subject to potentially critical bias, due to its retrospective nature, unmeasured confounders and patient characteristics that were not adjusted for. HES data also has significant limitations and is reliant on the accuracy of discharge coding. Essential data elements are missing from the registry. The EAG analysis recognises the following limitations [P65 EAG report]: • confounders that could not be adjusted for in the analysis: surgical risk group, patient anatomy characteristics, medication prior to procedure, operator learning curve / level of experience.	

				• patient anatomy characteristics informing device choice (for example, challenging vascular access, tortuosity, aortic valve and left ventricular outflow tract calcium burden and distribution) was not included. **We ask the Committee to note that there is a better chance of eliminating bias in RCTs than in registries.** The critical difference in the RCTs is that unmeasured confounders are equality distributed in both treatment groups. Proper performance of pivotal RCTs has formed the platform for FDA regulatory device approval in the US – in the view of the FDA, single arm registries have not provided sufficient evidence for demonstration of safety and efficacy for TAVI. As a result, RCTs are required for regulatory approval in the US; 6 prospective, large scale RCTs have been performed; 3 comparing Sapien with surgery and 3 comparing CoreValve Evolut with surgery over the past decade and published in NEJM. These pivotal RCTs have been excluded from this analysis. RCTs have provided additional trial oversight to mitigate bias, including: • Patient selection committees to ensure that appropriate patients were included in the study. • Internationally recognised study principal and clinical site co-principal investigators to provide technical expertise on the procedure. • Independent Clinical Event Committee for primary and secondary event adjudication. • Data and Safety Monitoring Committees to provide trial oversight for trial compliance and safety. • Echocardiographic Core Laboratories to provide long term hemodynamic comparison.	

				• High levels of adjudicated (approximately 90%) follow-up to 5 years after the procedure. The UK TAVI Registry does not include surgical risk, external adjudication, or extended clinical follow-up, these factors are very important to understand overall validity of the data and assessment of outcomes. Of these missing factors, surgical risk and its surrogate of STS PROM or EuroScore are the most critical factor in understanding late outcomes Whilst we acknowledge the value of real-world evidence to complement RCT findings, we suggest that, due to the substantial limitations and risk of bias in registry and HES data, the current multivariate analysis is not reliable for decision making on relative treatment effects of different TAVI valves and **ask that the EAG conduct an analysis incorporating the published RCTs.** We believe that the totality of the RCT evidence comparing TAVR and surgery (i.e.,PARTNER 1a, 2a, 3, CoreValve High Risk, Intermediate Risk, Low Risk with Corevalve/SAPIEN), and the results of smaller RCTs that randomized patients to either Sapien or CoreValve/Evolut (i.e.,CHOICE, SOLVE TAVI, SMART) demonstrate that the early (1 year) and later (5 year) mortality rates are similar or lower with CoreValve/Evolut than Sapien. All-cause mortality incorporates the totality of adverse procedure events (PVL, pacemakers with CoreValve/Evolut and higher gradients, thrombus, stroke with Sapien). Based on the totality of the RCT evidence, there should be parity in all-cause mortality with Sapien and Evolut in the proposed economic models.	
70				**We recommend the EAG perform a systematic literature review and consider the level of evidence available for each TAVI valve**	LSA Interim process and methods guide permits pragmatic searches.

	Medtronic UK Ltd			**platform (1st and current generation valves), for example by updating the search from NG208.** Medtronic is concerned that the EAG did not perform a systematic search and instead relied upon the companies to provide all evidence. We approached our initial submission under the assumption that standard HTA methods would be applied yet the lack of systematic search and limited regard for hierarchy of evidence demonstrates these standard approaches have not been followed. We strongly recommend that a systematic search is performed to ensure all evidence is captured in a non-biased fashion. It is critical that the EAG consider the Level of Evidence provided when evaluating the clinical evidence base for different TAVI devices. Sole reliance of the UK TAVI Registry would place the evidence at Level B for the ESC Guidelines. Criteria for Level of Evidence were provided with the ESC/EACTS Valvular Guidelines (Vahanian 2021 European Heart Journal) Level 1: Data derived from multiple randomized clinical trials or meta-analyses. Level 2: Data derived from a single randomized clinical trial or large non-randomized studies. Level 3: Consensus of opinion of the experts and/or small studies, retrospective studies, registries. Accordingly, we respectfully request that the Level of Evidence generated by multiple large-randomised trials be considered as well (Level of Evidence A) in addition to the UK TAVI Registry.	

HealthTech Programme

Transcatheter heart valves for transcatheter aortic valve implantation in people with aortic stenosis: Late Stage

External Assessment Report, User Preference Report and economic model – Collated comments

71	Medtronic UK Ltd	Protocol p9		**We recommend that SAVR is reinstated as a relevant comparator as discussed during the scoping workshop and published in the scope** The inclusion of SAVR as a comparator was discussed at the scoping workshop and it was agreed that, given the body of evidence for TAVI, it was important to include. The availability of RCT data in its totality is important for the overall assessment of quality of evidence and valve performance in the longer term. It was also discussed that new data has been published for low-risk patients since NG208 and so the NG208 cost-effectiveness models could be updated with contemporary data as well as assessing how different TAVI valves perform in economic modelling versus SAVR in these patient populations.	Not factual inaccuracy on the LSA report, as this comment refers to the published protocol. The agreed decision problem is based on selection of TAVI (when a clinical decision has been made that TAVI is appropriate); the role of LSA is not to repeat analysis of NG208 to determine cost-effectiveness of TAVI versus SAVR. Clinical Experts have advised that uptake of TAVI in surgically low-risk patients remains low in the NHS. SAVR is included in the model as a treatment that patients may subsequently experience, to resolve complications. No changes made.
72	Medtronic UK Ltd			**Some of the statistical methods within the EAG analysis of the UK TAVI registry should be improved/ addressed.** 1. We believe that the use of complete cases for modelling is a substantial weakness of the analysis. This means that every patient had to have complete data on 19+ fields; a single missing field would exclude the entire record from the analysis. It is established that complete case analysis generally leads to biased inference unless data are missing *completely* at random (Knol et al. 2010) - this assumption is very unlikely to hold in the registry data, and the resulting bias will propagate into the economic model. The EAG have acknowledged this weakness, but we believe it has not been fully addressed via the brief acknowledgement in the report, and we believe that this should have been explored in more detail with alternative models and assumptions. We have a number of further comments around the issue of missing data: a. Even if the missing at random assumption does not hold, multiple imputation would have likely reduced bias	1a. Not a factual inaccuracy. This could be explored to determine the impact on analysis if the committee so wishes. 1b. The numbers of data points available for each row in tables are given in the tables themselves, which should give an indication of the fields most likely to contribute to exclusion of procedures from the complete case analysis. Where specific data fields had high levels of missingness, they were not selected for inclusion in the cleaned dataset and tables, or the multivariate analysis. 1c. Data was designated as “missing” if it was entered as “Unknown” or the field was left blank. “Missing” as a response itself is not an option, in line with the data fields specification for the UK TAVI Registry, available online. The EAG agree that leaving a field blank could constitute “not present” but considers it less likely when a suitable option (that is, “unknown”) is available

				versus the complete case approach taken. An argument was made by the EAG for not using multiple imputation methods, but ignoring a large chunk of the registry data leaves the analysis open to bias. We believe multiple imputation should be attempted rather than discarding records with missing data. b. Missing data in the NICOR registries can be driven by one or two key fields (e.g., PA systolic, eGFR had considerable missingness in the Adult Cardiac Surgery registry). It would be helpful to understand which variables in the complete cases analysis drove the high number of subjects excluded from the original dataset. c. Some sites / implanters may be using missing as a proxy for "not present" based on our experience with site database managers. This was one of the reasons several fields were automatically imputed in other NICOR registries (Hickey et al. 2013). 2. Ideally, the regression models should account for site-level variation using random effects modelling (or other equivalent statistical methods). One of the aspects that NICOR leads is the reporting of healthcare provider outcomes, and even after adjustment there can be big differences (Hickey et al. 2014). This is important here because sites (or consultants) often have certain purchase agreements with companies. 3. All regression adjustment and extrapolation methods are susceptible to bias in the presence of unmeasured / unadjusted confounders, and in TAVR there are many. We have a number of comments regarding the approach taken here: a. We believe the ***single*** regression approach taken is problematic because the EAG assume the same predictors for each outcome – that is not necessarily going to be true. b. Not allowing for interaction terms with valve model means that it is assumed a constant level of risk in each	for selection. The EAG has clarified its treatment of missing data in section 5.3.1 Quality appraisal. 2. The EAG acknowledges potential variation at the level of NHS Trusts, sites, and individual operators, but the assessment of these falls outside of the scope of this work, which was to compare TAVI devices themselves to support procurement decisions in the NHS, and by maintaining focus on this, the results remain as generalisable as possible to the NHS. The EAG acknowledges that using mixed effects models to account for potential loss of independence for cases from the same centre is an alternative approach, but not a matter of factual accuracy. 3a. The EAG was advised by a Clinical Expert that the subset of key variables were potential confounders in all outcomes of interest. In addition, for the economic model it was required to use predictions from several regression models simultaneously (one for each clinical parameter), thus requiring that the regression models were trained on the same data set, with the same covariates. 3b. The EAG acknowledges that adding interactions between covariates (not limited to valves) may improve model fit, but at the expense of complexity of interpretation. Not a matter of factual inaccuracy. 3c. Propensity score methods risk the introduction of bias and diminished statistical power in studies with rare outcomes (Wilkinson et al. 2022). Matching would have risked discarding further data for unmatches. 4. Annular diameter was included as a covariate in the model

				valve cohort for the baseline measures. This might not be true for anatomical measures. c. One benefit of propensity score adjustment (whether matching, IPTW, etc.) is that overfitting is less of a concern. Here, we are restricting adjustment to these 19 fields only. Propensity adjustment would have been a worthwhile approach to explore. 4. Valve size was included as a covariate in the multivariate model. However, it is not appropriate to categorise by size which is not interchangeable between valves given the difference in design, notably supra versus intra annular. As published by Hahn et al (2019), valves should be compared based on the native patient annular size and resulting mean gradient and effective orifice area post implantation. Hahn et al reported for all Evolut R valve sizes, the mean EOA was 2.01cm ^{2} with a mean gradient of 7.52 mm Hg. Comparatively For all SAPIEN 3 valve sizes, the mean EOA was 1.66 cm ^{2} with a mean gradient of 11.18mm Hg. Post-implant EOA were progressively larger for each quintile of baseline annular area for both valves, however when compared on the native annular size, Evolut R implantation conferred a superior valve performance versus Sapien 3. 5. There are various modelling assumptions that we think need to be assessed more formally: a. (Multi)collinearity (especially with regard to valve size vs. Annular diameter). b. The linearity of continuous measures (for example, weight is not usually linear, but can be U-shaped). c. Proportional hazards for the Cox proportional hazards regression models.	5a) Correlation between covariates was explored in Figure 10 and no significant correlations were found. b) Whilst it is possible that annular diameter and valve size are correlated collinearity would only inflate estimated variance between those two variables. Assumption of linearity is in log space i.e. assumption is that the continuous variables are linear with respect to odds, which was verified through inspection of plots. c) Proportionality assumptions of each Cox proportional hazards model were assessed through inspection of scaled Schoenfield residuals. 6. The EAG considered it appropriate to censor patients at reintervention, such that any adverse outcomes reported were as a result of their first TAVI procedure only. It is acknowledged that adverse events are more likely following a reintervention, and because the device used for the reintervention would not be known, the EAG did not want to risk unfairly attributing adverse events following reintervention to the original TAVI device used. Furthermore, reintervention is such a rare event in itself that any further deaths would likely have negligible impact on results. 7. Wide confidence intervals reflect rarity of events and hence uncertainty in the estimates.

				6. We do not agree that patients should be right-censored for events such as mortality at the time of reintervention, as this will lead to loss of signal from post-reintervention deaths. 7. Some of the hazard ratios presented in Table 23 are implausibly large (e.g., nearly 500 million for 'valve size – large'; hazard ratios of 0 with infinite confidence intervals). These results strongly suggest that the models have not adequately converged and should be refit. In some cases, there are such small event rates (i.e., insufficient data) that the models proposed should not be fitted at all. **References** • Hickey, Graeme L, Stuart W Grant, Rebecca Cosgriff, Ioannis Dimarakis, Domenico Pagano, Arie Pieter Kappetein, and Ben Bridgewater. 'Clinical Registries: Governance, Management, Analysis and Applications'. European Journal of Cardio-Thoracic Surgery 44, no. 4 (2013): 605–14. • Hickey, Graeme L, Rebecca Cosgriff, Stuart W Grant, Graham Cooper, John E Deanfield, James C Roxburgh, and Ben Bridgewater. 'A Technical Review of the United Kingdom National Adult Cardiac Surgery Governance Analysis 2008-11'. European Journal of Cardio-Thoracic Surgery 45, no. 2 (February 2014): 225–33. • Hickey, Graeme L, Ben Bridgewater, Stuart W Grant, John E Deanfield, John Parkinson, Alan J Bryan, Malcolm Dalrymple-Hay, Neil E Moat, Iain Buchan, and Joel Dunning. 'National Registry Data and Record Linkage to Inform Postmarket Surveillance of Prosthetic Aortic Valve Models over 15 Years'. JAMA Internal Medicine 177, no. 1 (2017): 79–86. https://doi.org/10.1001/jamainternmed.2016.6936. • Knol, Mirjam J, Kristel J M Janssen, A. Rogier T Donders, Antoine C G Egberts, E Rob Heerdink, Diederick E Grobbee,	

				Karel G M Moons, and Mirjam I Geerlings. 'Unpredictable Bias When Using the Missing Indicator Method or Complete Case Analysis for Missing Confounder Values: An Empirical Example'. Journal of Clinical Epidemiology 63, no. 7 (2010): 728–36. • Hahn RT, Leipsic J, Douglas PS, Jaber WA, Weissman NJ, Pibarot P, Blanke P, Oh JK. Comprehensive Echocardiographic Assessment of Normal Transcatheter Valve Function. JACC Cardiovasc Imaging. 2019 Jan;12(1):25-34. doi: 10.1016/j.jcmg.2018.04.010. Epub 2018 Jun 13. PMID: 29909110.	
73	Medtronic UK Ltd	P36		**Information Bias.** The EAG and clinical lead identified a key limitation linked to 'poor reporting of device model in the registry' as a likely consequence of local reporting systems not updating device model options when uploading to the national systems (as such, earlier generation devices may be selected even when a later generation device was used) - if data is being entered/ selected incorrectly by local teams when procedures are carried out, this leaves room for significant margin of error in device reporting and potentially introduces a measurement error or misclassification of device/s. Despite efforts to check with manufacturers and clean data/ correct for this error, due to the length of time that has past, there is a level of uncertainty that cannot be accounted for. **We are concerned that this has caused information bias and ask the Committee to consider this limitation in the registry evidence.**	The EAG took device serial number and checked these with manufacturers (different data field to device model). Only rows where the device model could not be confirmed with companies (or where companies confirmed an out of scope device was used) were omitted. The EAG has acknowledged the limitation of this approach in the report, however this remains the largest device level analysis within the UK NHS setting, and the EAG can be confident that for those procedures included, patient and procedural characteristics, and outcomes, are attributed to the correct devices. No changes made.
74	Medtronic UK Ltd	38		**Given the differences in patient populations, it is imperative that the tables, analyses and results (both clinical and economic) for balloon-expandable and self-expandable valves should be presented entirely separately in order to avoid misinterpretation.**	Binary logistic regression requires reference case which we chose based on the most frequently used TAVI device. Separate modelling for self-expanding devices was shown in section 5.3.2 'Device subgroups'.

