National Institute for Health and Care Excellence

Draft

Heart valve disease presenting in adults: investigation and management

[J] Evidence review for anticoagulant and/or antiplatelet therapy for biological prosthetic valves and after valve repair

NICE guideline

Intervention evidence review underpinning recommendations 1.7.1 to 1.7.3 and research recommendations in the NICE guideline

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Draft for Consultation

This evidence review was developed by the National Guideline Centre

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1 Anticoagulant and antiplatelet use after biological valve replacement and valve repair

1.1 Review question: What is the clinical and cost effectiveness of anticoagulant and/or antiplatelet therapy for adults with transcatheter or surgical biological prosthetic valves or after valve repair?

1.2 Introduction

Anticoagulation is essential for patients with mechanical prosthetic heart valves. However, controversy exists in clinical practice regarding the use of anticoagulant and/or antiplatelet therapy for transcatheter or surgical prosthetic valves. Consequently, it is important to determine the clinical and cost effectiveness of anticoagulant and/or antiplatelet therapy in this setting, examining the associated risks and benefits.

1.3 PICO table

For full details see the review protocol in Appendix A:.

Table 1: PICO characteristics of review question

Population	Adults aged 18 years and over with repaired valves or biological prosthetic valves stratified by type of intervention: • Transcatheter intervention • Surgical intervention. Exclusion: • Children (aged <18 years). • Adults with congenital heart disease (excluding bicuspid aortic valves). • Tricuspid stenosis and pulmonary valve disease. • Adults who have had a mechanical valve replacement.
Interventions	Oral anticoagulation therapy: • Vitamin K antagonists (VKA) (including: warfarin, acenocoumarol and phenindione) • Direct acting oral anticoagulants (DOAC) (including: dabigatran, rivaroxaban, apixaban and edoxaban) Oral antiplatelet therapy: • Single antiplatelet therapy (SAPT) (including: aspirin, clopidogrel, ticagrelor or prasugrel) • Dual antiplatelet therapy (DAPT) (the combination of aspirin with either clopidogrel, ticagrelor or prasugrel) Combined oral anticoagulation and oral antiplatelet therapy.
Comparisons	Other active comparator listed above. Placebo. No treatment or standard care (for example, treatment with all other required medication post-valve replacement apart from anticoagulants/antiplatelets).

Outcomes	Primary outcomes: • All-cause mortality at ≤12 months and >1 year (dichotomous) • Health-related quality of life at ≤12 months and >1 year (continuous) • Major bleeding at ≤12 months and >1 year (dichotomous) • Minor bleeding at ≤12 months and >1 year (dichotomous) • Arterial thromboembolic events at ≤12 months and >1 year (dichotomous) Secondary outcomes: • Hospital re-admission at 12 months (dichotomous) • Withdrawal due to adverse events at 12 months (dichotomous) • Thrombus on imaging at <12 months (dichotomous) • Need for intervention at medium term (6 months to 1 year) and long term (>1 year) (time-to-event) • Valve degeneration (mean transvalvular gradient) at ≥1 year (continuous)
Study design	RCTs or Systematic Reviews of RCTs

1.4 Clinical evidence

1.4.1 Included studies

A search was conducted for randomised controlled trials comparing the effectiveness of antithrombotic agents (including anticoagulants and antiplatelet therapies) against other antithrombotic agents, placebo or no treatment with antithrombotic agents.

Ten studies reported in 11 publications were included in the review;[15, 18, 19, 23, 31, 50, 57, 62, 68, 73, 75] these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary tables below (Table 3, Table 4, Table 5,Table 6, Table 7 and Table 8).

The evidence covered the following populations and comparisons:

Surgical valve replacement

- DOAC versus VKA: 1 study[23]
- VKA versus SAPT: 2 studies[18, 57]
- VKA and SAPT versus VKA alone: 1 study[73]

Transcatheter valve implantation

- SAPT versus DAPT: 3 primary studies[62, 68, 75], and 1 individual patient data meta analysis[31]
- direct-acting oral anticoagulant (+single antiplatelet therapy for 3 months) vs. single antiplatelet therapy alone (+clopidogrel for 3 months): 1 study[19]
- oral anticoagulant + single antiplatelet therapy vs. oral anticoagulant alone: 1 study[50]

One individual patient data (IPD) meta-analysis[31] was included, which contained two studies identified during the search[68, 75]. The risk of bias for this systematic review was assessed using the ROBIS checklist, and the primary studies were also assessed. Only additional outcomes (not included in the IPD) were extracted from the individual studies.

No studies were included that discussed antithrombotic therapy in heart valve repair.

See also the study selection flow chart in Appendix C:, study evidence tables in Appendix D:, forest plots in Appendix E: and GRADE tables in Appendix F:.

1.4.2 Excluded studies

See the excluded studies list in Table 20.

A Cochrane review[46] was identified but could not be included as it included studies with people who had mechanical prosthetic valves and biological prosthetic valves. The studies did not separate the people with mechanical prosthetic valves and biological prosthetic valves and so were not applicable to our protocol. All included studies were cross-checked for inclusion in this review.

1.4.8 Summary of clinical studies included in the evidence review

2 **Table 2: Summary of studies included in the evidence review**

Study	Intervention and comparison	Population	Outcomes	Comments
Surgical valve replacement, direct-acting oral anticoagulant vs. vitamin K antagonist				
Duraes 2016[23]	**Dabigatran** 110mg orally twice daily. If on warfarin prior they underwent a washout period and dabigatran was introduced when INR <2.5. For up to 3 months. **Warfarin** Oral. Target INR between 2.0 and 3.0. For up to 3 months.	Adults 18-64 years old (mean age in dabigatran arm: 48.8±10.4 mean age in warfarin arm: 45.7±6) who underwent mitral and/or aortic bioprosthetic valve replacement (underlying preoperative valve disease not discussed) in the 3 months prior to entering the study and had documented atrial fibrillation postoperatively. 1 patient had diabetes mellitus. Preoperatively 8 patients were classified as NYHA class III-IV. Mean LVEF was 40±12 in the dabigatran arm and 50±10 in the warfarin arm.	All-cause mortality at 3 months Bleeding at 3 months Arterial thromboembolic events at 3 months Hospital re-admission at 3 months Thrombus on imaging at 3 months	DAWA trial No funding noted
Surgical valve replacement, vitamin K antagonist vs. single antiplatelet therapy				
Colli 2007[18]	**Warfarin, followed by aspirin** Oral. Warfarin for up to 3 months. Target INR between 2.0 and 3.0.	Adults (mean age in aspirin arm: 70.7±3.7, mean age in warfarin arm: 69.5±3.3) who required, for the first time, isolated aortic valve	All-cause mortality at 6 months Major bleeding at 6 months	WoA Epic trial Principle author funded by industry (Andrea Colli was a

	After 3 months the warfarin was stopped and aspirin (100mg/day) was started for up to a further 3 months. **Aspirin** **100mg/day orally for up to 6 months.**	replacement (50 people had preoperative aortic stenosis, 8 had aortic insufficiency, 11 had mixed aortic valve disease) and were in sinus rhythm before implantation. No patients had atrial fibrillation at the start of the study. 22 patients had diabetes mellitus. 20 patients had dyslipidaemia. Preoperatively, 53 (78%) people were classified as New York Heart Association (NYHA) class III-IV. Mean left ventricular ejection fraction (LVEF) was 53.6±11.6 in the aspirin arm and 52.5±10.2 in the warfarin arm.	Arterial thromboembolic events at 3 months and 6 months	clinical investigator for St. Jude Medical, Minneapolis, MN, USA).
Rafiq 2017[57]	**Warfarin** 5mg orally initial dose. Target INR between 2.0 and 3.0. **Aspirin** 150mg orally Patients who underwent a coronary artery bypass grafting (CABG) surgery at the same time as intervention received warfarin and aspirin 75mg or aspirin 150mg only.	Adults aged ≥60 years (mean age in warfarin arm: 73.1±6.4, mean age in aspirin arm: 72.7±7.2) referred for first time aortic valve replacement (underlying preoperative valve disease not discussed) with or without CABG surgery in sinus rhythm. People were excluded from the study if they had a history of AF or atrial flutter, liver cirrhosis or were on	All-cause mortality at 3 months Major bleeding at 3 months Arterial thromboembolic events at 3 months Hospital re-admission at 3 months Thrombus on imaging at 3 months	No funding noted.

		renal dialysis. 67 (20.4%) had diabetes mellitus. 187 (57.0%) had dyslipidaemia. The median NYHA score for both arms was 2 (ranging from 1 to 4). The mean LVEF was 51.4±12.5 for the warfarin arm and 52.6±10.5 in the aspirin arm.		
Surgical valve replacement, vitamin K antagonist + single antiplatelet therapy vs. vitamin K antagonist alone				
Turpie 1993[73]	**Warfarin and aspirin** Warfarin orally. Target INR 3.0-4.5. Aspirin 100mg/day orally. **Warfarin and placebo** **Warfarin orally. Target INR 3.0-4.5.**	Adults with mechanical or tissue replacement valves and preoperative atrial fibrillation or a history of thromboembolism. 172 (46%) patients had aortic valve replacement, 162 (44%) patients had mitral valve replacement and 36 (10%) had multiple valves replaced.	Arterial thromboembolic event/Vascular mortality at 6 months.	Reports major systemic embolism or death from vascular causes for mechanical and bioprosthetic valves separately.
Transcatheter valve implantation, single antiplatelet therapy vs. dual antiplatelet therapy				
Brouwer 2020[15]	**Aspirin only** 80-100 mg daily for duration of trial and advised to take it on a lifelong basis. Loading dose of 300 mg aspirin prior to TAVI procedure for those that had not previously taken aspirin. **Aspirin and clopidogrel**	Adults (mean age ~80 years in both groups) scheduled to undergo TAVI (majority for normal-flow high-gradient or low-flow low-gradient aortic stenosis) and no current indication for long-term oral anticoagulation. Details of number with atrial fibrillation not clear, but likely excluded as this group only	All-cause mortality at 12 months Major bleeding at 12 months Minor bleeding at 12 months Arterial thromboembolic events at 12 months (stroke, myocardial infarction and lung embolism reported separately) Valve thrombosis at 12 months	POPular TAVI trial cohort A Said to be no industry involvement in the trial.

	Aspirin at a dose of 80-100 mg daily with 75 mg clopidogrel daily for 3 months, followed by aspirin alone at dose of 80-100 mg daily for rest of trial duration. Patients were advised to take aspirin on a lifelong basis. Loading dose of 300 mg aspirin prior to TAVI procedure for those that had not previously taken aspirin. An initial single loading dose of 300 mg clopidogrel was given the day before or on the day of the TAVI procedure.	included those with no current indication for oral anticoagulation. Mean estimated glomerular filtration rate was ~58 ml/min/1.73 m^2 in both groups. 24-25% had diabetes mellitus and >70% had hypertension in both groups. Ejection fraction was >31-50% in 22% vs. 20% and ≤30% in 4% vs. 7%.	Mean aortic valve gradient (valve degeneration) at 6 months	
Hassell 2015[31]	**Aspirin only** 81-100mg orally for up to 3-6 months. **Aspirin and clopidogrel** Aspirin 81-100mg orally for up to 3-6 months. **Clopidogrel 75mg orally for up to 3-6 months.**	Studies including patients with aortic stenosis treated by TAVI (transcatheter aortic valve implantation) with a clear explanation of postprocedural antithrombotic treatment including one group treated with single antiplatelet therapy and another treated with dual antiplatelet therapy for a minimum follow-up of 1 month. Mean age of patients in the Stabile study was 80±5.2 and in the Ussia study was 81±5.1. No patients had AF in the Stabile study, while 10	All-cause mortality at 6 months Major bleeding at 6 months Arterial thromboembolic events at 6 months	Systematic review with pooled analysis of individual patient data. Includes 2 RCTs (Stabile 2014[68] and Ussia 2011[75]) and 2 observational studies, which were analysed separately in their study (and not included in the analysis of this guideline as per the protocol (Appendix A)). No funding noted. All relevant studies were included.

		(12.7%) had preoperative AF in the Ussia study. 54 (45%) patients had renal disease in the Stabile study, while 11 (13.9%) had renal disease in the Ussia study. 34 (28.3%) patients had diabetes mellitus in the Stabile study, while 21 (26.6%) had diabetes mellitus in the Ussia study. All patients in the Stabile study classified as NYHA class III-IV preoperatively, while 60 (75.9%) patients were classified as such in the Ussia study. In the Stabile study, LVEF was 30-50% in 46 (38.3%) patients and <30% in 5 (4.2%) patients. In the Ussia study, LVEF was 30-50% in 50 (63.3%) patients, and <30% in 4 (5.1%) patients.		
Rodes-Cabau 2017[62]	**Aspirin alone** 80-100mg/day orally. **Aspirin and clopidogrel** Aspirin 80-100mg/day orally. Clopidogrel 75mg/day orally.	Adults (mean age: 79±9) with clinical indications for TAVR (does not explicitly express the type of valve disease. However, 41 (19%) people had moderate aortic regurgitation) with a balloon-expandable Edwards SAPIEN XT or SAPIEN 3 valve.	All-cause mortality at 3 months Major bleeding at 3 months Arterial thromboembolic events at 3 months	The ARTE trial Principle author and several other authors were funded by industry and the study was funded by industry (a grant from Edwards Lifesciences) and from academic sources.

		No patients had atrial fibrillation at the start of the study.140 (63%) patients (63%) had chronic renal failure (GFR <60mL/min). 173 (78%) patients had hypertension. 77 (35%) patients had diabetes mellitus. Preoperative ejection fraction was 55±12 in the clopidogrel and aspirin arm and 54±13 in the aspirin only arm.		
Stabile 2014[68]	**Aspirin only** 81mg orally for 3 months. **Aspirin and clopidogrel or ticlopidine** Aspirin 81mg orally for 3 months. Clopidogrel 75mg orally or Ticlopidine 500mg twice a day orally for 3 months. Unable to determine how many patients had clopidogrel and how many had ticlopidine.	Adults (mean age in single antiplatelet arm: 81.1±4.8, mean age in dual antiplatelet arm: 80.2±5.7) with severe aortic stenosis treated with TAVI. No patients had atrial fibrillation at the start of the study. Please see Hassell 2015 for further information.	As in Hassell[31] study (no additional outcomes)	SAT-TAVI trial Included in Hassell 2015[31] – the outcomes reported for this study are not included in the systematic review[31]. Non-principle authors were funded by industry (G. Sorropago and P. Rubino were proctors for Edwards Lifesciences).
Ussia 2011[75]	**Aspirin only** 100mg orally for 6 months. **Aspirin and clopidogrel** Aspirin 100mg orally for 6 months.	Adults (mean age 81±4) with severe aortic stenosis treated with TAVI. 10 patients (13%) had permanent atrial fibrillation. 1 patient had liver cirrhosis.	Minor bleeding at 6 months	Included in Hassell 2015[31] – the outcomes reported for this study are not included in the systematic review[31]. Principle author funded by industry (Dr Ussia was a proctor

	Clopidogrel 75mg orally for up to 6 months.	11 patients (14%) had chronic kidney disease. Please see Hassell 2015 for further information.		physician for Medtronic Incorporation).
Transcatheter valve implantation, direct-acting oral anticoagulant (+single antiplatelet therapy for 3 months) vs. single antiplatelet therapy alone (+clopidogrel for 3 months)				
Dangas 2020[19]	**Rivaroxaban (+aspirin for 3 months)** Rivaroxaban at 10 mg daily with aspirin at 75-100 mg daily for 3 months, followed by rivaroxaban monotherapy at 10 mg daily. In those that developed atrial fibrillation, rivaroxaban received at 20 mg once daily (or 15 mg if eGFR 30-50 ml/min/1.73 m^2). Median treatment duration with rivaroxaban was 428 days and with aspirin was 90 days. **Aspirin (+clopidogrel for 3 months)** Aspirin at 75-100 mg daily with clopidogrel at 75 mg daily for 3 months, followed by aspirin monotherapy at 75-100 mg daily. Initial loading dose of ≥300 mg clopidogrel recommended for those that had not previously received it.	Adults (mean age: 80-81 years in the two groups) that underwent successful TAVI for aortic stenosis. Current or previous atrial fibrillation with ongoing indication for oral anticoagulant treatment was an exclusion criterion. Mean estimated glomerular filtration rate was 73 ml/min/1.73 m^2 in both groups. 87.2% vs. 85.2% had hypertension. ~29% patients had diabetes mellitus in both groups. Post-TAVI ejection fraction was 57.4±10.9% vs. 58.2±11.2%.	All-cause mortality at median 428 days Major bleeding at median 428 days Minor bleeding at median 428 days Arterial thromboembolic events at median 428 days (stroke, myocardial infarction, pulmonary embolism and systemic embolism reported separately) Premature study drug discontinuation due to adverse events during trial Symptomatic valve thrombosis at median 428 days	GALILEO trial Study funded by industry (Bayer ad Janssen Pharmaceuticals).

	Patients that developed atrial fibrillation received vitamin K antagonists (INR 2-3) to replace clopidogrel within 3 months or to replace aspirin thereafter. Median treatment duration with aspirin was 474 days and with clopidogrel was 90 days.			
Transcatheter valve implantation, oral anticoagulant + single antiplatelet therapy vs. oral anticoagulant alone				
Nijenhuis 2020[50]	**Vitamin K antagonist or direct-acting oral anticoagulant + clopidogrel** Patients continued anticoagulation were receiving prior to randomisation, which could be VKA or DOAC. 70.5% were on a VKA and 29.5% were on a DOAC. Randomised to receive clopidogrel for 3 months in addition to their oral anticoagulation. Loading dose of 300 mg clopidogrel administered 1 day prior to or on day of TAVI, followed by 75 mg daily for 3 months. **Vitamin K antagonist or direct-acting oral anticoagulant** Patients continued anticoagulation were receiving prior to randomisation, which	Adults (mean age: ~81 years in the two groups) that underwent TAVI (majority for normal-flow high-gradient or low-flow low-gradient aortic stenosis) and already had an existing long-term indication for oral anticoagulation. >90% in each group had atrial fibrillation at baseline. Mean estimated glomerular filtration rate was 55.6 vs. 53.4 ml/min/1.73 m^2 in the two groups. 67.3% vs. 73.2% had hypertension. 29.5 vs. 27.4% patients had diabetes mellitus. Ejection fraction was 31-50% in 29.5% vs. 24.4% and ≤30% in 8.3% vs. 7.6%.	All-cause mortality at 12 months Major bleeding at 12 months Minor bleeding at 12 months Arterial thromboembolic events at 12 months (stroke and myocardial infarction reported separately) Mean aortic valve gradient (valve degeneration) at 6 months	POPular TAVI trial cohort B Said to be no industry involvement in the trial.

	could be VKA or DOAC. 75.2% were on a VKA and 23.6% were on a DOAC. Randomised not to receive clopidogrel for 3 months in addition to their oral anticoagulation.			

See Appendix D:for full evidence tables.

1.4.3 Quality assessment of clinical studies included in the evidence review

1.4.4.1 Surgical valve replacement

Table 3: Clinical evidence summary: DOAC versus VKA in surgical valve replacement

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with VKA	Risk difference with DOAC (95% CI)
All-cause mortality at ≤12 months	27 (1 study) 3 months	⨁⨁⊖⊖ LOW[b] due to imprecision	Peto OR 0.11 (0 to 5.44)	83 per 1000	8 fewer per 1000 (from 28 fewer to 11 more)[a]
Health-related quality of life at ≤12 months - not measured	0		Not estimable		
Major bleeding at ≤12 months	27 (1 study) 3 months	⨁⨁⊖⊖ LOW[b] due to imprecision	Peto OR 0.79 (0.05 to 13.6)	83 per 1000	16 fewer per 1000 (from 78 fewer to 469 more)
Minor bleeding at ≤12 months - not measured	0		Not estimable		

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with VKA	Risk difference with DOAC (95% CI)
Arterial thromboembolic events at ≤12 Arterial thromboembolic events at ≤12 months	27 (1 study) 3 months	⨁⨁⨀⨀ LOW[b] due to imprecision	Peto OR 0.79 (0.05 to 13.6)	83 per 1000	16 fewer per 1000 (from 78 fewer to 469 more)
Hospital re-admission at 12 months	27 (1 study) 3 months	⨁⨁⨀⨀ LOW[b] due to imprecision	Peto OR 0.79 (0.05 to 13.6)	83 per 1000	16 fewer per 1000 (from 78 fewer to 469 more)
Thrombus on imaging at ≤12 months	27 (1 study) 3 months	⨁⨁⨀⨀ LOW[b] due to imprecision	Peto OR 0.11 (0 to 5.44)	83 per 1000	8 fewer per 1000 (from 28 fewer to 11 more)[a]
All-cause mortality at >12 months - not measured	0		Not estimable		
Health-related quality of life at >12 months - not measured	0		Not estimable		
Major bleeding at >12 months - not measured	0		Not estimable		
Minor bleeding at >12 months - not measured	0		Not estimable		
Arterial thromboembolic events at >12 months - not measured	0		Not estimable		

[a] Absolute effect calculated manually using risk difference as zero events in one arm of the study
[b] Downgraded by 2 increments as the confidence interval crossed two MIDs ±

Table 4: Clinical evidence summary: VKA versus SAPT in surgical valve replacement

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with SAPT	Risk difference with VKA (95% CI)
All-cause mortality at ≤12 months	397 (2 studies) 3-6 months	⨁⊖⊖⊖ VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 1.22 (0.49 to 3.04)	47 per 1000	10 more per 1000 (from 24 fewer to 96 more)
Health-related quality of life at ≤12 months - not reported	0		Not estimable		
Major bleeding at ≤12 months	397 (2 studies) 3-6 months	⨁⊖⊖⊖ VERY LOW[a,b,d] due to risk of bias, indirectness, imprecision	RR 2.94 (0.97 to 8.95)	24 per 1000	47 more per 1000 (from 1 fewer to 191 more)
Minor bleeding at ≤12 months - not measured	0		Not estimable		
Arterial thromboembolic events at ≤12 months	397 (2 studies) 3-6 months	⨁⊖⊖⊖ VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 0.82 (0.37 to 1.76)	63 per 1000	11 fewer per 1000 (from 40 fewer to 48 more)
Hospital re-admission at 12 months	328 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW[b,c] due to indirectness, imprecision	RR 1.15 (0.67 to 1.97)	130 per 1000	19 more per 1000 (from 43 fewer to 126 more)
Thrombus on imaging at ≤12 months	328 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW[b,c] due to indirectness, imprecision	Peto OR 0.13 (0 to 6.58)	6 per 1000	10 fewer per 1000 (from 20 fewer to 10 more)[e]
All-cause mortality at >12 months - not measured	0		Not estimable		

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with SAPT	Risk difference with VKA (95% CI)
Health-related quality of life at >12 months - not measured	0		Not estimable		
Major bleeding at >12 months - not measured	0		Not estimable		
Minor bleeding at >12 months - not measured	0		Not estimable		
Arterial thromboembolic events at >12 months - not measured	0		Not estimable		

[a] Downgraded by 1 increment as the majority of the evidence was at high risk of bias
[b] Downgraded by 1 increment as one study included people who had a CABG while having the valve replacement surgery. The people in the intervention arm were subsequently given warfarin and aspirin, instead of just warfarin.
[c] Downgraded by 2 increments as the confidence interval crossed both MIDs
[d] Downgraded by 1 increment as the confidence interval crossed one MID
[e] Absolute effect calculated manually using risk difference as zero events in one arm of the study

Table 5: Clinical evidence summary: VKA and SAPT versus VKA alone in surgical valve replacement

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with VKA	Risk difference with VKA and SAPT (95% CI)
All-cause mortality at ≤12 months - not measured	0		Not estimable		
Health-related quality of life at ≤12 months - not measured	0		Not estimable		
Major bleeding at ≤12 months - not measured	0		Not estimable		
Minor bleeding at ≤12 months - not measured	0		Not estimable		

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with VKA	Risk difference with VKA and SAPT (95% CI)
Major systemic embolism or death from vascular causes at ≤12 months	89 (1 study)	⨁⊖⊖⊖ VERY LOW[a,b] due to indirectness, imprecision	RR 0.49 (0.09 to 2.53)	91 per 1000	46 fewer per 1000 (from 83 fewer to 139 more)
All-cause mortality at >12 months - not measured	0		Not estimable		
Health-related quality of life at >12 months - not measured	0		Not estimable		
Major bleeding at >12 months - not measured	0		Not estimable		
Minor bleeding at >12 months - not measured	0		Not estimable		
Arterial thromboembolic events at >12 months - not measured	0		Not estimable		

[a] Downgraded by 1 increment as the evidence reported thromboembolic events/vascular mortality and did not report the protocol outcome of thromboembolic events excluding mortality
[b] Downgraded by 2 increments as the confidence interval crossed both MIDs

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1.4.4.2 Transcatheter valve implantation

3 **Table 6: Clinical evidence summary: SAPT versus DAPT in biological transcatheter valve implantation**

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with DAPT	Risk difference with SAPT (95% CI)
All-cause mortality at ≤12 months	1086 (4 studies)	⨁⊖⊖⊖ VERY LOW[b,c]	OR 0.94 (0.56 to 1.6)[a]	56 per 1000	3 fewer per 1000

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with DAPT	Risk difference with SAPT (95% CI)
	3-12 months	due to risk of bias, imprecision			(from 24 fewer to 31 more)
Health-related quality of life at ≤12 months - not measured	0		Not estimable		
Major bleeding at ≤12 months	1086 (4 studies) 3-12 months	⨁⨁⨁⨀ MODERATE[b] due to risk of bias	OR 0.48 (0.3 to 0.77)[a]	100 per 1000	49 fewer per 1000 (from 21 fewer to 68 fewer)
Minor bleeding at ≤12 months	744 (2 studies) 6-12 months	⨁⨁⨀⨀ LOW[b,d] due to risk of bias, imprecision	RR 0.64 (0.43 to 0.94)	131 per 1000	47 fewer per 1000 (from 8 fewer to 75 fewer)
Arterial thromboembolic events at ≤12 months	222 (3 studies) 3-6 months	⨁⨀⨀⨀ VERY LOW[b,c] due to risk of bias, imprecision	OR ranged from 0.21 to 2.24[a,e]	Not estimable	
Stroke (arterial thromboembolic events) at 12 months	665 (1 study) 12 months	⨁⨀⨀⨀ VERY LOW[b,c] due to risk of bias, imprecision	RR 0.9 (0.48 to 1.71)	57 per 1000	6 fewer per 1000 (from 30 fewer to 40 more)
Myocardial infarction (arterial thromboembolic events) at 12 months	665 (1 study) 12 months	⨁⨀⨀⨀ VERY LOW[b,c] due to risk of bias, imprecision	RR 0.67 (0.19 to 2.36)	18 per 1000	6 fewer per 1000 (from 15 fewer to 24 more)
All-cause mortality at >12 months - not measured	0		Not estimable		
Health-related quality of life at >12 months - not measured	0		Not estimable		
Major bleeding at >12 months - not measured	0		Not estimable		
Minor bleeding at >12 months - not measured	0		Not estimable		
Arterial thromboembolic events at >12 months - not measured	0		Not estimable		

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with DAPT	Risk difference with SAPT (95% CI)
Hospital readmission at 12 months - not measured	0		Not estimable		
Withdrawal due to adverse events at 12 months - not measured	0		Not estimable		
Symptomatic clinical aortic valve thrombosis (thrombus on imaging) at 12 months	665 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[b,c] due to risk of bias, imprecision	OR 2.76 (0.39 to 19.65)	3 per 1000	5 more per 1000 (from 2 fewer to 53 more)
Need for reintervention at 6-12 months - not measured	0		Not estimable		
Need for reintervention at >12 months - not measured	0		Not estimable		
Mean aortic valve gradient (valve degeneration) at ≤12 months	665 (1 study) 6 months	⨁⨁⨁⊖ MODERATE[b,f] due to risk of bias		The mean aortic valve gradient (valve degeneration) at ≤12 months in the control groups was 10.8 mmHg	The mean aortic valve gradient (valve degeneration) at ≤12 months in the intervention groups was 0.20 lower (1.09 lower to 0.69 higher)

[a] Odds ratio used because this summary statistic was reported for the two studies included in the IPD MA
[b] Downgraded by 1 increment as the majority of the evidence was at high risk of bias
[c] Downgraded by 2 increments as the confidence interval crossed both MIDs
[d] Downgraded by 1 increments as the confidence interval crossed one MID
[e] Outcome reported as a range of odds ratios due to heterogeneity between studies with a large difference in point estimates without sufficient study number to form valid subgroups
[f] MIDs used to assess imprecision were ±2.60

Table 7: Clinical evidence summary: DOAC (+ aspirin for 3 months) versus aspirin (+ clopidogrel for 3 months) in biological transcatheter valve implantation

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with aspirin (+clopidogrel for 3 months) post TAVI	Risk difference with DOAC (+aspirin for 3 months) (95% CI)
All-cause mortality at ≤12 months - not measured	0		Not estimable		
Health-related quality of life at ≤12 months - not measured	0		Not estimable		
Major bleeding at ≤12 months - not measured	0		Not estimable		
Minor bleeding at ≤12 months - not measured	0		Not estimable		
Arterial thromboembolic events at ≤12 months - not measured	0		Not estimable		
All-cause mortality at >12 months - median treatment duration 428 days	1644 (1 study) 428 days	⨁⨁⨀⨀ LOW[a,b] due to risk of bias, imprecision	RR 1.67 (1.13 to 2.46)	47 per 1000	31 more per 1000 (from 6 more to 69 more)
Health-related quality of life at >12 months - not measured	0		Not estimable		

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with aspirin (+clopidogrel for 3 months) post TAVI	Risk difference with DOAC (+aspirin for 3 months) (95% CI)
Major bleeding at >12 months - VARC-2 life-threatening, disabling or major bleeding - median treatment 428 days	1644 (1 study) 428 days	⨁⨁⨀⨀ LOW[a,b] due to risk of bias, imprecision	RR 1.47 (0.94 to 2.29)	38 per 1000	18 more per 1000 (from 2 fewer to 49 more)
Major bleeding at >12 months - BARC type 2, 3 or 5 bleeding - median treatment 428 days	1644 (1 study) 428 days	⨁⨁⨁⨀ MODERATE[a] due to risk of bias	RR 1.72 (1.34 to 2.21)	104 per 1000	75 more per 1000 (from 35 more to 126 more)
Major bleeding at >12 months - ISTH major bleeding - median treatment 428 days	1644 (1 study) 428 days	⨁⨁⨀⨀ LOW[a,b] due to risk of bias, imprecision	RR 1.62 (1.04 to 2.52)	37 per 1000	23 more per 1000 (from 1 more to 56 more)
Minor bleeding at >12 months - TIMI major or minor bleeding - median treatment 428 days	1644 (1 study) 428 days	⨁⨀⨀⨀ VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 1.73 (1.06 to 2.83)	29 per 1000	21 more per 1000 (from 2 more to 53 more)
Stroke (arterial thromboembolic events) at >12 months - median treatment 428 days	1644 (1 study) 428 days	⨁⨀⨀⨀ VERY LOW[a,d] due to risk of bias, imprecision	RR 1.19 (0.71 to 2)	31 per 1000	6 more per 1000 (from 9 fewer to 31 more)
Myocardial infarction (arterial thromboembolic events) at >12 months - median treatment 428 days	1644 (1 study) 428 days	⨁⨀⨀⨀ VERY LOW[d,e] due to risk of bias, imprecision	RR 1.34 (0.72	21 per 1000	7 more per 1000 (from 6 fewer to 31 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with aspirin (+clopidogrel for 3 months) post TAVI	Risk difference with DOAC (+aspirin for 3 months) (95% CI)
			to 2.49)		
Pulmonary embolism (arterial thromboembolic events) at >12 months - median treatment 428 days	1644 (1 study) 428 days	⨁⊖⊖⊖ VERY LOW[d,e] due to risk of bias, imprecision	OR 1.48 (0.26 to 8.55)	2 per 1000	1 more per 1000 (from 1 fewer to 15 more)
Systemic embolism (arterial thromboembolic events) at >12 months- median treatment 428 days	1644 (1 study) 428 days	⨁⊖⊖⊖ VERY LOW[d,e] due to risk of bias, imprecision	OR 0.99 (0.06 to 15.85)	1 per 1000	0 fewer per 1000 (from 1 fewer to 15 more)
Hospital readmission at 12 months - not measured	0		Not estimable		
Premature study drug discontinuation (withdrawal due to adverse events - thromboembolic, bleeding or other adverse events) at 12 months - median treatment duration 428 days	1644 (1 study) 428 days	⨁⨁⊖⊖ LOW[e] due to risk of bias	RR 2.01 (1.6 to 2.54)	111 per 1000	112 more per 1000 (from 67 more to 171 more)
Symptomatic valve thrombosis (thrombus on imaging) at <12 months - median treatment duration 428 days	1644 (1 study) 428 days	⨁⊖⊖⊖ VERY LOW[a,d] due to risk of bias, imprecision	OR 0.44 (0.13 to 1.54)	9 per 1000	5 fewer per 1000 (from 8 fewer to 5 more)
Need for reintervention at 6-12 months - not measured	0		Not estimable		

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with aspirin (+clopidogrel for 3 months) post TAVI	Risk difference with DOAC (+aspirin for 3 months) (95% CI)
Need for reintervention at >12 months - not measured	0		Not estimable		
Valve degeneration (mean transvalvular gradient) at ≥12 months - not measured	0		Not estimable		

[a] Downgraded by 1 increment as the majority of the evidence was at high risk of bias
[b] Downgraded by 1 increments as the confidence interval crossed one MID
[c] Combines major and minor bleeding rather than reporting minor bleeding events separately
[d] Downgraded by 2 increments as the confidence interval crossed both MIDs
[e] Downgraded by 2 increments as the majority of the evidence was at very high risk of bias

Table 8: Clinical evidence summary: Anticoagulant (VKA or DOAC) + SAPT (clopidogrel) versus anticoagulant (VKA or DOAC) alone in biological transcatheter valve implantation

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with anticoagulant alone post TAVI	Risk difference with Anticoagulant (VKA or DOAC) + clopidogrel (95% CI)
All-cause mortality at ≤12 months	313 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 1.15 (0.67 to 1.98)	134 per 1000	20 more per 1000 (from 44 fewer to 131 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with anticoagulant alone post TAVI	Risk difference with Anticoagulant (VKA or DOAC) + clopidogrel (95% CI)
Health-related quality of life at ≤12 months - not measured	0		Not estimable		
Major bleeding at ≤12 months - VARC-2 life-threatening, disabling or major bleeding (major bleeding) at 12 months	313 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[a,b,d] due to risk of bias, indirectness, imprecision	RR 1.87 (1.01 to 3.44)	89 per 1000	77 more per 1000 (from 1 more to 217 more)
Minor bleeding at ≤12 months - VARC-2 minor bleeding (minor bleeding) at 12 months	313 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[a,b,d] due to risk of bias, indirectness, imprecision	RR 1.41 (0.83 to 2.39)	127 per 1000	52 more per 1000 (from 22 fewer to 177 more)
Stroke (arterial thromboembolic events) at ≤12 months	313 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 1.01 (0.41 to 2.47)	57 per 1000	1 more per 1000 (from 34 fewer to 84 more)
Myocardial infarction (arterial thromboembolic events) at ≤12 months	313 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[b,c,e] due to risk of bias,	OR 1.01 (0.06 to 16.16)	6 per 1000	0 more per 1000 (from 6 fewer to 83 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with anticoagulant alone post TAVI	Risk difference with Anticoagulant (VKA or DOAC) + clopidogrel (95% CI)
		indirectness, imprecision			
All-cause mortality at >12 months - not measured	0		Not estimable		
Health-related quality of life at >12 months - not measured	0		Not estimable		
Major bleeding at >12 months - not measured	0		Not estimable		
Minor bleeding at >12 months - not measured	0		Not estimable		
Arterial thromboembolic events at >12 months - not measured	0		Not estimable		
Hospital readmission at 12 months - not measured	0		Not estimable		
Withdrawal due to adverse events at 12 months - not measured	0		Not estimable		
Thrombus on imaging at <12 months - not measured	0		Not estimable		
Need for reintervention at 6-12 months - not measured	0		Not estimable		

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with anticoagulant alone post TAVI	Risk difference with Anticoagulant (VKA or DOAC) + clopidogrel (95% CI)
Need for reintervention at >12 months - not measured	0		Not estimable		
Mean aortic valve gradient (valve degeneration - transvalvular gradient) at ≥12 months	264 (1 study) 6 months	⨁⊖⊖⊖ VERY LOW[a,d,e,f] due to risk of bias, indirectness, imprecision		The mean aortic valve gradient (valve degeneration - transvalvular gradient) at ≥12 months in the control groups was 9 mmHg	The mean aortic valve gradient (valve degeneration - transvalvular gradient) at ≥12 months in the intervention groups was 1.5 higher (0.29 to 2.71 higher)

[a]Downgraded by 1 increment as the majority of the evidence was at high risk of bias
[b] Anticoagulation includes a mixture of some receiving VKAs and some receiving DOACs, whereas ideally aimed to look at these groups separately
[c] Downgraded by 2 increments as the confidence interval crossed both MIDs
[d] Downgraded by 1 increment as the confidence interval crossed one MID
[e] Downgraded by 2 increments as the majority of the evidence was at very high risk of bias
[f] MIDs used to assess imprecision ±2.55

1

1.4.4.3 Valve repair

3 No information available.

4 See Appendix F: for full GRADE tables.

5

1.5 Economic evidence

1.5.1 Included studies

No health economic studies were included.

1.5.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix G:.

1.5.8 Summary of studies included in the economic evidence review

No economic evidence identified.

1.5.14 Health economic modelling

This question was not prioritised for economic modelling.

1.5.15 Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Table 9: UK costs of anticoagulant and antiplatelet drugs

Drug class	Drug	Daily dose	Cost – per day
Vitamin K antagonist	Warfarin tablet	5mg daily [(a)]	£0.01
	Acenocoumarol	4mg daily [(b)]	£0.18
	Phenindione	100mg daily [(c)]	£76.88
Direct acting anticoagulants (DOACs)	Dabigatran capsule	110mg-150mg twice daily	£1.70
	Rivaroxaban tablet	20mg once daily	£1.80
	Apixaban tablet	2.5-5mg twice daily	£1.90
	Edoxaban tablet	60mg once daily	£1.75
Antiplatelet	Aspirin tablet	75mg once daily	£0.05
	Clopidogrel	75mg once daily	£0.05
	Ticagrelor	90mg twice daily [(d)]	£1.95
	Prasugrel	5mg once daily [(e)]	£1.70

Source: BNF 2019[37]

(a) Assumed here to be an average daily dose of 5mg. Initially 5–10 mg, to be taken on day 1; subsequent doses dependent on the prothrombin time, reported as INR (international normalised ratio), a lower induction dose can be given over 3–4 weeks in patients who do not require rapid anticoagulation, elderly patients to be given a lower induction dose; maintenance 3–9 mg daily, to be taken at the same time each day.

(b) 4mg used for calculation but BNF states daily dose is 1-8mg depending on response.

(c) 100mg daily dose used for calculation but guidance is for 50-100mg

(d) 180mg loading dose also required

(e) Based on guidance for >75 year olds. 60mg loading dose also required

1.5.16 Monitoring

For warfarin there is also the cost of monitoring. In the previous update of the guideline (CG178), the annual cost of warfarin monitoring (anticoagulation clinic) was reported in the costing template as £241.54 a year (2014 cost year). This equates to a daily cost of £0.66, or £0.67 when including the drug cost of warfarin as well.

1.6 Evidence statements

1.6.1 Clinical evidence statements

See the summary of evidence in Table 3, **Table 4**, **Table 5**, **Table 6**, **Table 7** and **Table 8**.

1.6.2 Health economic evidence statements

- No relevant economic evaluations were identified.

1.7 The committee's discussion of the evidence

1.7.1 Interpreting the evidence

1.7.1.1 The outcomes that matter most

The critical outcomes were all-cause mortality, health-related quality of life, major bleeding, minor bleeding and arterial thromboembolic events (including myocardial infarction, stroke and transient ischaemic attack). These events were considered critical due to their consequences to people with heart valve disease. The important outcomes were hospital re-admission, withdrawal from the study due to adverse events, thrombus on imaging of the valve, need for re-intervention and valve degeneration.

Thrombus on valve imaging was considered important by the committee as this is believed to reduce valve durability by provoking earlier valve degeneration (measured by transvalvular gradient). This will affect patients in the long-term as it will mean they require re-intervention earlier. Valve degeneration can present in multiple ways, including a drop in mean calculated effective valve area and development of valvular regurgitation, but valve degeneration as measured by transvalvular gradient was prioritised for inclusion in this review.

Health-related quality of life, need for re-intervention and valve degeneration were not reported in any of the studies, possibly because the length of follow-up in the studies was short and studies did not aim to measure these types of outcomes where any effects would take longer to occur, with the longest follow-up being ~12 months.

1.7.1.2 The quality of the evidence

Eleven studies, including one systematic review (with individual patient data) and ten randomised controlled trials were included in this review. No relevant clinical studies for antithrombotic therapy in valve repair were identified. Evidence was available for the following comparisons:

- Biological surgical valve replacement
  - DOAC versus VKA
  - VKA versus SAPT
  - VKA and SAPT versus VKA alone
- Transcatheter valve implantation
  - SAPT versus DAPT
  - DOAC (+SAPT for 3 months) versus SAPT (DAPT for 3 months)
  - Anticoagulant (VKA or DOAC) + SAPT versus anticoagulant alone (VKA or DOAC)

Most of the evidence ranged from low to very low quality. Three outcomes in the transcatheter valve group were of moderate quality: major bleeding and mean aortic valve gradient at short term time points for SAPT versus DAPT, major bleeding at >12 months for DOAC (+ aspirin for 3 months) versus aspirin (+ clopidogrel for 3 months). Evidence quality was often downgraded due to the risk of bias and imprecision. Common problems leading to risk of bias were issues with selection bias, including groups not being comparable at baseline for all reported factors in some studies and some studies where allocation concealment was not described, and incomplete outcome data due to missing data rates being high or not well reported.. The majority of the analyses were based on data from a small number of participants and some outcomes had low event rates resulting in uncertainty. One study was downgraded for indirectness because participants were given a mixture of medications included in our protocol and a medication excluded from our protocol without a way to separate out the cases affected.

Based on the limitations of the evidence, including the population being limited to older adults, lack of a placebo comparison and a lack of data longer than 12 months follow-up, the strength of the recommendation made for single antiplatelet therapy after transcatheter intervention was limited to consider. A strong do not offer recommendation was made against the use of anticoagulation after surgical biological valve replacement supported by evidence of very low quality, but also based on the clinical experience of the committee.

1.7.12.3 Benefits and harms

Direct acting oral anticoagulants compared to vitamin K antagonists following surgical biological valve replacement

For the comparison of direct acting oral anticoagulants compared to vitamin K antagonists after surgical biological valve replacement, the committee agreed that there were no clinically significant differences for major bleeding, arterial thromboembolic events, hospital readmission and thrombus on imaging. A small benefit of direct acting oral anticoagulants was seen for reduced all-cause mortality. However, this effect estimate was based on a very small sample size (27 people) and a very low event rate reported during the follow up period of 3 months, and so the committee did not have confidence in this finding. The population of the study consisted of people who had atrial fibrillation post-operatively. This would alter the risk of arterial thromboembolic events compared to the population without atrial fibrillation and it was likely that the anti-thrombotic treatment was primarily used to manage the atrial fibrillation rather than the valve disease.

Based on this information and the lack of applicable evidence the committee agreed that they could not make a recommendation on the choice between vitamin K antagonists and direct acting oral anticoagulants for biological surgical valve replacement, and have included these treatment options in a recommendation for research (see Appendix J.1.5 for details), including long term outcomes. However, a recommendation was made on the use of anticoagulants in general based on the evidence discussed in the paragraph below and the experience of the committee.

Vitamin K antagonists compared to single antiplatelet therapy following surgical biological valve replacement

For the comparison of vitamin K antagonists with single antiplatelet therapy after surgical biological valve replacement, a clinically important benefit was seen for single antiplatelet therapy in reducing major bleeding events. The evidence also suggested a possible small benefit of single antiplatelet therapy in reducing all-cause mortality but there was too much uncertainty in the effect estimate to conclude whether or not this was a clinically important effect. This was associated with no clinically important difference between the two

interventions for arterial thromboembolic events, hospital re-admission and thrombus on imaging.

One of the included studies compared four treatment arms, where two groups had simultaneous coronary artery bypass grafting surgery and surgical valve replacement, while the others did not. The population who had coronary artery bypass grafting surgery would be at a greater risk of adverse events compared to the population having valve replacement alone, which made the evidence more difficult to interpret.

Both studies consisted of people without atrial fibrillation taking warfarin for three months. In one study, the people taking warfarin switched to aspirin after this time and continued this for three months while the other study concluded after three months. Therefore, the committee could not assess the long-term efficacy of treatment and made a research recommendation (see Appendix J.1.5 for details). The committee could not make a consensus recommendation.

Based on the evidence of an increased bleeding risk with vitamin K antagonists and no apparent reduction in risk for other outcomes, such as mortality or thromboembolic events, the lack of clinical difference between vitamin K antagonists and direct acting oral anticoagulants (as discussed in the paragraph above) and supported by clinical experience, the committee made a recommendation not to use anticoagulants after surgical biological valve replacement unless there are other indications for anticoagulant therapy. Where this is the case, the committee recommended following the existing guidelines for the relevant indication.

Combined anticoagulant and antiplatelet therapy compared to anticoagulant therapy alone following surgical biological valve replacement

For the comparison of combined vitamin K antagonists and single antiplatelet therapy compared to single antiplatelet therapy alone following surgical biological valve replacement, the evidence suggested a reduction in the composite outcome of major systemic embolism or death from vascular causes with the combination therapy, although there was great uncertainty around the effect estimate. However, the committee discussed that this study was not relevant to the population based on the target INR being much higher than that used in standard practice and the fact that all participants had to have atrial fibrillation or a thromboembolic event prior to surgery. Most importantly, the study was conducted in patients with mechanical and biological valve replacement. The populations were combined for all outcomes apart from “major systemic embolism or death from vascular causes”. Due to the indirectness of this outcome and the imprecision of the effect size based on one study with a small sample size, the committee agreed that it was not possible to make any recommendations based on this evidence. Additionally, given limited evidence for whether any form of anticoagulation/antiplatelet is needed, research recommendations were prioritised to compare treatments with placebo rather than to each other or combinations. It was not possible to make a consensus recommendation.

Single antiplatelet therapy compared to dual antiplatelet therapy following transcatheter valve implantation

For the comparison of single antiplatelet therapy to dual antiplatelet therapy after transcatheter aortic valve implantation a clinically important benefit was seen with single antiplatelet in reducing major and minor bleeding events. A small but clinically significant effect of single antiplatelet therapy in reducing mortality compared to dual antiplatelet therapy was also observed, however there was uncertainty in this effect estimate and the difference was very small so the committee were not confident in this finding. Arterial thromboembolic events were reported as a range of odds ratios due to heterogeneity on inspection of the forest plot, with large effect estimates in opposite directions between the included studies, and the inability to form adequate subgroups with the limited number of studies. A separate study also reported only small differences between the two groups in terms of stroke,

myocardial infarction, symptomatic clinical aortic valve thrombosis and valve degeneration (mean aortic valve gradient), with uncertainty in the direction of effect present for all of these outcomes. Therefore, in addition to the uncertainty around the effect estimates, it was not possible to determine whether there was a benefit to either treatment for these outcomes.

The committee noted that all the included studies were conducted in an older population (people aged over 70 years), who may already be at a higher risk of major bleeding and arterial thromboembolic events, with a lower window for benefit, than a younger population. This included people with comorbidities, including chronic kidney disease. While this may influence the results, the committee felt that this was applicable to people in the United Kingdom.

The committee raised the lack of comparison to placebo, which meant that, while they could say there was a benefit of taking single antiplatelet therapy rather than dual antiplatelet therapy, they could not say that single antiplatelet therapy was preferable to no antiplatelet therapy.

There was no evidence for long-term outcomes, with the studies included having a duration of up to 12 months. This meant that the committee were uncertain on the long-term efficacy of the treatment. The committee noted that antiplatelet agents used over the long term may reduce the risk of valve thrombosis and have a positive effect on valve durability. Some evidence for this may come from observational studies that were excluded in this protocol. These factors contributed to the research recommendations.

Based on the higher bleeding risk observed with dual antiplatelet therapy compared to single antiplatelet therapy, especially in the elderly population, and supported by clinical experience, the committee made a recommendation to consider single antiplatelet therapy following transcatheter aortic valve implantation. The recommendation was specifically for aspirin, as this was the drug usually used in practice and was used in all of the studies. Clopidogrel was included in the recommendation as the alternative if aspirin was not tolerated, in line with current practice. However, given the lack of evidence, clopidogrel was also included within the research recommendation (see Appendix J.1.1 for details).

The committee agreed that in practice it would be normal for the majority of patients having transcatheter aortic valve implantation to have at least a single antiplatelet agent, with many receiving dual antiplatelet therapy.

Rivaroxaban (+aspirin for 3 months) compared to aspirin (+clopidogrel for 3 months) following transcatheter valve implantation

One study with 1644 participants was included that compared outcomes with rivaroxaban (a DOAC) to aspirin, with a median treatment duration of 428 days in the rivaroxaban group. In both groups, the first 3 months involved a combined treatment, with aspirin taken alongside rivaroxaban and clopidogrel taken alongside aspirin in those randomised to rivaroxaban and aspirin, respectively.

The absolute effects for the majority of the outcomes favoured the aspirin group, with a clinically important harm of rivaroxaban demonstrated for mortality, major bleeding and withdrawal due to adverse events. The same direction of effect was seen for the outcomes of minor bleeding, stroke, myocardial infarction and pulmonary embolism, though there was more uncertainty in these results and the effect sizes were smaller.

The only outcome that favoured the rivaroxaban group was symptomatic valve thrombosis; however, the effect was small and there was uncertainty in this result.

Evidence from this study, including moderate quality evidence for major bleeding being higher in the DOAC group, further supports the recommendation made to consider single

antiplatelet therapy (aspirin) following transcatheter valve implantation as rivaroxaban did not appear to be a better option based on this study.

Anticoagulant (VKA or DOAC) + clopidogrel compared to anticoagulant (VKA or DOAC) alone following transcatheter valve implantation

One study compared outcomes between an anticoagulant + single antiplatelet therapy in the form of clopidogrel and an anticoagulant alone in those with an existing indication for long-term oral anticoagulation. The results suggested a clinically significant harm of anticoagulant plus clopidogrel for mortality and major and minor bleeding, though there was uncertainty in these results. No clinically significant differences were identified for the other reported outcomes of stroke, myocardial infarction and mean aortic valve gradient (valve degeneration), with uncertainty in the direction of the effect.

This evidence did not contribute to any recommendations made as it was based on a single, moderately sized study with uncertainty in the effects for all of the reported outcomes. In addition, recommendations for anticoagulants following transcatheter valve implantation were not made due to the limited evidence and this study assessing whether an anticoagulant combined with clopidogrel is preferable to an anticoagulant alone did not add anything further that could be used to inform recommendations on anticoagulants following transcatheter valve implantation. However, the population of this study was covered by one of the recommendations made, as it was agreed that for those with other indications for anticoagulation or antiplatelet therapy, such as atrial fibrillation or chronic heart failure, the respective NICE guidelines should be followed.

Key uncertainties

There is no evidence comparing anticoagulant or antiplatelet therapy to placebo, which means there was no clear evidence that antithrombotic therapy is required after surgical biological valve replacement or valve repair. Therefore, there was insufficient evidence to make a recommendation based on this. The committee agreed that this is an area that requires more research as there is a large variance in clinical practice across the country and currently no high-quality evidence to support any consensus recommendation on antithrombotic therapy. This led to a research recommendation (see Appendix J.1.1 for details). The committee noted the reasonable clinical rationale for single antiplatelet therapy after surgical biological and transcatheter valve implantation, as well as surgical valve repair, but the requirement for antithrombotic therapy has not been tested in a clinical trial.

No evidence was available to assess the long-term efficacy of any antithrombotic therapy after any surgical or transcatheter procedure. Currently the duration of antithrombotic therapy in this population is unclear with no high-quality evidence to support a consensus recommendation. This led to a research recommendation (see Appendix J.1.5 for details).