				The EAG states that they "did not compare balloon- and self-expanding TAVI devices" yet all the analyses, tables and the economic model use Sapien 3 Ultra as the reference case. We ask that all the tables, analyses and results are presented separately in order to avoid misinterpretation of the report. It is however important to note that the clinical advisors correctly advised that many patients can be treated with either an SE or BE valve. We are concerned that the report has the tendency to niche the SE patients into the more complex patient group which is not necessarily the case, demonstrated by the fact that SE valves are implanted in the majority of patients across Europe as well as in some centres in the UK.	
75	Medtronic UK Ltd			**Only 35% of patients in the UK TAVI Registry were included in the EAG analysis and some of the valves were only available in certain sizes between April 2021 and March 2023 meaning that the limited number of patients included in this analysis are not reflective of the current market and therefore the analysis is unreliable for supporting procurement and commissioning decisions?** **LSA aims to assess technologies that are in widespread or established use in the NHS to support procurement and commissioning decisions.** We have some concerns regarding the flow of data from the registry. At the outset, there were more than 14,000 records, which is then reduced to around 7,000 (Figure 1): a. 10% of cases were excluded due to missing pathology, MGV, valve area, delivery approach. b. 25% of Cohort 1 were excluded due to "device unverified". There are algorithms that can be applied to reduce this somewhat, e.g., Hickey et al. (2017).	The data available represents the largest available UK data set at the time the LSA was conducted. The EAG further notes that any newer devices introduced since March 2023 would have very short follow-up available and hence, would be of limited value for decision-making should a later data cut have been available. The latest data from UK TAVI registry was analysed, and the univariate results from analysis conducted prior to linkage are reported in Table 16 and 17 of the updated report – this reflects current NHS practice from 32 TAVI centres across England, Wales and Northern Ireland. The EAG has acknowledged the limitation of the data completeness throughout the report, and whilst a large number of procedures have been omitted not all cases were omitted due to missing data: a proportion are removed at the start due to restricting to aortic

				c. Around 1,000 records were excluded due to HES matching (not unexpected, plus complex due to regions). d. Another ~40% of data were excluded due to the complete cases requirement (Section 5.3.2). The impact of these points collectively could be major bias, leading to inappropriate estimates of treatment effects and event risks in the economic analysis. Only 3,917/ 11076 (35%) of TAVI registry procedures were included in the multivariate analysis (62% of those recorded as having TAVI in the native valve), which may introduce significant bias and imprecision as acknowledged by EAG. The TAVI registry reports 85.8% of devices included however this number of procedures suggests a total of (12,909) is significantly less (4,309) that the number reported in HES (17,218). This adds further to risk of bias and imprecision. To assess whether the patients analysed by the EAG are reflective of the UK TAVI patient population, we ask that a table is produced similar to Tables 13 and 14 outlining patient characteristics and outcomes for the whole UK TAVI registry (n = 11,076) along with statistical testing regardless of missing data.	stenosis and transfemoral approach, and some used older version of devices. All exclusions are quantified in Figures 1, 3 and 4. In all results tables, it is also clearly stated how many cases had that field completed. Where appropriate, the proportion of missing entries is quantified for specific fields. The analysis presented remains the largest device comparison (of almost 4000 patients) in a UK NHS setting. The EAG does not consider it appropriate or helpful to compare the suggested 11,076 UK TAVI Registry procedures with the 7,116 included in Tables 16 and 17, because the differences between the two populations are the exclusion of valves that could not be identified, were outside of NICE's scope or were used outside of the instructions for use.
76	Medtronic UK Ltd			Can you please share how many valves were identified as being Evolut Pro and Evolut FX? The analysis currently estimated that 19% of the valves were either Evolut R or Evolut Pro+ which does not reflect the Evolut UK market share of 25% reported in the BCIS annual audit report for data from 2021 to 2022. [redacted]	The UK TAVI Registry data available was until 31 March 2023, and the EAG acknowledge that the 3 Evolut FX (Section 5.3.2. Cohort identification) devices included in this extract were from before it was formally launched. This data represents the most recent available from a UK setting from 32 contributing NHS centres.

				We would also like to remind the EAG that, as described in our initial submission, Evolut PRO and Evolut PRO+ are the same in terms of valve design; only the delivery systems differ in terms of profile. Therefore, in populations where patient vasculature is matched, you may observe different major vascular complication rate but, since all other valve features remained the same, all other outcomes would be expected to be similar between PRO and PRO+. **We ask the Committee to consider that the 35% of valves included in the analysis are not reflective of the current market and therefore the analysis is unreliable for identifying differences between valves and cannot be relied upon for supporting procurement and commissioning decisions? It is also important to note that the LSA should include assessment of all listed valves, including those without registry data available, otherwise NICE will be unable to answer NHS England's decision problem**.	Because the Evolut Pro is not listed in the Final Scope for this topic, the EAG has not considered it in the report. However, Medtronic did provide the EAG with device models corresponding to the serial numbers found in the UK TAVI Registry, and this could be used to establish how many were Evolut Pro. Although the EAG has acknowledged limitations around availability of data for some devices included in the Final Scope, the approach taken provides the most generalisable evidence available for this topic, and can be strengthened by the availability of more data in the future.
77	Medtronic UK Ltd			**The EAG have excluded all data on our first-generation device, CoreValve and so miss the vital opportunity to assess long-term outcomes. It may be misinterpreted that all data on earlier generation valves are irrelevant due to variation in <u>some outcomes</u>. In some cases, certain design features, applied to newer valves, will improve some but not all patient outcomes. We ask that the EAG performs critical appraisal of these design changes over time and engages KOLs to understand which outcomes are likely to have improved and which should be assumed consistent until new data can prove otherwise.** Whilst the EAG make some attempt to consider the differences between valve iterations (mentioned on page 54), they make no attempt to consider what has remained the same over time. Therefore, this section provides justification that, where available and where design features have remained consistent, long-term outcomes (e.g. durability and	

				survival) should form an important part of the assessment and economic modelling. Where valve platforms do not have long-term data available, the model results should reflect this uncertainty**.** Whilst the EAG make some attempt to consider the differences between valve iterations (mentioned on page 54), they fail to consider what has remained the same over time. Therefore, this section provides justification that, where available and where design features have remained consistent, long-term outcomes (e.g. durability and survival) should form an important part of the assessment and economic modelling. Where valve platforms do not have long-term data available, the model results should reflect this uncertainty. **The Evolut product family (Evolut R / Pro / Pro Plus / Evolut FX) is built on the proven Corevalve ™ platform and, as such, long-term clinical evidence for the CoreValve system should be considered applicable to the later Evolut valves (Evolut R / Pro / Pro Plus / Evolut FX).** The CoreValve system, acquired by Medtronic from CoreValve Inc. in April 2009, was CE marked on November 8, 2006 and was discontinued on November 7, 2018. The following unique combination of design attributes have remained unchanged since the original CoreValve system and have been extensively scrutinised in over 12,000 patients in over 25 sponsored clinical trials globally, demonstrating excellent clinical outcomes for patients: • **Supra-annular design:** The supra-annular valve design keeps the working portion of the valve above, and unconstrained by, the native annulus, optimizing blood flow through the valve and resulting in excellent hemodynamic outcomes and low rates of structural valve deterioration (SVD)[1]	

				• **Hour-glass Shape:** The supra-annular hour-glass design decreases the size and impact of the neo-sinus (region between native and transcatheter aortic valve leaflets), allowing adequate washing behind the native leaflets and thereby reducing the risk of thrombosis[2]. • **Self-expanding nitinol frame:** The frame is composed of proprietary blend of Nitinol, providing a compact design and low delivery profile which conforms to the patient's anulus for consistent radial force across a wide and treatable annulus range. It is biocompatible as well as MRI conditional. Additionally, individual frame cells are sized to allow for passage of 10 Fr catheters for future coronary access. • **Porcine pericardial tissue that are reverse canted to reduce leaflet stress:** The tissue is half of the thickness of bovine pericardium, enabling a low delivery profile. • **AOA tissue treatment:** Medtronic Alpha-aminooleic acid (AOA) treatment is a biocompatible anti-calcification treatment that has been used in the Medtronic surgical portfolio for over 25 years. It is an established biochemical approach to mitigating calcification in the wall and leaflets of tissue valves. It is distinguished from other tissue treatments by its unique interaction and covalent bonding with the free aldehydes of glutaraldehyde. The unique features of the CoreValve/Evolut platform results in better bioprosthetic valve performance, including prothesis-patient mismatch (PPM) which is present when the Effective Orifice Area (EOA) of the prosthetic valve is too small in relation to the body size[3]. PPM has been associated with clinical outcomes and patients without PPM have a higher survival versus those without ≥ moderate PPM[4].	

				Thanks to the self-expanding, supra-annular, hourglass design of all previous and current device iterations, CoreValve / Evolut TAVI has consistently demonstrated excellent hemodynamics compared to SAVR in randomised clinical trials[5-9]. Large EOAs and low gradients have been consistently demonstrated in both early and contemporary RCTs, suggesting that the hemodynamic performance of CoreValve has been *at least* maintained as new iterations of Evolut TAVI have been introduced over time. Collectively, the fundamental design of the CoreValve and Evolut R systems which has been carried forward to newer generations for Evolut PRO, PRO+ and FX, strongly suggest that the longer term clinical outcomes demonstrated with CoreValve and Evolut R is applicable for all iterations of the Evolut platform. • CoreValve TAVI system is the only valve with 10-year RCT data (NOTION RCT). The study confirms the durable performance of the CoreValve platform out to 10 years, showing no difference in the composite outcome of death, myocardial infarction and stroke (65.5% vs 65.5%, p=0.93)[6]. The study also showed statistically lower rates of severe SVD and severe bioprosthetic valve dysfunction (BVD) with CoreValve versus surgery out to 10 years. • SVD has been defined as one of the four failure modes of bioprosthetic valve dysfunction[10,11]. CoreValve/Evolut platform is the first and only TAVI platform to demonstrate statistically lower rates of SVD versus SAVR at 5 years: a vital consideration as patients with SVD have an approximate two-fold risk of death or rehospitalization for valve disease or worsening heart failure at 5 years[12]. Data used in this analysis included RCT and single arm data from Pivotal and single arm studies for extreme, high, and intermediate risk populations. In the RCTs, CoreValve was used in 998 patients	

				(88.5%) and Evolut R was used in 130 patients (11.5%). In the single arm studies, CoreValve was used in all patients. • Hemodynamic performance also differentiates Medtronic from other TAV platforms, including Edwards Lifesciences SAPIEN™* 3 valve. The Evolut platform has been shown to have lower gradients and larger EOAs than SAPIEN 3 out to 5 years[13]. Additionally, a recent meta-analysis showed statistically lower rates of SVD in self-expanding TAVI valves (of which CoreValve/Evolut valves constituted approximately 87%) when compared to both SAVR and balloon expandable TAVI valves (exclusively Edwards Lifesciences SAPIEN™*, SAPIEN XT™*, and SAPIEN 3 valves). Furthermore, the balloon-expandable TAVI valves demonstrated statistically worse rates of SVD when compared to SAVR alone[14]. Given this determination, we would like to assert that all clinical data associated with these specific valve models (Corevalve Evolut, Evolut R, Evolut Pro, Evolut Pro Plus, Evolut FX remain entirely applicable and should be considered as part of the Late-stage assessment. **The EAG are correct to acknowledge that newer valve iterations may demonstrate better outcomes but we feel it is important to understand that the long term outcomes from previous generations are a helpful baseline and to understand which specific design features have changed, why these were implemented and which outcomes these features are likely and proven to improve, and which outcomes will not change as a result.** Over the past 15 years, Medtronic has expanded the CoreValve platform, introducing Evolut™ R, Evolut™ PRO, Evolut™ PRO+ and Evolut FX. Whilst the CoreValve™ Evolut™ TAVI platform design has fundamentally remained consistent in terms of the self-expanding, supra-annular design, the platform has undergone several iterations since the original CoreValve™ system. Each new design feature has been introduced to	

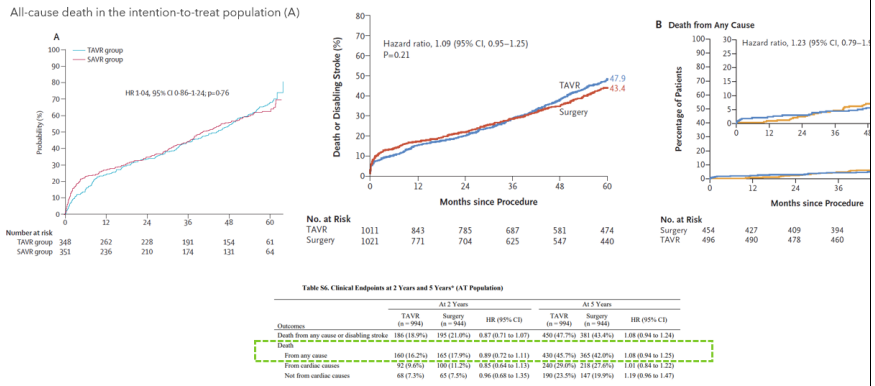
				improve patient outcomes and user experience. However, in the context of this Late Stage Assessment it is important to note that these changes listed below, were not intended to change or improve blood flow through the valve: • **Recapturability:** The original CoreValve™ system was not recapturable meaning that the valve could not be repositioned in the most optimal position subsequently impacting outcomes such as paravalvular leak (PVL) and pacemaker implantation. Recapturability was introduced with Evolut™ R via modifications to the attachment mechanism between the valve frame and the delivery system. • **External pericardial wrap:** Evolut PRO received CE mark in 2017 and included the external pericardial wrap for Evolut PRO 23, 26, and 29 mm TAVs. The Evolut PRO+ system (CE mark in 2021) allowed for the inclusion of the pericardial wrap on all four valve sizes (23, 26, 29, and 34 mm). This pericardial wrap was not present in the earlier CoreValve™ and Evolut™ R iterations. • **Delivery system profile:** The PRO+ 23-29 mm TAVs are designed for use with the Evolut PRO+ DCS that was downsized from 16 eFr (EnVeo PRO) to 14 eFr (PRO+) to allow patients with access vessels of ≥5.0 mm to be treated. For the size 34 mm TAV, the PRO+ DCS is an EnVeo PRO delivery system was upsized from 16 eFr to 18 eFr (22Fr), and the EnVeo PRO LS was upsized to 18 eFr (22 Fr) to accommodate loading of the larger size TAV. • **Gold markers for visualisation of the implant:** Evolut™ FX includes radiopaque gold markers at the inflow region of the frame to enhance visualization during deployment to aid with commissure alignment.	

				• **Delivery System updates for Evolut™ FX:** The delivery system for Evolut™ FX has been redesigned to improve stability, deliverability and flexibility. **References:** 1 O'Hair D, Yakubov SJ, Grubb KJ, et al. Structural Valve Deterioration After Self-Expanding Transcatheter or Surgical Aortic Valve Implantation in Patients at Intermediate or High Risk. *JAMA Cardiol*. Feb 1 2023;8(2):111-119. doi:10.1001/jamacardio.2022.4627 2 Midha PA, Raghav V, Sharma R, Condado JF, Okafor IU, Rami T, Kumar G, Thourani VH, Jilaihawi H, Babaliaros V, Makkar RR, Yoganathan AP. The Fluid Mechanics of Transcatheter Heart Valve Leaflet Thrombosis in the Neosinus. Circulation. 2017 Oct 24;136(17):1598-1609. doi: 10.1161/CIRCULATIONAHA.117.029479. Epub 2017 Jul 19. PMID: 28724752. 3 Pibarot P, Dumesnil JG. Prosthesis-patient mismatch: definition, clinical impact, and prevention. Heart. 2006 Aug;92(8):1022-9. doi: 10.1136/hrt.2005.067363. Epub 2005 Oct 26. PMID: 16251232; PMCID: PMC1861088. 4 Kornyeva A, Burri M, Lange R, Ruge H. Self-expanding vs. balloon-expandable transcatheter heart valves in small aortic annuli. Front Cardiovasc Med. August 3, 2023;10:1175246. 5 Gleason TG, Reardon MJ, Popma JJ, Deeb GM, Yakubov SJ, Lee JS, et al. 5-Year Outcomes of Self-Expanding Transcatheter Versus Surgical Aortic Valve Replacement in High-Risk Patients. Journal of the American College of Cardiology. 2018;72(22):2687-96. 6 Hans Gustav Hørsted Thyregod, Troels Højsgaard Jørgensen, Nikolaj Ihlemann, Daniel Andreas	

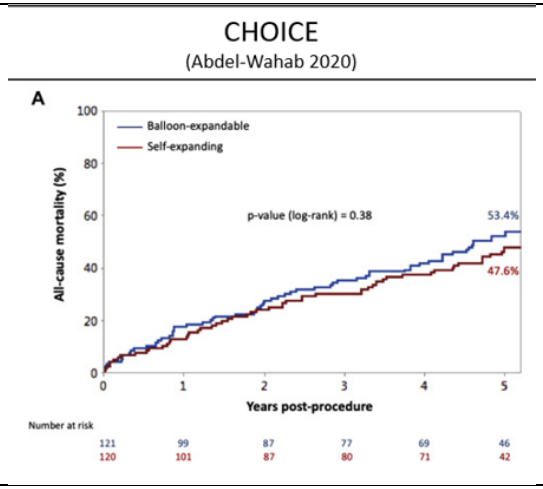
					Steinbrüchel, Henrik Nissen, Bo Juel Kjeldsen, Petur Petursson, Ole De Backer, Peter Skov Olsen, Lars Søndergaard, Transcatheter or surgical aortic valve implantation: 10-year outcomes of the NOTION trial, European Heart Journal, Volume 45, Issue 13, 1 April 2024, Pages 1116–1124, https://doi.org/10.1093/eurheartj/ehae043	
				7	Van Mieghem NM, Deeb GM, Søndergaard L, et al; SURTAVI Trial Investigators. Self-expanding Transcatheter vs Surgical Aortic Valve Replacement in Intermediate-Risk Patients: 5-Year Outcomes of the SURTAVI Randomized Clinical Trial. JAMA Cardiol. 2022 Oct 1;7(10):1000-1008. doi: 10.1001/jamacardio.2022.2695. PMID: 36001335; PMCID: PMC9403849.	
				8	Forrest JK, Deeb GM, Yakubov SJ, Gada H, Mumtaz MA, Ramlawi B, Bajwa T, Teirstein PS, Tchétché D, Huang J, Reardon MJ; Evolut Low Risk Trial Investigators. 4-Year Outcomes of Patients With Aortic Stenosis in the Evolut Low Risk Trial. J Am Coll Cardiol. 2023 Nov 28;82(22):2163-2165. doi: 10.1016/j.jacc.2023.09.813. Epub 2023 Oct 24. PMID: 37877907.	
				9	Reardon 2023 Evolut Surgical Replacement and Transcatheter Aortic Valve implantation in Low Risk Patients – Evolut Low Risk, presented at TCT, San Fransisco 2023. Slides publicy available here: https://www.acc.org/Latest-in-Cardiology/Clinical-Trials/2019/03/15/18/34/EVOLUT-Low-Risk	
				10	VARC-3 Writing Committee, et al. Valve Academic Research Consortium 3: Updated endpoint definitions for aortic valve clinical research. *J Am Coll Cardiol*. June 1, 2021;77(21):2717-2746.	