1.7.2 Cost effectiveness and resource use

No economic evidence was found for this review. The unit costs of drugs were presented. The committee noted that the daily cost of these interventions was typically low but that the price varied between different drugs. Aspirin and clopidogrel, for example, have a daily cost of £0.05 whilst ticagrelor has a daily cost of £1.90. According to committee consensus, broad current practice is to give dual antiplatelet therapy after valve intervention but some clinics may choose other interventions or give no treatment.

For vitamin K antagonists compared to single antiplatelet therapy following surgical biological valve replacement**,** a do not use recommendation was made for vitamin K antagonists. This was based on the evidence of an increased bleeding risk with vitamin K antagonists and no

apparent reduction in risk for other outcomes, such as mortality or thromboembolic events. Savings are possible from reduced use of anticoagulation clinics and fewer bleeding events. The recommendation does not specify exactly which drugs should be given as the evidence concerned broader drug classes. It was therefore not possible to make more detailed recommendation for particular drugs.

The committee also recommended single antiplatelet therapy over dual antiplatelet therapy for transcatheter aortic valve implantation. The resource impact of this recommendation will depend on the type of single antiplatelet therapy used. Although most of current practice is to use dual antiplatelet therapy, for the smaller number of clinics that do not currently give any treatment there will be an initial cost in procurement of drugs. However, these costs might be offset by a reduction in major and minor bleeding events, although no evidence was found that included placebo or no treatment as a comparator.

1.7.3 Other factors the committee took into account

The committee discussed that while there may be no evidence to support anticoagulant therapy after surgical biological valve replacement that clinicians should still provide anticoagulant therapy for other indications (for example, atrial fibrillation) as appropriate according to the relevant guidance.

The committee recognised that the BNF states that dabigatran is contraindicated for prosthetic heart valves. However, they believed that this contraindication is based on evidence from the mechanical valve population and does not necessarily apply to people with biological prosthetic heart valves. The evidence found in this review did not support or oppose this.

The committee noted that guidelines for direct oral anticoagulation medication for atrial fibrillation use the term “non-valvular atrial fibrillation” to refer to atrial fibrillation that is not coexistent with mitral stenosis. Atrial fibrillation coexistent with mitral stenosis is named “valvular atrial fibrillation”. Furthermore, the committee noted that in the presence of mechanical prosthetic valves with coexistent atrial fibrillation the anticoagulation requirements for the mechanical prosthetic valves prevails.

Although not the subject of this review, the committee noted the widespread use of warfarin or antiplatelets for 3 months after biological valve replacement, which was thought to be based on a clinical rationale but limited evidence.

No evidence was identified as part of this review that could be used to inform recommendations specifically in pregnant women with heart valve disease or women who may become pregnant in the future.

1.8 Recommendations supported by this evidence review

This evidence review supports recommendations 1.7.1-1.7.3 and the research recommendations for antithrombotic therapy.

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Appendices

Appendix A: Review protocols

Table 10: Review protocol: Clinical protocol for anticoagulant and/or antiplatelet therapy for biological prosthetic valves

ID	Field	Content
0.	PROSPERO registration number	Not registered
1.	Review title	5.1 What is the clinical and cost effectiveness of anticoagulant and/or antiplatelet therapy for adults with transcatheter or surgical biological prosthetic valves or after valve repair?
2.	Review question	What is the clinical and cost effectiveness of anticoagulant and/or antiplatelet therapy for adults with transcatheter or surgical biological prosthetic valves or after valve repair?
3.	Objective	To assess and compare the clinical and cost-effectiveness of anticoagulant and/or antiplatelet therapy in people with biological prosthetic valves as a result of transcatheter or surgical intervention, and with repaired valves after surgical intervention.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • English language • Human studies • Letters and comments are excluded • Validated study filters for systematic reviews and RCTs • No date restrictions applied

		Other searches: • Inclusion lists of systematic reviews will be checked by the reviewer The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.
5.	Condition or domain being studied	Diagnosed heart valve disease in adults aged 18 years and over: Aortic (including bicuspid) stenosis, aortic regurgitation, mitral stenosis, mitral regurgitation and tricuspid regurgitation.
6.	Population	Inclusion: Adults aged 18 years and over with repaired valves or biological prosthetic valves stratified by type of intervention: • transcatheter replacement • surgical replacement. • transcatheter repair • surgical repair Exclusion: • Children (aged <18 years) • Adults with congenital heart disease (excluding bicuspid aortic valves) • Tricuspid stenosis and pulmonary valve disease • Adults who have had a mechanical valve replacement
7.	Intervention/Exposure/Test	Oral anticoagulation therapy: • Vitamin K Antagonists (including: warfarin, acenocoumarol and phenindione) • Direct acting oral anticoagulants (DOACs) (including: dabigatran, rivaroxaban, apixaban and edoxaban) Oral antiplatelet therapy: • Single therapy (including aspirin, clopidogrel, ticagrelor and prasugrel) • Dual therapy (the combination of aspirin with either clopidogrel, ticagrelor or prasugrel). Combined oral anticoagulation and oral antiplatelet therapy

		A class effect will be used for analysis, combining all interventions within each drug class listed above. Warfarin will be analysed separately to DOACs, single antiplatelet therapy will be analysed separately to dual antiplatelet therapy. Primary studies with a mixed intervention (some in the 'active' arm received the intervention of interest and some a different intervention) will be included if at least 90% received the intervention of interest.
8.	Comparator/Reference standard/Confounding factors	Other active comparator listed above. Placebo. No treatment or standard care (for example, treatment with all other required medication post-valve replacement apart from anticoagulants/antiplatelets).
9.	Types of study to be included	Randomised control trials (RCTs) or systematic reviews of RCTs. If no RCT data are available, observational data will not be considered. This is due to the risk of confounding variables influencing the study results, reducing our confidence in the review results.
10.	Other exclusion criteria	Exclusion criteria: • Crossover studies will not be included as variations in coagulation propensity will occur over the follow-up period which would make interventions non-comparable. • Conference abstracts will be excluded because they are unlikely to contain enough information to assess whether the population matches the review question in terms of previous medication use, or enough detail on outcome definitions, or on the methodology to assess the risk of bias of the study. • Studies including any participants with mechanical valves. • Non-randomised studies/observational studies. • Non-English language studies.
11.	Context	N/A.
12.	Primary outcomes (critical outcomes)	• All-cause mortality (dichotomous) • Health-related quality of life (continuous) • Major bleeding (dichotomous) • Minor bleeding (dichotomous) • Arterial thromboembolic events (dichotomous)

		Follow-up: All outcomes reported within the following time points will be pooled. The latest time points in each category will be used if multiple time points are reported in a single study. The categories include: • Short-medium term: ≤12 months • Long term: >12 months.
13.	Secondary outcomes (important outcomes)	• Hospital re-admission at 12 months (dichotomous). • Withdrawal due to adverse events at 12 months (dichotomous). • Thrombus on imaging at <12 months (dichotomous). • Need for reintervention at medium term (6 months to 12 months) and long term (>12 months) (time-to-event). • Valve degeneration (mean transvalvular gradient) at ≥12 months (continuous).
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. An in-house developed database; EviBase, will be used for data extraction. A standardised form is followed to extract data from studies (see Developing NICE guidelines: the manual section 6.4) and for undertaking assessment of study quality. Summary evidence tables will be produced including information on: study setting; study population, participant demographics and baseline characteristics; details of the intervention and control interventions; study methodology' recruitment and missing data rates; outcomes and times of measurement; and critical appraisal ratings. 10% of the sifting and extractions will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third party. MS Excel will be used for data extraction and critical appraisal for health economic studies.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. Checklists used in this intervention review are as follows for different types of study design: • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0)

		A 10% sample of the risk of bias assessments will be independently quality assured by a second reviewer. Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third party where necessary.
16.	Strategy for data synthesis	• Where possible, data will be meta-analysed. Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5) to combine the data given in all studies for each of the outcomes stated above. A fixed effect meta-analysis, with weighted mean differences for continuous outcomes and risk ratios for binary outcomes will be used, and 95% confidence intervals will be calculated for each outcome. • Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. We will consider an I^2 value greater than 50% indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented using random-effects. • GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. • WinBUGS will be used for network meta-analysis, if possible given the data identified. A network meta-analysis will be considered if sufficient evidence is available to form a network. • Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. If significant heterogeneity is detected during meta-analysis, subgroups will be analysed. Subgroups were selected before initial searches were completed, and are listed in section 17 of this appendix. A second reviewer will quality assure 10% of the data analyses. Discrepancies will be identified and resolved through discussion (with a third party where necessary). Groups from the equality impact assessment were considered. It was decided that, while anticoagulation in women of childbearing age and pregnant women with prosthetic heart valves is of importance, they will not be considered separately in this question. This is as they are likely to have received mechanical prostheses instead of biological and so fall outside of the scope of the question.
17.	Analysis of sub-groups	• Age (<75 versus ≥75) • Sex (male versus female) • Renal function (normal versus abnormal [as defined by individual studies]) • Hepatic function (normal versus abnormal [as defined by individual studies]) • Atrial fibrillation (atrial fibrillation versus no atrial fibrillation)

		• Replaced/repaired valve location (aortic, mitral or tricuspid) Studies will be assigned to different subgroups using a threshold of 75% - for example, a study in which 80% of the population is older than 75 and 20% are younger than 75 would be assigned to the age ≥75 group (if their individual data cannot be separated from the study) when subgrouping for this factor.			
18.	Type and method of review	☒	Intervention		
		☐	Diagnostic		
		☐	Prognostic		
		☐	Qualitative		
		☐	Epidemiologic		
		☐	Service Delivery		
		☐	Other (please specify)		
19.	Language	English			
20.	Country	England			
21.	Anticipated or actual start date	09/05/2019			
22.	Anticipated completion date	17/06/2021			
23.	Stage of review at time of this submission	Review stage		Started	Completed
		Preliminary searches		☑	☑
		Piloting of the study selection process		☑	☑
		Formal screening of search results against eligibility criteria		☑	☑
		Data extraction		☑	☑

		Risk of bias (quality) assessment	☑	☑
		Data analysis	☑	☑
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail HVD@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre		
25.	Review team members	From the National Guideline Centre: Sharon Swain [Guideline lead] Eleanor Samarasekera [Senior systematic reviewer] Nicole Downes [Systematic reviewer] George Wood [Systematic reviewer] Robert King [Health economist] Jill Cobb [Information specialist] Katie Broomfield [Project manager]		
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.		
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of		

		the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10122	
29.	Other registration details	N/A	
30.	Reference/URL for published protocol	N/A	
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Acenocoumarol; Anticoagulation; Antiplatelet; Aspirin; Biological heart valve; Clopidogrel; Heart valve disease; Intervention; Phenindione; Prasugrel; Surgical valve repair; Surgical valve replacement; Ticagrelor; Transcatheter valve repair; Transcatheter valve replacement; Warfarin	
33.	Details of existing review of same topic by same authors	N/A	
34.	Current review status	☐	Ongoing
		☒	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued

35.	Additional information	N/A
36.	Details of final publication	www.nice.org.uk

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Table 11: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2004, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[49] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).

	• OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2004 or later that depend on unit costs and resource data entirely or predominantly from before 2004 will be rated as 'Not applicable'. • Studies published before 2004 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B: Literature search strategies

Heart valve disease – search strategy 10 - anticoagulant and/or antiplatelet therapy for biological prosthetic valves and after valve repair

This literature search strategy was used for the following review:

- What is the clinical and cost effectiveness of anticoagulant and/or antiplatelet therapy for adults with transcatheter or surgical biological prosthetic valves or after valve repair?

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[49]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 12: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 - 14 October 2020	Exclusions Randomised controlled trials Systematic review studies
Embase (OVID)	1974 - 14 October 2020	Exclusions Randomised controlled trials Systematic review studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2020 Issue 10 of 12 CENTRAL to 2020 Issue 10 of 12	None

Medline (Ovid) search terms

1.	exp Heart Valve Diseases/
2.	exp heart valves/
3.	((primary or secondary) adj valv* disease*).ti,ab.
4.	((valv* or flap* or leaflet*) adj1 (heart or cardiac) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
5.	((mitral or aortic or tricuspid or pulmon*) adj (valv* or flap* or leaflet*) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
6.	((mitral or aortic or tricuspid or pulmon*) adj3 (prolapse or regurgitation or stenos?s or atresia or insufficienc*)).ti,ab.
7.	Heart Valve Prosthesis/
8.	((mechanical or artificial or prosthe* or bioprosthe* or biological or tissue) adj (valv* or flap* or leaflet*)).ti,ab.
9.	valve-in-valve.ti,ab.
10.	(transcatheter adj2 (valve or valves)).ti,ab.
11.	exp Heart Murmurs/
12.	((heart or cardiac) adj murmur*).ti,ab.
13.	or/1-12
14.	letter/
15.	editorial/
16.	news/
17.	exp historical article/
18.	Anecdotes as Topic/
19.	comment/
20.	case report/
21.	(letter or comment*).ti.
22.	or/14-21
23.	randomized controlled trial/ or random*.ti,ab.

24.	22 not 23
25.	animals/ not humans/
26.	exp Animals, Laboratory/
27.	exp Animal Experimentation/
28.	exp Models, Animal/
29.	exp Rodentia/
30.	(rat or rats or mouse or mice).ti.
31.	or/24-30
32.	13 not 31
33.	limit 32 to English language
34.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
35.	33 not 34
36.	randomized controlled trial.pt.
37.	controlled clinical trial.pt.
38.	randomi#ed.ti,ab.
39.	placebo.ab.
40.	randomly.ti,ab.
41.	Clinical Trials as topic.sh.
42.	trial.ti.
43.	or/36-42
44.	Meta-Analysis/
45.	exp Meta-Analysis as Topic/
46.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
47.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
48.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
49.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
50.	(search* adj4 literature).ab.
51.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
52.	cochrane.jw.
53.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
54.	or/44-53
55.	35 and (43 or 54)
56.	exp Anticoagulants/
57.	anticoag*.ti,ab.
58.	anti coag*.ti,ab.
59.	"antivitamin k".ti,ab.
60.	acenocoumarol.ti,ab.
61.	aspirin*.ti,ab.
62.	clopidogrel.ti,ab.
63.	Phenindione.ti,ab.
64.	Phytomenadione.ti,ab.
65.	warfarin.ti,ab.

66.	Heparin.ti,ab.
67.	((novel or direct) adj oral anticoag*).ti,ab.
68.	exp Platelet Aggregation Inhibitors/
69.	antiplatelet*.ti,ab.
70.	anti platelet*.ti,ab.
71.	antiaggregant*.ti,ab.
72.	anti aggregant*.ti,ab.
73.	platelet antagonist*.ti,ab.
74.	(platelet adj2 inhibitor*).ti,ab.
75.	Cangrelor.ti,ab.
76.	dipyridamole.ti,ab.
77.	Prasugrel.ti,ab.
78.	Ticagrelor.ti,ab.
79.	or/56-78
80.	55 and 79

1 **Embase (Ovid) search terms**

1.	exp valvular heart disease/
2.	exp heart valve/
3.	((primary or secondary) adj valv* disease*).ti,ab.
4.	((valv* or flap* or leaflet*) adj1 (heart or cardiac) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
5.	((mitral or aortic or tricuspid or pulmon*) adj (valv* or flap* or leaflet*) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
6.	((mitral or aortic or tricuspid or pulmon*) adj3 (prolapse or regurgitation or stenos?s or atresia or insufficienc*)).ti,ab.
7.	exp heart valve prosthesis/
8.	((mechanical or artificial or prosthe* or bioprosthe* or biological or tissue) adj (valv* or flap* or leaflet*)).ti,ab.
9.	valve-in-valve.ti,ab.
10.	(transcatheter adj2 (valve or valves)).ti,ab.
11.	exp heart murmur/
12.	((heart or cardiac) adj murmur*).ti,ab.
13.	or/1-12
14.	letter.pt. or letter/
15.	note.pt.
16.	editorial.pt.
17.	Case report/ or Case study/
18.	(letter or comment*).ti.
19.	or/14-18
20.	randomized controlled trial/ or random*.ti,ab.
21.	19 not 20
22.	animal/ not human/
23.	Nonhuman/
24.	exp Animal Experiment/
25.	exp Experimental animal/

26.	Animal model/
27.	exp Rodent/
28.	(rat or rats or mouse or mice).ti.
29.	or/21-28
30.	13 not 29
31.	limit 30 to English language
32.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
33.	31 not 32
34.	random*.ti,ab.
35.	factorial*.ti,ab.
36.	(crossover* or cross over*).ti,ab.
37.	((doubl* or singl*) adj blind*).ti,ab.
38.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
39.	crossover procedure/
40.	single blind procedure/
41.	randomized controlled trial/
42.	double blind procedure/
43.	or/34-42
44.	systematic review/
45.	meta-analysis/
46.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
47.	((systematic or evidence) adj3 (review* or overview*)).ti,ab.
48.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
49.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
50.	(search* adj4 literature).ab.
51.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
52.	((pool* or combined) adj2 (data or trials or studies or results)).ab.
53.	cochrane.jw.
54.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
55.	or/44-53
56.	33 and (43 or 55)
57.	exp anticoagulant agent/
58.	anticoag*.ti,ab.
59.	anti coag*.ti,ab.
60.	antivitamin K/
61.	"antivitamin k".ti,ab.
62.	acenocoumarol/
63.	acenocoumarol.ti,ab.
64.	aspirin*.ti,ab.
65.	clopidogrel/
66.	clopidogrel.ti,ab.
67.	phenindione/
68.	Phenindione.ti,ab.

69.	phytomenadione/
70.	phytomenadione.ti,ab.
71.	warfarin/
72.	warfarin.ti,ab.
73.	heparin/
74.	heparin.ti,ab.
75.	((novel or direct) adj oral anticoag*).ti,ab.
76.	exp antithrombocytic agent/
77.	antithrombocytic.ti,ab.
78.	antiplatelet*.ti,ab.
79.	anti platelet*.ti,ab.
80.	antiaggregant*.ti,ab.
81.	anti aggregant*.ti,ab.
82.	platelet antagonist*.ti,ab.
83.	(platelet adj2 inhibitor*).ti,ab.
84.	cangrelor/
85.	Cangrelor.ti,ab.
86.	dipyridamole/
87.	dipyridamole.ti,ab.
88.	prasugrel/
89.	Prasugrel.ti,ab.
90.	ticagrelor/
91.	Ticagrelor.ti,ab.
92.	or/57-91
93.	56 and 92

1 **Cochrane Library (Wiley) search terms**

#1.	MeSH descriptor: [Heart Valve Diseases] explode all trees
#2.	MeSH descriptor: [Heart Valves] explode all trees
#3.	((primary or secondary) NEXT valv* disease*):ti,ab
#4.	((valv* or flap* or leaflet*) near/1 (heart or cardiac) NEXT (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)):ti,ab
#5.	((mitral or aortic or tricuspid or pulmon*) NEXT (valv* or flap* or leaflet*) NEXT (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)):ti,ab
#6.	((mitral or aortic or tricuspid or pulmon*) NEAR/3 (prolapse or regurgitation or stenos?s or atresia or insufficienc*)):ti,ab
#7.	MeSH descriptor: [Heart Valve Prosthesis] explode all trees
#8.	((mechanical or artificial or prosthe* or bioprosthe* or biological or tissue) NEXT (valv* or flap* or leaflet*)):ti,ab
#9.	valve-in-valve:ti,ab
#10.	(transcatheter NEAR/2 (valve or valves)):ti,ab
#11.	MeSH descriptor: [Heart Murmurs] explode all trees
#12.	((heart or cardiac) NEXT murmur*):ti,ab
#13.	(or #1-#12)
#14.	MeSH descriptor: [Anticoagulants] explode all trees

#15.	anticoag*:ti,ab
#16.	anti coag*:ti,ab
#17.	antivitamin k:ti,ab
#18.	acenocoumarol:ti,ab
#19.	aspirin*:ti,ab
#20.	clopidogrel:ti,ab
#21.	Phenindione:ti,ab
#22.	Phytomenadione:ti,ab
#23.	warfarin:ti,ab
#24.	Heparin:ti,ab
#25.	((novel or direct) NEXT oral anticoag*):ti,ab
#26.	MeSH descriptor: [Platelet Aggregation Inhibitors] explode all trees
#27.	antiplatelet*:ti,ab
#28.	anti platelet*:ti,ab
#29.	antiaggregant*:ti,ab
#30.	anti aggregant*:ti,ab
#31.	platelet antagonist*:ti,ab
#32.	(platelet NEAR/2 inhibitor*):ti,ab
#33.	Cangrelor:ti,ab
#34.	dipyridamole:ti,ab
#35.	Prasugrel:ti,ab
#36.	Ticagrelor:ti,ab
#37.	(or #14-#36)
#38.	#13 and #37

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to heart valve disease population in NHS Economic Evaluation Database (NHS EED) – (this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) – (this ceased to be updated after March 2018) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics.

Table 13: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	01 January 2014 – 15 October 2020	Exclusions Health economics studies
Embase	01 January 2014 – 15 October 2020	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - Inception – 31 March 2018 NHSEED - Inception to 31 March 2015	None

Medline (Ovid) search terms

1.	exp Heart Valve Diseases/
2.	exp heart valves/

3.	((primary or secondary) adj valv* disease*).ti,ab.
4.	((valv* or flap* or leaflet*) adj1 (heart or cardiac) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
5.	((mitral or aortic or tricuspid or pulmon*) adj (valv* or flap* or leaflet*) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
6.	((mitral or aortic or tricuspid or pulmon*) adj3 (prolapse or regurgitation or stenos?s or atresia or insufficienc*)).ti,ab.
7.	Heart Valve Prosthesis/
8.	((mechanical or artificial or prosthe* or bioprosthe* or biological or tissue) adj (valv* or flap* or leaflet*)).ti,ab.
9.	valve-in-valve.ti,ab.
10.	(transcatheter adj2 (valve or valves)).ti,ab.
11.	exp Heart Murmurs/
12.	((heart or cardiac) adj murmur*).ti,ab.
13.	or/1-12
14.	letter/
15.	editorial/
16.	news/
17.	exp historical article/
18.	Anecdotes as Topic/
19.	comment/
20.	case report/
21.	(letter or comment*).ti.
22.	or/14-21
23.	randomized controlled trial/ or random*.ti,ab.
24.	22 not 23
25.	animals/ not humans/
26.	exp Animals, Laboratory/
27.	exp Animal Experimentation/
28.	exp Models, Animal/
29.	exp Rodentia/
30.	(rat or rats or mouse or mice).ti.
31.	or/24-30
32.	13 not 31
33.	limit 32 to English language
34.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
35.	33 not 34
36.	Economics/
37.	Value of life/
38.	exp "Costs and Cost Analysis"/
39.	exp Economics, Hospital/
40.	exp Economics, Medical/

41.	Economics, Nursing/
42.	Economics, Pharmaceutical/
43.	exp "Fees and Charges"/
44.	exp Budgets/
45.	budget*.ti,ab.
46.	cost*.ti.
47.	(economic* or pharmaco?economic*).ti.
48.	(price* or pricing*).ti,ab.
49.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
50.	(financ* or fee or fees).ti,ab.
51.	(value adj2 (money or monetary)).ti,ab.
52.	or/36-51
53.	35 and 52

1 **Embase (Ovid) search terms**

1.	exp valvular heart disease/
2.	exp heart valve/
3.	((primary or secondary) adj valv* disease*).ti,ab.
4.	((valv* or flap* or leaflet*) adj1 (heart or cardiac) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
5.	((mitral or aortic or tricuspid or pulmon*) adj (valv* or flap* or leaflet*) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)).ti,ab.
6.	((mitral or aortic or tricuspid or pulmon*) adj3 (prolapse or regurgitation or stenos?s or atresia or insufficienc*)).ti,ab.
7.	exp heart valve prosthesis/
8.	((mechanical or artificial or prosthe* or bioprosthe* or biological or tissue) adj (valv* or flap* or leaflet*)).ti,ab.
9.	valve-in-valve.ti,ab.
10.	(transcatheter adj2 (valve or valves)).ti,ab.
11.	exp heart murmur/
12.	((heart or cardiac) adj murmur*).ti,ab.
13.	or/1-12
14.	letter.pt. or letter/
15.	note.pt.
16.	editorial.pt.
17.	Case report/ or Case study/
18.	(letter or comment*).ti.
19.	or/14-18
20.	randomized controlled trial/ or random*.ti,ab.
21.	19 not 20
22.	animal/ not human/
23.	Nonhuman/
24.	exp Animal Experiment/
25.	exp Experimental animal/
26.	Animal model/

27.	exp Rodent/
28.	(rat or rats or mouse or mice).ti.
29.	or/21-28
30.	13 not 29
31.	limit 30 to English language
32.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
33.	31 not 32
34.	health economics/
35.	exp economic evaluation/
36.	exp health care cost/
37.	exp fee/
38.	budget/
39.	funding/
40.	budget*.ti,ab.
41.	cost*.ti.
42.	(economic* or pharmaco?economic*).ti.
43.	(price* or pricing*).ti,ab.
44.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
45.	(financ* or fee or fees).ti,ab.
46.	(value adj2 (money or monetary)).ti,ab.
47.	or/34-46
48.	33 and 47