				11 Capodanno D, Petronio AS, Prendergast B, et al. Standardized definitions of structural deterioration and valve failure in assessing long-term durability of transcatheter and surgical aortic bioprosthetic valves: a consensus statement from the European Association of Percutaneous Cardiovascular Interventions (EAPCI) endorsed by the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J.* December 1, 2017;38(45):3382-3390. 12 O'Hair D, Yakubov SJ, Grubb KJ, et al. Structural valve deterioration after self-expanding transcatheter or surgical aortic valve implantation in patients at intermediate or high risk. *JAMA Cardiol.* Published online December 14, 2022. doi:10.1001/jamacardio.2022.4627. 13 Abdel-Wahab M, Landt M, Neumann FJ, et al. 5-Year Outcomes After TAVR With Balloon-Expandable Versus Self-Expanding Valves: Results From the CHOICE Randomized Clinical Trial. *JACC Cardiovasc Interv*. May 11 2020;13(9):1071-1082. doi:10.1016/j.jcin.2019.12.026 14 Ueyama H et al. Meta-Analysis Comparing Valve Durability Among Different Transcatheter and Surgical Aortic Valve Bioprosthesis. *Am J Cardiol.* 2021 Nov 1;158:104-111	
78	Medtronic UK Ltd			**The EAG raised concerns that RCT data was 'limited by short term follow up" yet appear to have excluded all data on our first-generation device (CoreValve) therefore missing the vital opportunity to assess long-term outcomes. The differences in mortality rates between devices, from the multivariate analysis of**	The EAG could explore uncertainties around mortality using additional longer follow-up data from HES to determine the impact on results, if the committee so wishes.

				the registry data, are driving the differences in Net Monetary Benefit in the economic analysis. This difference in event rates is improbable and is at odds with the totality of RCT data in over 10,000 patients, It is likely that this mortality difference is due to the confounders for mortality that have not been adjusted for in the registry data model. Well-designed, prospective randomised controlled trials provide information related to specific "efficacy" questions: How do the 5-year mortality rates compare with Sapien versus surgery in various surgical risk strata? How do the 5-year mortality rates compare with Evolut versus surgery in various surgical risk strata? How do late mortality rates compare with Corevalve /Evolut and Sapien/Sapien3 in randomised populations? We believe that consideration of prior randomised controlled trials (RCT) that address late term mortality after TAVI versus surgery is a critical concern for UK patients and physicians. Randomised controlled clinical trials in patients with aortic stenosis have provided the highest level of scientific evidence for clinicians, patients, and societal guidelines, as the "standard of care" for severe aortic stenosis, (i.e., surgical aortic valve replacement), was directly compared with transcatheter aortic valve replacement in various levels of surgical risk. To date, only the Corevalve/Evolut supra-annular valve and the Sapien/Sapien XT/Sapien 3 transcatheter valves have provided long-term outcome for patients randomized to TAVI or surgery in high risk, intermediate risk, or low risk patients for surgery**. Relative to surgery, these studies have shown comparable (or better) 5 -year mortality with CoreValve/Evolut compared with the Sapien for each surgical risk strata (Level of Evidence A).** In addition, three studies, two investigator initiated RCTs (CHOICE 5 year; SOLVE TAVI 5 years) and one industry sponsored RCT in patients with small annuli (SMART 1 Year) showed similar or lower numerical mortality for CoreValve	The EAG cannot assume equivalence between CoreValve and the devices listed in the scope (Evolut R, Evolut Pro+, Evolut FX); differences in outcomes have been identified and summarised in the report (see section 5.2, 5.2.6). The EAG has acknowledged the long-term data available for the Evolut family of devices (see section 5.2.2). The EAG has also summarised the technical differences between CoreValve (first generation) and Evolut R, Pro, and FX (see Table 2 and Table 3). The EAG note that CoreValve, Evolut Pro and Evolut R at the end of the year are not available on NHS Supply Chain. The EAG could explore manufacturer as a grouping factor in future analysis, if the committee so wishes. The EAG has reviewed the title and abstract of the 3 RCTs highlighted by the company: - Abdel-Wahab et al. 2020 (CHOICE, investigator initiated, NCT01645202; setting: Germany) compared transfemoral TAVI with CoreValve (n=120; 56 alive at 5 years) with Sapien XT (n=121; 61 alive at 5 years); neither valve is currently available. The study was powered to detect a 10% difference in 1-year mortality between arms (50% power (which suggests that this is a post-hoc power calculation rather than an a-priori one, which in turn raises questions about biases within the study), 5% significance level; Abdel-Wahab et al. 2015). Patients had to be anatomically suitable for treatment with both balloon- and self-expanding valves, which was defined as a native aortic valve annulus

				compared with Sapien at 5 years (Level of Evidence A). We believe that these findings should be considered in the NICE Tech Analysis and should be deemed equivalent early and late term mortality with Sapient and Evolut for the economic analysis. **All Cause Mortality: Evidence Summary** While statistically non inferior to surgery, both the Partner IIA (intermediate risk) and Partner III (low risk) randomised trials show crossing of the all-cause mortality curves at 3 years, with numerically higher mortality rates with Sapien compared to surgery at 5 years. **Five year mortality with Sapien (PIA High Risk), Sapient XT (PIIA intermediate risk) and Sapien 3 (PIII Low Risk) compared with surgery** PARNER (Sapien) Randomised Controlled Trials : All-Cause Mortality  Table S6. Clinical Endpoints at 2 Years and 5 Years* (AT Population) | Outcomes	At 2 Years: TAVR (n = 994)	At 2 Years: Surgery (n = 944)	At 2 Years: HR (95% CI)	At 5 Years: TAVR (n = 994)	At 5 Years: Surgery (n = 944)	At 5 Years: HR (95% CI)
---	---	---	---	---	---	---
Death from any cause or disabling stroke	186 (18.9%)	195 (21.0%)	0.87 (0.71 to 1.07)	450 (47.7%)	381 (43.4%)	1.08 (0.94 to 1.24)
Death						
From any cause	160 (16.2%)	165 (17.9%)	0.89 (0.72 to 1.11)	430 (45.7%)	365 (42.0%)	1.08 (0.94 to 1.25)
From cardiac causes	92 (9.6%)	100 (11.2%)	0.85 (0.64 to 1.13)	240 (29.0%)	218 (27.6%)	1.01 (0.84 to 1.22)
Not from cardiac causes	68 (7.3%)	65 (7.5%)	0.96 (0.68 to 1.35)	190 (23.5%)	147 (19.9%)	1.19 (0.96 to 1.47)	 1. In contrast, the CoreValve studies showed numerically lower mortality rates through the first four years in the CoreValve High Risk study, similar mortality rates in the CoreValve Intermediate Risk study, and numerically diverging mortality curves with a trend toward lower mortality rate with Evolut than surgery at 4 years (P=0.07).	- measuring between 20 to 27 mm in diameter on pre-operative imaging. This study showed no difference in all-cause death, cardiovascular death, stroke, repeat hospitalisation for heart failure, bleeding (life-threatening, major or minor severity treated separately), major or minor vascular complication at 5 years; but acknowledged limited statistical power. However, there were statistical differences in new pacemaker (excluding patients with pacemaker at baseline) were different between arms; 40.4% CoreValve, 25.4% Sapien XT; p=0.01. The EAG note that this RCT also had statistically significant differences in the proportion of male sex at baseline (71.7% male in CoreValve, 57.0% in Sapien). - SOLVE is a 2x2 factorial randomised study (NCT02737150) of 447 patients undergoing transfemoral TAVI to Evolut R or Sapien 3, but also randomised to general anaesthesia or conscious sedation (Thiele et al. 2020). The study was powered for equivalence (equivalence margin 10% with significance level 0.05) of a composite primary outcome (all-cause mortality, stroke, MI, infection requiring antibiotics, and AKI at 30 days). The authors acknowledge that choice of anaesthetic drugs was left to the discretion of the anaesthetist which may have been a confounder, and that the study was underpowered for other endpoints. The EAG has identified an abstract (EuroPCR 2024)

				Five-year mortality with CoreValve High Risk, CoreValve Intermediate Risk, and Evolut Low Risk  To further support these findings, two randomized studies evaluating CoreValve versus Sapien and Evolut with Sapien three showed comparable mortality rates at the 5 years and 1 year respectively.	- reporting 5-year results; no difference in all-cause mortality (48.5% compared with 47.6%), moderate to severe paravalvular leak (9% compared with 5.8%) or need for pacemaker (29.6% compared with 22.8%). However higher incidence of stroke in Sapien 3 group (4.8% compared with 0.5%; p=0.001). - Hermann et al. 2024 (SMART RCT) compared self-expanding (Evolut Pro, Pro+ or FX; n=355) to balloon-expanding (Sapien 3, Sapien 3 Ultra; n=361) in patients with small annuli (aortic valve annulus area of 430 mm2 or less) up to 1 year. This study was already included in the EAG review of published evidence (see section 5.2.5). The EAG consider that none of these publications would be considered higher quality evidence, or more relevant to the decision problem, than that already summarised in the EAG report.

					
79	Medtronic UK Ltd			**Where data is available, we strongly recommend that the EAG use the RCT data to perform economic modelling of each TAVI device versus SAVR. We would also like to flag some studies that were not captured by the EAG.** On page 147 and in Appendix B6, the EAG references 3 French economic models. The 2 in French language were published by the French HTA agency, Haute Autorite de Sante in 2021 and were the result of company-driven submissions for the low-risk indications for Evolut and Sapien TAVI. As part of their assessment, the HAS performed critical appraisal of both of these models and the Evolut model was assessed favourably (receiving no "major concerns") and the Sapien model received a "major concern" (methodological concern on utility data) meaning it was not accepted by the HAS. Manuscripts were later published in peer-reviewed journals for each – Gilard et al. 2022 based on 1-year outcomes from Partner 3 trial (as correctly identified by the EAG) and Tchetche 2023 based on the 1-year outcomes from the Evolut Low Risk trial which was not picked up by the EAG. Both	

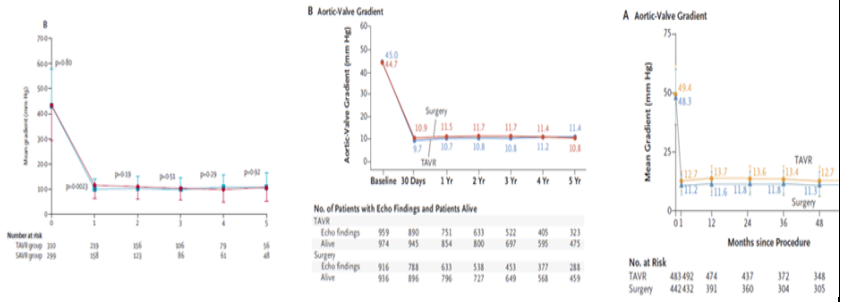
				analyses found TAVI to be cost-effective in France however, the projected QALY gains differ substantially. Medtronic feel it is important to note that the Gilard et al. 2022 model (& most other published CEAs based on the PARTNER 3 Trial) used a TAVI-favourable methodology in terms of survival extrapolation beyond the trial-observed period (1-year) whereas Tchetche 2023 took a more conservative approach whereby the trial-observed mortality benefit was assumed to fade out to no difference in survival between TAVI and SAVR beyond 1 year, thus contributing towards the difference in incremental QALYs between the 2 studies. In the French context we also feel it is relevant to flag that Accurate Neo valve was assessed by Haute Autorite de Sante and subsequently removed from the French market due to unfavourable clinical data. At EuroPCR 2024, Blackman et al, presented UK & US cost-effectiveness analysis of TAVI incorporating long-term survival from Evolut Low Risk 4-year follow-up (see appendix 1) which was based on the Tchetche 2023 model and adapted for the UK NHS. Based on 4-year follow-up, which showed the survival curves continue to diverge in numerical favour of Evolut TAVI, the base-case lifetime ICER was £19,613 with a projected survival benefit of 0.36 LYs and 0.25 incremental QALYs. By comparison, a similar analysis based on previously relied-upon 1-year follow-up data resulted in survival benefit of 0.14 years, 0.13 QALYs gained, and an ICER of £35,044 per QALY gained, which demonstrates that the 4 year follow-up data is more favourable than earlier modelling assumptions based on 1 year follow-up. [redacted] [redacted]	

				[redacted] Due to the limited follow-up period of the UK TAVI registry analysis and given the decision to remove SAVR as a comparator, the EAG are unable to accurately project the long-term outcomes of specific devices which we feel is a significant shortcoming of the EAR. We understand that the model used by the EAG was based on the high-risk NG208 model and, whilst we have not performed recent CEA using the high risk trials, similar patterns play out in the survival curves between PARTNER 1a trial and CoreValve High Risk Trial and so we would again expect to see differences in QALYs accrued over the longer term. There have also been differences in long-term thrombotic complications in randomized trials comparing Sapien and CoreValve/Evolut. In the CHOICE trial that randomized 241 patients with severe aortic stenosis to a balloon-expandable Sapien XT or treatment with CoreValve (Abdel-Wahab, JACC 2020). After 5 years, there were no statistically significant differences between BE and SE valves in the cumulative incidence of death from any cause (53.4% vs. 47.6%; p = 0.38), although clinical valve thrombosis occurred in 7 balloon expandable patients (7.3%) and 1 self expanding patient (0.8%; p = 0.06) and moderate or severe structural valve deterioration in 6 BE patients (6.6%) and no SE patient (0%; p = 0.018). In the randomized SOLVE TAVI study in patients, the 5 year stroke rate was 4.8% in the Evolut group and 15.5% in the Sapien3 group (p=0.001) (Feistritzer EuroPCR LBCT 2024) **References**	

				• Tchétché D, de Gennes CD, Cormerais Q, Geisler BP, Dutot C, Wilquin-Bequet F, Breau-Brunel M, Lueza B, Pietzsch JB. Cost-effectiveness of transcatheter aortic valve implantation in patients at low surgical risk in France: a model-based analysis of the Evolut LR trial. Eur J Health Econ. 2024 Apr;25(3):447-457. doi: 10.1007/s10198-023-01590-x. Epub 2023 May 30. PMID: 37254006; PMCID: PMC10972970. • Gilard M, et al., Cost Effectiveness Analysis of SAPIEN 3 Transcatheter Aortic Valve Implantation Procedure Compared With Surgery in Patients With Severe Aortic Stenosis at Low Risk of Surgical Mortality in France Value Health 25 (4) (2022) 605–613 • Blackman et al,. 2024, Cost-effectiveness of TAVI incorporating long-term survival from Evolut Low Risk 4-year follow-up, presented at euroPCR 2024	
80	Medtronic UK Ltd			**Whilst earlier versions of CoreValve/Evolut TAVI did elicit higher rates of aortic regurgitation, the differences between Evolut and Sapien observed in the EAG analysis, are not shown in contemporary RCT data directly comparing Evolut Pro/Pro+/FX with Sapien 3/Ultra therefore indicating that the UK registry differences are driven by confounders rather than differences in valve design. Despite this, the EAG's CEA models odds ratios of 8.51 and 9.78 for Evolut R and Evolut Pro+ respectively vs. Sapien 3 Ultra for AR and these patients are then subject to an annual mortality hazard of 2.44 which is at odds with the totality of RCT evidence.** It is well recognised that residual aortic regurgitation after TAVR is associated with a worsened outcome. The initial CoreValve device had higher rates of residual aortic regurgitation than surgery, resulting in a higher earlier reintervention rate. The Evolut R (repositionable,	The study Grubb et al. 2024 was published after the literature search conducted by the EAG, and pools data from RCTs and single arm studies. See Final Protocol for reasons as to why comparisons with SAVR and network meta-analysis were considered inappropriate by the EAG. The SMART study (Herrman et al. 2024) is already within the included the EAG report clinical published evidence (see section 5.2.5). Real-world data reflects varying demographics, treatment settings and demonstrates how TAVI performs under typical conditions within an English NHS hospital compared to RCTs which are often highly selective by nature and are completed in a

				conformable frame inflow with higher outward radial force) and Evolut Pro/Pro-/Fx have a pericardial wrap to further reduce paravalvaular regurgitation. In a recent publication, Grubb and colleagues (Grubb JACC CV Interv 2024) demonstrated the reduced rates of re-intervention Evolut compared with CoreValve from the randomized Clinical Trials. Pooled data from CoreValve and Evolut R/PRO (Medtronic) randomized trials and single-arm studies encompassed 5,925 TAVR (4,478 CoreValve and 1,447 Evolut R/PRO) and 1,832 SAVR patients. The cumulative incidence of reintervention through 5 years was higher with TAVR vs SAVR (2.2% vs 1.5%; *P* = 0.017), with differences observed early (≤1 year; adjusted subdistribution HR: 3.50; 95% CI: 1.53-8.02) but not from >1 to 5 years (adjusted subdistribution HR: 1.05; 95% CI: 0.48-2.28). The most common reason for reintervention was paravalvular regurgitation after TAVR and endocarditis after SAVR. Evolut had a significantly lower incidence of reintervention than CoreValve (0.9% vs 1.6%; *P* = 0.006) at 5 years with differences observed early (adjusted subdistribution HR: 0.30; 95% CI: 0.12-0.73) but not from >1 to 5 years (adjusted subdistribution HR: 0.61; 95% CI: 0.21-1.74). The 5-year incidence of reintervention was similar for Evolut vs SAVR (0.9% vs 1.5%; *P* = 0.41). A low incidence of reintervention was observed for CoreValve/Evolut R/PRO and SAVR through 5 years. Reintervention occurred most often at ≤1 year for TAVR and >1 year for SAVR. Most early reinterventions were with the first-generation CoreValve and managed percutaneously. Reinterventions were more common following CoreValve TAVR compared with Evolut TAVR or SAVR. In the SMART study (Herrmann NEJM 2024), mild or greater total aortic regurgitation at 12 months was present in 14.1% of patients in the Evolut group and 20.3% of patients in the Sapien valve group (difference, −6.2 percentage points; 95% CI, −12.3 to −0.2). **References**	setting which is not reflective of the English healthcare system. Furthermore, this study included 3917 patients, which is infeasible to be included in an RCT and therefore is much better placed at detecting rare outcomes such as AR (only occurred in 46 procedures)

				• Grubb KJ, Lisko JC, O'Hair D, Merhi W, Forrest JK, Mahoney P, Van Mieghem NM, Windecker S, Yakubov SJ, Williams MR, Chetcuti SJ, Deeb GM, Kleiman NS, Althouse AD, Reardon MJ. Reinterventions After CoreValve/Evolut Transcatheter or Surgical Aortic Valve Replacement for Treatment of Severe Aortic Stenosis. JACC Cardiovasc Interv. 2024 Apr 22;17(8):1007-1016. doi: 10.1016/j.jcin.2024.01.292. Epub 2024 Apr 3. PMID: 38573257. • Herrmann HC, Mehran R, Blackman DJ, et al., on behalf of the SMART Trial Investigators. Self-Expanding or Balloon-Expandable TAVR in Patients With a Small Aortic Annulus. N Engl J Med 2024;390:1959-71.	
81	Medtronic UK Ltd	Page 75 – Table 14		**We ask that the EAG investigates and addresses the factual inaccuracies in the gradients data** We ask that the EAG externally validate the Sapien mean pressure gradient recorded in the Table 14. The EAR reports mean pressure gradient 6mmHg (Sapien 3) and 8mmhg (Sapien 3 Ultra) which is not consistent with any externally validated echocardiographic readings from the EDW RCT core lab which is consistently 10-12mmHg as illustrated below.	This is not a factual inaccuracy. The EAG has carried out additional analysis on the 14,401 procedures in the UK TAVI Registry, pre-cohort identification and cleaning and found mean post-procedure pressure gradients, consistent with results presented in Table 14 (now Table 16 in the updated report), as follows: **ALL** Mean (sd): 8.6 (6) Median [IQR]: 7 [5 to 11] Range: 0 to 81 **Sapien 3** Mean (sd): 7.9 (5.3) Median [IQR]: 6 [5 to 10] Range: 0 to 81 **Sapien 3 Ultra** Mean (sd): 10.2 (5.9)

				PARNER (Sapien) Randomised Controlled Trials : Haemodynamic Outcomes  	Median [IQR]: 9 [6 to 13] Range: 0 to 55 Note, results above use the valve model entered at data entry site (hospital), and not those verified by serial number. The EAG is therefore satisfied that the analysis of the data received from the UK TAVI Registry is appropriate and correct. Differences between values reported in the registry and literature may be within measurement error. The EAG does note that 28.4% of entries for this data field were missing from the UK TAVI Registry, and acknowledge that with technical difficulties around measuring mean gradient, especially in a real world setting, these results are likely to be within acceptable measurement error limits. The EAG also notes that the PARTNER 3 trial was in patients at low risk from surgery, who differ fundamentally from those undergoing TAVI according to NICE Guidance in the UK.
82	Medtronic UK Ltd	Page 33		We concur with the Clinical Experts that “while many patients can be treated with any TAVI device, there are some subgroups, such as those with a small annulus, who may be better suited to a particular device for its specific features, such as expansion type or intra- or supra-annular leaflets”. We are concerned that the current data analysis in the current report does not sufficiently consider the needs of these patient subgroups and does not consider the adequate economic value of this benefit. **RCT Reference**	

				• Herrmann HC, Mehran R, Blackman DJ, et al., on behalf of the SMART Trial Investigators. Self-Expanding or Balloon-Expandable TAVR in Patients With a Small Aortic Annulus. N Engl J Med 2024;390:1959-71. **Supportive/complementary UK Reference:** • Ali N, Hildick-Smith D, Parker J, Malkin CJ, Cunnington MS, Gurung S, Mailey J, MacCarthy PA, Bharucha A, Brecker SJ, Hoole SP, Dorman S, Doshi SN, Wiper A, Buch MH, Banning AP, Spence MS, Blackman DJ. Long-term durability of self-expanding and balloon-expandable transcatheter aortic valve prostheses: UK TAVI registry. Catheter Cardiovasc Interv. 2023 Apr;101(5):932-942. doi: 10.1002/ccd.30627. Epub 2023 Mar 15. PMID: 36924015. • Kalogeras K, Jabbour RJ, Pracon R, Kabir T, Shannon J, Duncan A, Quarto C, Heng EL, Rahbi H, Oikonomou E, Katsianos E, Patel N, Chandra N, Vavuranakis MA, Cadiz S, Bougiakli M, Smith RD, Siasos G, Vavuranakis M, Davies S, Dalby M, Panoulas V. Midterm Outcomes in Patients With Aortic Stenosis Treated With Contemporary Balloon-Expandable and Self-Expanding Valves: Does Valve Size Have an Impact on Outcome? J Am Heart Assoc. 2023 Jun 6;12(11):e028038. doi: 10.1161/JAHA.122.028038. Epub 2023 May 26. PMID: 37232270; PMCID: PMC10382012.	
83	Medtronic UK Ltd			**Some key outcomes appear not to have been assessed, such as Bioprosthetic Valve Dysfunction (BVD), a metric for valve performance and long-term durability recommended by VARC3. We request that the EAG considers BVD within the clinical assessment and the economic model, especially in preparation for**	The EAG has explicitly stated that some key variables which contribute to VARC-3 are not in the UK TAVI Registry (Appendix C4) and HES (Appendix D2). BVD is not an outcome listed in the Final Scope, and the

				upcoming data from RCTs such as the SMART Trial which are expected to prove the link between BVD and hard clinical outcomes. The EAG references VARC3 but has not included Bioprosthetic Valve Dysfunction, a vital metric for valve performance and long-term durability. Valve performance, evaluated as bioprosthetic valve dysfunction (BVD) is composed of structural valve deterioration (SVD), non-structural valve dysfunction (NSVD), clinical valve thrombosis and infectious endocarditis. BVD significantly increases the risk for death or hospitalitisation at 5 years and Corevalve/Evolut is the only valve to demonstrate a 43% relative reduction of BVD compared to surgery (Yakubov, 2024). Furthermore using the UK TAVI registry Ali et al showed a significantly higher incidence of severe Structural Valve Deterioration (SVD) amongst patients treated with the balloon-expandable SAPIEN valve compared to the SEV Corevalve / Evolut. The authors conclude the difference relates to the fundamental design characteristics of the two valve platforms. They state the CoreValve / Evolut is a supra-annular valve, in contrast to the intra-annular SAPIEN, resulting in a larger effective orifice area (EOA) and typically lower transvalvular gradients, which may confer an advantage with respect to long-term durability. **References** • Herrmann HC, Mehran R, Blackman DJ, et al., on behalf of the SMART Trial Investigators. Self-Expanding or Balloon-	report has been reviewed by Clinical Expert SCMs who have not challenged omission of this outcome. Furthermore, the scope and consequently the EAG has concentrated on clinical outcomes of direct relevance to the decision problem, rather than surrogate and proxies for these outcomes.

				Expandable TAVR in Patients With a Small Aortic Annulus. N Engl J Med 2024;390:1959-71. • Yakubov, S and McConnell J. Impact of Bioprosthetic Valve Performance on 5-Year Clinical Outcomes after Self-Expanding TAVI or Surgery in Patients at Intermediate or Great Surgical Risk, Presented at New York Valves, 2024 • Ali N, Hildick-Smith D, Parker J, Malkin CJ, Cunnington MS, Gurung S, Mailey J, MacCarthy PA, Bharucha A, Brecker SJ, Hoole SP, Dorman S, Doshi SN, Wiper A, Buch MH, Banning AP, Spence MS, Blackman DJ. Long-term durability of self-expanding and balloon-expandable transcatheter aortic valve prostheses: UK TAVI registry. Catheter Cardiovasc Interv. 2023 Apr;101(5):932-942. doi: 10.1002/ccd.30627. Epub 2023 Mar 15. PMID: 36924015.	
84	Medtronic UK Ltd		Table 27 & 39	**Recent publications including Evolut FX should be added to the assessment:** • Bajwa T, Attizzani GF, Gada H, Chetcuti SJ, Williams MR, Ahmed M, Petrossian GA, Saybolt MD, Allaqaband SQ, Merhi WM, Stoler RC, Bezerra H, Mahoney P, Wu W, Jumper R, Lambrecht L, Tang GHL. Use and performance of the evolut FX transcatheter aortic valve system. Cardiovasc Revasc Med. 2024 Apr 7:S1553-8389(24)00145-3. doi: 10.1016/j.carrev.2024.04.002. Epub ahead of print. PMID: 38599918. • Attizzani, G, Gabasha, S, Ukaigwe, A. et al. Coronary Cannulation, Commissure, and Coronary Alignment Post-TAVR With Evolut FX System: CANNULATE TAVR Study. J Am Coll	These papers were published after EAG literature searches. Bajwa et al. 2024 summarises a survey conducted in the US, of Evolut FX users in 23 centres with extensive experience in Evolut TAVI devices (n=285 patients), and 46 centres with broad balloon and self-expanding experience (n=254 patients). Outcomes included amount of resistance when compared to the Evolut Pro+ during insertion and advancing of the valve system from vascular access to the annulus, predictable deployment, and pre-deployment to post-deployment valve movement. These outcomes were not in the Final Scope.

				Cardiol Intv. 2024 Mar, 17 (6) 825–827. https://doi.org/10.1016/j.jcin.2023.10.033	Attizzani et al. 2024 is a letter; reports commissural alignment in 50 consecutive patients treated with Evolut FX in a US setting. This outcome is not listed in the final scope and larger cohorts using Evolut FX have been included in the EAG report.
85	British Cardiovascular Society	1	1	This is a comprehensive analysis of the published studies and registries and of the UK TAVI registry aiming to assess the performance of different TAVI devices and their cost effectiveness. The report is complete and balanced; a tremendous effort has been made to cover the literature and to analyze the data of the UK TAVI registry. The limitations of the existing data have been acknowledged, extensively discussed and were taken into account in the conclusions. The conclusions in terms of the performances of different devices and in terms of their cost effectiveness are supported by the provided evidence. I have no comment to make. It is apparent that there is a need to improve the quality of the data that we enter in the UK TAVI registry and this is the main EAG recommendation.	

Section B: Comments on the User Preference Report

HealthTech Programme

Transcatheter heart valves for transcatheter aortic valve implantation in people with aortic stenosis: Late Stage

External Assessment Report, User Preference Report and economic model – Collated comments

Comment no.	Name	Page no.	Section no.	Comment	NICE response
1	Edwards Lifesciences		Entire document	Edwards is grateful for the participation of the clinicians involved in this process although it appears that most of their input, or preference, has already been captured in the EAG model. User Preference is not mentioned in the NICE manual and was only introduced in the revised interim methods and process, several months after the TAVI LSA had commenced. MCDA already has questionable validity in NICE methods and observing that some decisions in this report were originally based on an attendance n=3, this brings further doubt into its value in this process. There is a noticeable absence of input from patient representatives, TAVI nurses and other healthcare professionals in the care pathway who may bring other considerations into choice of device used such as education, training and support. By definition, MCDA / user preference enables a holistic assessment by a systematic, transparent and explicit consideration of multiple aspects beyond the traditional criteria used by HTA	Thank you for your comment. Late-stage assessment (LSA) is currently in the pilot phase of the programme, and as such new methods are being trialled to assess their suitability for addressing the aims of LSA. It is important to note that we are not conducting a formal MCDA in LSA. Instead, we are using MCDA methods to capture and present preferences of users in a more systematic fashion. The rationale for capturing user preferences as part of this process has been outlined in section 4 of the LSA interim methods and processes. During scoping, experts advised that interventional cardiologists were the only speciality who would use the technology and are directly involved in the decision to choose one technology over another. Therefore, only interventional cardiologists were included as experts in the user preference elicitation. It is our understanding that patients and TAVI nurses would not normally be involved in this decision.
2	Boston Scientific	6, 27-30	Results, Appendix B	We understand that it is difficult to recruit a sample of users (interventional cardiologists) completely free of direct financial interests. Only 5 to 9 users participated in different stages of this Multicriteria Decision Analysis (MCDA). And 6 out of 9 users provided data on which TAVI devices had been available to them. However, for ACURATE neo2, only 2 users provided such preference data. We suggest increasing the sample size for each TAVI device to be between 5 and 10 in the MCDA.	Thank you for your comment. It is important to note that we are not conducting a formal MCDA in LSA. Instead, we are using MCDA methods to capture and present preferences of users in a more systematic fashion. We will however consider the number of users included in the user preference process for future late-stage assessment topics.

HealthTech Programme

Transcatheter heart valves for transcatheter aortic valve implantation in people with aortic stenosis: Late Stage

External Assessment Report, User Preference Report and economic model – Collated comments

3	Boston Scientific	20, 23-26	Results, Appendix A	Overall, the 4-stage MCDA approach is very typical. However, it lacks a scenario analysis or a one-way deterministic analysis to address the uncertainty. The authors only described 4 main sources of uncertainty at the end of Results section as well as in Appendix A. Adding a scenario analysis or one-way deterministic analysis would address uncertainty in the weighting of the criteria (stage 3), the scoring stage, or the lack of consensus among the experts on the performance rules (stage 2).	Thank you for your comment. It is important to note that we are not conducting a formal MCDA in LSA. Instead, we are using MCDA methods to capture and present preferences of users in a more systematic fashion. We will consider the feasibility and added benefit of including scenario and sensitivity analyses for future user preference reports.
4	Boston Scientific	11-12	Results, Table 4	In Table 4, it seems the 18-month and 24-month mortality rates are lower for ACURATE neo2 compared with other valve products (95% confidence intervals slightly overlap with the reference product Sapien 3 Ultra). The report says mortality data were derived from the UK TAVI Registry, which only had a maximum follow-up of 24 months. 24-month (2-year) mortality may not be defined as 'long-term mortality' as Criterion 1, given the time frame/horizon of the economic model is 15 years.	Thank you for your comment. The presented values are extracted from the external assessment report (EAR) and represent the best available data in the EAR to address the criterion. Given these limitations, the external assessment group (EAG) applied the value for 2-year mortality across the whole time horizon of the economic model.
5	Boston Scientific	26	Conclusion, Appendix A	Note the general theme of valve selection being driven by the patient's clinical presentation, which accounts for most of the weight in the matrix, thus, challenging the applicability of User Preference. Additionally, the differences in the patient populations across devices in the UK TAVI Registry data linked with HES are significant, supporting this claim.	Thank you for your comment. This limitation is described in the conclusion of the UP report: "There was a question raised by a user about the applicability of the user preference assessment, due to valve selection being driven solely by clinical presentation."
6	Meril Life Sciences Pvt. Ltd	9 of 32	Results	In the paragraph, it is mentioned that **3 criteria had a weight less than 5% and were removed from the list leaving 7 criteria on the list** We noticed that the after considering top 10 criteria and weights were recalculated. Then again, the criteria with less than 5% were removed from the list. So as per this there will be 4 criteria with weights less	Thank you for your comment. The report states "after truncation, and recalculation of weights" 3 criteria had a weight less that 5%. So the process was: • Truncate to top ten • Recalculate weights for the top ten

				than 5% that needs to be removed i.e., criteria of **minimum vessel size for access** with weight of 4.6%.	• Remove all criteria with a recalculated weight under 5% • Recalculate weights for remaining criteria This means that criteria 7 which had a pre-truncated weight of 4.6%. Then had a recalculated weight of 5.1% *when looking at the top ten only*. Then when the other criteria below 5% were removed, criterion 7 had its weight recalculated to 6%. (note these calculations are not included in the report as they are not necessary, and are reproducible using the raw data in the appendices) The report is accurate as it stands it requires no amendment.
7	Meril Life Sciences Pvt. Ltd	14 of 32	Criterion 2: procedural stroke (24%)	The non-inferiority RCT by Baumbach et al. (2024) compared Myval (n=379; combination of Myval n=336, Myval Octacor n=32, with the remainder crossover contemporary valve implanted, and 1 Portico device) with a contemporary TAVI group (n= 377; Sapien 3 n=108, Sapien 3 Ultra n=87, Evolut R n=71, Evolut Pro n=106, Evolut Pro+ n=10, Evolut FX n=5, with 5 patients having Myval implanted). Please change the values as per 30 days ITT 1. 381 in Myval THV Series 2. 381 in Contemporary THV Series However, there were six subjects who were randomised but did not undergo randomisation due to death and one subject was implanted with non-study device. This accounts to 755 patients, including 15 cross-overs in the Myval arm and 5 cross-overs in the contemporary	Thank you for your comment. This has been amended in line with amends to the EAR.