1 **NHS EED and HTA (CRD) search terms**

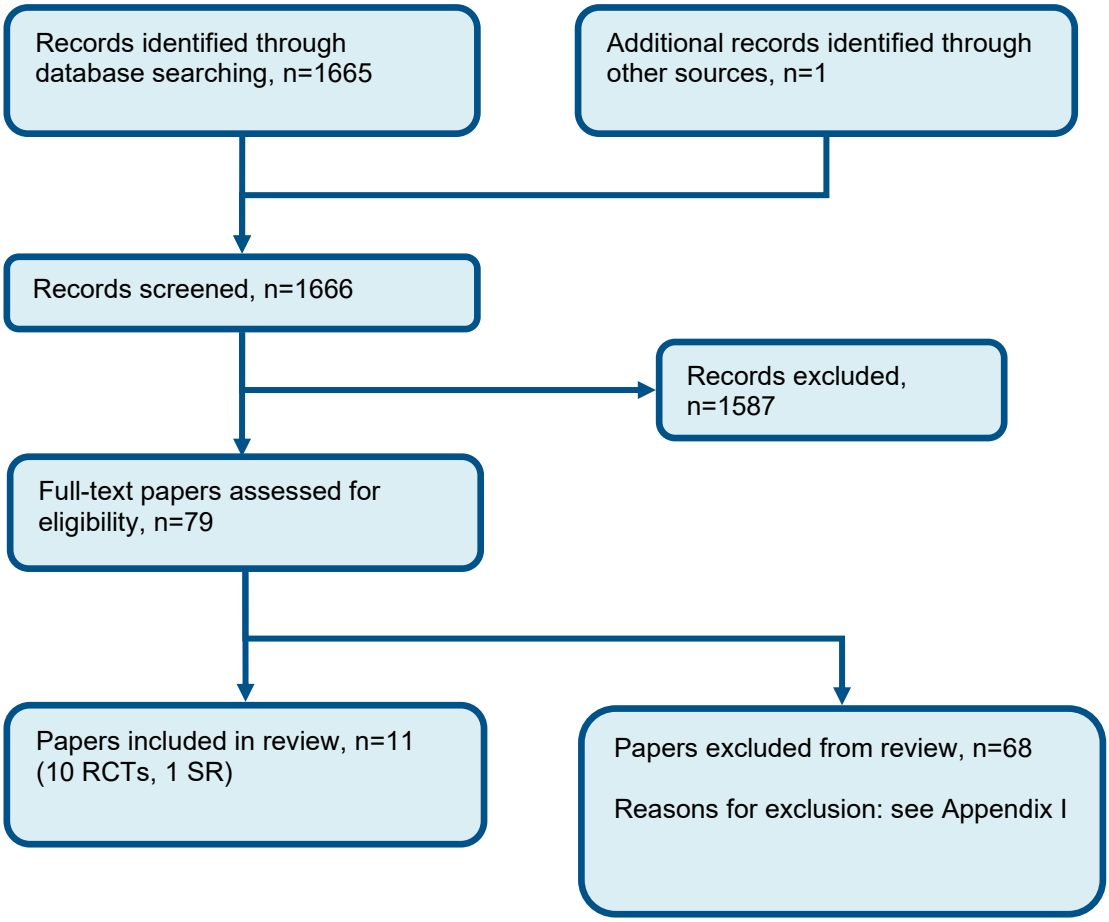
#1.	MeSH DESCRIPTOR Heart Valve Diseases EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Heart Valves EXPLODE ALL TREES
#3.	(((primary or secondary) adj Valv* adj disease*))
#4.	(((valv* or flap* or leaflet*) adj (heart or cardiac) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)))
#5.	((heart or cardiac) adj (valv* or flap* or leaflet*) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*))
#6.	(((mitral or aortic or tricuspid or pulmon*) adj (valv* or flap* or leaflet*) adj (disease* or disorder* or failure or failed or dysfunction* or insufficien* or repair* or replace* or damage* or leak*)))
#7.	(((mitral or aortic or tricuspid or pulmon*) adj3 (prolapse or regurgitation or stenos?s or atresia or insufficienc*)))
#8.	MeSH DESCRIPTOR Heart Valve Prosthesis EXPLODE ALL TREES
#9.	(((mechanical or artificial or prosthe* or bioprosthe* or biological or tissue) adj (valv* or flap* or leaflet*)))
#10.	(valve-in-valve)
#11.	((transcatheter adj2 (valve or valves)))
#12.	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11

2

3

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review anticoagulation and antiplatelet use after biological valve replacement and valve repair



Appendix D: Clinical evidence tables

Study	POPular TAVI trial cohort A trial: Brouwer 2020[15]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=690 (665 analysed))
Countries and setting	Conducted in Belgium, Czech Republic, Luxembourg, Netherlands; Setting: Secondary care/outpatient
Line of therapy	1st line
Duration of study	Intervention time: All had data for 12 months follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Confirmed to have undergone TAVI
Stratum	Transcatheter replacement: Those scheduled to undergo TAVI and no indication for long-term oral anticoagulation
Subgroup analysis within study	Not applicable
Inclusion criteria	Provide written informed consent; scheduled to undergo TAVI; no indication for long-term oral anticoagulation
Exclusion criteria	Long-term indication for oral anticoagulation; drug-eluting stent implantation within 3 months of the TAVI procedure; bare-metal stent implantation within 1 month prior to TAVI; allergy, intolerance or contraindication to aspirin or clopidogrel.
Recruitment/selection of patients	All of those matching inclusion criteria, unclear if consecutive
Age, gender and ethnicity	Age - Mean (SD): Aspirin alone, 80.4 (6.2) years; aspirin + clopidogrel, 79.5 (6.4) years. Gender (M:F): Aspirin alone, 167/164; aspirin + clopidogrel, 174/160. Ethnicity: Not reported

Further population details	1. Age (<75 vs ≥75): 75 years or over (Mean age >75 years in both groups). 2. Atrial fibrillation: No atrial fibrillation (Group with no existing indication for long-term oral anticoagulation). 3. Hepatic function : Not stated / Unclear (No details provided). 4. Renal function: Abnormal (Estimated glomerular filtration rate <60 ml/min/1.73 m2 in both groups - moderate dysfunction?)). 5. Sex: Mixed (Roughly equal proportions in each group). 6. Valve position: Aortic (TAVI performed in all cases).
Extra comments	NYHA class III or IV, 64.0% vs. 65.9%; body mass index, mean (SD): 27.0 (4.7) vs. 27.1 (4.6) kg/m²; STS risk score, median (IR): 2.6 (1.6-3.7) vs. 2.4 (1.7-3.7); indication for TAVI: normal-flow high-gradient AS (76.4% vs. 75.1%), low-flow low-gradient AS (19.3% vs. 17.4%), pure AR (2.4% vs. 2.1%) and combination (1.8% vs. 5.4%); hypertension, 73.4% vs. 76.3%; diabetes mellitus, 23.6% vs. 25.4%; coronary artery disease, 40.5% vs. 41.3%; previous myocardial infarction, 8.5% vs. 9.3%; peripheral artery disease, 14.2% vs. 20.4%; previous stroke, 5.4% vs. 3.6%; estimated golmerular filtration rate, mean (SD): 57.5 (18.1) vs. 57.9 (19.7) ml/min/1.73 m²; COPD, 15.7% vs. 22.2%; previous CABG, 18.4% vs. 19.5%; previous aortic valve surgery, 6.9% vs. 6.0%; LVEF >50% (73.7% vs. 73.4%), 31-50% (22.4% vs. 19.5%) and ≤30% (3.9% vs. 7.2%); type of valve: Sapien XT (1.5% vs. 1.8%), Sapien 3 (45.0% vs. 44.0%), Sapien Ultra (0.0% vs. 0.3%), CoreValve (3.3% vs. 3.0%), COreValve Evolut R (27.2% vs. 25.%), CoreValve Evolut Pro (11.2% vs. 10.5%), Engager (0.0% vs. 0.3%), Accurate Neo (4.5% vs. 3.9%), Lotus (3.9% vs. 4.8%), JenaValve (0.9% vs. 2.4%), Portico (1.5% vs. 3.3%) and Direct Flow (0.9% vs. 0.3%); maximal aortic valve gradient at discharge, mean (SD): 16.8 (9.5) vs. 17.3 (8.4) mmHg; mean aortic valve gradient at discharge, mean (SD): 9.1 (5.5) vs. 9.2 (4.9) mmHg; aortic valve area at discharge, mean (SD): 2.1 (0.7) vs. 2.2 (0.7) cm²; administration of oral anticoagulation during trial, 13.3% vs. 9.6%;
Indirectness of population	No indirectness
Interventions	(n=343) Intervention 1: Single antiplatelet therapy - Aspirin. Aspirin alone. Aspirin at a dose of 80-100 mg daily for duration of trial and advised to take it on a lifelong basis. For those that had not previously taken aspirin, a loading dose of 300 mg aspirin was administered within 1 day prior to the TAVI procedure. For those receiving clopidogrel prior to enrollment for medical reasons, the physician was contacted about the possibility of switching to aspirin and if permission was denied clopidogrel was continued at a dose of 75 mg daily (4.8% - these received clopidogrel alone for the entire study duration). For those assigned to aspirin, if a stroke occurred during the trial, at the attending physician's discretion they could be switched to clopidogrel. Duration 12 months. Concurrent medication/care: All other actively prescribed antiplatelet agents were discontinued at least 5 days prior to TAVI. TAVI procedures performed according to local protocol at each site. During TAVI, unfractionated heparin use recommended with the goal of an activated clotting time of >250 seconds. In those that developed AF following TAVI, oral anticoagulation was initiated with a vitamin K antagonist or DOAC according to local practice. The protocol recommended that the oral anticoagulant should replace aspirin and, if applicable, be prescribed with clopidogrel. Indirectness: No indirectness

	(n=347) Intervention 2: Dual antiplatelet therapy - Asprin + clopidogrel. Aspirin + clopidogrel (3 months with clopidogrel). Aspirin at a dose of 80-100 mg daily with 75 mg clopidogrel daily for 3 months, followed by aspirin alone at a dose of 80-100 mg daily for rest of trial duration. Patients were advised to take aspirin on a lifelong basis. For those that had not previously taken aspirin, a loading dose of 300 mg aspirin was administered within 1 day prior to the TAVI procedure. An initial single loading dose of 300 mg clopidogrel was given the day before or on the day of the TAVI procedure, followed by 75 mg daily for 3 months, with discretionary allowance for discontinuation of clopidogrel 1 month earlier (3.4%) or later than 3 months (34.5%). For those receiving clopidogrel prior to enrollment for medical reasons, the physician was contacted about the possibility of switching to aspirin and if permission was denied clopidogrel was continued at a dose of 75 mg daily (3.0% - these received clopidogrel for trial duration and aspirin for 3 months). For those assigned to aspirin, if a stroke occurred during the trial, at the attending physician's discretion they could be switched to clopidogrel. Duration 12 months. Concurrent medication/care: TAVI procedures performed according to local protocol at each site. During TAVI, unfractionated heparin use recommended with the goal of an activated clotting time of >250 seconds. In those that developed AF following TAVI, oral anticoagulation was initiated with a vitamin K antagonist or DOAC according to local practice. The protocol recommended that the oral anticoagulant should replace aspirin and, if applicable, be prescribed with clopidogrel. Indirectness: No indirectness
Funding	Other (Other (Sponsored by Netherlands Organization for Health Research and Development. No industry involvement in the trial.))

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ASPIRIN versus ASPRIN + CLOPIDOGREL (CLOPIDOGREL FOR 3 MONTHS)

Protocol outcome 1: All-cause mortality at ≤12 months
- Actual outcome for Transcatheter replacement: All-cause mortality at 12 months; Group 1: 21/331, Group 2: 19/334; Comments: RR of 1.12 (95% CI, 0.61 to 1.04) reported
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Blinding: unclear if outcome assessors were blinded but committee that adjudicated events were blinded.; Indirectness of outcome: No indirectness ; Baseline details: Some slight differences but all within <10% difference; Group 1 Number missing: 12, Reason: Withdrew informed consent (n=1); died prior to TAVI procedure (n=4); no initiation of TAVI, TAVI procedure aborted or converted to open surgery (n=2); and screening failure (n=5); Group 2 Number missing: 13, Reason: Withdrew informed consent (n=3); no initiation of TAVI, TAVI procedure aborted or converted to open surgery (n=6); and screening failure (n=4)

Protocol outcome 2: Major bleeding at ≤12 months

- Actual outcome for Transcatheter replacement: Major, life-threatening or disabling bleeding according to VARC-2 at 12 months; Group 1: 17/331, Group 2: 19/334; Comments: RR of 0.48 (95% CI, 0.27-0.83) reported
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Blinding: unclear if outcome assessors were blinded but committee that adjudicated events were blinded.; Indirectness of outcome: No indirectness ; Baseline details: Some slight differences but all within <10% difference; Group 1 Number missing: 12, Reason: Withdrew informed consent (n=1); died prior to TAVI procedure (n=4); no initiation of TAVI, TAVI procedure aborted or converted to open surgery (n=2); and screening failure (n=5); Group 2 Number missing: 13, Reason: Withdrew informed consent (n=3); no initiation of TAVI, TAVI procedure aborted or converted to open surgery (n=6); and screening failure (n=4)

Protocol outcome 3: Minor bleeding at ≤12 months
- Actual outcome for Transcatheter replacement: Minor bleeding according to VARC-2 at 12 months; Group 1: 33/331, Group 2: 53/334; Comments: RR of 0.63 (95% CI, 0.42-0.94) reported
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Blinding: unclear if outcome assessors were blinded but committee that adjudicated events were blinded.; Indirectness of outcome: No indirectness ; Baseline details: Some slight differences but all within <10% difference; Group 1 Number missing: 12, Reason: Withdrew informed consent (n=1); died prior to TAVI procedure (n=4); no initiation of TAVI, TAVI procedure aborted or converted to open surgery (n=2); and screening failure (n=5); Group 2 Number missing: 13, Reason: Withdrew informed consent (n=3); no initiation of TAVI, TAVI procedure aborted or converted to open surgery (n=6); and screening failure (n=4)

Protocol outcome 4: Arterial thromboembolic events at ≤12 months
- Actual outcome for Transcatheter replacement: Stroke at 12 months; Group 1: 17/331, Group 2: 19/334; Comments: RR of 0.90 (95% CI, 0.48-1.71) reported
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Blinding: unclear if outcome assessors were blinded but committee that adjudicated events were blinded.; Indirectness of outcome: No indirectness ; Baseline details: Some slight differences but all within <10% difference; Group 1 Number missing: 12, Reason: Withdrew informed consent (n=1); died prior to TAVI procedure (n=4); no initiation of TAVI, TAVI procedure aborted or converted to open surgery (n=2); and screening failure (n=5); Group 2 Number missing: 13, Reason: Withdrew informed consent (n=3); no initiation of TAVI, TAVI procedure aborted or converted to open surgery (n=6); and screening failure (n=4)
- Actual outcome for Transcatheter replacement: Myocardial infarction at 12 months; Group 1: 4/331, Group 2: 6/334; Comments: RR of 0.67 (95% CI, 0.19-2.36) reported
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Blinding: unclear if outcome assessors were blinded but committee that adjudicated events were blinded.; Indirectness of outcome: No indirectness ; Baseline details: Some slight differences but all within <10% difference; Group 1 Number missing: 12, Reason: Withdrew informed consent (n=1); died prior to TAVI procedure (n=4); no initiation of TAVI, TAVI procedure aborted or converted to open surgery (n=2); and screening failure (n=5); Group 2 Number missing: 13, Reason: Withdrew informed consent (n=3); no initiation of TAVI, TAVI procedure aborted or converted to open surgery (n=6); and screening failure (n=4)
- Actual outcome for Transcatheter replacement: Lung embolism at 12 months; Group 1: 1/331, Group 2: 0/334
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover -

Low, Subgroups - Low, Other 1 - Low, Comments - Blinding: unclear if outcome assessors were blinded but committee that adjudicated events were blinded.; Indirectness of outcome: No indirectness ; Baseline details: Some slight differences but all within <10% difference; Group 1 Number missing: 12, Reason: Withdrew informed consent (n=1); died prior to TAVI procedure (n=4); no initiation of TAVI, TAVI procedure aborted or converted to open surgery (n=2); and screening failure (n=5); Group 2 Number missing: 13, Reason: Withdrew informed consent (n=3); no initiation of TAVI, TAVI procedure aborted or converted to open surgery (n=6); and screening failure (n=4) Protocol outcome 5: Thrombus on imaging at ≤12 months - Actual outcome for Transcatheter replacement: Valve thrombosis at 12 months; Group 1: 3/331, Group 2: 1/334 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Blinding: unclear if outcome assessors were blinded but committee that adjudicated events were blinded.; Indirectness of outcome: No indirectness ; Baseline details: Some slight differences but all within <10% difference; Group 1 Number missing: 12, Reason: Withdrew informed consent (n=1); died prior to TAVI procedure (n=4); no initiation of TAVI, TAVI procedure aborted or converted to open surgery (n=2); and screening failure (n=5); Group 2 Number missing: 13, Reason: Withdrew informed consent (n=3); no initiation of TAVI, TAVI procedure aborted or converted to open surgery (n=6); and screening failure (n=4) Protocol outcome 6: Valve degeneration (transvalvular gradient) at ≤12 months - Actual outcome for Transcatheter replacement: Mean aortic valve gradient at Mean (SD): 6 (3) months; Group 1: mean 10.6 mmHg (SD 6.2); n=331, Group 2: mean 10.8 mmHg (SD 5.5); n=334; Comments: Values at discharge from TAVI: 9.1 (5.5) vs. 9.2 (4.9) mmHg Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Blinding: unclear if outcome assessors were blinded but committee that adjudicated events were blinded.; Indirectness of outcome: No indirectness; Baseline details: Some slight differences but all within <10% difference; Group 1 Number missing: 55, Reason: Withdrew informed consent (n=1); died prior to TAVI procedure (n=4); no initiation of TAVI, TAVI procedure aborted or converted to open surgery (n=2); screening failure (n=5); and missing data for this outcome at follow-up (n=43); Group 2 Number missing: 59, Reason: Withdrew informed consent (n=3); no initiation of TAVI, TAVI procedure aborted or converted to open surgery (n=6); screening failure (n=4); and missing data for this outcome at follow-up (n=46)	
Protocol outcomes not reported by the study	All-cause mortality at >12 months; Quality of life at ≤12 months; Quality of life at >12 months; Major bleeding at >12 months; Minor bleeding at >12 months; Arterial thromboembolic events at >12 months; Hospital re-admission at 12 months; Withdrawal due to adverse events at 12 months; Need for valve re-intervention at ≤12 months; Valve degeneration (transvalvular gradient) at >12 months

Study	Colli 2007[18]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=69)
Countries and setting	Conducted in Spain; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Post-operative after aortic valve replacement
Stratum	Surgical replacement
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged at least 18 years who required, for the first time, isolated aortic valve replacement and were in sinus rhythm before implantation (patients receiving the EPIC porcine bioprosthesis)
Exclusion criteria	The presence of a previously implanted prosthetic valve; double valve implantation; concomitant coronary artery bypass grafting; intra-aortic balloon pump at any time before, during or after intervention; the use of ASA or VKA therapy or any other antithrombotic drug; a recent positive pregnancy test, breast-feeding or the possibility of future pregnancy; active infective endocarditis; aortic dissection; a history of cerebral ischaemia; coagulopathy; a history of gastrointestinal bleeding or increased bleeding risk; vascular disease requiring medical or surgical treatment; previous chronic anticoagulation therapy; and allergy or contraindication to ASA and/or VKA.
Recruitment/selection of patients	No further details given in the paper
Age, gender and ethnicity	Age - Mean (SD): ASA arm: 70.7±3.7, Warfarin arm: 69.5±3.3. Gender (M:F): 59:10. Ethnicity: Not stated
Further population details	1. Age (<75 vs ≥75): <75 years (ASA arm: 70.7±3.7, Warfarin arm: 69.5±3.3). 2. Atrial fibrillation: No atrial fibrillation (No AF pre-randomisation). 3. Hepatic function: Not stated / Unclear 4. Renal function: Not stated / Unclear 5. Sex: Mixed (Predominantly male (59:10) but is mixed). 6. Valve position: Aortic
Indirectness of population	No indirectness
Interventions	(n=34) Intervention 1: Vitamin K antagonist - Warfarin. On day 1 after surgery all received a single, body weight-adjusted dose of prophylactic LMWH. Warfarin began from day 2 with target INR 2.0-3.0. Duration 3 months, then aspirin (100mg/day) for 3 months. Concurrent medication/care: Not reported. LMWH was given until the INR was within the target range. A number of patients in each group had comorbid hypertension, diabetes and dyslipidaemia so could have been receiving relevant medication for this. Comments: At 3 months switches from warfarin to aspirin 100mg/day for 3 months (n=35) Intervention 2: Single antiplatelet therapy - Aspirin. On day 1 after surgery all received a single, body

	weight-adjusted dose of prophylactic LMWH. From day 2 aspirin was given 100mg/day. Duration 6 months. Concurrent medication/care: Not reported. LMWH was given until active mobilisation was achieved. A number of patients in each group had comorbid hypertension, diabetes and dyslipidaemia so could have been receiving relevant medication for this. Indirectness: No indirectness
Funding	Principal author funded by industry (Andrea Colli is a clinical investigator for St. Jude Medical, Minneapolis, MN, USA (this paper is investigating the St. Jude Medical heart valve))
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WARFARIN versus ASPIRIN Protocol outcome 1: All-cause mortality at ≤12 months - Actual outcome for Surgical replacement: Death at follow up at 6 months; Group 1: 2/34, Group 2: 2/35 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Less females in the warfarin arm (M:F = 33:1 vs. 26:9); Group 1 Number missing: 0, Reason: 6 patients were likely randomised but excluded from analysis as they developed permanent atrial fibrillation. They did not report which arms those patients were from.; Group 2 Number missing: 0 Protocol outcome 2: Major bleeding at ≤12 months - Actual outcome for Surgical replacement: Major bleeding (as per guidelines in reference 3 of the article - Edmunds et al. Guidelines for reporting morbidity and mortality after cardiac valvular operations. Ann Thorac Surg 1988;46:257-259) at 6 months; Group 1: 3/34, Group 2: 1/35 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: Less females in the warfarin arm (M:F = 33:1 vs. 26:9); Group 1 Number missing: 0, Reason: 6 patients were likely randomised but excluded from analysis as they developed permanent atrial fibrillation. They did not report which arms those patients were from.; Group 2 Number missing: 0 Protocol outcome 3: Arterial thromboembolic events at ≤12 months - Actual outcome for Surgical replacement: Postoperative cerebral ischaemia at 6 months; Group 1: 1/34, Group 2: 2/35; Comments: Reports at 24h to 3 months and at >3 months. Numbers were added together to determine the total at 6 months. Does not report any other arterial thromboembolic events. Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Baseline details: Less females in the warfarin arm (M:F = 33:1 vs. 26:9); Group 1 Number missing: 0, Reason: 6 patients were likely randomised but excluded from analysis as they developed permanent atrial fibrillation. They did not report which arms those patients were from.; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	All-cause mortality at >12 months; Quality of life at ≤12 months; Quality of life at >12 months; Major bleeding at >12 months; Minor bleeding at ≤12 months; Minor bleeding at >12 months; Arterial thromboembolic events at >12 months; Hospital re-admission at 12 months; Withdrawal due to adverse events at 12 months; Thrombus on imaging at ≤12 months; Need for valve re-intervention at ≤12 months; Valve degeneration (transvalvular gradient) at ≤12 months; Valve degeneration (transvalvular gradient) at >12 months

Study	GALILEO trial: Dangas 2020[19]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1644)
Countries and setting	Conducted in Austria, Belgium, Canada, Czech Republic, Denmark, France, Germany, Italy, Netherlands, Norway, Poland, Spain, Sweden, Switzerland, United Kingdom, USA; Setting: Secondary care/outpatient
Line of therapy	1st line
Duration of study	Intervention time: Median trial duration was 17 months (IQR, 13-21)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: TAVI performed and success determined by echocardiography
Stratum	Transcatheter replacement: Those that received successful TAVI for treatment of aortic stenosis
Subgroup analysis within study	Not applicable
Inclusion criteria	≥18 years; successful TAVI (correct positioning of single prosthetic heart valve into proper anatomical location, intended performance of the valve as defined by mean aortic valve gradient <20 mmHg, peak transvalvular velocity <3.0 m/s and no severe or moderate aortic valve regurgitation, and absence of periprocedural complications including stroke, life-threatening bleeding, acute coronary obstruction requiring intervention, major vascular complication needing intervention, unresolved acute valve thrombosis and any requirement of a repeat procedure) for aortic stenosis (either native or valve-in-valve procedure); iliofemoral or

	subclavian access used; TAVI performed with any approved/marketed device; and written informed consent obtained
Exclusion criteria	Current or previous atrial fibrillation with an ongoing indication for oral anticoagulant treatment; any other indication for continued treatment with any oral anticaogulant; known bleeding diathesis (including but not limited to active internal bleeding, clinically significant bleeding, bleeding at a non-compressible site or bleeding diathesis, platelet count ≤50,000 mm³ at screening, haemoglobin level <8.5 g/dl, history of intracranial haemorrhage or subdural haematoma, major surgery, biopsy of a parenchymal organ or serious trauma within 30 days prior to randomisation, and active peptic ulcer or known upper GI bleeding within last 3 months); ongoing indication for dual-antiplatelet therapy at time of screening that is unrelated to TAVI procedure; known hypersensitivity or contraindication to acetylsalicylic acid, clopidogrel or rivaroxaban or hypersensitivity to contrast media that could not be solved by switching to alternative contrast media or by pre-treating with appropriate medication; routine use of NSAIDs; concomitant treatment with systemic drugs that are strong inhibitors of cytochrome P450 3A4 and P-gp; concomitant treatment with drugs that are strong CYP3A4 inducers; concomitant therapy with omeprazole or esomeprazole that cannot be switched to an alternative medication; planned coronary or vascular intervention or major surgery; clinically overt stroke within last 3 months; severe renal impairment (eGFR <30 ml/min/1.73 m²) or on dialysis, or post-TAVI unresolved acute kidney injury with renal dysfunction stage 2 or above; moderate and severe hepatic impairment or any hepatic disease associated with coagulopathy; active infective endocarditis; active malignancy (diagnosed within 5 years) apart from adequately treated non-melanoma skin cancer or other non-invasive or in situ neoplasm; dementia or forgetfulness affecting compliance with medication intake or other study procedures; cannot provide informed consent; previous (30 days prior to enrollment) or concomitant participation in another clinical study with medicinal products being investigated; previous assignment to treatment during this study; close affiliation with the investigational site; female of childbearing potential
Recruitment/selection of patients	Unclear if consecutive patients
Age, gender and ethnicity	Age - Mean (SD): Rivaroxaban, 80.4 (7.1); antiplatelet, 80.8 (6.0). Gender (M:F): Define. Ethnicity: Not reported
Further population details	1. Age (<75 vs ≥75): 75 years or over (Mean age in both groups >75 years). 2. Atrial fibrillation: No atrial fibrillation (Atrial fibrillation listed as an exclusion criterion). 3. Hepatic function : Normal (Moderate or severe hepatic dysfunction listed as an exclusion criterion). 4. Renal function: Not stated / Unclear (Severe renal dysfunction listed as an exclusion criterion, unclear how many with milder forms of renal dysfunction may be included. Mean values for eGFR consistent with mild dysfunction). 5. Sex: Mixed (Males and females included). 6. Valve position: Aortic (TAVI performed in all patients).

Extra comments	Body mass index, mean (SD): 28.1 (5.5) vs. 28.2 (5.7); hypertension, 87.2% vs. 85.2%; diabetes mellitus, 28.6% vs. 28.7%; EuroSCORE II, mean (SD): 4.1 (3.9) vs. 4.1 (3.7); STS risk score, mean (SD): 4.0 (3.2) vs. 4.3 (3.5); congestive heart failure, 47.7%vs. 46.5%; NYHA class III or IV, 30.3% vs. 27.1%; coronary artery disease, 39.3% vs. 37.3%; previous stroke, 6.2% vs. 4.3%; peripheral artery disease, 10.0% vs. 10.0%; previous venous thromboembolism, 2.2% vs. 1.8%; permanent pacemaker, 9.7% vs. 9.8%; COPD, 13.3% vs. 10.8%; glomerular filtration rate, mean (SD): 73.4 (23.8) vs 73.2 (23.2) ml/min/1.73 m²; TAVI valve type: Sapien XT (1.6% vs. 1.6%), Spaien 3 (46.6% vs. 42.3%), CoreValve (4.0% vs. 4.3%), CoreValve Evolut R (24.9% vs. 27.5%), Lotus (5.3% vs. 4.9%), Portico (5.3% vs. 4.9%), Acurate Neo (9.9% vs. 10.9%) and other (2.3% vs. 3.7%); valve-in-valve procedure, 5.1% vs. 6.0%); aortic valve area post-TAVI, mean (SD): 1.8 (0.6) vs. 1.9 (0.5) cm²; mean aortic valve gradient post TAVI, mean (SD): 10.0 (4.7) vs. 10.1 (4.6) mmHg; LVEF post-TAVI, mean (SD): 57.4 (10.9)% vs. 58.2 (11.2)%; mild paravalvular aortic regurgitation post-TAVI, 19.0% vs. 20.5%; moderate or severe paravalvular aortic regurgitation post-TAVI, 1.2% vs. 1.2%
Indirectness of population	No indirectness
Interventions	(n=826) Intervention 1: Direct oral anticoagulants (DOACs) - Rivaroxaban. Rivaroxaban at 10 mg daily + aspirin at 75-100 mg daily for 3 months, followed by rivaroxaban monotherapy 10 mg daily. In those that developed atrial fibrillation, rivaroxaban at 20 mg was received once daily (or 15 mg for those with estimated glomerular filtration rate 30-50 ml/min/1.73 m²). Median exposure to rivaroxaban was 428 days (IQR, 171-581) and median exposure to aspirin was 90 days (IQR, 84-94). Duration Median treatment with rivaroxaban 428 days. Concurrent medication/care: Reports that various medications were allowed concomitantly but no information on the number that were taking concomitant medications/treatments. Indirectness: No indirectness (n=818) Intervention 2: Single antiplatelet therapy - Aspirin. Antiplatelet group received aspirin 75-100 mg daily + clopidogrel 75 mg daily for 3 months (patients that had not previously received clopidogrel were recommended to have a single loading dose of ≥300 mg), followed by aspirin monotherapy (75-100 mg daily). Median exposure to aspirin was 474 days (IQR, 298-603) and median exposure to clopidogrel was 90 days (IQR, 85-93). Duration Median treatment with aspirin 474 days. Concurrent medication/care: Reports that various medications were allowed concomitantly but no information on the number that were taking concomitant medications/treatments. Patients that developed atrial fibrillation received vitamin K antagonists (targeting INR ratio of 2-3) to replace clopidogrel within 3 months or to replace aspirin thereafter. Indirectness: No indirectness
Funding	Study funded by industry (Supported by Bayer and Janssen Pharmaceuticals. Sponsors involved in design and supervision of trial.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RIVAROXABAN (+ASPIRIN FOR FIRST 3 MONTHS) versus ASPIRIN (+ CLOPIDOGREL FOR FIRST 3 MONTHS)

Protocol outcome 1: All-cause mortality at >12 months
- Actual outcome for Transcatheter replacement: All-cause deaths during follow-up. Includes all deaths within study, some of which will have occurred prior to 12 months. at Median treatment duration 428 days; Group 1: 64/826, Group 2: 38/818; Comments: HR of 1.69 (95% CI, 1.13-2.53) reported. Causes of death - sudden death (1.7% vs. 1.0%), congestive heart failure of cardiogenic shock (0.6% vs. 1.0%), intracranial haemorrhage (0.1% vs. 0.1%), ischaemic stroke (0% vs. 0.4%), myocardial infarction (0.2% vs. 0%), non-intracranial haemorrhage (0.1% vs. 0%), dysrhythmia (0.2% vs. 0%), directly related to cardiac procedure or surgery (0.4% vs. 0.2%), unknown death (0.8% vs. 0.6%), cancer (1.2% vs. 0.5%), respiratory failure (1.0% vs. 0.4%), liver failure (0.1% vs. 0.1%), infection or sepsis (0.7% vs. 0.2%), renal failure (0.4% vs. 0.1%) accident or trauma (0.1% vs. 0%).
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness; Baseline details: Some slight differences between groups but only 2-3% difference at most; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Major bleeding at >12 months
- Actual outcome for Transcatheter replacement: Life-threatening, disabling or major bleeding, according to VARC-2, during follow-up. Includes all events within study, some of which will have occurred prior to 12 months. at Median treatment duration 428 days; Group 1: 46/826, Group 2: 31/818; Comments: Rivaroxaban: 18 life-threatening or disabling bleeding, 2 fatal bleeding and 30 major bleeding; aspirin: 17 life-threatening or disabling bleeding, 1 fatal bleeding and 15 major bleeding.
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Some slight differences between groups but only 2-3% difference at most; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Transcatheter replacement: Major bleeding according to ISTH, during follow-up. Includes all events within study, some of which will have occurred prior to 12 months. at Median treatment duration 428 days; Group 1: 49/826, Group 2: 30/818
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Some slight differences between groups but only 2-3% difference at most; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Transcatheter replacement: BARC type 2, 3 or 5 bleeding, during follow-up. Includes all events within study, some of which will have occurred prior to 12 months. at Median treatment duration 428 days; Group 1: 148/826, Group 2: 85/818
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness; Baseline details: Some slight differences between groups but only 2-3% difference at most; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Minor bleeding at >12 months
- Actual outcome for Transcatheter replacement: Major or minor bleeding according to TIMI, during follow-up. Includes all events within study, some of which will have occurred prior to 12 months. at Median treatment duration 428 days; Group 1: 42/826, Group 2: 24/818

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: Serious indirectness, Comments: Does not report number of minor events separately - combined with major events.; Baseline details: Some slight differences between groups but only 2-3% difference at most; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Arterial thromboembolic events at >12 months
- Actual outcome for Transcatheter replacement: Stroke during follow-up. Includes all events within study, some of which will have occurred prior to 12 months. Includes ischaemic and haemorrhagic. at Median treatment duration 428 days; Group 1: 30/826, Group 2: 25/818
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness; Baseline details: Some slight differences between groups but only 2-3% difference at most; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Transcatheter replacement: Myocardial infarction during follow-up. Includes all events within study, some of which will have occurred prior to 12 months. at Median treatment duration 428 days; Group 1: 23/826, Group 2: 17/818
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Some slight differences between groups but only 2-3% difference at most; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Transcatheter replacement: Pulmonary embolism during follow-up. Includes all events within study, some of which will have occurred prior to 12 months. at Median treatment duration 428 days; Group 1: 3/826, Group 2: 2/818
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Some slight differences between groups but only 2-3% difference at most; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Transcatheter replacement: Systemic embolism during follow-up. Includes all events within study, some of which will have occurred prior to 12 months. at Median treatment duration 428 days; Group 1: 1/826, Group 2: 1/818
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Some slight differences between groups but only 2-3% difference at most; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 5: Withdrawal due to adverse events at 12 months
- Actual outcome for Transcatheter replacement: Premature study drug discontinuation due to adverse events - includes any discontinuation with any of the following occurring within 30 days before the discontinuation: thromboembolic events (stroke, myocardial infarction, symptomatic valve thrombosis, systemic embolism not involving the CNS, deep vein thrombosis or pulmonary embolism), life-threatening, disabling or major bleeding and other adverse events. Does not include deaths. at Median treatment duration 428 days; Group 1: 185/826, Group 2: 91/818; Comments: Rivaroxaban: 23 due to thromboembolic events, 68 due to bleeding events and 94 due to other adverse events. Aspirin: 21 due to thromboembolic events, 9 due to bleeding events and 61 due to other adverse events.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Measurement - types of events included under 'other adverse events' not reported; Indirectness of outcome: No indirectness ; Baseline details: Some slight differences between groups but only 2-3% difference at most; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 6: Thrombus on imaging at ≤12 months - Actual outcome for Transcatheter replacement: Symptomatic valve thrombosis (confirmed on echocardiography). Defined as any thrombus attached to or near an implanted valve that occludes part of blood flow path, interferes with valve function or is sufficiently large to warrant treatment. at Median treatment duration 428 days; Group 1: 3/826, Group 2: 7/818 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - ; Indirectness of outcome: No indirectness, Comments: May include some events occurring >12 months but unclear; Baseline details: Some slight differences between groups but only 2-3% difference at most; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	All-cause mortality at ≤12 months; Quality of life at ≤12 months; Quality of life at >12 months; Major bleeding at ≤12 months; Minor bleeding at ≤12 months; Arterial thromboembolic events at ≤12 months; Hospital re-admission at 12 months; Need for valve re-intervention at ≤12 months; Valve degeneration (transvalvular gradient) at ≤12 months; Valve degeneration (transvalvular gradient) at >12 months

Study	Duraes 2016[23]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=27)
Countries and setting	Conducted in Brazil; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention + follow up: 90 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Post-surgical patients (up to 3 months post-operatively)
Stratum	Surgical replacement
Subgroup analysis within study	Not applicable
Inclusion criteria	18-64 years old, who underwent mitral and/or aortic bioprosthetic valve replacement at least 3 months prior to entering the study and had documented AF postoperatively.
Exclusion criteria	Exclusion of atrial thrombus or valve prosthesis thrombosis by TEE. CT without haemorrhagic or findings of acute cerebral infarction on the last 2 days of screening.
Recruitment/selection of patients	No additional information
Age, gender and ethnicity	Age - Mean (SD): Dabigatran arm: 48.8±10.4; Warfarin arm: 45.7±6. Gender (M:F): 10:17. Ethnicity: Not stated
Further population details	1. Age (<75 vs ≥75): <75 years (Mean age 48.8±10.4 (dabigatran) and 45.7±6 (warfarin)). 2. Atrial fibrillation: Atrial fibrillation (Patients were included if they had post-operative atrial fibrillation). 3. Hepatic function: Not stated / Unclear 4. Renal function: Not stated / Unclear 5. Sex: Mixed (10:17 (male to female)). 6. Valve position: Mixed (Aortic and mitral).
Indirectness of population	No indirectness
Interventions	(n=15) Intervention 1: Direct oral anticoagulants (DOACs) - Dabigatran. 110mg twice daily. Duration 90 days. Concurrent medication/care: None noted. However, some patients had diabetes and hypertension and so could have been on other medications. Indirectness: No indirectness Comments: People with previous use of warfarin underwent washout with immediate introduction of dabigatran once the international normalised ratio (INR) was <2.5. (n=12) Intervention 2: Vitamin K antagonist - Warfarin. Target INR 2.0-3.0 (doses between 5 and 10mg in the first days for most individuals). Duration 90 days. Concurrent medication/care: None noted. However, some patients had diabetes and hypertension and so could have been on other medications. Indirectness: No indirectness
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DABIGATRAN versus WARFARIN

Protocol outcome 1: All-cause mortality at ≤12 months
- Actual outcome for Surgical replacement: Death at 90 days; Group 1: 0/15, Group 2: 1/12
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Blinding details: Warfarin patients would have had INR blood tests while dabigatran patients would not. Some patients had previously had warfarin.; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Major bleeding at ≤12 months
- Actual outcome for Surgical replacement: Bleeding at 90 days; Group 1: 1/15, Group 2: 2/12
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Blinding details: Warfarin patients would have had INR blood tests while dabigatran patients would not. Some patients had previously had warfarin.; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Arterial thromboembolic events at ≤12 months
- Actual outcome for Surgical replacement: Stroke or systemic embolism at 90 days; Group 1: 1/15, Group 2: 1/12; Comments: Reports stroke and systolic embolism (1 event in the warfarin arm, 0 events in the dabigatran arm) and reversible ischaemic neurological deficit (0 events in the warfarin arm, 1 event in the dabigatran arm).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Blinding details: Warfarin patients would have had INR blood tests while dabigatran patients would not. Some patients had previously had warfarin.; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Hospital re-admission at 12 months
- Actual outcome for Surgical replacement: Hospitalisation at 90 days; Group 1: 1/15, Group 2: 1/12
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Blinding details: Warfarin patients would have had INR blood tests while dabigatran patients would not. Some patients had previously had warfarin.; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 5: Thrombus on imaging at ≤12 months
- Actual outcome for Surgical replacement: Intracardiac thrombus at 90 days; Group 1: 0/15, Group 2: 1/12
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Blinding details: Warfarin patients would have had INR blood tests while dabigatran patients would not. Some patients had previously had warfarin.; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	All-cause mortality at >12 months; Quality of life at ≤12 months; Quality of life at >12 months; Major bleeding at >12 months; Minor bleeding at ≤12 months; Minor bleeding at >12 months; Arterial thromboembolic events at >12 months; Withdrawal due to adverse events at 12 months; Need for valve re-

intervention at ≤12 months; Valve degeneration (transvalvular gradient) at ≤12 months; Valve degeneration (transvalvular gradient) at >12 months	

Study	Hassell 2015[31]
Study type	Systematic Review
Number of studies (number of participants)	2 (n=199)
Countries and setting	Conducted in Italy; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention + follow up: Up to 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Studies containing patients with aortic stenosis after being treated with TAVI
Stratum	Transcatheter replacement
Subgroup analysis within study	Not applicable
Inclusion criteria	Studies containing patients with aortic stenosis after being treated with TAVI, clear description of postprocedural antithrombotic treatment including one group treated with single antiplatelet therapy and another treated with dual antiplatelet therapy, and a minimum follow-up of 1 month.
Exclusion criteria	If only one intervention was considered or when the treatment groups mere included dual versus single antiplatelet therapy in combination with vitamin K antagonist treatment.
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): Stabile: 80±5.2. Ussia: 81±5.1. Gender (M:F): 76:123. Ethnicity: Not stated
Further population details	1. Age (<75 vs ≥75): 75 years or over (Stabile: 80±5.2. Ussia: 81±5.1.). 2. Atrial fibrillation: Mixed (0 patients in Stabile study. 10 patients in Ussia study (12.7% or 10:69). (AF: not AF)). 3. Hepatic function: Not stated / Unclear 4. Renal function: Mixed (Stabile: 54 (45% or 54:66), Ussia: 11 (13.9% or 11:68) (renal impairment: normal renal function)). 5. Sex: Mixed (Stabile: 80 (66.7% or 40:80), Ussia: 43 (54.4% or 36:43) (M:F)). 6. Valve position: Aortic
Extra comments	Paper also includes observational studies but the RCTs are reported separately.
Indirectness of population	No indirectness
Interventions	(n=99) Intervention 1: Single antiplatelet therapy - Aspirin. Stabile: 81mg OD orally; Ussia: 100mg OD orally. Duration Lifelong. Concurrent medication/care: None stated. Indirectness: No indirectness (n=100) Intervention 2: Dual antiplatelet therapy - Aspirin + clopidogrel. Stabile: 75mg clopidogrel OD orally, 81mg aspirin OD orally. Ussia: 75mg clopidogrel OD orally, 100mg aspirin OD orally. Both studies included a preloading dose of 300mg clopidogrel 1 day preprocedural. Duration Aspirin lifelong. Stabile: Clopidogrel for 6 months. Ussia: Clopidogrel for 3 months. Concurrent medication/care: None stated. Indirectness: No indirectness
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ASPIRIN versus ASPIRIN + CLOPIDOGREL Protocol outcome 1: All-cause mortality at ≤12 months - Actual outcome for Transcatheter replacement: All-cause mortality at 3-6 months; Group 1: 4/99, Group 2: 5/100; Comments: OR for Stabile: 1.00 (0.06-16.37) OR for Ussia: 0.75 (0.16-3.59) Risk of bias: All domain – High: unclear if all relevant studies have been identified and biases in primary studies not assessed or accounted for; Indirectness of outcome: No indirectness ; Baseline details: Doesn't report this for the RCTs alone. The individual studies appear comparable to themselves, and accounted for in the analysis.; Blinding details: From the primary study reports: unblinded and the care was comparable.; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Major bleeding at ≤12 months - Actual outcome for Transcatheter replacement: Life-threatening and major bleeding at 3-6 months; Group 1: 8/99, Group 2: 10/100; Comments: OR for Stabile: 0.83 (0.24-2.90) OR for Ussia: 0.75 (0.16-3.59). Stabile: Bleeding events lead to withdrawal of the clopidogrel in 1 person (due to muscular haematoma). There was withdrawal of ticlopidine in 1 person due to thrombocytopenia but no explicit report of bleeding as a consequence. Risk of bias: All domain - High: unclear if all relevant studies have been identified and biases in primary studies not assessed or accounted for; Indirectness of outcome: No indirectness ; Baseline details: Doesn't report this for the RCTs alone. The individual studies appear comparable to themselves, and accounted for in the analysis.; Blinding details: From the primary study reports unblinded and the care was comparable.; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Arterial thromboembolic events at ≤12 months - Actual outcome for Transcatheter replacement: ACS and Stroke at 3-6 months; Group 1: 4/99, Group 2: 2/100; Comments: OR for Stabile: 2.03 (0.18-23.06) OR for Ussia: 2.11 (0.18-24.24) No ACS events in either arms. 4 strokes in the aspirin arm, 2 strokes in the aspirin and clopidogrel arm. Risk of bias: All domain – High: unclear if all relevant studies have been identified and biases in primary studies not assessed or accounted for; Indirectness of outcome: No indirectness ; Baseline details: Doesn't report this for the RCTs alone. The individual studies appear comparable to themselves, and accounted for in the analysis.; Blinding details: From the primary study reports unblinded and the care was comparable.; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	All-cause mortality at >12 months; Quality of life at ≤12 months; Quality of life at >12 months; Major bleeding at >12 months; Minor bleeding at ≤12 months; Minor bleeding at >12 months; Arterial thromboembolic events at >12 months; Hospital re-admission at 12 months; Withdrawal due to adverse events at 12 months; Thrombus on imaging at ≤12 months; Need for valve re-intervention at ≤12 months; Valve degeneration (transvalvular gradient) at ≤12 months; Valve degeneration (transvalvular gradient) at >12 months

Study
POPular TAVI cohort B trial: Nijenhuis 2020[50]

Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=326 (313 analysed))
Countries and setting	Conducted in Belgium, Czech Republic, Luxembourg, Netherlands; Setting: Secondary care/outpatient
Line of therapy	1st line
Duration of study	Intervention time: All followed for at least 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Confirmed to have undergone TAVI
Stratum	Transcatheter replacement: Those suitable for TAVI, based on dedicated heart team at each institution, eligible for enrollment (this study covers those with an existing indication for long-term oral anticoagulation)
Subgroup analysis within study	Not applicable
Inclusion criteria	Long-term indication for oral anticoagulation; underwent TAVi procedure; written informed consent provided
Exclusion criteria	Drug-eluting stent implantation within 3 months prior to TAVI; bare-metal stent implantation within 1 month prior to TAVI; allergy, intolerance or contraindication to oral anticoagulation or clopidogrel.
Recruitment/selection of patients	All of those matching inclusion criteria, unclear if consecutive
Age, gender and ethnicity	Age - Mean (SD): Oral anticoagulation + clopidogrel, 81 (5.5) years; oral anticoagulation only, 80.9 (6.2) years. Gender (M:F): Oral anticoagulation + clopidogrel, 83/73; oral anticoagulation only, 88/69. Ethnicity: Not reported
Further population details	1. Age (<75 vs ≥75): 75 years or over (Mean age in both groups >75 years). 2. Atrial fibrillation: Atrial fibrillation (>90% in each group have atrial fibrillation at baseline). 3. Hepatic function : Not stated / Unclear (No details provided). 4. Renal function: Abnormal (Estimated glomerular filtration rate <60 ml/min/1.73 m2 in both groups - moderate dysfunction?). 5. Sex: Mixed (Males and females included). 6. Valve position: Aortic (TAVI performed in all cases).

Extra comments	Oral anticoagulant therapy: vitamin K antagonist, 70.5% vs. 75.2% (acenocoumarol, 58.3% vs. 61.8%, phenprocomon, 10.3% vs. 11.5% and warfarin, 1.9% vs. 1.9%); DOAC, 29.5% vs. 23.6% (apixaban, 16.0% vs. 8.9%; dabigatran, 2.6% vs. 4.5%; edoxaban, 2.6% vs. 2.5%; and rivaroxaban, 7.6% vs. 7.6%); and low molecular weight heparin, 0% vs. 1.3%. NYHA class III or IV, 70.5% vs. 75.8%; body mass index, mean (SD): 27.5 (5.1) vs. 27.4 (5.3); logistic EuroSCORE, median (IQR): 14.1 (10.6-22.8) vs. 15.6 (9.2-23.8); STS risk score, median (IQR): 3.1 (2.3-4.5) vs. 3.2 (2.2-4.8); indication for TAVI: normal-flow high-gradient AS (62.8% vs. 62.4%), low-flow low-gradient AS (32.1% vs. 32.5%), pure AR (2.6% vs. 3.8%) or combination (2.6% vs. 1.3%); atrial fibrillation, 94.2% vs. 95.5%; hypertension, 67.3% vs. 73.2%; diabetes mellitus, 29.5% vs. 27.4%; coronary artery disease, 44.2% vs. 41.4%; previous myocardial infarction, 12.8% vs. 8.9%; peripheral artery disease, 17.9% vs. 19.1%; previous stroke, 9.6% vs. 9.6%; estimated GFR, mean (SD): 55.6 (17.1) vs. 53.4 (17.7) ml/min/1.73 m²; COPD, 19.2% vs. 21.0%; previous CABG, 19.2% vs. 19.1%; previous aortic valve surgery, 5.8% vs. 4.5%; LVEF >50%, 62.2% vs. 58.0%; LVEF 31-50%, 29.5% vs. 34.4%; LVEF ≤30%, 8.3% vs. 7.6%; transfemoral TAVI approach, 84.6% vs. 86.6%; transapical TAVI approach, 11.5% vs. 9.6%; direct aortic TAVI approach, 3.2% vs. 3.8%; trans-subclavia TAVI approach, 0.6% vs. 0%; unfractionated heparin during TAVI, 100% vs. 100%; valve type: Sapien XT (2.6% vs. 4.5%), Sapien 3 (52.6% vs. 41.4%), CoreValve (7.7% vs. 2.5%), CoreValve Evolut R (23.1% vs. 28.7%), CoreValve Evolut Pro (3.2% vs. 5.7%), Engager (1.9% vs. 1.3%), Lotus (4.5% vs. 6.4%), JenaValve (1.9% vs. 3.2%), Portico (0.6% vs. 1.3%) and Direct Flow (1.9% vs. 3.2%); VARC-2 vascular complication, 22.4% vs. 12.7%; red blood cell transfusion following TAVI, 8.3% vs. 7.0%; mild PV leak at discharge, 26.9% vs. 28.7%; moderate PV leak at discharge, 2.6% vs. 1.9%; severe PV leak at discharge, 0% vs. 0%; maximal aortic valve gradient at discharge, mean (SD): 17.0 (10.2) vs. 15.8 (8.0) mmHg; mean aortic valve gradient at discharge, mean (SD): 8.8 (5.6) vs. 8.6 (4.6) mmHg; aortic valve area at discharge, mean (SD): 2.2 (0.8) vs. 2.1 (0.7) cm²
Indirectness of population	No indirectness
Interventions	(n=162) Intervention 1: Anti-coagulation + antiplatelet therapy – VKA/DOAC + clopidogrel. Oral anticoagulation (vitamin K antagonist or DOAC) + clopidogrel. Patients continued using the oral anticoagulation they were receiving prior to randomisation, which could be a vitamin K antagonist or a DOAC. Randomised prior to TAVI to receive clopidogrel for 3 months in addition to their oral anticoagulation. Loading dose of 300 mg clopidogrel administered 1 day prior to or on the day of TAVI ocedure, followed by 75 mg once daily for 3 months. There was a discretionary allowance of cessation of clopidogrel 1 month earlier or later than 3 months. Adherence to clopidogrel was 95.5% for the period of 3 months. 70.5% were on a vitamin K antagonist and 29.5% were on a DOAC. No patients in this group discontinued oral anticoagulation. Duration 3 months. Concurrent medication/care: TAVI procedures performed according to local protocol at each site. Protocol advised physicians to continue oral anticoagulation during admission for the TAVi procedure with a target of INR 2.0 for vitamin K antagonists, but the choice to continue or interrupt oral anticoagulation periprocedurally was left to discretion of attending physician. During TAVI, unfractionated

	heparin use recommended with the goal of an activated clotting time of >250 seconds or >200 seconds in patients with continued oral anticoagulation therapy. Indirectness: Serious indirectness; Indirectness comment: Includes a mixture of those receiving vitamin K antagonists and DOACs under the term 'oral anticoagulation', whereas in protocol ideally wanted to separate vitamin K antagonists and DOACs (n=164) Intervention 2: Anti-coagulation – VKA/DOAC. Oral anticoagulation (vitamin K antagonist or DOAC) alone. Patients continued using the oral anticoagulation they were receiving prior to randomisation, which could be a vitamin K antagonist or a DOAC. Randomised prior to TAVI not to receive clopidogrel for 3 months in addition to their oral anticoagulation. 75.2% were on a vitamin K antagonist and 23.6% were on a DOAC. 2 patients discontinued oral anticoagulation during the trial. Duration 3 months. Concurrent medication/care: TAVI procedures performed according to local protocol at each site. Protocol advised physicians to continue oral anticoagulation during admission for the TAVi procedure with a target of INR 2.0 for vitamin K antagonists, but the choice to continue or interrupt oral anticoagulation periprocedurally was left to discretion of attending physician. During TAVI, unfractionated heparin use recommended with the goal of an activated clotting time of >250 seconds or >200 seconds in patients with continued oral anticoagulation therapy. Two patients in this group were discharged with low molecular weight heparin, which was used until an adequate INR with vitamin K antagonist was obtained. Indirectness: Serious indirectness; Indirectness comment: Includes a mixture of those receiving vitamin K antagonists and DOACs under the term 'oral anticoagulation', whereas in protocol ideally wanted to separate vitamin K antagonists and DOACs
Funding	Other (Sponsored by Netherlands Organization for Health Research and Development. No industry involvement in the trial.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL ANTICOAGULATION (VITAMIN K OR DOAC) + CLOPIDOGREL versus ORAL ANTICOAGULATION (VITAMIN K ANTAGONIST OR DOAC) ALONE

Protocol outcome 1: All-cause mortality at ≤12 months
- Actual outcome for Transcatheter replacement: All-cause mortality at 12 months; Group 1: 24/156, Group 2: 21/157
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Some larger differences between groups, e.g. history of myocardial infarction, LVEF and type of anticoagulant being used; Group 1 Number missing: 6, Reason: Withdrew consent, n=1; no initiation of TAVI or procedure was aborted or converted to open surgery, n=3; and screening failure, n=2.; Group 2 Number missing: 7, Reason: Withdrew consent, n=4; no initiation of TAVI or procedure was aborted or converted to open surgery, n=2; and screening failure, n=1.