				arm, who were treated with different generations of study devices summarised below: 1. Myval THV: 336 2. Myval Octacor THV: 32 3. Sapien 3: 108 4. Sapien 3 Ultra: 87 5. Evolut R: 71 6. Evolut Pro+: 116 (including Evolut Pro:106) 7. Evolut FX: 5	
8	Meril Life Sciences Pvt. Ltd	14 of 32	Criterion 2: procedural stroke (24%)	A retrospective non-randomised trial (Santos-Martinez et al. 2022) comparing multiple valves (n=834) versus the earlier generation Myval valve (n=135) recorded no in-hospital cerebrovascular events with Myval. Please modify the multiple valves count from 834 to 996, as this study compared the 996 patients with multiple valves to 135 of Myval THV.	Thank you for your comment, we will amend this error.
9	Meril Life Sciences Pvt. Ltd	14 of 32	Criterion 2: procedural stroke (24%)	It is reported here that Delgado-Arana et al. 2022 study with n=205 a propensity matched study between Myval and Sapien 3 Please change the n from 205 to 206 in the above propensity matched study between Myval and Sapien 3 by Delgado-Arana et al. 2022	Thank you for your comment, we will amend this error.
10	Meril Life Sciences Pvt. Ltd	14 of 32	Criterion 2: procedural stroke (24%)	The EAG noted a number of design issues with the Baumbach et al. (2024) study. Kawashima et al. 2021 published the LANDMARK Trial design in American Heart Journal followed by a letter to editor for update in the study protocol by Tobe et al. 2024. The primary combined safety and effectiveness endpoint was presented as a late breaking trial in EuroPCR 2024 and published in the Lancet by Baumbach et al. 2024	Thank you for your comment. This report only reproduces or summarises what the EAG have stated in the external assessment that could be considered to address the criterion. Please see EAG responses to comments on their assessment of this trial.

				in a very transparent manner. The trial is well powered randomised controlled trial with an absolute non-inferiority margin 10.44% and expected event rate of 26.1%. The primary endpoint showed non-inferiority of the Myval (25%) compared with contemporary THV (27%), with a risk difference of -2.3% (one-sided upper 95% CI 3.8, $p_{non\text{-}inferiority}<0.0001$). The study has been well accepted among the experts from the EuroPCR, American Heart Journal and the Lancet communities. References: 1. Kawashima H, Soliman O, Wang R, Ono M, Hara H, Gao C, Zeller E, Thakkar A, Tamburino C, Bedogni F, Neumann FJ. Rationale and design of a randomized clinical trial comparing safety and efficacy of myval transcatheter heart valve versus contemporary transcatheter heart valves in patients with severe symptomatic aortic valve stenosis: The LANDMARK trial. American heart journal. 2021 Feb 1;232:23-38. 2. Tobe A, Onuma Y, Soliman O, Baumbach A, Serruys PW. LANDMARK trial: update in study protocol. American heart journal. 2024 Apr;270:162-3.	
11	Abbott Medical	13	Criterion 2: procedural stroke (24%)	*"In this analysis, people treated with Sapien 3, Evolut R, Evolut Pro+, and Navitor were found to have statistically significantly higher odds of in-hospital stroke relative to Sapien 3 Ultra (Table 5)."* Navitor Valve was identified as the lowest device with the use of cerebral circulation protection device(s) – 6.6%, the highest rate of previous CABG (11.9%), and the highest rate of presence of extracardiac arteriopathy (15.9%) (page 73, Table 13 Summary of patient and procedural characteristics from UK TAVI Registry for TAVI in native aortic valve between 01 April 2021 and 31 March 2023).	Thank you for your comment. The data presented in this table are derived from the EAG's analysis of the linked UK TAVI registry and HES dataset (see tables 17 and 18 in the EAR). We will ensure that key differences in the baseline characteristics of people in this dataset are sufficiently highlighted to committee in the meeting.

				Prescribed NOACs and other antithrombotic were the lowest (24.9% and 4.4% respectively) Table 14, page 75, Summary of results from UK TAVI Registry for TAVI in native aortic valve (01 April 2021 to 31 March 2023). We believe that these measures are important and that it is important to analyse the criterion holistically in procedural management and patient selection.	
12	Abbott Medical	15	Criterion 3: severe paravalvular leak (15%)	"Table 7. Results from the binomial model for in-hospital aortic regurgitation (OR [95% CI])" The source of the data in the table is not clear and we recommend that this is added.	Thank you for your comment. This data is obtained from the EAG's multivariate analysis of the linked UK TAVI registry as stated in the text.
13	Abbott Medical	20	Sources of uncertainty	*"There were 4 main sources of uncertainty in this user preference assessment: engagement levels, interests of users, levels of agreement between users, and the lack of consensus when developing performance rules. Despite efforts to improve engagement, the levels of engagement varied and were lower through the stages of ranking, weighting, and performance rule setting (6 in stage 2, 5 in stage 3, and 7 in stage 4)."* We strongly agree with all the above and believe that these sources of uncertainty could cause large inaccuracies in outputs.	Thank you for your comment. The committee will consider the uncertainty when making their recommendations.
14	Abbott Medical	22	Conclusion	*"There was a question raised by a user about the applicability of the user preference assessment, due to valve selection being driven solely by clinical presentation."* This relates back to the point 12 above. We believe that device choice based on clinical features leads to an unfair comparison in devices. Some patient characteristics will inherently lead to greater rates of	Thank you for your comment. The committee will consider the limitations and uncertainties in the analysis when making their recommendations.

				complications and therefore devices used for patients with these characteristics have a disadvantage in a head to head comparison if results are not adjusted to account for this.	
15	Abbott Medical	22	Conclusion	*"Direct financial interests were common in the users and availability of valves available to users was not equal across the sample. Given the limitations in this user preference assessment, the findings should be interpreted with caution."* We believe this poses a real risk of bias and reduces the credibility of the outputs.	Thank you for your comment. We have highlighted this as a source of bias to allow the committee to consider it when making recommendations. Unfortunately conflicts of interest are common in the field and the decision was made to allow participation in this exercise as it is not a decision-making role. Experts were recruited in line with NICE's policies
16	Medtronic UK Ltd	7	Table 1	NICE LSA Interim methods and Process (May 24) section 4.27 *"So, users of these technologies can comment on the importance of characteristics or features of these technologies* ***that may not be captured elsewhere in the evidence base."*** Criteria 1-5 and 16-23 in Table 1: long-term mortality, procedural stroke, severe paravalvular leak, safety and effectiveness in annulus/left ventricular outflow tract calcium, vascular complications, length of stay, including ICU stay, health related QoL, reintervention rate, conversion to surgery, cost, atrial fibrillation, acute kidney injury, endocarditis, are all **clinical outcomes that should be captured in the cost effectiveness analysis and are inappropriate for inclusion in the user preference assessment.** After truncation (Table 2), and application of performance rules, the performance matrix is reduced to a single criterion that isn't captured in the model i.e. minimum vessel size for access. This was the lowest ranked criterion and carried only 6% of the weight. The EAG states that "this criterion was the only one to be a physical feature of the TAVI devices and not a measure of clinical performance	Thank you for your comment. We acknowledge that the majority of factors identified by users were captured in the EAG's report, and this is stated in the user preference report. The report has been published to provide transparency on the process and to reinforce the finding that most of the factors that influence decisions on which valve to use are based on clinical factors. The committee will consider this information as part of its decision-making process.

				(either generally or in a specific clinical presentation). However, it is linked to the available size range of the valves and so may not truly reflect the value offered by each model if considered in isolation". Given that 94% of the weight in the performance matrix was made up of measures of clinical performance and users felt that choice was always driven by clinical presentation and clinician experience of using different valves to meet that presentation, it is clear that this preference assessment process has been unsuccessful in determining characteristics or features of these technologies that may not be captured elsewhere in the evidence base and therefore the user preference report cannot be used to inform decision making. **We therefore ask that the user preference report is withdrawn from this LSA process.**	

Section C: Comments on the economic model

Issue	Name	Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)	EAG or NICE response
1	Edwards Lifesciences	The EAG modified the NG208 economic model structure such that both short-term and long-term outcomes are captured. It is acknowledged that the updated model allows for more transparency (i.e., no hidden nested decision trees as in the previous model) and transitions that try to reflect the patient pathway in a real-world setting, it appears complex. Although assumptions are essential components in economic modelling, those will increase as the model becomes more complex. The model presents many health states transactions and multiple coexisting health states that patients can experience. However, some important health states (namely, disabling stroke and atrial fibrillation) have	For the stroke health state, our recommendation is to distinguish between disabling and non-disabling stroke and to account for the former only, as it enables additional follow-up costs. Atrial fibrillation (AF) health state and related transitions from other health states (e.g., from AF to disabling stroke) should also be considered, reflecting the health states considered in recent cost-utility publications (Gilard et al. 2022, Mennini et al. 2022, Vázquez Rodríguez et al. 2023, Kuck et al. 2023, Dubois et al. 2023, Eerdekens et al. 2024).	Based on the stroke before discharge incidence rates from Table 14 (UK TAVI registry) and from Table 18 (UK TAVI registry linked to HES), which are lower for SAPIEN 3 Ultra vs. SAPIEN 3 (1.2% vs. 2.0%) and (1.9% and 1.1%) respectively, we expect a positive impact on the NMB for SAPIEN 3 Ultra (vs. SAPIEN 3). Atrial fibrillation rates might not vary significantly across the different TAVI valves, so this might have a minor impact on results.	Additional state would add additional complexity, and modified Rankin Score was missing in 90.2% of procedures recorded in the UK TAVI registry. The EAG followed the approach taken for the economic model for NG208, which considered atrial fibrillation to be periprocedural outcome only, with short term outcomes and costs, expected to be already captured by the HRG cost used in the base case scenario. This has now been clarified in the report.

		not been considered. Previously published Markov-based models/analyses consider those as relevant health states, especially for patients at low risk of surgical mortality (Gilard et al. 2022, Mennini et al. 2022, Vázquez Rodríguez et al. 2023, Kuck et al. 2023, Dubois et al. 2023, Eerdekens et al. 2024).			
2	Edwards Lifesciences	Section 6.3. Base case results are reported in Table 33 for male and 34 for female.	The Probability of the highest NMB at £20k WTP value is SAPIEN 3 with 76% for male and 74% for female respectively, which is much higher for our latest TAVI device generation SAPIEN 3 Ultra with 4% and 9% respectively. As the cost of the device are the same, this should be driven only by QALY gained. When looking at the driver of the QALYs, which are mortality, PVL (AR), PPI and Stroke, we		See the EAG response to consultation comment 5.

			would expect higher QALYs with SAPIEN 3 Ultra than with SAPIEN 3, based not only on the literature highlighted earlier in the document but also in the Tables reporting the UK TAVI registry (Table 14) and the one linking with the HES data (Table 18).		
3	Edwards Lifesciences	In section 6.2.3 with the description of the cost parameters used in the economic model (page 162), the EAG noted that whilst the majority of costs remained at 2021/22, it was not consistent across each resource item. The EAG acknowledged that this will tend to underestimate costs and hence increase the NMB for each procedure. We would expect consistency across the various resources and cost inputs indexation (NHS Reference Costs 2017-2018 inflated to 2021/22 vs. Unit costs of health and social	We recommend that EAG considers our observations on costs using an approach that is more consistent and transparent		The EAG have acknowledged the limitation that inflation was not applied consistently across all costs; this was due to time constraints and will be addressed in future analyses. However, the EAG would consider these to have low impact on results. The cost of the valve used was the Net SSDP and Trust Rebate price provided by NHS Supply Chain on 22 January 2024. We have lifted redaction on this description to clarify. The economic model used was an extension of the NG208 economic model, and therefore the same approach was used in terms of hospital costs. This information is provided in the reproducible economic model and described in the Appendix F3.

		care 2023) to limit the impact on results. We also notice that no details are presented in the methodology used to calculate the costs of the intervention in relation to the proportion of elective vs. non-elective cases (e.g., procedure cost recalculated excluding the hospital stay component = NHS reference cost - excess bed day cost x average length of stay, based on the same methodology used in the NG208 economic model). It seems also that the costs of rehabilitation after TAVI are not being accounted for. Although we understand that EAG has redacted costs (and the majority of their corresponding sources) in order to prevent backwards calculation of the price of TAVI device valves, it is not clear what valve price was used in the base case scenario. In contrast, it's clearly reported that the deterministic sensitivity analysis (DSA) included three options for the cost of			Rehabilitation costs for home-rehabilitation and intermediate care costs were excluded from the economic model as the discharge location was not available from the UK TAVI Registry, therefore differences between devices could not be modelled using UK data.

		TAVI device were (transacted price, £17,500 based on NG208, and £15,000 threshold analysis in NG208) to test the robustness of model estimates.			
4	Boston Scientific	Selection of TAVI valve is mainly driven by clinical presentation, i.e., specific clinical situation of each patient. However, because of a lack of patient-level data enabling adjustment for these differences, multivariate analysis and subsequent economic modelling were not possible for TAVI devices with no data, or minimal data, in the Registry (as described in the External Assessment Report – page 13).	It would be better to use patient-level real-world data (e.g., electronic health record) that includes clinical presentation information and the factors associated with device selection in the multivariate analysis. Then the economic modelling can incorporate adjusted parameters for these population differences.	We support the recommendation of EAG listed on page 190 of adapting data fiels in the UK TAVI Registry to support subgroup analysis in the future. Incorporating patient-level data that influences device choice will further address the limitation of uncertainty, and make the modelling results robust.	Agrees with EAG recommendation.
5	Medtronic UK Ltd	Given the level of redaction in the report and the 5-day turnaround, we were unable to perform full assessment of the model. Costs are largely redacted and redacted details in	We ask that each company receives a model with unredacted inputs and results available for their own devices. Otherwise it will be impossible to run a transparent and	Errors in model may be identified by stakeholders that change the outputs of the model	NICE comment: Unfortunately the cost inputs cannot be unredacted, as this could enable back-calculation of competitor pricing, given that each company will be aware of the pricing arrangements that it uses for the NHS.

		Tables 33, 34 make it impossible to assess the accuracy of the assumptions. Table 35 is also heavily redacted, as is much of the appendix.	fair public consultation process.		
6	Medtronic UK Ltd	Our biggest concern regarding the model is the reliance upon the flawed UK TAVI Registry analysis to inform the model. Please refer to Section A for detail and recommendations	As per comments	This would remove any major differences in NMB that are not driven by device price.	
7	Medtronic UK Ltd	Given the differences in patient populations, it is imperative that 2 separate economic models are built: one economic comparing BEVs to other BEVs. and one economic model comparing SEVs to other SEVs in order to avoid misinterpretation. Please refer to section A for details.	Where the UK TAVI registry data is primarily informing the model, the EAG should have 2 separate models using one BE reference case and one SE reference case.	Patient populations should be more comparable – although this should be verified with the clinical experts.	Thank you for the suggestion, however one benefit of Net Monetary Benefit is that arms can be omitted and the remaining options ranked assuming the options are equally comparable.
8	Medtronic UK Ltd	The EAG appear to have excluded all data on our first-generation device, CoreValve and so miss the vital opportunity to assess long-term outcomes that are of importance and are not	Where available and where design features have remained consistent, long-term outcomes (e.g. durability and survival)	This would remove any major differences in NMB that are not driven by device price.	The EAG cannot assume clinical equivalence between device generations (and have acknowledged differences in outcomes between generations).

		available or (where available) are not consistent between valves. Whilst the EAG make some attempt to consider the differences between valve iterations (mentioned on page 54), they fail to consider what has remained the same over time. Please refer to Section A, comment no. 8 for more detail.	should form an important part of the assessment and economic modelling. Where valve platforms do not have long-term data available, the model results should reflect this uncertainty.		
9	Medtronic UK Ltd	The EAG report states that "mean cost per patient across the 6 devices ranged between £23,764 and £29,011; and mean QALYs ranged between 1.52 and 3.15. Whilst the heavy redaction has meant we cannot perform full assessment of the model, this range in QALYs (+1.63) appears entirely implausible and should indicate that the model is not fit for purpose. In the following comments, we outline that the QALY	Apply RCT data rather than registry data to the model	As the QALY difference is implausible the model is not reliable for decision making. An updated model would remove any major differences in NMB that are not driven by device price.	Not a factual inaccuracy. However, the EAG agree that the QALY difference is driven by the mortality difference. The EAG will review the impact of uncertainty in survival estimates on QALYs and cost-effectiveness.

		difference between Sapien and Evolut appears to be driven by a mortality difference that is not observed in any published RCT. In NG208, the QALY gain between TAVI and SAVR in high-risk patients was only +0.12 in favour of TAVI. In the most recent UK cost-effectiveness analysis based on the Evolut Low Risk 4-year follow-up (Blackman et al.), outlined in Section A and in appendix 1, the QALY gain was +0.25 for TAVI.			
10	Medtronic UK Ltd	Due to the limited follow-up period of the UK TAVI registry analysis and given the decision to remove SAVR as a comparator, the EAG are unable to accurately project the long-term outcomes of specific devices which is a significant shortcoming of the EAR.	Where data is available, we strongly recommend that the EAG use the RCT data to perform economic modelling of each TAVI device versus SAVR.	This would remove any major differences in NMB that are not driven by device price.	See response to comment 8.

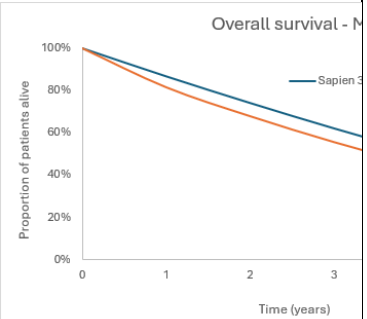
		Please refer to Section A, comment numbers 9 & 10 for more detail.			
11	Medtronic UK Ltd	Appendix F4 gives the expected mortality projections (from the economic model) for each valve up to 15 years. From this, we can derive survival curves which show the differences in survival over the model horizon (below - for Evolut R and Sapien 3, separately for males and females). The curves diverge almost immediately, and the substantial difference in predicted survival after 3 years (~7% to 9%) propagates through the model, leading to a sustained survival benefit for Sapien 3 over Evolut R. Using the area under the curve approach, mean survival can be estimated from these curves, giving an estimated (undiscounted) gain of 0.46 life-years (males) and 0.60 years	We strongly recommend that the EAG use RCT data as the basis for modelling patient survival in the economic model, accurately reflecting short and long-term mortality for each device.	This would remove any major differences in NMB that are not driven by device price.	See response to comment 8. The economic model uses predicted events from multivariable modelling (after correcting for other factors).

		(females) for Sapien 3 versus Evolut R. As noted in our previous comment in Section A (Comment 9 above), the substantial body of RCT evidence has demonstrated no difference in short- or long-term survival between devices. We believe that these projections (resulting from the inappropriate use of registry data which are confounded and therefore biased) do not reflect the mortality outcomes observed in RCTs. Given the relatively low predicted incidence of stroke and heart failure in the model (as events which influence quality of life), we conclude that the implausible survival differences modelled are what is driving the difference in NMB for the different devices.			

HealthTech Programme

Transcatheter heart valves for transcatheter aortic valve implantation in people with aortic stenosis: Late Stage

External Assessment Report, User Preference Report and economic model – Collated comments

					
12	Medtronic UK Ltd	**It is important that the survival traces in the model are reflective of NHS practice. Given the level of redaction in the model it is very difficult to pinpoint causality however the use of hazard ratios for death following aortic regurgitation/PVL, pacemaker, stroke and**	Remove double-counting and ensure the survival models are reflective of the data feeding the model.	As the QALY difference is implausible the model is not reliable for decision making. An updated model would remove any major differences in NMB that are not driven by device price.	The EAG replicated the base case of NG208 economic model and found no evidence of double counting. For clarification Table 22 reports unadjusted events, from which the Kaplan-Meier curves have been plotted. The values in Appendix F4 are predicted events using adjusted multi-variable analyses (after correcting for other factors).

		dialysis may be introducing double-counting of mortality. In comparing the Kaplan-Meier (KM) survival curve in figure 5 (page 93) with the number of patients in the "dead" absorbing state of the model (appendix F3), patients appear to die much more quickly in the model than observed in the HES-linked analysis. It also appears that the delta between the KM and the model is smallest for Sapien 3 and greater for both Evolut Pro+ and Evolut R which is likely contributing towards the unrealistic QALY differences between valves. Without unredacted access to the model it is difficult to pinpoint the reason for this but one cause could be the hazard ratios applied to patients suffering aortic regurgitation (2.41), pacemaker (1.17), stroke (3.21), post-stroke (1.58) and/or dialysis (2.81). All RCTs comparing Sapien to CoreValve Evolut have so far			

		shown no significant difference in long-term mortality and as such the model should not include any differences either. Data from Table 19 Device / % dead at 1 year / % dead at 2 Evolut Pro + / 9.3% / 16.0% Evolut R / 8.0% / 18.5% Sapien 3 / 8.1% / 16.9% Sapien 3 Ultra / 7.7% / 16.9% In terms of UK data, and for UK complementary / validation purposes only given the limitations of registry data, the EAG may also wish to consider conclusions from Kalogeras et al. This retrospective registry using newer iterations of Evolut and Sapien valves demonstrated similar survival up to 3 years' follow-up. However, in propensity matched patients with small transcatheter heart valves, the authors observed a trend for improved survival among those treated with Evolut valves.			

		Reference (for complementary validation only): • Kalogeras K, Jabbour RJ, Pracon R, Kabir T, Shannon J, Duncan A, Quarto C, Heng EL, Rahbi H, Oikonomou E, Katsianos E, Patel N, Chandra N, Vavuranakis MA, Cadiz S, Bougiakli M, Smith RD, Siasos G, Vavuranakis M, Davies S, Dalby M, Panoulas V. Midterm Outcomes in Patients With Aortic Stenosis Treated With Contemporary Balloon-Expandable and Self-Expanding Valves: Does Valve Size Have an Impact on Outcome? J Am Heart Assoc. 2023 Jun 6;12(11):e028038. doi: 10.1161/JAHA.122.028038. Epub 2023			

		May 26. PMID: 37232270; PMCID: PMC10382012.			
13	Medtronic UK Ltd	Some key outcomes have not been included in the model; Patient-prosthesis mismatch (PPM), Structural Valve Deterioration (SVD) and Bioprosthetic valve dysfunction (BVD) which significantly increases the risk for death or hospitalisation at 5 years. Please refer to Section A, comment no. 16 for more detail. You will also find further detail in our original submission in response to NICE's request for information.	If the EAG are applying hazard ratios for the risk of mortality and hospitalisation following PVL, AR, PPI and dialysis, they should also Consider PPM, BVD and SVD in the economic model. However, please note our comment above regarding double-counting of mortality. We would recommend the EAG include these within the economic model, in accordance with VARC3, especially in preparation for upcoming data from RCTs such as the SMART Trial which is expected to prove the link between BVD and hard clinical outcomes.	More certainty around the economic modelling.	These outcomes are not listed in Final Scope, nor recorded in the Registry or available in HES.

HealthTech Programme

Transcatheter heart valves for transcatheter aortic valve implantation in people with aortic stenosis: Late Stage

External Assessment Report, User Preference Report and economic model – Collated comments

14	Medtronic UK Ltd	**Given that the commercial models and rebate structure differs substantially between companies, they are not comparable, and we therefore strongly suggest that the transacted price should be used in the base-case of the cost-effectiveness analysis & greatly impact the results in terms of NMB. This will be most informative for NHS England / NHS supply chain and provide a much more comparable basis for decision making. For scenario analysis, we ask that the quantification of all rebates are verified by NHS supply chain for all valves.** We ask that the EAG confirm how the price methodology is applied unilaterally across all suppliers when we know there are differences in:	We strongly suggest that the transacted price should be used in the base-case of the cost-effectiveness analysis & greatly impact the results in terms of NMB. For scenario analysis, we ask that the quantification of all rebates are verified by NHS supply chain for all valves.	This will be most informative for NHS England / NHS supply chain and provide a much more comparable basis for decision making.	Note that the source of valve costs has had the redaction lifted for transparency. NICE have confirmed that the prices were correct as of 04 June

		• The availability of value-add schemes • How the schemes are applied within the market (different go to market strategies). • Rebates that are directed towards NHS Trusts and / or towards NHSE. • Rebates that are applied on the basis of volume, at the trust and/or NHSE level. In table 35, there is a scenario analysis that uses the transacted cost of the valve which is described as "not accounting for rebates given based on volume of sales, (which did differ by valve) did change the relative probabilities" and substantially impacts the cost-effectiveness results.			

HealthTech Programme

Transcatheter heart valves for transcatheter aortic valve implantation in people with aortic stenosis: Late Stage

External Assessment Report, User Preference Report and economic model – Collated comments

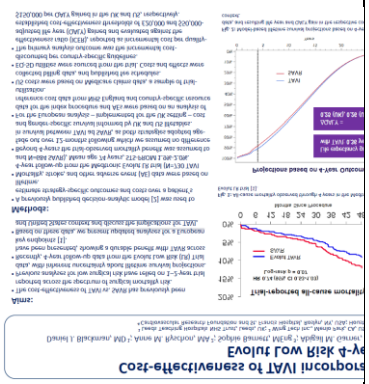
		[redacted]			

		[redacted] [image] [redacted]			

HealthTech Programme

Transcatheter heart valves for transcatheter aortic valve implantation in people with aortic stenosis: Late Stage

External Assessment Report, User Preference Report and economic model – Collated comments

15	Medtronic UK Ltd	Given the extremely tight turnaround time of 5 days, along with the heavy redaction in the model, Medtronic have been unable to perform full appraisal of all assumptions within the economic model. Therefore, the EAG should not assume that Medtronic agree with all other elements of the economic model at this stage.	Minimum 2 weeks consultation time and minimal redaction.	Errors in model may be identified by stakeholders that change the outputs of the model	
16	Medtronic UK Ltd	**Appendix 1.** For detail please see Section A, Comment 10 			Thank you for providing this information. However, the EAG has not included SAVR as a comparator (see Final Scope).
17	British Cardiova	1	1	The selection of the criteria for assessing cost effectiveness and the	

	scular Society			performance of the TAVI devices seems appropriate.	

NICE National Institute for Health and Care Excellence

Late-stage assessment

Transcatheter heart valves for transcatheter aortic valve implantation (TAVI) in people with aortic stenosis

User preference report

Produced by: NICE

Date completed: 3 July 2024, updated 16 July 2024

Contains confidential information: No

Number of attached appendices: 4

Table of Contents

Introduction

Transcatheter aortic valve implantation (TAVI) is a procedure used to replace the aortic valve, accessed through a blood vessel in the leg or chest. TAVI is now considered standard care for people with aortic stenosis at high surgical risk, and is increasingly used in people at low and intermediate surgical risk as an alternative to open heart surgery. There are 11 TAVI devices from 8 manufacturers included in the late-stage assessment of TAVI for people with aortic stenosis.

NICE is looking at user preferences when choosing a TAVI valve for people with aortic stenosis alongside the evaluation of the clinical and cost benefits. This user preference assessment considers the following:

- the criteria that are important to users when choosing a TAVI valve
- the relative importance of the criteria
- and how the criteria can be measured.

This report presents the key findings of a user preference assessment and how the technologies in scope perform against the criteria. This report should be read alongside the external assessment report (EAR) as a supplement.

Methods

This user preference assessment was done in line with NICE's Interim methods and process statement for late-stage assessment. The aim of capturing user preferences is to transparently collect and present information to the committee on the criteria that users consider important when deciding which technology to choose. Users are defined as those who will use the technology and are directly involved in the decision to choose one technology over another.

Purposive sampling was employed to select interventional cardiologists, because during NICE's scoping phase they were identified as the main users and decision makers when selecting a TAVI device to use. Interventional cardiologists were recruited in line with NICE's Interim methods and process

statement for late-stage assessment. NICE's policy on declaring and managing interests for NICE advisory committees was considered during the recruitment process.

All participants were registered according to the NICE health technology evaluation process and submitted declarations for confidentiality agreement and conflicts of interest. The register of declared interests can be accessed along with other project documents on the topic's page on the NICE website.

Due to how TAVI services are organised and the common occurrence of industry funded assistance for education and proctorship programmes, it was not possible to recruit a sample of relevant users who were all completely free of direct financial interests. Users who were directly employed by a company were excluded from the process. Users who benefited financially from lecturing fees, consultancy, advisory board membership or proctorship were not excluded. Further detail can be found in the register of declarations of interests.

The user preference assessment has been designed with Multicriteria Decision Analysis (MCDA) principles (ISPOR Task Force Report, 2016). Data on user preference was collated through participation in 2 online workshops and through communication via email. The process followed 4 stages:

- Stage 1: identifying and defining criteria
- Stage 2: ranking criteria in order of importance
- Stage 3: weighting of criteria
- Stage 4: development of performance rules.

Stage 1: identifying and defining criteria

Users were asked to identify key factors that are important when choosing a TAVI valve. A list of criteria and definitions were identified and agreed on during an online workshop with users. The criteria identified by the users were subsequently cross-referenced and combined, where appropriate, with the key outcomes listed in the EAR.

Stage 2: ranking criteria in order of importance

Users were then asked to rank the criteria in order of importance to them via email. Ranked lists from all respondents were collated, averaged and ordered from most important to least important, creating a final ranked list of criteria and definitions (using the SMART ranking technique; see appendix C for a detailed definition).

Stage 3: weighting criteria

Users were asked to weight the criteria to show how much more important 1 criterion was compared with the criterion ranked below (using the swing weighted technique, see appendix C for a detailed definition). To weight the criteria, users were asked to give each criterion a score from 0 to 100%. A score of 0% meant that there was no difference in importance between a criterion and the criterion ranked below and a score of 100% meant that it was considered twice as important. Weighted lists for all respondents were collated, averaged and weights were calculated. To ensure only criteria with meaningful impact on decision-making were included, the list was truncated to the top 10 criteria and weights recalculated. Any criteria with a weight lower than 5% were then removed and weights recalculated again.

Stage 4: developing performance rules

Stage 4 included the development of rules to establish the performance of each technology against each criterion at a workshop. Consensus on the rules was then sought from the group of users by email. Finally, a performance matrix was produced. In cases where consensus on a rule was not reached, the criterion remained in the performance matrix but would not be used to assess the technology. The criterion was retained to indicate how important it is to users (that is, its relative weight). Criteria that were relevant to a specific subgroup and not the general population of people receiving the technology were presented separately to demonstrate their importance in the respective subgroup.

When technologies were assessed against a criterion or performance rule that overlapped with the external assessment group (EAG)'s evaluation, the relevant section of the EAR was referenced.

Results

A total of 9 consultant interventional cardiologists took part in the user preference exercise. Their engagement varied at each stage as follows: 9 interventional cardiologists participated in stage 1, 6 in stage 2, 5 in stage 3, and 7 in stage 4.

In terms of experience, 6 of 9 users provided complete data on which TAVI devices had been available to them to use in their daily practice. The order of availability was: Sapien 3 Ultra (n=6), Sapien 3 (n=5), Navitor (n=5), Evolut FX (n=4), Evolut R (n=4), Myval Octacor (n=4), Trilogy (n=4), Evolut Pro+ (n=3), Allegra (n=2), ACURATE neo2 (n=2), and Hydra (n=0). Raw data can be found in Appendix B.

A total of 23 criteria were set and agreed by 9 interventional cardiologists. Each of the criteria was ranked in order of importance and a weight was then assigned to show how much more important 1 criterion was over another. Table 1 shows the full list of criteria with associated weights.

Table 1. List of identified criteria and the outcomes and parameters from the health economic evaluation after ranking and weighting

Order of importance	Criteria	Weight (%)
1	long-term mortality	21.9
2	procedural stroke	19.2
3	severe paravalvular leak	12.3
4	safety and effectiveness in annulus/left ventricular outflow tract calcium	9.9
5	vascular complications	6.9
6	predicted post-procedural haemodynamics/risk of patient prothesis mismatch	5.3
7	minimum vessel size for access	4.6
8	long-term durability data	4.2
9	ease of coronary access/What is later coronary access like?	3.3
10	flexibility and deliverability of valve system to be able to deal with tortuosity, calcification, and angulated aortas	2.8
11	risk of post procedural conduction abnormality	2.0
12	treatable annulus size range	1.8
13	pacemaker implantation rate	1.3
14	risk of coronary compromise (obstruction, create difficult later access)	1.1
15	length of hospital stay, including intensive care unit stay	0.7
16	health-related quality of life	0.7

17	heart failure	0.5
18	reintervention rate	0.4
19	conversion to surgery	0.3
20	cost	0.3
21	atrial fibrillation	0.2
22	acute kidney injury	0.2
23	endocarditis	0.1

After truncation and recalculation of the weights, 3 criteria had a weight less than 5% and were removed from the list leaving 7 criteria on the list. The weights for the remaining 7 criteria were recalculated and the performance rules for these 7 criteria were then established. Table 2 presents the resulting performance matrix. Anonymised raw data of the ranking and weighting stages can be found in Appendix B.

Table 2. Performance matrix

Order of importance	Weight (%)	Criteria	Performance rule
1	27	long-term mortality	Criterion is captured in model
2	24	procedural stroke	Criterion is captured in model
3	15	severe paravalvular leak	Device has moderate to severe paravalvular leak rate of less than 5%, 3%, 1% (note: rate of aortic regurgitation, which includes paravalvular leak, is captured in model)
4	12	safety and effectiveness in annulus/left ventricular outflow tract calcium	Lack of consensus on performance rule
5	9	vascular complications	Criterion is captured in model
6	7	predicted post-procedural haemodynamics/risk of patient prothesis mismatch	Lack of consensus on performance rule
7	6	minimum vessel size for access	Having a minimal vessel size access for smallest device 5mm, largest device 5.5 mm

In the performance matrix consensus was achieved on 5 and not achieved on 2 criteria, namely 'safety and effectiveness in annulus/left ventricular outflow tract calcium' and 'predicted post-procedural haemodynamics/risk of patient prothesis mismatch'. In addition, there was no consensus on the 3 criteria which were considered important when choosing a TAVI device, but were specifically applicable to a sub-population (Table 3). Hence, these 3 subgroup criteria and the 2 matrix criteria without consensus were not used for technology assessment. Further information on the lack of consensus can be found in Appendix A.