Protocol outcome 2: Major bleeding at ≤12 months
- Actual outcome for Transcatheter replacement: Major, life-threatening or disabling bleeding according to VARC-2 at 12 months; Group 1: 26/156, Group 2:

14/157; Comments: Anticoagulation +clopidogrel: 13 life-threatening or disabling and 13 major bleeding; anticoagulation alone, 6 life-threatening or disabling and 8 major bleeding.
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Some larger differences between groups, e.g. history of myocardial infarction, LVEF and type of anticoagulant being used; Group 1 Number missing: 6, Reason: Withdrew consent, n=1; no initiation of TAVI or procedure was aborted or converted to open surgery, n=3; and screening failure, n=2.; Group 2 Number missing: 7, Reason: Withdrew consent, n=4; no initiation of TAVI or procedure was aborted or converted to open surgery, n=2; and screening failure, n=1.

Protocol outcome 3: Minor bleeding at ≤12 months
- Actual outcome for Transcatheter replacement: Minor bleeding according to VARC-2 at 12 months; Group 1: 28/156, Group 2: 20/157
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Some larger differences between groups, e.g. history of myocardial infarction, LVEF and type of anticoagulant being used; Group 1 Number missing: 6, Reason: Withdrew consent, n=1; no initiation of TAVI or procedure was aborted or converted to open surgery, n=3; and screening failure, n=2.; Group 2 Number missing: 7, Reason: Withdrew consent, n=4; no initiation of TAVI or procedure was aborted or converted to open surgery, n=2; and screening failure, n=1.

Protocol outcome 4: Arterial thromboembolic events at ≤12 months
- Actual outcome for Transcatheter replacement: Stroke. Includes ischaemic and haemorrhagic. at 12 months; Group 1: 9/156, Group 2: 9/157
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Some larger differences between groups, e.g. history of myocardial infarction, LVEF and type of anticoagulant being used; Group 1 Number missing: 6, Reason: Withdrew consent, n=1; no initiation of TAVI or procedure was aborted or converted to open surgery, n=3; and screening failure, n=2.; Group 2 Number missing: 7, Reason: Withdrew consent, n=4; no initiation of TAVI or procedure was aborted or converted to open surgery, n=2; and screening failure, n=1.
- Actual outcome for Transcatheter replacement: Myocardial infarction at 12 months; Group 1: 1/156, Group 2: 1/157
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Some larger differences between groups, e.g. history of myocardial infarction, LVEF and type of anticoagulant being used; Group 1 Number missing: 6, Reason: Withdrew consent, n=1; no initiation of TAVI or procedure was aborted or converted to open surgery, n=3; and screening failure, n=2.; Group 2 Number missing: 7, Reason: Withdrew consent, n=4; no initiation of TAVI or procedure was aborted or converted to open surgery, n=2; and screening failure, n=1.

Protocol outcome 5: Valve degeneration (transvalvular gradient) at ≤12 months
- Actual outcome for Transcatheter replacement: Mean aortic valve gradient at mean (SD) follow-up 6(3) months; Group 1: mean 10.5 mmHg (SD 5.3); n=129, Group 2: mean 9 mmHg (SD 4.7); n=135; Comments: Values at discharge from TAVI: anticoagulation + clopidogrel, 8.8 (5.6) mmHg; anticoagulation alone, 8.6 (4.6) mmHg.
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Some larger differences between groups, e.g. history of myocardial infarction, LVEF and type of anticoagulant being used; Group 1 Number missing: 33, Reason: Withdrew consent, n=1; no initiation of TAVI or procedure was aborted or converted to open surgery, n=3; screening failure, n=2; further n=27 with missing data at follow-up; Group 2 Number

missing: 29, Reason: Withdrew consent, n=4; no initiation of TAVI or procedure was aborted or converted to open surgery, n=2; and screening failure, n=1; further n=22 with missing data at follow-up	
Protocol outcomes not reported by the study	All-cause mortality at >12 months; Quality of life at ≤12 months; Quality of life at >12 months; Major bleeding at >12 months; Minor bleeding at >12 months; Arterial thromboembolic events at >12 months; Hospital re-admission at 12 months; Withdrawal due to adverse events at 12 months; Thrombus on imaging at ≤12 months; Need for valve re-intervention at ≤12 months; Valve degeneration (transvalvular gradient) at >12 months

Study	Rafiq 2017[57]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=328)
Countries and setting	Conducted in Denmark; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention + follow up: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Post-operative patients
Stratum	Surgical replacement
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients referred for first time aortic valve replacement with or without concomitant coronary artery bypass grafting surgery aged 60 years or older and in sinus rhythm.
Exclusion criteria	Other concomitant procedures, active endocarditis, history of atrial fibrillation or flutter, previous TIA or stroke, neurological deficits, coagulopathy, haematological disorders/cancers, permanent pacemaker, HIV/AIDS, liver cirrhosis, renal dialysis, narcotics or alcohol abuse, not able to give informed consent, patients from Greenland and Faroe Islands (not available for follow-up).
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): Warfarin arm: 73.1±6.4, Aspirin arm: 72.7±7.2. Gender (M:F): 229:99. Ethnicity: Not stated
Further population details	1. Age (<75 vs ≥75): Mixed (Warfarin arm: 73.1±6.4, Aspirin arm: 72.7±7.2. Crosses the line due to the confidence interval.). 2. Atrial fibrillation: No atrial fibrillation 3. Hepatic function : Normal (No liver cirrhosis (sufficient?)). 4. Renal function: Normal (Not on renal dialysis (sufficient?)). 5. Sex: Mixed (Predominantly male but by a 2:1 ratio.). 6. Valve position: Aortic
Indirectness of population	No indirectness
Interventions	(n=167) Intervention 1: Vitamin K antagonist - Warfarin. Initial dose 5mg orally. Target INR of 2.0 to 3.0. Duration 3 months. Concurrent medication/care: Enoxaparin 40mg SC once daily until INR stabilised for 2 days. Indirectness: Very serious indirectness; Indirectness comment: 63 patients had a CABG while having the valve replacement surgery and so were put on warfarin and aspirin 75mg once a day post-operatively. (n=161) Intervention 2: Single antiplatelet therapy - Aspirin. 150mg orally. Duration 3 months. Concurrent medication/care: Enoxaparin 40mg SC once daily was given for the first 3 days. Indirectness: No indirectness Comments: 56 patients had a CABG at the same time. They received the same treatment otherwise.
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WARFARIN versus ASPIRIN

Protocol outcome 1: All-cause mortality at ≤12 months
- Actual outcome for Surgical replacement: Total mortality at 3 months; Group 1: 8/167, Group 2: 6/161
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0, Reason: Some patients developed AF and were switched to use warfarin. These patients were analysed by ITT.

Protocol outcome 2: Major bleeding at ≤12 months
- Actual outcome for Surgical replacement: Major bleeding at 3 months; Group 1: 9/167, Group 2: 3/161
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0, Reason: Some patients developed AF and were switched to use warfarin. These patients were analysed with ITT.

Protocol outcome 3: Arterial thromboembolic events at ≤12 months
- Actual outcome for Surgical replacement: Thromboembolic complications at 3 months; Group 1: 10/167, Group 2: 11/161; Comments: They included MI, DVT, TCI/Stroke and other thromboembolic complications. This included 2 MIs in the warfarin arm, 5 MIs in the aspirin arm, 8 TCIs/Strokes in the warfarin arm and 4 TCIs/Strokes in the aspirin arm. We did not include the other thromboembolic complications reported, which included a pulmonary embolus (as this would not be a relevant arterial thromboembolic event in this scenario) and intramural cardiac thrombus (as this is counted in another outcome).
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0, Reason: Some patients developed AF and were switched to use warfarin. These patients were analysed with ITT.

Protocol outcome 4: Hospital re-admission at 12 months
- Actual outcome for Surgical replacement: Re-admission to hospital at 3 months; Group 1: 25/167, Group 2: 21/161
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0, Reason: Some patients developed AF and were switched to use warfarin. These patients were analysed with ITT.

Protocol outcome 5: Thrombus on imaging at ≤12 months
- Actual outcome for Surgical replacement: Left ventricle mural thrombus at 3 months; Group 1: 0/167, Group 2: 1/161
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0, Reason: Some patients developed AF and were switched to use warfarin. These patients were analysed with ITT.

Protocol outcomes not reported by the study	All-cause mortality at >12 months; Quality of life at ≤12 months; Quality of life at >12 months; Major bleeding at >12 months; Minor bleeding at ≤12 months; Minor bleeding at >12 months; Arterial thromboembolic events at >12 months; Withdrawal due to adverse events at 12 months; Need for valve re-

intervention at ≤12 months; Valve degeneration (transvalvular gradient) at ≤12 months; Valve degeneration (transvalvular gradient) at >12 months	

Study	Rodes-Cabau 2017[62]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=222)
Countries and setting	Conducted in Canada, Chile, Spain, Switzerland; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention + follow up: 3 months (90 days)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Post-operative patients
Stratum	Transcatheter replacement
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with clinical indications for TAVR with a balloon-expandable Edwards SAPIEN XT or SAPIEN 3 valve
Exclusion criteria	Need for chronic anticoagulation treatment, major bleeding within the 3 months before the TAVR procedure, allergy to clopidogrel and/or aspirin.
Recruitment/selection of patients	Selected from 9 centers across Canada, Europe and South America
Age, gender and ethnicity	Age - Mean (SD): 79±9. Gender (M:F): 129:93. Ethnicity: Not stated
Further population details	1. Age (<75 vs ≥75): Mixed (79±9 - Crosses the middle point). 2. Atrial fibrillation: No atrial fibrillation 3. Hepatic function: Not stated / Unclear 4. Renal function: Mixed (140 patients (70 in each arm) had chronic renal failure (GFR <60mL/min)). 5. Sex: Mixed (129:93 (male:female)). 6. Valve position: Aortic
Indirectness of population	No indirectness
Interventions	(n=111) Intervention 1: Single antiplatelet therapy - Aspirin. Aspirin 80-100mg per day. Duration 3 months. Concurrent medication/care: Not stated. No specific recommendations regarding proton pump inhibitors. Indirectness: No indirectness (n=111) Intervention 2: Dual antiplatelet therapy - Asprin + clopidogrel. Aspirin 80-100mg per day, Clopidogrel 75mg per day. Duration 3 months. Concurrent medication/care: Not stated. No specific recommendations regarding proton pump inhibitors. Indirectness: No indirectness
Funding	Principal author funded by industry (The study was also funded by industry (a grant from Edwards Lifesciences) and from academic sources (the Foundation of the Research Center of the Quebec Heart and Lung Institute). Several authors had funding from industry.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ASPIRIN versus ASPRIN + CLOPIDOGREL	

Protocol outcome 1: All-cause mortality at ≤12 months - Actual outcome for Transcatheter replacement: Death at 3 months; Group 1: 4/111, Group 2: 7/111 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Major bleeding at ≤12 months - Actual outcome for Transcatheter replacement: Life threatening/major bleeding at 3 months; Group 1: 3/111, Group 2: 5/111; Comments: Bleeding events lead to withdrawal of clopidogrel in 8 people. Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Arterial thromboembolic events at ≤12 months - Actual outcome for Transcatheter replacement: Stroke and MI at 3 months; Group 1: 2/111, Group 2: 7/111; Comments: MIs in aspirin arm: 1, MIs in aspirin and clopidogrel arm: 4 Strokes in aspirin arm: 1, Strokes in aspirin and clopidogrel arm: 3 No TIAs in both arms. Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	All-cause mortality at >12 months; Quality of life at ≤12 months; Quality of life at >12 months; Major bleeding at >12 months; Minor bleeding at ≤12 months; Minor bleeding at >12 months; Arterial thromboembolic events at >12 months; Hospital re-admission at 12 months; Thrombus on imaging at ≤12 months; Need for valve re-intervention at ≤12 months; Valve degeneration (transvalvular gradient) at ≤12 months; Valve degeneration (transvalvular gradient) at >12 months; Withdrawal due to adverse events at 12 months

Study	Stabile 2014[68]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=120)
Countries and setting	Conducted in Italy; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Patients with severe AS, cardiac symptoms (NYHA ≥2, syncope) and high surgical risk.
Stratum	Transcatheter replacement
Subgroup analysis within study	Not applicable
Inclusion criteria	Severe AS (echo-derived AVA <0.8cm² and mean AVG >40mmHg or peak jet velocity >4.0m/s), cardiac symptoms (NYHA functional class ≥2) or high surgical risk (predicted risk of operative mortality ≥15% as determined by surgeon and cardiology or STS scope ≥10
Exclusion criteria	Aortic annulus diameter <18mm or >25mm; aortic dissection or iliac-femoral dimensions or disease precluding safe sheath insertion; untreated coronary artery disease requiring revascularisation; severe aortic regurgitation or mitral regurgitation or prosthetic valve (any location); acute myocardial infarction within 1 month; upper gastrointestinal bleeding within 3 months; cerebrovascular accident or transient ischaemic attack within 6 months; any cardiac procedure, other than balloon aortic valvuloplasty within 1 month or within 6 months for drug eluting stent; indication for oral anticoagulation therapy (i.e. atrial fibrillation); aspirin intolerance/allergy; thienopiridine intolerance/allergy
Recruitment/selection of patients	144 consecutive patients, scheduled for TAVI, were screened.
Age, gender and ethnicity	Age - Mean (SD): ASA arm: 81.1±4.8, DAPT arm: 80.2±5.7. Gender (M:F): 40:80. Ethnicity: Not specified
Further population details	1. Age (<75 vs ≥75): 75 years or over (ASA arm: 81.1±4.8, DAPT arm: 80.2±5.7). 2. Atrial fibrillation: No atrial fibrillation 3. Hepatic function: Not stated / Unclear 4. Renal function: Not stated / Unclear 5. Sex: Mixed (40:80 - predominantly female, but not exclusively). 6. Valve position: Aortic
Extra comments	.
Indirectness of population	No indirectness
Interventions	(n=60) Intervention 1: Single antiplatelet therapy - Aspirin. 75-160mg/day. Duration 6 months. Concurrent medication/care: Patients received unfractionated heparin at the start of the procedure and were given additional heparin at the operator's discretion. Indirectness: No indirectness (n=60) Intervention 2: Dual antiplatelet therapy - Asprin + clopidogrel. Aspirin 75-160mg/day. Clopidogrel 75mg four times a day OR ticlopidine 500mg twice a day. Duration 6 months. Concurrent medication/care:

	Patients received unfractionated heparin at the start of the procedure and were given additional heparin at the operator's discretion. Indirectness: Serious indirectness; Indirectness comment: Ticlopidine 500mg twice a day. Not able to distinguish patients who took ticlopidine instead of clopidogrel.
Funding	Other author(s) funded by industry (G. Sorropago and P. Rubino are proctors for Edwards Lifesciences.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ASPIRIN versus ASPRIN + CLOPIDOGREL No additional outcomes reported	
Protocol outcomes not reported by the study	All-cause mortality at ≤12 months; All-cause mortality at >12 months; Quality of life at ≤12 months; Quality of life at >12 months; Major bleeding at ≤12 months; Major bleeding at >12 months; Minor bleeding at ≤12 months; Minor bleeding at >12 months; Arterial thromboembolic events at ≤12 months; Arterial thromboembolic events at >12 months; Hospital re-admission at 12 months; Thrombus on imaging at ≤12 months; Need for valve re-intervention at ≤12 months; Valve degeneration (transvalvular gradient) at ≤12 months; Valve degeneration (transvalvular gradient) at >12 months; Withdrawal due to adverse events at 12 months

Study	Turpie 1993[73]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=In trial: 370, with bioprosthetic valves: 89)
Countries and setting	Conducted in Canada; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention + follow up: Mean 2.5 years, maximum 4 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Surgery was performed with specific valves.
Stratum	Surgical replacement
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with mechanical or bioprosthetic valves plus pre-operative atrial fibrillation or a history of thromboembolism. Patients with replacements in the aortic, mitral or tricuspid positions (singly or in combination) were potentially eligible, as were patients who had concurrent coronary artery bypass graft surgery.
Exclusion criteria	Allergy to aspirin; contraindication to either anticoagulant or antiplatelet therapy; were geographically inaccessible for follow up; were not willing to give consent
Recruitment/selection of patients	Consecutive patients from 3 different Canadian hospitals
Age, gender and ethnicity	Age - Mean (range): Study in total: Aspirin arm 58.1 (26-82), Placebo arm: 58.1 (22-79). Gender (M:F): Total for study 187:183. Not able to distinguish for patients with biological valves only. Ethnicity: Not stated
Further population details	1. Age (<75 vs ≥75): Not stated / Unclear (Unclear for our strata, generally <75). 2. Atrial fibrillation: Not stated / Unclear (Unclear for our strata. One of the inclusion criteria included the presence of AF as a possible option.). 3. Hepatic function: Not stated / Unclear 4. Renal function: Not stated / Unclear 5. Sex: Not stated / Unclear (Unclear for our strata, generally mixed). 6. Valve position: Mixed (Aortic and mitral).
Extra comments	. Am not able to distinguish ages and sex of the people in the biological valve arm.
Indirectness of population	No indirectness
Interventions	(n=45) Intervention 1: Vitamin K antagonist - Warfarin. Warfarin and aspirin (100mg OD). Target INR 3.0-4.5. Duration Mean 2.4 years. Concurrent medication/care: Low-dose heparin postoperatively until 3 days after oral anticoagulant started. Indirectness: No indirectness (n=44) Intervention 2: Vitamin K antagonist - Warfarin. dose/quantity, brand name, extra details. Duration Mean 2.4 years. Concurrent medication/care: Low-dose heparin postoperatively until 3 days after oral anticoagulant started. Indirectness: No indirectness
Funding	Academic or government funding (Grant from the Heart and Stroke Foundation or Ontario.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: WARFARIN AND ASPIRIN versus WARFARIN Protocol outcome 1: Arterial thromboembolic events at ≤12 months - Actual outcome for Surgical replacement: Major systemic embolism OR death from vascular causes at Mean follow up 2.4 months; Group 1: 2/45, Group 2: 4/44 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: Serious indirectness, Comments: Includes vascular mortality. Appeared to fit better into this outcome than the all-cause mortality outcome.; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	All-cause mortality at ≤12 months; All-cause mortality at >12 months; Quality of life at ≤12 months; Quality of life at >12 months; Major bleeding at ≤12 months; Major bleeding at >12 months; Minor bleeding at ≤12 months; Minor bleeding at >12 months; Arterial thromboembolic events at >12 months; Hospital re-admission at 12 months; Withdrawal due to adverse events at 12 months; Thrombus on imaging at ≤12 months; Need for valve re-intervention at ≤12 months; Valve degeneration (transvalvular gradient) at ≤12 months; Valve degeneration (transvalvular gradient) at >12 months

Study	Ussia 2011[75]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=79)
Countries and setting	Conducted in Italy; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Patients after TAVI insertion
Stratum	Transcatheter replacement
Subgroup analysis within study	Not applicable
Inclusion criteria	Criteria for inclusion of a TAVI (previously reported). Patients with severe symptomatic aortic stenosis with a valve area <1cm². Eligibility for TAVI was established at each centre by the consensus of a local multidisciplinary team. All procedures were approved for compassionate use in patients with no reasonable surgical option.
Exclusion criteria	Additional exclusion factors were: previous percutaneous coronary intervention or ACS requiring DAPT, the need for oral anticoagulation therapy, and allergy or intolerance to any of the study drugs.
Recruitment/selection of patients	Consecutive patients who met the anatomic and clinical criteria.
Age, gender and ethnicity	Age - Mean (SD): 81±4. Gender (M:F): 36:43. Ethnicity: Not stated
Further population details	1. Age (<75 vs ≥75): 75 years or over (81±4). 2. Atrial fibrillation: Mixed (Permanent AF in 10 patients (13%)). 3. Hepatic function: Mixed (1 patient with liver cirrhosis, otherwise normal hepatic function). 4. Renal function: Mixed (11 patients (14%) with CKD). 5. Sex: Mixed (36:43 (M:F)). 6. Valve position: Aortic
Indirectness of population	No indirectness
Interventions	(n=40) Intervention 1: Dual antiplatelet therapy - Asprin + clopidogrel. Oral aspirin 100mg OD and oral clopidogrel 75mg OD. Loading dose of 300mg clopidogrel on the day before TAVI. Duration Aspirin lifelong. Clopidogrel for 3 months. Concurrent medication/care: Not stated. Indirectness: No indirectness (n=39) Intervention 2: Single antiplatelet therapy - Aspirin. Oral aspirin 100mg OD. Duration Lifelong. Concurrent medication/care: Not stated. Indirectness: No indirectness
Funding	Principal author funded by industry (Dr Ussia is a proctor physician for Medtronic Incorporation. All other authors have no conflicts of interest to declare.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ASPRIN + CLOPIDOGREL versus ASPIRIN	

Protocol outcome 1: Minor bleeding at ≤12 months - Actual outcome for Transcatheter replacement: Minor bleeding at 6 months; Group 1: 3/40, Group 2: 4/39 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: The dual antiplatelet group generally has more patients that would fall into a higher clinical risk bracket (ex. diabetes, heart failure, peripheral vascular disease, previous PCI, COPD, previous valvuloplasty); Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	All-cause mortality at ≤12 months; All-cause mortality at >12 months; Quality of life at ≤12 months; Quality of life at >12 months; Major bleeding at ≤12 months; Major bleeding at >12 months; Minor bleeding at >12 months; Arterial thromboembolic events at ≤12 months; Arterial thromboembolic events at >12 months; Hospital re-admission at 12 months; Withdrawal due to adverse events at 12 months; Thrombus on imaging at ≤12 months; Need for valve re-intervention at ≤12 months; Valve degeneration (transvalvular gradient) at ≤12 months; Valve degeneration (transvalvular gradient) at >12 months

Appendix E: Forest plots

E.1 Surgical Valve Replacement

E.1.1 DOAC versus VKA

Figure 2: All-cause mortality at ≤12 months for DOAC versus VKA in biological surgical valve replacement

Figure 3: Major bleeding at ≤12 months for DOAC versus VKA in biological surgical valve replacement

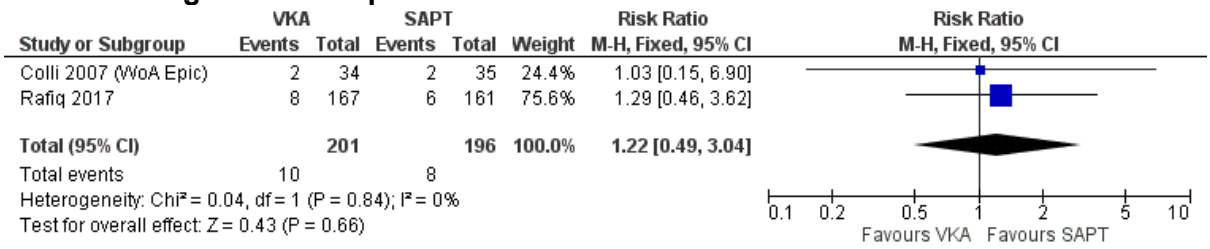
Figure 4: Arterial thromboembolic events at ≤12 months for DOAC versus VKA in biological surgical valve replacement

Figure 5: Hospital re-admission at 12 months for DOAC versus VKA in biological surgical valve replacement

Figure 6: Thrombus on imaging at ≤12 months for DOAC versus VKA in biological surgical valve replacement

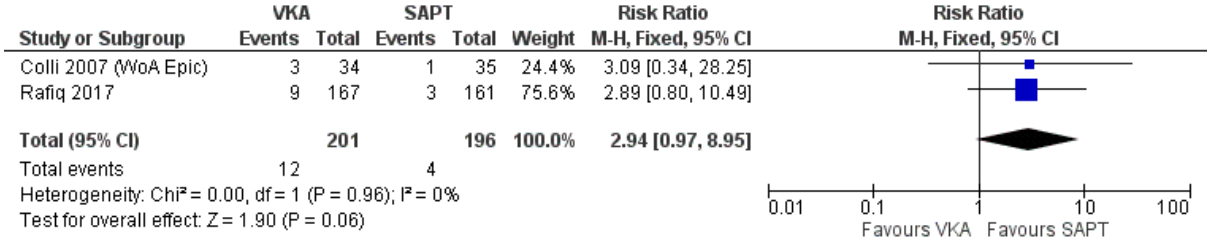
E.1.12 VKA versus SAPT

Figure 7: All-cause mortality at ≤12 months for VKA versus SAPT in biological surgical valve replacement