Table 3. Sub-population criteria with performance rules

Criteria	Performance rule
Safety and effectiveness in bicuspid anatomy	Lack of consensus on performance rule
Can be used for TAVI in surgical aortic valve replacement due to failed surgical aortic valve replacement	Lack of consensus on performance rule
Can be used for TAVI in TAVI due to failed TAVI	Lack of consensus on performance rule

Criteria captured by the EAG's clinical review and economic modelling

Of the seven most important criteria to users when selecting a TAVI device, five (including the top three) were captured in the EAG's assessment, and there was a lack of consensus on 2 criteria. So, any differences between valves with regards to the factors important to users should be reflected in the outcomes of the EAG's clinical review and economic modelling.

The only criterion which was not captured in the economic model and had consensus on the scoring rule was criterion 7 (minimal vessel size for access). This was the lowest ranked criterion and carried only 6% of the weight. Criterion 6 (predicted post-procedural haemodynamics/risk of patient prothesis mismatch) was also not captured by the EAG's model, but there was no consensus on the performance rule. This criterion was the second

lowest ranked and carried 7% of the weight. This means that the model captured 87% of the weight of users' decision making either directly or indirectly.

The criteria captured either directly or indirectly are discussed below. Evidence identified in the EAR is summarised here for convenience and was not available to participants during the user preference elicitation process. This will be discussed further at the committee meeting.

Criterion 1: long-term mortality (27%)

Mortality was a parameter within the EAG's health economic model, which had a time horizon of 15 years in the base case.

The EAG obtained mortality estimates for Navitor (Abbott), ACURATE neo2 (Boston Scientific), Sapien 3 and Sapien 3 Ultra (Edwards) and Evolut R and Evolut Pro+ (Medtronic) from an aggregated TAVI cohort of procedures (N=6,508) followed in the Hospital Episode Statistics (HES) Admitted Patient Care/Civil Registrations of Deaths dataset, linked to data from the UK TAVI Registry (the linked dataset). This dataset had a maximum follow-up of 2 years. Information on the strengths and limitations of this dataset can be found in Sections 5 and 8 of the EAR.

A univariate analysis of the linked dataset showed no significant differences in the long-term mortality up to 2 years between the devices (Table 4). A multivariate analysis did not find a significant difference in the odds of mortality post-discharge between valves (see Table 21 in the EAR).

Table 4: Mortality in the linked dataset (% [95% CI])

Parameter	Sapien 3 (n=1121)	Sapien 3 Ultra (n=3589)	ACURATE neo2 (n=295)	Evolut R (n=247)	Evolut Pro+ (n=845)	Navitor (n=170)
Median [Q1,Q3] length of follow-up, days	521.5 [354, 725.25]	502 [354,705]	403 [275, 634]	730 [529.5, 832.5]	417 [292, 558]	343 [279, 443.25]

Parameter	Sapien 3 (n=1121)	Sapien 3 Ultra (n=3589)	ACURATE neo2 (n=295)	Evolut R (n=247)	Evolut Pro+ (n=845)	Navitor (n=170)
Death (total = 751)	-	-	-	-	-	-
30 days	0.4 [0.0 to 0.7]	0.7 [0.4 to 0.9]	0.7 [0.0 to 1.6]	0.0 [0.0 to 0.0]	0.8 [0.2 to 1.5]	1.2 [0.0 to 2.9]
6 months	3.9 [2.7 to 5.0]	3.6 [3.0 to 4.2]	4.5 [2.1 to 6.0]	4.6 [1.9 to 7.2]	5.5 [4.0 to 7.1]	6.1 [2.4 to 9.7]
12 months	8.1 [6.4 to 9.7]	7.7 [6.8 to 8.6]	7.8 [4.5 to 11.0]	8.0 [4.5 to 11.4]	9.3 [7.2 to 11.3]	7.3 [3.2 to 11.2]
18 months	12.7 [10.5 to 14.8]	11.8 [10.6 to 13.0]	9.2 [5.4 to 12.8]	14.5 [9.8 to 19.0]	13.4 [10.5 to 16.2]	10.1 [3.2 to 16.6]
24 months	16.9 [14.1 to 19.6]	16.9 [15.2 to 18.5]	11.4 [6.66 to 16.0]	18.5 [13.1 to 23.6]	16.0 [11.8 to 19.9]	-

As data on Allegra (Biosensors), Hydra (SMT), Myval Octacor (Meril) and Trilogy (Jenavalve) were not available in the UK TAVI registry and hence in the linked dataset, the EAG considered evidence on mortality rates from published literature.

The longest available evidence for Allegra was in a single arm study reporting outcomes for 103 patients extracted from the Swiss TAVI Registry from a single centre (Wolfrum et al. 2023). All-cause mortality and cardiovascular mortality from Kaplan-Meier analysis were 31.4% and 18.8% respectively (no confidence intervals were reported) to 3 years.

The longest follow-up for SMT's Hydra was from Aidietis et al. (2022) who reported 1-year outcomes for 157 people in 18 centres across Europe and Asia. At 1 year, there were 23 (14.6%) deaths, including 13 (8.3%) cardiovascular deaths.

No long-term evidence was available for Myval Octacor, as it is a new generation of the Myval TAVI device. The longest follow-up for the earlier Myval generation was 2 years reported by Moscarella et al. (2024) that retrospectively compared 108 patients treated with Evolut R with 58 patients

treated with Myval. No significant differences in all-cause mortality or cardiovascular mortality between arms were observed. However, the EAG noted that reporting of baseline demographics between arms was lacking and no adjustments were made to account for any difference in populations.

No study evidence for Jenavalve's Trilogy was identified, although studies of a predecessor device used for transapical TAVI did report 1-year outcomes. As most TAVI procedures in the NHS are done transfemorally and no evidence was found comparing the predecessor device with the Trilogy device, the EAG considered that results from these studies may not be generalisable to the UK NHS population. Therefore, the performance of Trilogy has not been described for any of the clinical performance-related criteria.

Criterion 2: procedural stroke (24%)

In-hospital stroke was a parameter within the EAG's health economic model. A binomial model was fitted to the data from the linked dataset for the valves with data available. In this analysis, people treated with Sapien 3, Evolut R, Evolut Pro+ and Navitor were found to have statistically significantly higher odds of in-hospital stroke relative to Sapien 3 Ultra (Table 5). The results for ACURATE neo2 were not significant.

Table 5. Results from the binomial model for in-hospital stroke (odds ratio [95% CI])

Device	In-hospital stroke
Sapien 3 Ultra	Reference
Sapien 3	3.26 (1.23, 8.64)*
ACURATE neo2	0.97 (0.13, 7.51)
Evolut R	5.44 (1.49, 19.91)*
Evolut Pro+	5.21 (2.02, 13.46)*
Navitor	5.22 (1.59, 17.15)*

*significant at 5%

A statistically significant difference between the valves was also observed in a univariate analysis of the linked dataset (Table 6).

Table 6. In-hospital stroke in linked dataset

Sapien 3 (n=1,121)	Sapien 3 Ultra (n=3,589)	ACURATE neo2 (n=295)	Evolut R (n=247)	Evolut Pro+ (n=845)	Navitor (n=170)	p-value (adjusted)
20/1,038 (1.9%)	38/3,316 (1.1%)	2/245 (0.8%)	5/227 (2.2%)	20/726 (2.8%)	6/147 (4.1%)	0.025*

*significant at 5%

As with mortality, the EAG also considered evidence from published literature for the valves that were not present in the UK TAVI registry.

The non-inferiority randomised controlled trial (RCT) by Baumbach et al. (2024) compared Myval (n=384 randomised, 381 ITT at 30 days; combination of Myval and Myval Octacor, including 15 crossover and Portico=1) with a contemporary TAVI group (n= 384, 381 ITT at 30 days; including combination of Sapien 3, Sapien 3 Ultra, Evolut R, Evolut Pro, Evolut Pro+, Evolut FX, and 5 patients having Myval implanted). No statistically significant differences between groups on stroke outcomes up to 30 days were observed, although the EAG noted a number of design issues with the study. A retrospective non-randomised trial (Santos-Martinez et al. 2022) comparing multiple valves (n=996) versus the earlier generation Myval valve (n=135) recorded no in-hospital cerebrovascular events with Myval. However, this study did not adjust for differences in baseline characteristics between devices. Two propensity-matched studies also did not find any difference in 30-day stroke outcomes between Myval and Sapien 3 (Delgado-Arana et al. 2022; n=206) or between Myval and Evolut R or Pro (Halim et al. 2023; n=182), although the EAG noted issues with propensity matching for both studies (see section 5.4.21 in the EAR).

Santos-Martinez et al. (2022) also included 103 people who received the Allegra valve, of which 5.8% had in-hospital cerebrovascular events

(p=0.006 vs Myval). For the Hydra device, Aidietis et al (2022) reported 1 case of stroke within 30 days after implantation.

There was a large amount of disagreement between the users in the weighting exercise over how important procedural stroke was compared to severe paravalvular leak.

Criterion 3: severe paravalvular leak (15%)

Severe paravalvular leak was not captured specifically in the health economic model, but the EAG used the datafield "aortic regurgitation at end of procedure by echo or angio", which includes paravalvular leak. In the multivariate analysis of the linked dataset, people treated with Evolut R, Evolut Pro+, ACURATE neo2 and Navitor all had statistically significantly higher odds of in-hospital aortic regurgitation relative to Sapien 3 Ultra (Table 7). The result for people treated with Sapien 3 was not statistically significant compared to Sapien 3 Ultra.

Table 7. Results from the binomial model for in-hospital aortic regurgitation (OR [95% CI])

Device	Aortic regurgitation
Sapien 3 Ultra	Reference
Sapien 3	1.58 (0.41, 6.1)
ACURATE neo2	5.60 (1.11, 28.32)*
Evolut R	8.51 (2.1, 34.47)*
Evolut Pro+	9.78 (3.11, 30.76)*
Navitor	24.56 (7.04, 85.67)*

*significant at 5%

A statistically significant difference between the valves was also observed in a univariate analysis of the linked dataset (Table 8).

Table 8: Aortic regurgitation at end of procedure in linked dataset

Sapien 3 (n=1,121)	Sapien 3 Ultra (n=3,589)	ACURATE neo2 (n=295)	Evolut R (n=247)	Evolut Pro+ (n=845)	Navitor (n=170)	p-value (adjusted)
11/1,077 (1.0%)	33/3,442 (1.0%)	8/257 (3.1%)	12/239 (5.0%)	38/827 (4.6%)	6/162 (3.7%)	0.011*

*significant at 5%

The EAG also considered evidence from published literature where valves did not have data in the UK TAVI registry.

For the Allegra valve, Wolfrum et al. (2023) reported that moderate to severe paravalvular leak was observed in 2% of patients at 30 days.

Baumbach et al. (2024) reported no statistically significant differences in moderate or severe valve regurgitation between Myval/Myval Octacor and the combined contemporary valve arm (Evolut or Sapien series). For the predecessor Myval valve, Delgado-Arana et al. (2022) found no statistically significant difference in moderate-to-severe paravalvular aortic regurgitation between Myval (n=103) and Sapien 3 (n=103). Similarly, Halim et al. (2023) found no statistically significant difference in moderate to severe paravalvular leak between Myval (n=91) and Evolut R or Pro (n=91).

In Aidietis et al. (2022), moderate or severe paravalvular leak was 5.3%, 6.3% and 6.9% post-procedure, at 30 days and at 1 year for SMT's Hydra valve.

Criterion 4: safety and effectiveness in annulus/left ventricular outflow tract calcium (12%)

There was no consensus reached by the users on a performance rule for this criterion. The main reason driving the lack of consensus was the view that RCTs frequently exclude people with severe left ventricular outflow tract calcium, and if they are included it was unlikely for the rupture rate to be reported at the sub-group level. One user suggested that the safety and effectiveness of valves in this subgroup should be based on clinical opinion and experience of the user group, rather than published evidence.

As this is a clinical presentation this means that the UK TAVI registry data would have included people with this presentation. Experts advised that the choice of valve is likely affected by factors including the calcium burden, but as this is not recorded in the registry the EAG was unable to adjust for calcification in the analysis.

The only evidence identified by the EAG on the effect of calcification on the performance of specific valves was from Rao et al. (2023), which reported differences in the distribution of calcium in 10 people receiving the 34mm Evolut Pro+ between those where infolding occurred and those where it did not. However, no statistical analysis was reported.

The EAG examined a scenario using 'extensive calcification of the ascending aorta' as a surrogate measure for aortic valve calcification. In this scenario, Sapien 3 was the most likely to have the highest net monetary benefit of the valves modelled although this was reduced from the base case – see section 6.3.3 of the EAR for more detail.

Criterion 5: vascular complications (9%)

Vascular complication was a parameter in the economic model. In the multi-variate analysis of the linked dataset, the odds of experiencing major vascular complications for people treated with Navitor (Abbott), ACURATE neo2 (Boston Scientific), Sapien 3 and Sapien 3 Ultra (Edwards) and Evolut R and Evolut Pro+ (Medtronic) were not statistically significantly different (Table 9).

Table 9. Results from the binomial model for in-hospital major vascular complications (OR [95% CI))

Device	Major vascular complication
Sapien 3 Ultra	Reference
Sapien 3	0.60 (0.17, 2.17)
ACURATE neo2	3.10 (0.92, 10.39)
Evolut R	0.66 (0.11, 4.05)

Evolut Pro+	0.73 (0.2, 2.67)
Navitor	2.54 (0.62, 10.36)

*significant at 5%

The rate of major vascular complications was described in the univariate analysis of the linked dataset (Table 10).

Table 10: Major vascular complications in linked dataset

Sapien 3 (n=1,121)	Sapien 3 Ultra (n=3,589)	ACURATE neo2 (n=295)	Evolut R (n=247)	Evolut Pro+ (n=845)	Navitor (n=170)	p-value (adjusted)
12/1,051 (1.1%)	34/3,340 (1.0%)	7/244 (2.9%)	9/232 (3.9%)	12/724 (1.7%)	4/159 (2.5%)	0.025*

*significant at 5%

Baumbach et al. (2024) reported no statistically significant difference in major vascular complications between Myval/Myval Octacor and the combined contemporary valve arm (Evolut or Sapien series). For the predecessor Myval valve, neither Delgado-Arana et al. (2022) or Halim et al. (2023) found a statistically significant difference in major vascular complications between Myval and the comparators. Santos-Martinez et al. (2022) reported no cases of major vascular complications.

For Allegra, Santos-Martinez et al. (2022) reported a major vascular complication rate of 10.7% ($p<0.001$ vs. Myval), while Wolfrum et al. reported 7.8%. Aidietis et al. (2022) reported a major vascular complication rate of 4.5% for the SMT Hydra.

Sub-population criteria: can be used for TAVI in surgical aortic valve replacement due to failed surgical aortic valve replacement, and can be used for TAVI in TAVI due to failed TAVI

There was no consensus reached by the users on performance rules for these criteria. Currently, 6 of 11 TAVI devices included in this late-stage

assessment are indicated for TAVI-in-SAVR: Sapien 3, Sapien 3 Ultra, Allegra, Evolut R, Evolut Pro+ and Evolut FX. Only Sapien 3 and Sapien 3 Ultra are indicated for TAVI-in-TAVI.

Because of the small number of procedures observed in the UK TAVI registry (3.5% TAVI-in-SAVR, 0.4% TAVI-in-TAVI), differences in demographics and presentation (when compared with TAVI in native aortic valve) and because not all TAVI devices are explicitly indicated for TAVI-in-TAVI or TAVI-in-SAVR, the EAG was unable to conduct multivariate analysis on these populations (to adjust for population differences). Therefore, these populations were not modelled.

Sub-population criterion: safety and effectiveness in bicuspid anatomy

There was no consensus reached by the users on a performance rule for this criterion. There was disagreement if the performance rules should follow CE marking or the users' own knowledge from clinical experience and unpublished evidence. Clinical experts have reported that they use valves based on their own clinical experience because the published literature does not fully represent UK practice.

Similar to criterion 4, as this is a clinical presentation this means that the UK TAVI Registry data would have included people with bicuspid anatomy, but these data were not reported separately. This means that this criterion may be captured indirectly in the health economic model, but it is unclear which devices were used. This is because bicuspid aortic morphology is explicitly contraindicated in 2 devices (ACURATE neo2, Allegra), and any other leaflet configuration other than tricuspid is explicitly contraindicated in 1 device (Navitor). For the 3 devices manufactured by Medtronic (Evolut R, Evolut Pro+, Evolut FX) their instructions for use state that use in bicuspid aortic valves is explicitly indicated when the patient is at intermediate or high surgical risk. For the remaining 5 devices, no explicit indication or contraindication of aortic valve morphology is listed in the device instructions for use.

Assessment of technologies against the performance matrix

From a total of 7 criteria included in the performance matrix, 5 criteria with consensus on their performance rules were used to evaluate the technologies. Of the 5 criteria, 4 were covered in the EAG's report (see above). So, in this user preference report, performance rules were only used to assess valves against criterion 7, as shown in Table 11.