2

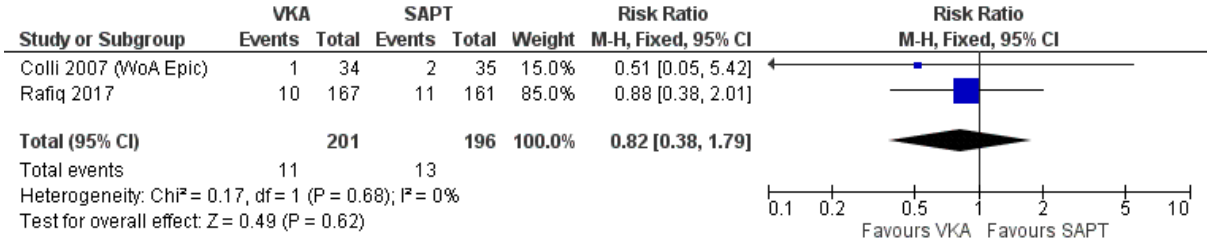
Figure 8: Major bleeding at ≤12 months for VKA versus SAPT in biological surgical valve replacement



3

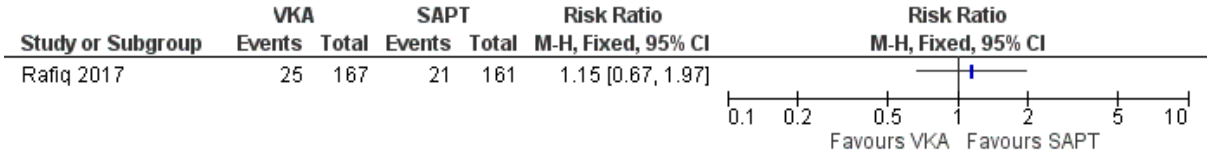
4

Figure 9: Arterial thromboembolic events at ≤12 months for VKA versus SAPT in biological surgical valve replacement



5

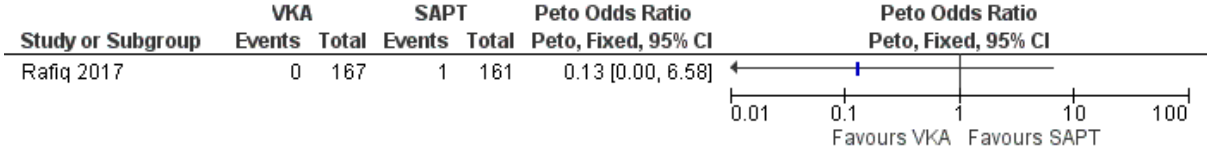
Figure 10: Hospital re-admission at 12 months for VKA versus SAPT in biological surgical valve replacement



1

2

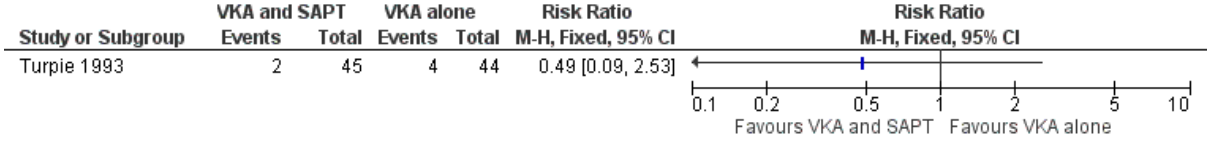
Figure 11: Thrombus on imaging at ≤12 months for VKA versus SAPT in biological surgical valve replacement



3

E.13 VKA and SAPT versus VKA alone in surgical valve replacement

Figure 12: Major systemic embolism or death from vascular causes at ≤12 months for VKA and SAPT versus VKA alone in biological surgical valve replacement

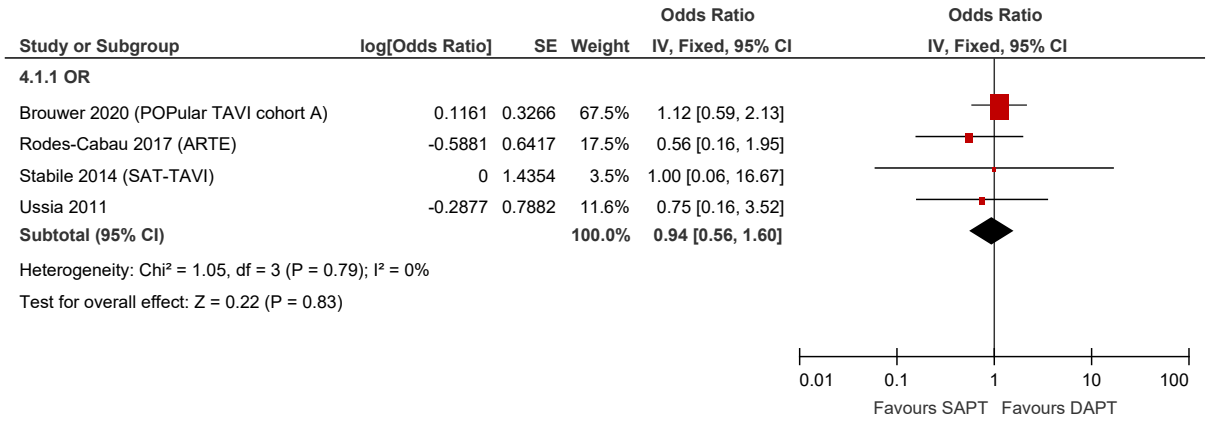


5

E.2 Transcatheter valve implantation

E.21 SAPT versus DAPT

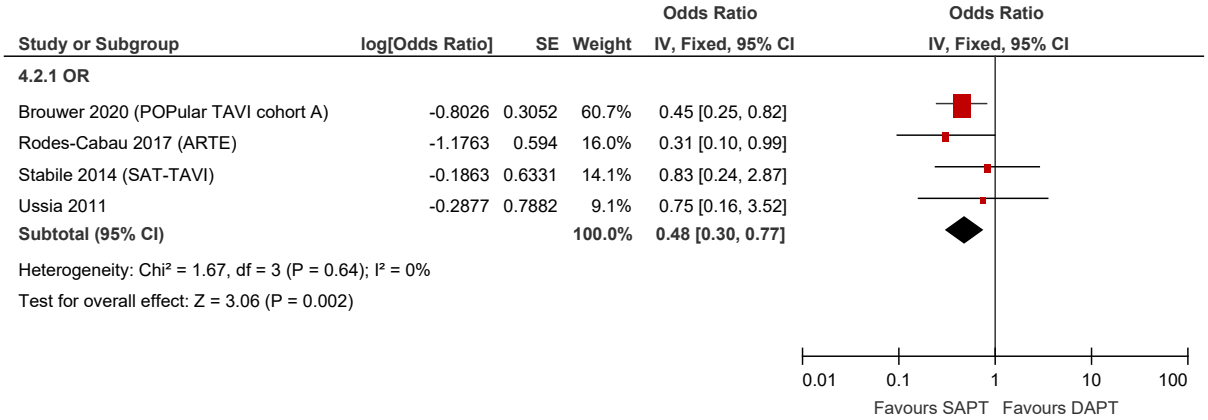
Figure 13: All-cause mortality at ≤12 months for SAPT versus DAPT in transcatheter valve implantation



Note: Odds ratio used because this summary statistic was reported for the two studies included in the IPD MA.

1

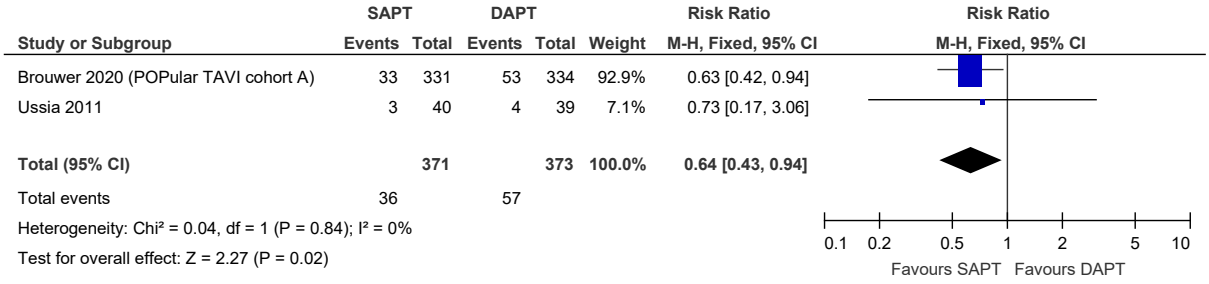
Figure 14: Major bleeding at ≤12 months for SAPT versus DAPT in transcatheter valve implantation



Note: Odds ratio used because this summary statistic was reported for the two studies included in the IPD MA.

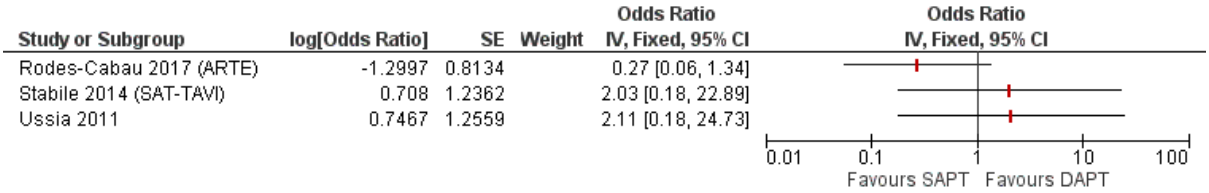
2

Figure 15: Minor bleeding at ≤12 months for SAPT versus DAPT in transcatheter valve implantation



3

Figure 16: Arterial thromboembolic events at ≤12 months for SAPT versus DAPT in transcatheter valve implantation



Note: Reported as a range of odds ratios due to heterogeneity between studies with a large difference in point estimates without sufficient study number to form valid subgroups. Odds ratio used because this summary statistic was reported for the two studies included in the IPD MA.

Figure 17: Stroke (arterial thromboembolic events) at 12 months for SAPT versus DAPT in transcatheter valve implantation

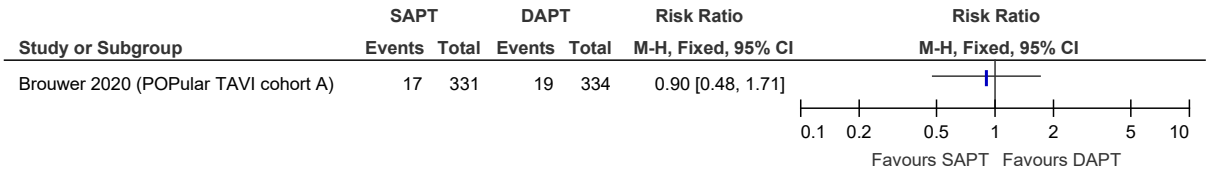


Figure 18: Myocardial infarction (arterial thromboembolic events) at 12 months for SAPT versus DAPT in transcatheter valve implantation

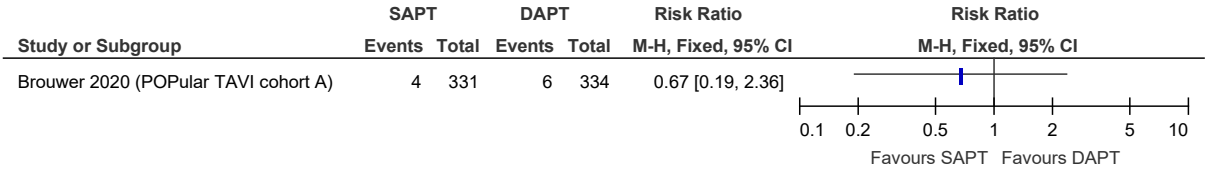


Figure 19: Symptomatic clinical aortic valve thrombosis (thrombus on imaging) at 12 months for SAPT versus DAPT in transcatheter valve implantation

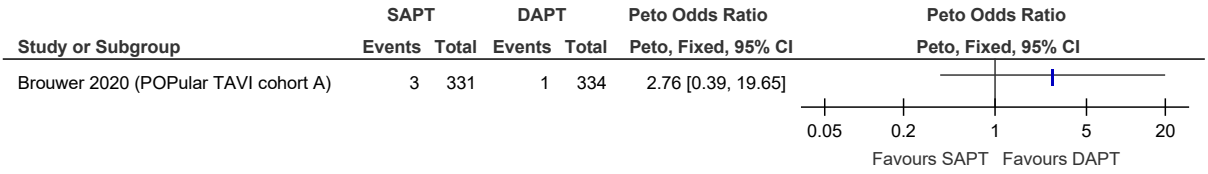
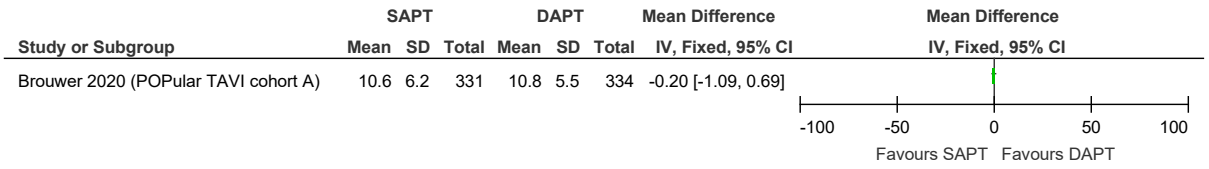


Figure 20: Mean aortic valve gradient (valve degeneration) at 6 months for SAPT versus DAPT in transcatheter valve implantation

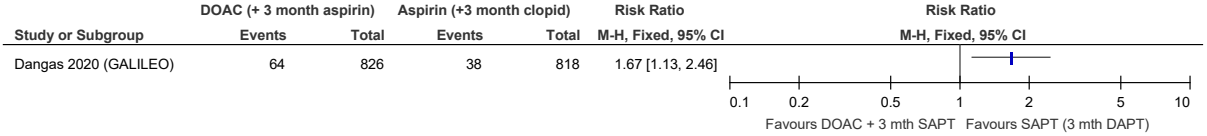


MIDs used to assess imprecision were calculated by multiplying the median baseline SD across study arms (5.2) by 0.5 and were ±2.60.

E.2.12 DOAC (+ aspirin for 3 months) versus aspirin (+ clopidogrel for 3 months)

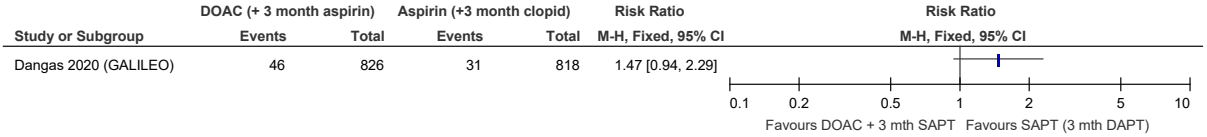
2

Figure 21: All-cause mortality at median treatment duration of 428 days



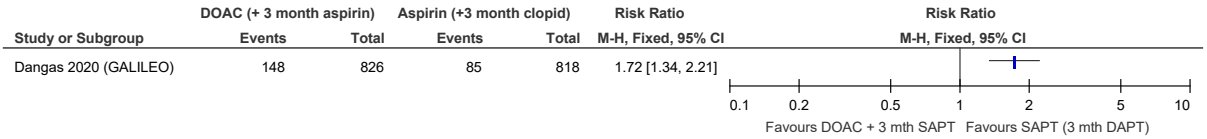
1

Figure 22: Major bleeding (VARC-2 life-threatening, disabling or major bleeding) at median treatment duration of 428 days



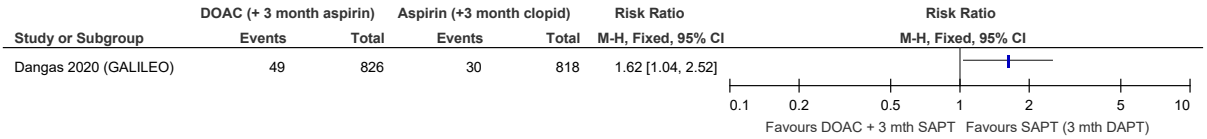
2

Figure 23: Major bleeding (BARC type 2, 3 or 5 bleeding) at median treatment duration of 428 days



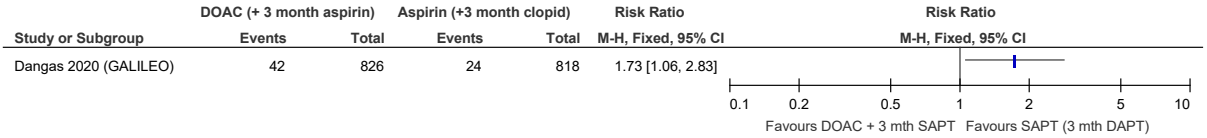
3

Figure 24: Major bleeding (ISTH major bleeding) at median treatment duration of 428 days



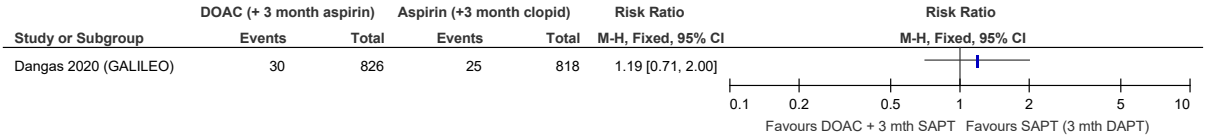
4

Figure 25: Major/minor bleeding (TIMI major or minor bleeding) at median treatment duration of 428 days



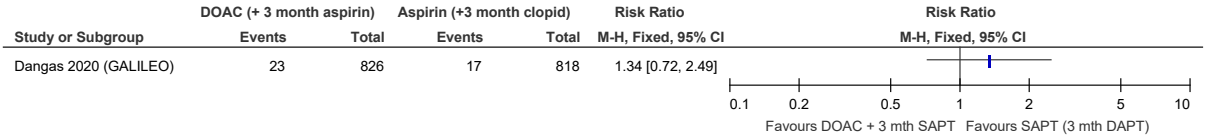
1

Figure 26: Stroke (arterial thromboembolic events) at median treatment duration of 428 days



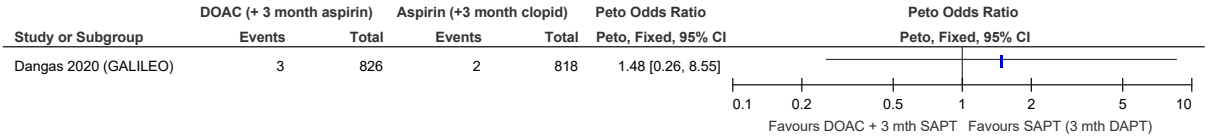
2

Figure 27: Myocardial infarction (arterial thromboembolic events) at median treatment duration of 428 days



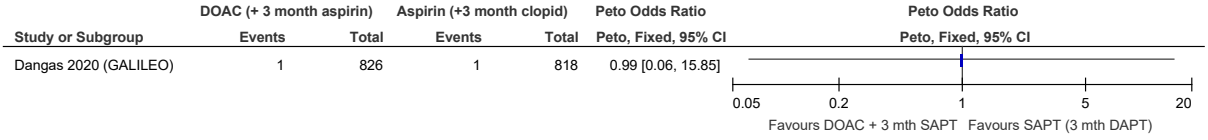
3

Figure 28: Pulmonary embolism (arterial thromboembolic events) at median treatment duration of 428 days



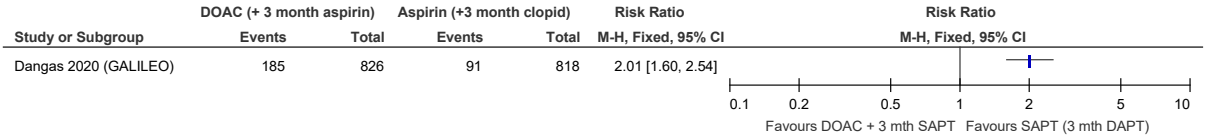
4

Figure 29: Systemic embolism (arterial thromboembolic events) at median treatment duration of 428 days



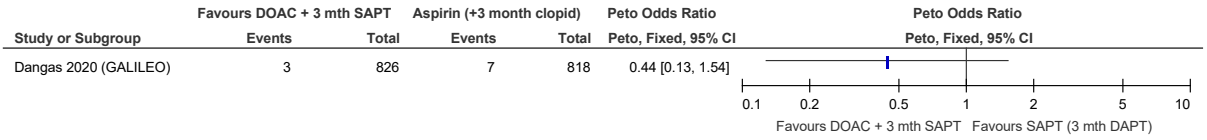
5

Figure 30: Premature study drug discontinuation due to adverse events (thromboembolic, bleeding or other adverse events) at median treatment duration of 428 days



1

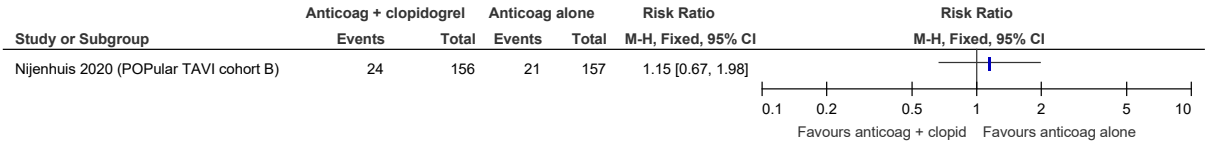
Figure 31: Symptomatic valve thrombosis (thrombus on imaging) at median treatment duration of 428 days



2

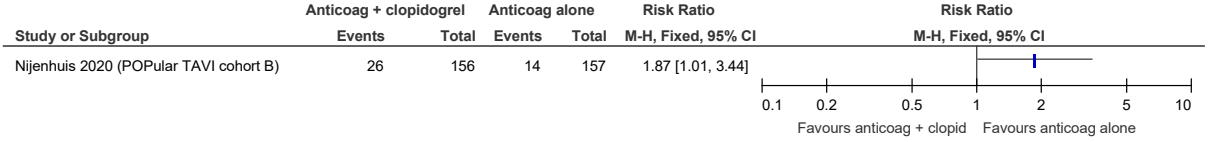
E.23 Anticoagulant (VKA or DOAC) + SAPT (clopidogrel) versus anticoagulant (VKA or DOAC) alone

Figure 32: All-cause mortality at 12 months



5

Figure 33: Major bleeding (VARC-2 life-threatening, disabling or major bleeding) at 12 months

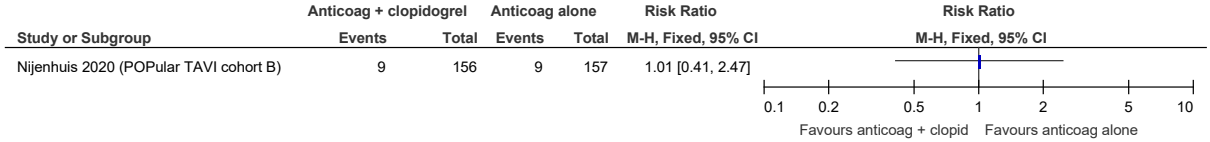


6

Figure 34: Minor bleeding (VARC-2 minor bleeding) at 12 months

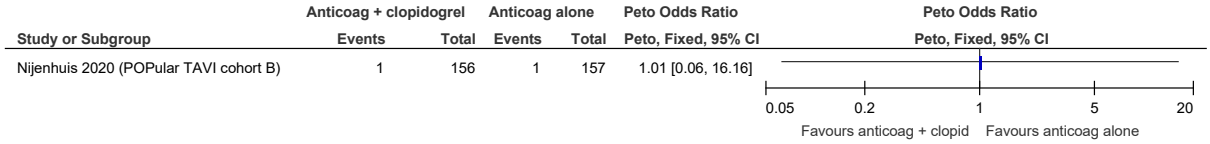
1

Figure 35: Stroke (arterial thromboembolic events) at 12 months



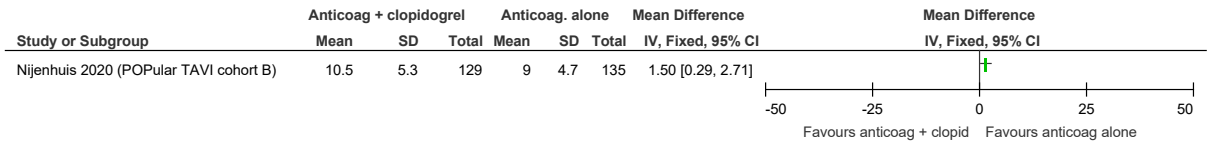
2

Figure 36: Myocardial infarction (arterial thromboembolic events) at 12 months



3

Figure 37: Mean aortic valve gradient (valve degeneration – transvalvular gradient) at 6 months



MIDs used to assess imprecision were calculated by multiplying the median baseline SD across study arms (5.1) by 0.5 and were ± 2.55.