Table 11. Individual TAVI scores against performance matrix

Valve name	Minimum vessel size for access of smallest device (minimum of 5 mm required)	Minimum vessel size for access of largest device (minimum of 5.5 mm required)
Sapien 3	No (5.5)	No (6.0)*
Sapien 3 Ultra	No (5.5)	Yes (5.5)
Myval Octacor	No (5.5)	Unclear**
Navitor	Yes (5.0)	Yes (5.5)
Allegra	No (6.0)	No (6.0)
ACURATE neo2	No (5.5)	Yes (5.5)
Trilogy	No (7.0)	No (7.0)
Evolut R	Yes (5.0)	No (6.0)
Evolut Pro+	Yes (5.0)	No (6.0)
Evolut FX	Yes (5.0)	No (6.0)
Hydra	Yes (5.0)	Yes (5.5)

*The Sapien 3 is available in 29 mm valve size, while the largest Ultra is 26 mm

**The largest device is 32 mm

Sources of uncertainty

There were 4 main sources of uncertainty in this user preference assessment: engagement levels, interests of users, levels of agreement between users, and the lack of consensus when developing performance rules. Despite efforts to improve engagement, the levels of engagement varied and were lower through the stages of ranking, weighting, and performance rule setting (6 in stage 2, 5 in stage 3, and 7 in stage 4).

Seven out of the 9 users had direct financial interests, often with multiple relevant companies. These included speaker's fees, assistance with education, consultancy agreements, advisory board membership and proctorship fees. Companies which users had interests with included Medtronic, Edwards, Boston Scientific, Biosensors and Abbott. There were no users who had financial interests with SMT, JenaValve or Meril.

The level of agreement was generally consistent among the group for both the ranking and weighting exercises. Criterion 1 (mortality) was consistently the highest ranked criterion, but there was a large amount of disagreement between the users in the weighting exercise over how important procedural stroke was compared to severe paravalvular leak. For more detail see Appendix A.

Lastly, there was a lack of consensus on a number of the performance rules due to differing opinions within the group of users. Further information on the lack of consensus can be found in Appendix A.

Conclusion

Nine interventional cardiologists took part in a user preference assessment to determine the most important criteria when selecting a TAVI device to use. After ranking and weighting, 7 criteria were listed in the performance matrix. Of these, the top 3 (mortality, stroke, and severe paravalvular leak) had a combined weighting of 66% in their decision making.

Three criteria from the performance matrix were captured directly by the EAG's health economic model (mortality, stroke, vascular complications). One of the criteria (severe paravalvular leak) was captured indirectly by the model as aortic regurgitation at the end of the procedure. One of the criteria (safety and effectiveness in annulus/left ventricular outflow tract calcium) was not well reported in the UK TAVI registry or in the published literature, but the EAG did a scenario analysis using ascending aortic calcification as a surrogate measure. For a full description of how these factors were incorporated into the assessment and the results of the economic model, please see the EAR.

Only two criteria from the performance matrix (predicted post-procedural haemodynamics/risk of patient prothesis mismatch and minimal vessel size for access) were not captured either directly or indirectly in the model. However, they ranked lowest and second lowest in terms of importance and had a combined weight of 13%. One of these criteria (minimal vessel size for access) was the only one to be a physical feature of the TAVI devices and not a measure of clinical performance (either generally or in a specific clinical presentation). However, it is linked to the available size range of the valves and so may not truly reflect the value offered by each model if considered in isolation.

There was a question raised by a user about the applicability of the user preference assessment, due to valve selection being driven solely by clinical presentation. This view of what drives device choice is in line with expert opinion captured in the EAG's evaluation. It is also reflected in the fact that 94% of the weight in the performance matrix was made up of measures of clinical performance.

Direct financial interests were common in the users and availability of valves available to users was not equal across the sample. Given the limitations in this user preference assessment, the findings should be interpreted with caution.

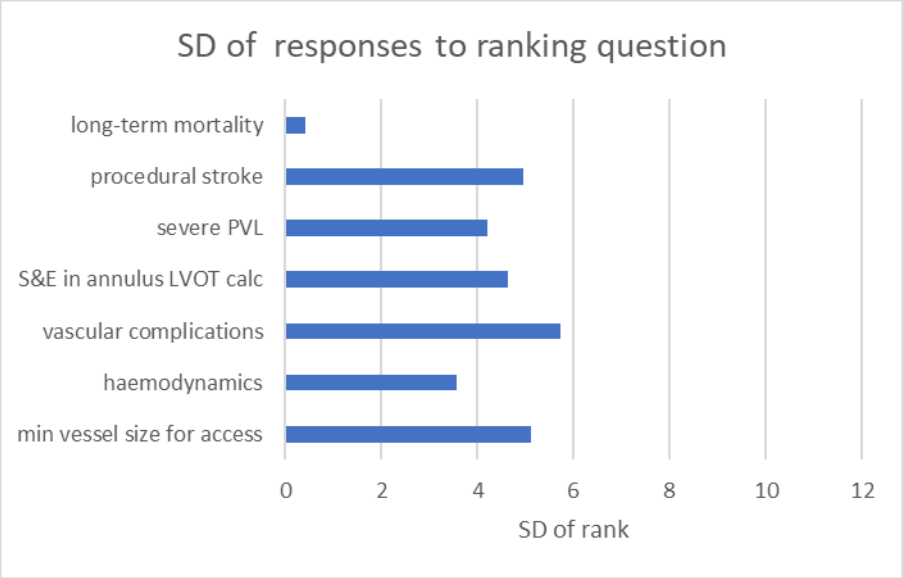
Appendix A. Uncertainty in the user preference exercise

Agreement of participants for ranking and weighting stage

Ranking stage

Figure 1 shows the standard deviation (SD) of responses representing the level of agreement between the users in their responses to the ranking exercise for the top 7 criteria. Six users contributed to the ranking exercise. There were 23 criteria ranked, therefore responses could have ranged from 1-23 meaning the maximum SD was approximately 11.5. The SD ranged from 0.4 for criterion 1 to 5.7 for criterion 5.

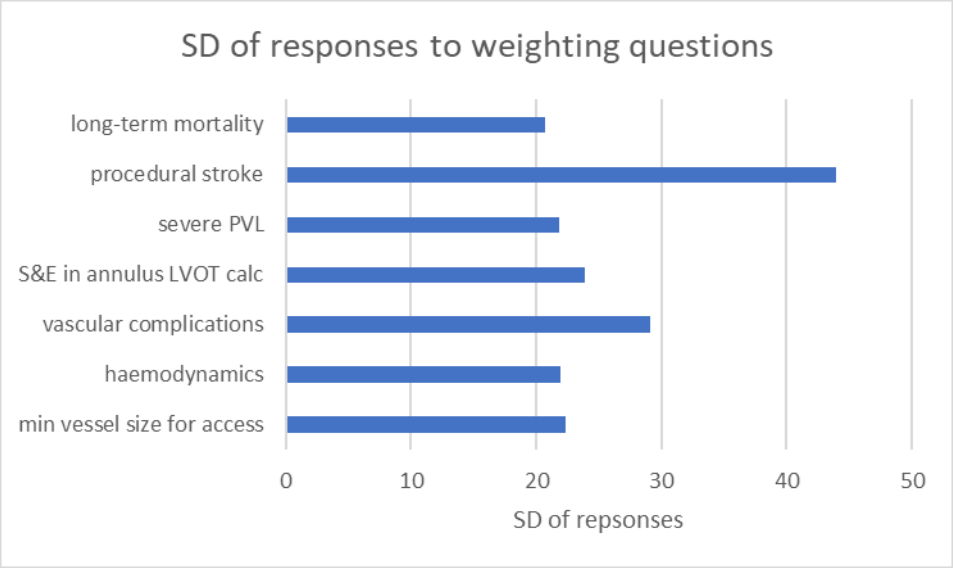
Figure 1. Standard deviation of mean of rank



Weighting stage

The SD of responses representing the level of agreement between the users in their responses to the ranking exercise for the top 7 criteria is in Figure 2. Five users contributed to the weighting exercise. Responses could range from 0-100 meaning the maximum SD was approximately 50. The SD of first 7 weighting responses ranged from 20.7 for criterion 1 to 43.4 for criterion 2.

Figure 2. Standard deviation of mean weight



Lack of consensus

Due to clinical commitments of users, attendance at the second workshop to develop the performance rules was low (n=3). The performance rules were therefore circulated among the rest of the group after the workshop for their consensus. There was a subsequent lack of consensus among the experts on five of the performance rules. Further attempts were made to achieve consensus, but these were unsuccessful. The criteria for which there was a lack of consensus on the performance rules were:

- Safety and effectiveness in annulus/left ventricular outflow tract calcium
- Predicted post-procedural haemodynamics/risk of patient prothesis mismatch
- Safety and effectiveness in for TAVI in failed TAVI
- Safety and effectiveness in bicuspid anatomy
- Safety and effectiveness for TAVI in failed SAVR.

Safety and effectiveness in annulus/left ventricular outflow tract calcium

The performance rule suggested at the workshop was: “There are data to support the device has a statistically significant lower annular rupture rate than competitors.”

There was disagreement from one user who questioned if annular rupture rate was a valid outcome measure to be using from published literature. They stated this was due to frequent exclusion of people with severe left ventricular outflow tract calcium from RCTs, and if they are included it was unlikely for the rupture rate to be reported at the sub-group level. They also suggested that the safety and effectiveness of valves in this sub-group should be based on clinical opinion and experience of the user group, rather than published evidence.

Predicted post-procedural haemodynamics/risk of patient prothesis mismatch

The performance rule suggested at the workshop was: “Are there data for mean gradient post procedure of value X” (a limit was not supplied).

There was disagreement from a user who questioned the validity of the using a mean gradient. They raised that using it was “full of difficulty” and that it was difficult to justify using it. Another user questioned whether haemodynamics was related to clinical outcomes, and noted that the relevance of patient prosthesis mismatch would vary with depending on the age of the person undergoing the procedure.

Safety and effectiveness in TAVI in failed TAVI, Safety and effectiveness in bicuspid anatomy, Safety and effectiveness for TAVI in failed SAVR

The performance rule suggested for each of these three criteria at the workshop was: “Is the valve CE marked for this indication?”

There was disagreement from two users who questioned the validity of relying solely on CE marking for these criteria. They both suggested that in clinical practice some more than one valve included in the scope of the LSA were regularly used for these indications. They felt that the clinical community informed their decision making using registry data, clinical experience and opinion. They requested that they (the participants in the user preference assessments) should be allowed to make an expert recommendation on which valves were the most suitable. In addition, they both said that the architecture of the failed valve can drive the choice of the replacement rather than the CE marking.

This view on use was consistent with expert opinion captured in the EAG report (see Section 2) where experts expressed that they relied on their own clinical opinion because they felt that the published evidence did not fully capture clinical experience and practice.

Concerns with applicability of user preference assessment

After the process was completed one user questioned the applicability of the user preference assessment for selecting a TAVI device. They felt that choice was always driven by clinical presentation and clinician experience of using different valves to meet that presentation. This was consistent with the expert opinion captured in the EAG report (see Sections 2 and 5 and 8 of the EAG report).

Appendix B. Raw data from ranking and weighting stages

Table 12. Raw data from ranking exercise

Criteria	User 1	User 2	User 3	User 4	User 5	User 6	Mean	SD	Final rank
long-term mortality	1	1	1	1	2	1	1.2	0.4	1
procedural stroke	9	2	13	2	1	2	4.8	5	2
severe paravalvular leak	4	4	8	3	4	14	6.2	4.2	3
safety and effectiveness in annulus/left ventricular outflow tract calcium	2	7	12	14	6	4	7.5	4.6	4
vascular complications	3	3	10	18	9	5	8	5.7	5
predicted post-procedural haemodynamics/risk of patient prothesis mismatch	11	12	7	6	7	15	9.7	3.6	6
minimum vessel size for access	6	16	3	15	8	11	9.8	5.1	7
long-term durability data	16	9	4	5	14	12	10	4.9	8
ease of coronary access/What is later coronary access like?	14	10	6	11	17	5	10.5	4.6	9
flexibility and deliverability of valve system to be able to deal with tortuosity, calcification, and angulated aortas	7	19	2	12	16	7	10.5	6.3	10
risk of post procedural conduction abnormality	10	5	11	13	18	7	10.7	4.6	11
treatable annulus size range	13	8	9	16	15	3	10.7	4.9	12
pacemaker implantation rate	5	5	15	7	22	10	10.7	6.7	13
risk of coronary compromise (obstruction, create difficult later access)	8	10	14	17	3	16	11.3	5.4	14
length of hospital stay, including ICU stay	12	14	19	10	10	9	12.3	3.7	15

health-related quality of life	18	18	18	8	5	-*	13.4	6.4	16
heart failure	17	13	22	4	11	-	13.4	6.7	17
reintervention rate	22	14	17	9	20	13	15.8	4.8	18
conversion to surgery	20	21	5	20	12	20	16.3	6.5	19
cost	19	16	16	19	21	23	19	2.8	20
atrial fibrillation	23	22	21	22	13	18	19.8	3.8	21
acute kidney injury	15	23	20	23	23	17	20.2	3.5	22
endocarditis	21	20	23	21	19	19	20.5	1.5	23

*missing data, user did not think these two criteria factored in their decision making so did not rank them

Table 13. Raw data from weighting exercise

Rank	Criteria	User 1	User 4	User 6	User 5	User 3	mean	SD	Overall weight
1	long-term mortality	10	50	0	0	10	14	20.74	0.219
2	procedural stroke	50	0	100	100	30	56	43.93	0.192
3	severe paravalvular leak	5	30	50	40	0	25	21.79	0.123
4	safety and effectiveness in annulus/left ventricular outflow tract calcium	30	20	50	80	30	42	23.87	0.099
5	vascular complications	20	0	50	70	10	30	29.15	0.069
6	predicted post-procedural haemodynamics/risk of patient prothesis mismatch	0	0	0	40	40	16	21.91	0.053

7	minimum vessel size for access	0	0	0	50	0	10	22.36	0.046
8	long-term durability data	30	30	0	50	20	26	18.17	0.042
9	ease of coronary access/ What is later coronary access like?	10	0	0	80	0	18	34.93	0.033
10	flexibility and deliverability of valve system to be able to deal with tortuosity, calcification, and angulated aortas	25	10	100	40	30	41	34.71	0.028
11	risk of post procedural conduction abnormality	10	10	0	20	20	12	8.37	0.02
12	treatable annulus size range	0	10	50	90	40	38	35.64	0.018
13	pacemaker implantation rate	15	10	33	0	20	15.6	12.22	0.013
14	risk of coronary compromise (obstruction, create difficult later access)	20	0	100	100	30	50	46.9	0.011
15	length of hospital stay, including ICU stay	30	0	0	20	10	12	13.04	0.007
16	health-related quality of life	0	0	100	80	40	44	45.61	0.007
17	heart failure	0	0	0	80	20	20	34.64	0.005
18	reintervention rate	0	0	0	100	20	24	43.36	0.004
19	conversion to surgery	50	10	0	10	10	16	19.49	0.003
20	cost	70	10	100	40	30	50	35.36	0.003
21	atrial fibrillation	0	0	0	20	20	8	10.95	0.002

22	acute kidney injury	0	0	0	40	20	12	17.89	0.002
23	endocarditis								0.001

*points are attributed to the criterion based on the mean importance relative to the criterion below. These are used to calculate the final weight

Table 14. TAVI devices available to users

User number	Sapien 3	Sapien 3 Ultra	Evolut R	Evolut Pro+	Evolut FX	Allegra	ACURATE neo2	Hydra	Myval Octacor	Navitor	Trilogy
1	X									X	
2*		X					X			X	X
3	X	X	X	X	X		X		X		
4	X	X	X		X					X	X
5	X	X	X	X	X	X			X	X	
6	X	X	X	X	X				X		
7^											
8		X				X			X	X	
9$											

* also stated “Medtronic – Evolut” but did not specify which model

^ only provided manufacturer: Edward, Boston, Medtronic

$ missing data

Appendix C. Glossary

Term	Definition
SMART ranking technique	Simple Multi-Attribute Rating Technique is a process mainly used in Multi Criteria Decision Analysis. It allows a group of alternatives to be ordered by importance. Individual responses from each member of the sample are collated and then meaned ensuring equal say among the group (Von Winterfeldt D, Edwards W. (1993) Decision analysis and behavioral research. Cambridge: Cambridge University Press).
Swing weighting technique	Swing weighting is also a process often used in Multi Criteria Decision Analysis. It is a method used for calculating and reporting the relative importance (weight) of each of the alternatives from a ranked group. Each member of the provides individual answers to questions asking them to decide (on a scale of 0-100%) how important each criterion is over the criterion below it. All of the responses from each member of the sample are then collated and meaned. After this, weights are calculated (Von Winterfeldt D, Edwards W. (1993) Decision analysis and behavioral research. Cambridge: Cambridge University Press).
Performance rule	A rule which describes how the users measure performance of the technology in question against the criteria.
Performance matrix	A list of the most important criteria to users, and the performance rules associated with these criteria.

Appendix D. Interventional cardiologist participants

Dr Clare Appleby, Liverpool Heart and Chest Hospital

Professor Adrian Banning, Oxford University Hospitals NHS Trust

Professor Dan Blackman, Leeds Teaching Hospitals NHS Trust

Professor David Hildick-Smith, University Hospitals Sussex

Professor Rajesh Kharbanda, Oxford University Hospitals NHS Trust

Dr Ranjit More, Blackpool Teaching Hospitals NHS Trust

Dr Douglas Muir, South Tees Hospitals NHS Foundation Trust

Dr Jaydeep Sarma, Manchester University Hospitals NHS Foundation Trust

Professor Azfar Zaman, Newcastle upon Tyne NHS Hospitals