4

E.3 Valve repair

5

6 No information available.

7

8

Appendix F: GRADE tables

F.1 Surgical valve replacement

Table 14: Clinical evidence profile: DOAC versus VKA in surgical valve replacement

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DOAC	VKA	Relative (95% CI)	Absolute		
All-cause mortality at ≤12 months (follow-up mean 3 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/15 (0%)	8.3%	Peto OR 0.11 (0 to 5.44)	8 fewer per 1000 (from 28 fewer to 11 more)[2]	⊕⊕OO LOW	CRITICAL
Health-related quality of life at ≤12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Major bleeding at ≤12 months (follow-up mean 3 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	1/15 (6.7%)	8.3%	Peto OR 0.79 (0.05 to 13.6)	16 fewer per 1000 (from 78 fewer to 469 more)	⊕⊕OO LOW	CRITICAL
Minor bleeding at ≤12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Arterial thromboembolic events at ≤12 months (follow-up mean 3 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	1/15 (6.7%)	8.3%	Peto OR 0.79 (0.05 to 13.6)	16 fewer per 1000 (from 78 fewer to 469 more)	⊕⊕OO LOW	CRITICAL
Hospital re-admission at 12 months (follow-up mean 3 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	1/15 (6.7%)	8.3%	Peto OR 0.79 (0.05 to 13.6)	16 fewer per 1000 (from 78 fewer to 469 more)	⊕⊕OO LOW	IMPORTANT
Thrombus on imaging at ≤12 months (follow-up mean 3 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/15 (0%)	8.3%	Peto OR 0.11 (0 to 5.44)	8 fewer per 1000 (from 28 fewer to 11 more)[2]	⊕⊕OO LOW	IMPORTANT
All-cause mortality at >12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Health-related quality of life at >12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Major bleeding at >12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL

Minor bleeding at >12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Arterial thromboembolic events at >12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL

[1] Downgraded by 2 increments as the confidence interval crossed two MIDs
[2] Absolute effect calculated manually using risk difference as zero events in one arm of the study

Table 15: Clinical evidence profile: VKA versus SAPT in surgical valve replacement

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**VKA**	**SAPT**	**Relative (95% CI)**	**Absolute**		
All-cause mortality at ≤12 months (follow-up 3-6 months)												
2	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	10/201 (5%)	4.7%	RR 1.22 (0.49 to 3.04)	10 more per 1000 (from 24 fewer to 96 more)	⊕OOO VERY LOW	CRITICAL
Health-related quality of life at ≤12 months - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Major bleeding at ≤12 months (follow-up 3-6 months)												
2	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4]	none	12/201 (6%)	2.4%	RR 2.94 (0.97 to 8.95)	47 more per 1000 (from 1 fewer to 191 more)	⊕OOO VERY LOW	CRITICAL
Minor bleeding at ≤12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Arterial thromboembolic events at ≤12 months (follow-up 3-6 months)												
2	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	11/201 (5.5%)	6.3%	RR 0.82 (0.37 to 1.76)	11 fewer per 1000 (from 40 fewer to 48 more)	⊕OOO VERY LOW	CRITICAL
Hospital re-admission at 12 months (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[3]	none	25/167 (15%)	13%	RR 1.15 (0.67 to 1.97)	19 more per 1000 (from 43 fewer to 126 more)	⊕OOO VERY LOW	IMPORTANT
Thrombus on imaging at ≤12 months (follow-up mean 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	very serious[3]	none	0/167 (0%)	0.6%	Peto OR 0.13 (0 to 6.58)	10 fewer per 1000 (from 20 fewer to 10 more)[5]	⊕OOO VERY LOW	IMPORTANT
All-cause mortality at >12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL

Health-related quality of life at >12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Major bleeding at >12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Minor bleeding at >12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Arterial thromboembolic events at >12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL

[1] Downgraded by 1 increment as the majority of the evidence was at high risk of bias
[2] Downgraded by 1 increment as one study included people who had a CABG while having the valve replacement surgery. The people in the intervention arm were subsequently given warfarin and aspirin, instead of just warfarin.
[3] Downgraded by 2 increments as the confidence interval crossed both MIDs
[4] Downgraded by 1 increment as the confidence interval crossed one MID
[5] Absolute effect calculated manually using risk difference as zero events in one arm of the study

Table 16: Clinical evidence profile: VKA and SAPT versus VKA alone in surgical valve replacement

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**VKA and SAPT**	**VKA**	**Relative (95% CI)**	**Absolute**		
All-cause mortality at ≤12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Health-related quality of life at ≤12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Major bleeding at ≤12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Minor bleeding at ≤12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Major systemic embolism or death from vascular causes at ≤12 months												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	2/45 (4.4%)	9.1%	RR 0.49 (0.09 to 2.53)	46 fewer per 1000 (from 83 fewer to 139 more)	⊕OOO VERY LOW	CRITICAL
All-cause mortality at >12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Health-related quality of life at >12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Major bleeding at >12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL

Minor bleeding at >12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Arterial thromboembolic events at >12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL

[1] Downgraded by 1 increment as the evidence reported thromboembolic events/vascular mortality and did not report thromboembolic events excluding mortality
[2] Downgraded by 2 increments as the confidence interval crossed both MIDs

F.2 Transcatheter valve implantation

Table 17: Clinical evidence profile: SAPT versus DAPT in transcatheter valve implantation

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SAPT	DAPT	Relative (95% CI)	Absolute		
All-cause mortality at ≤12 months (follow-up 3-12 months)												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	29/541 (5.4%)	5.6%	OR 0.94 (0.56 to 1.6)[3]	3 fewer per 1000 (from 24 fewer to 31 more)	⊕OOO VERY LOW	CRITICAL
Health-related quality of life at ≤12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Major bleeding at ≤12 months (follow-up 3-12 months)												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	28/541 (5.2%)	10%	OR 0.48 (0.3 to 0.77)[3]	49 fewer per 1000 (from 21 fewer to 68 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Minor bleeding at ≤12 months (follow-up 6-12 months)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	36/371 (9.7%)	13.1%	RR 0.64 (0.43 to 0.94)	47 fewer per 1000 (from 8 fewer to 75 fewer)	⊕⊕OO LOW	CRITICAL
Arterial thromboembolic events at ≤12 months (follow-up 3-6 months)												

3	randomised trials	serious[1]	no serious inconsistency	serious[5]	very serious[2]	none	0/111 (0%)	4%	OR ranged from 0.21 to 2.24[3,6]	-	⊕OOO VERY LOW	CRITICAL
Stroke (arterial thromboembolic events) at 12 months (follow-up mean 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	17/331 (5.1%)	5.7%	RR 0.9 (0.48 to 1.71)	6 fewer per 1000 (from 30 fewer to 40 more)	⊕OOO VERY LOW	CRITICAL
Myocardial infarction (arterial thromboembolic events) at 12 months (follow-up mean 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/331 (1.2%)	1.8%	RR 0.67 (0.19 to 2.36)	6 fewer per 1000 (from 15 fewer to 24 more)	⊕OOO VERY LOW	CRITICAL
All-cause mortality at >12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Health-related quality of life at >12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Major bleeding at >12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Minor bleeding at >12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Arterial thromboembolic events at >12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Hospital readmission at 12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		IMPORTANT
Withdrawal due to adverse events at 12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		IMPORTANT
Symptomatic clinical aortic valve thrombosis (thrombus on imaging) at 12 months (follow-up mean 12 months)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/331 (0.91%)	0.3%	OR 2.76 (0.39 to 19.65)	5 more per 1000 (from 2 fewer to 53 more)	⊕OOO VERY LOW	IMPORTANT
Need for reintervention at 6-12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		IMPORTANT
Need for reintervention at >12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		IMPORTANT
Mean aortic valve gradient (valve degeneration) at ≤12 months (follow-up mean 6 months; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[7]	none	331	334	-	MD 0.20 lower (1.09 lower to 0.69 higher)	⊕⊕⊕O MODERATE	IMPORTANT

[1] Downgraded by 1 increment as the majority of the evidence was at high risk of bias
[2] Downgraded by 2 increments as the confidence interval crossed both MIDs
[3] Odds ratio used because this summary statistic was reported for the two studies included in the IPD MA
[4] Downgraded by 1 increments as the confidence interval crossed one MID
[5] Downgraded by 1 increment as people in the Stabile study who received dual antiplatelet therapy could have received clopidogrel or ticlopidine (no information was provided on proportion of people receiving each drug).
[6] Outcome reported as a range of odds ratios due to heterogeneity between studies with a large difference in point estimates without sufficient study number to form valid subgroups
[7]MIDs used to assess imprecision were ±2.60

Table 18: Clinical evidence profile: DOAC (+ aspirin for 3 months) versus aspirin (+ clopidogrel for 3 months) in transcatheter valve implantation

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**DOAC (+aspirin for 3 months)**	**aspirin (+clopidogrel for 3 months) post TAVI**	**Relative (95% CI)**	**Absolute**		
All-cause mortality at ≤12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL

Health-related quality of life at ≤12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Major bleeding at ≤12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Minor bleeding at ≤12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Arterial thromboembolic events at ≤12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
All-cause mortality at >12 months - median treatment duration 428 days (follow-up median 428 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	64/826 (7.7%)	4.7%	RR 1.67 (1.13 to 2.46)	31 more per 1000 (from 6 more to 69 more)	⊕⊕OO LOW	CRITICAL
Health-related quality of life at >12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Major bleeding at >12 months - VARC-2 life-threatening, disabling or major bleeding - median treatment 428 days (follow-up median 428 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	46/826 (5.6%)	3.8%	RR 1.47 (0.94 to 2.29)	18 more per 1000 (from 2 fewer to 49 more)	⊕⊕OO LOW	CRITICAL
Major bleeding at >12 months - BARC type 2, 3 or 5 bleeding - median treatment 428 days (follow-up mean 428 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	148/826 (17.9%)	10.4%	RR 1.72 (1.34 to 2.21)	75 more per 1000 (from 35 more to 126 more)	⊕⊕⊕O MODERATE	CRITICAL
Major bleeding at >12 months - ISTH major bleeding - median treatment 428 days (follow-up median 428 days)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	49/826 (5.9%)	3.7%	RR 1.62 (1.04 to 2.52)	23 more per 1000 (from 1 more to 56 more)	⊕⊕OO LOW	CRITICAL
Minor bleeding at >12 months - TIMI major or minor bleeding - median treatment 428 days (follow-up median 428 days)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	serious[2]	none	42/826 (5.1%)	2.9%	RR 1.73 (1.06 to 2.83)	21 more per 1000 (from 2 more to 53 more)	⊕OOO VERY LOW	CRITICAL
Stroke (arterial thromboembolic events) at >12 months - median treatment 428 days (follow-up median 428 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	30/826 (3.6%)	3.1%	RR 1.19 (0.71 to 2)	6 more per 1000 (from 9 fewer to 31 more)	⊕OOO VERY LOW	CRITICAL
Myocardial infarction (arterial thromboembolic events) at >12 months - median treatment 428 days (follow-up median 428 days)												
1	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	very serious[4]	none	23/826 (2.8%)	2.1%	RR 1.34 (0.72 to 2.49)	7 more per 1000 (from 6 fewer to 31 more)	⊕OOO VERY LOW	CRITICAL
Pulmonary embolism (arterial thromboembolic events) at >12 months - median treatment 428 days (follow-up median 428 days)												
1	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	very serious[4]	none	3/826 (0.36%)	0.2%	OR 1.48 (0.26 to 8.55)	1 more per 1000 (from 1 fewer to 15 more)	⊕OOO VERY LOW	CRITICAL
Systemic embolism (arterial thromboembolic events) at >12 months- median treatment 428 days (follow-up median 428 days)												
1	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	very serious[4]	none	1/826 (0.12%)	0.1%	OR 0.99 (0.06 to 15.85)	0 fewer per 1000 (from 1 fewer to 15 more)	⊕OOO VERY LOW	CRITICAL
Hospital readmission at 12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		IMPORTANT
Premature study drug discontinuation (withdrawal due to adverse events - thromboembolic, bleeding or other adverse events) at 12 months - median treatment duration 428 days (follow-up median 428 days)												
1	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	185/826 (22.4%)	11.1%	RR 2.01 (1.6 to 2.54)	112 more per 1000 (from 67	⊕⊕OO LOW	IMPORTANT

										more to 171 more)		
Symptomatic valve thrombosis (thrombus on imaging) at <12 months - median treatment duration 428 days (follow-up median 428 days)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	3/826 (0.36%)	0.9%	OR 0.44 (0.13 to 1.54)	5 fewer per 1000 (from 8 fewer to 5 more)	⊕OOO VERY LOW	IMPORTANT
Need for reintervention at 6-12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		IMPORTANT
Need for reintervention at >12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		IMPORTANT
Valve degeneration (mean transvalvular gradient) at ≥12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		IMPORTANT

[1] Downgraded by 1 increment as the majority of the evidence was at high risk of bias
[2] Downgraded by 1 increments as the confidence interval crossed one MID
[3] Combines major and minor bleeding rather than reporting minor bleeding events separately
[4] Downgraded by 2 increments as the confidence interval crossed both MIDs
[5] Downgraded by 2 increments as the majority of the evidence was at very high risk of bias

Table 19: Clinical evidence profile: Anticoagulant (VKA or DOAC) + SAPT (clopidogrel) versus anticoagulant (VKA or DOAC) alone in transcatheter valve implantation

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Anticoagulant (VKA or DOAC) + clopidogrel	anticoagulant alone post TAVI	Relative (95% CI)	Absolute		
All-cause mortality at ≤12 months (follow-up mean 12 months)												

1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	24/156 (15.4%)	13.4%	RR 1.15 (0.67 to 1.98)	20 more per 1000 (from 44 fewer to 131 more)	⊕OOO VERY LOW	CRITICAL
Health-related quality of life at ≤12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Major bleeding at ≤12 months - VARC-2 life-threatening, disabling or major bleeding (major bleeding) at 12 months (follow-up mean 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4]	none	26/156 (16.7%)	8.9%	RR 1.87 (1.01 to 3.44)	77 more per 1000 (from 1 more to 217 more)	⊕OOO VERY LOW	CRITICAL
Minor bleeding at ≤12 months - VARC-2 minor bleeding (minor bleeding) at 12 months (follow-up mean 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4]	none	28/156 (17.9%)	12.7%	RR 1.41 (0.83 to 2.39)	52 more per 1000 (from 22 fewer to 177 more)	⊕OOO VERY LOW	CRITICAL
Stroke (arterial thromboembolic events) at ≤12 months (follow-up mean 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	9/156 (5.8%)	5.7%	RR 1.01 (0.41 to 2.47)	1 more per 1000 (from 34 fewer to 84 more)	⊕OOO VERY LOW	CRITICAL
Myocardial infarction (arterial thromboembolic events) at ≤12 months (follow-up mean 12 months)												
1	randomised trials	very serious[5]	no serious inconsistency	serious[2]	very serious[3]	none	1/156 (0.64%)	0.6%	OR 1.01 (0.06 to 16.16)	0 more per 1000 (from 6 fewer to 83 more)	⊕OOO VERY LOW	CRITICAL
All-cause mortality at >12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Health-related quality of life at >12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Major bleeding at >12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL

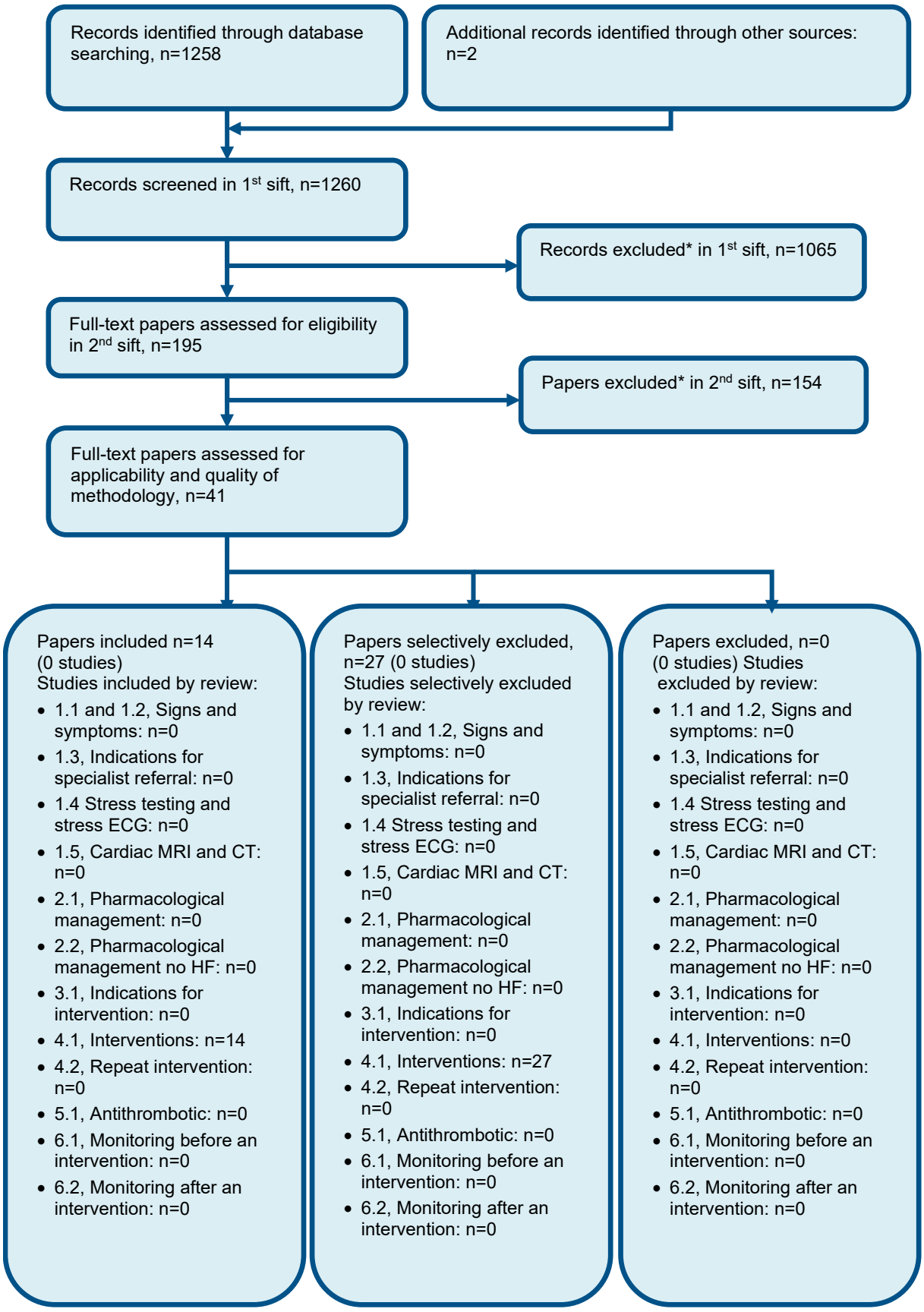
Minor bleeding at >12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Arterial thromboembolic events at >12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Hospital readmission at 12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		IMPORTANT
Withdrawal due to adverse events at 12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		IMPORTANT
Thrombus on imaging at <12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		IMPORTANT
Need for reintervention at 6-12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		IMPORTANT
Need for reintervention at >12 months - not measured												
0	-	-	-	-	-	none	-	-	-	-		IMPORTANT
Mean aortic valve gradient (valve degeneration - transvalvular gradient) at ≥12 months (follow-up mean 6 months; Better indicated by lower values)												
1	randomised trials	very serious[5]	no serious inconsistency	serious[2]	serious[4,6]	none	129	135	-	MD 1.5 higher (0.29 to 2.71 higher)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment as the majority of the evidence was at high risk of bias
[2] Anticoagulation includes a mixture of some receiving VKAs and some receiving DOACs, whereas ideally aimed to look at these groups separately
[3] Downgraded by 2 increments as the confidence interval crossed both MIDs
[4] Downgraded by 1 increment as the confidence interval crossed one MID
[5] Downgraded by 2 increments as the majority of the evidence was at very high risk of bias
[6] MIDs used to assess imprecision were ±2.55

F.3 Valve repair

No information available.

Appendix G: Health economic evidence selection



* Non-relevant population, intervention, comparison, design or setting; non-English language

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Appendix H: Health economic evidence tables

No economic studies were identified.

Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 20: Studies excluded from the clinical review

Study	Exclusion reason
Abuzaid 2018[1]	Less than minimum duration. Systematic review: study designs inappropriate
Ahmad 2018[2]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Al Halabi 2018[4]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate. Less than minimum duration
Al-Atassi 2012[3]	Incorrect study design
Alrifai 2018[5]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate. Less than minimum duration
Altman 1976[6]	Not review population. Incorrect study design. Adults who have had a mechanical valve replacement
An 2019[7]	Systematic review: study designs inappropriate. Less than minimum duration
Ando 2017[8]	Systematic review: quality assessment is inadequate. Less than minimum duration
Aramendi 1998[11]	Incorrect interventions. Incorrect study design
Aramendi 2005[9]	Incorrect interventions
Aramendi 2005[10]	Incorrect interventions
Aryal 2015[12]	Systematic review: quality assessment is inadequate. Systematic review: study designs inappropriate. Less than minimum duration
Avezum 2013[13]	Incorrect study design. Not review population
Banerjee 2017[14]	Systematic review: quality assessment is inadequate. Less than minimum duration
Burke 2018[16]	Systematic review is not relevant to review question or unclear PICO. Systematic review: study designs inappropriate. Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear. Inappropriate comparison. Less than minimum duration
Caldeira 2018[17]	Not review population. Systematic review: quality assessment is inadequate. Systematic review: study designs inappropriate. Less than minimum duration
De Caterina 2017[20]	Unabled to separate population and results for patients with valve replacement from patients with valve repair
De Souza Lima Bitar 2019[21]	Not review population. Less than minimum duration
Dong 2011[22]	Not review population. Adults who have had a mechanical valve replacement
Ezekowitz 2016[24]	Not review population
Farah 1981[25]	Incorrect study design. Adults who have had a mechanical valve replacement
Gandhi 2015[26]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate. Less than minimum duration

Geisler 2018[27]	Systematic review: study designs inappropriate. Systematic review is not relevant to review question or unclear PICO. Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear
Gherli 2004[28]	Incorrect study design
Guedeney 2019[29]	Systematic review: study designs inappropriate. Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review is not relevant to review question or unclear PICO. Systematic review: methods are not adequate/unclear
Guimaraes 2019[30]	This study does not appear to maintain randomisation
He 2019[32]	Not review population. Systematic review: quality assessment is inadequate. Systematic review is not relevant to review question or unclear PICO
Herold 2017[33]	Incorrect study design. Incorrect interventions. Inappropriate comparison
Hu 2018[34]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate. Less than minimum duration
Ichibori 2017[35]	Incorrect study design
Jamieson 2007[36]	Incorrect study design. Incorrect interventions
Kawazoe 1990[38]	Incorrect study design. Adults who have had a mechanical valve replacement. Incorrect interventions. Less than minimum duration
Kuno 2020[39]	Systematic review: study designs inappropriate
Lawley 2015[40]	Adults who have had a mechanical valve replacement. Systematic review: study designs inappropriate. Less than minimum duration
Liang 2020[41]	Systematic review: quality assessment is inadequate
Ma 2019[42]	Systematic review: quality assessment is inadequate
Maes 2018[43]	Systematic review: quality assessment is inadequate. Less than minimum duration
Malik 2019[44]	Systematic review: quality assessment is inadequate
Masri 2017[45]	Less than minimum duration. Systematic review: quality assessment is inadequate. Systematic review: study designs inappropriate
Massel 2001[47]	Not review population. Adults who have had a mechanical valve replacement. Systematic review: quality assessment is inadequate
Massel 2013[46]	Adults who have had a mechanical valve replacement. All studies included patients with mechanical valve replacement with very few including a small number of patients with bioprosthetic valve replacement. Unable to separate patients with bioprosthetic valve replacement from mechanical valve replacement
Mok 1985[48]	Not review population. Adults who have had a mechanical valve replacement. Incorrect interventions
Nijenhuis 2019[51]	Systematic review: study designs inappropriate. Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear. Less than minimum duration. Inappropriate comparison
Nowell 2007[52]	Systematic review: quality assessment is inadequate. Less than minimum duration. Systematic review: study designs inappropriate
Owais 2016[53]	Incorrect study design. Crossover study. Less than minimum duration. Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate

Pan 2017[54]	Not review population. Crossover study. Systematic review is not relevant to review question or unclear PICO. Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Paparella 2016[55]	Incorrect study design
Perleth 2001[56]	Adults who have had a mechanical valve replacement. Inappropriate comparison
Raheja 2018[58]	Less than minimum duration. Systematic review: quality assessment is inadequate. Systematic review: study designs inappropriate
Rajah 1979[59]	Abstract only. Incorrect interventions
Renda 2017[60]	Not review population. Systematic review: quality assessment is inadequate. Systematic review is not relevant to review question or unclear PICO
Riaz 2016[61]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Russmann 1997[63]	Inappropriate comparison. Incorrect interventions. Less than minimum duration
Sharma 2015[64]	Systematic review: study designs inappropriate. Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear. Less than minimum duration. Inappropriate comparison
Sharma 2018[65]	Letter/commentary
Sherwood 2018[66]	Systematic review: study designs inappropriate. Systematic review: literature search not sufficiently rigorous. Systematic review: quality assessment is inadequate. Systematic review: methods are not adequate/unclear. Inappropriate comparison. Less than minimum duration
Siddamsetti 2018[67]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate. Less than minimum duration
Sterling 2015[69]	Systematic review: quality assessment is inadequate. Systematic review: study designs inappropriate. Less than minimum duration
Taguchi 1975[70]	Adults who have had a mechanical valve replacement. Not review population. Incorrect study design. Incorrect interventions. Less than minimum duration
Thourani 2013[71]	Incorrect study design
Turgeon 2015[72]	Less than minimum duration. Systematic review: quality assessment is inadequate. Systematic review: study designs inappropriate
Ueyama 2020[74]	Systematic review: study designs inappropriate
Vavuranakis 2016[77]	Less than minimum duration. Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Vavuranakis 2018[76]	Systematic review is not relevant to review question or unclear PICO. Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Verdoia 2018[78]	Less than minimum duration. Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate
Zhou 2020[79]	Not review population
Zhu 2020[80]	Systematic review: study designs inappropriate
Zuo 2019[81]	Systematic review: study designs inappropriate. Systematic review: quality assessment is inadequate

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I.2 Excluded health economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2004 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

None.

Appendix J: Research recommendations

J.1 Anticoagulation and antiplatelet therapy

J.1.1 Research recommendation

What is the clinical and cost effectiveness of single or dual antiplatelet therapies or anticoagulants compared with placebo following transcatheter or surgical valve replacement (implantation) with biological prosthesis and following valve repair?

J.1.2 Why this is important

Biological surgical valve and transcatheter valve replacement/implantation

Cusp thrombosis is known to potentially occur occasionally in biological surgical valves and more often in transcatheter valves. It usually occurs in the first 3-6 months after valve replacement/implantation are in most cases it is subclinical at this stage, being identified on valve imaging by detecting thrombus on the affected valve cusp and reduced mobility of it. An immediate effect on valve function at the time of this diagnosis is rare and it manifests primarily through abrupt significant increase in transvalvular gradient and consequent decrease in calculated valve area, mainly in aortic valves. Commencement of anticoagulation at this stage has been found to result in gradual normalisation of valve function, as the thrombus resolves. Anticoagulation is only given as treatment in these rare cases of significant haemodynamic consequences of cusp thrombosis. However, there is concern that this cusp thrombosis even when undetected or subclinical may contribute to earlier degeneration of biological surgical and transcatheter valves. Consequently, it is thought that maybe preventive anticoagulation or dual antiplatelet therapy should be offered to prevent cusp thrombosis, to avoid early degeneration of the valve and premature need for redo intervention.

Valve repair

In the case of mitral valve repair, the rationale of offering an anticoagulant or dual antiplatelet drug early after the intervention would be to avoid the rarely occurring cerebrovascular or other arterial embolization of thrombus sometimes seen to form in the left atrium or suspected due to developed atrial fibrillation. This can be the result of reduction in mitral valve area as a result of mitral valve repair or mitral valve replacement with a biological surgical valve. As the experience with surgical mitral valve repair is larger, the phenomenon is recognised as rarely potential occurring in this case; however, it can also occur in patient having had transcatheter edge-to-edge mitral valve repair that decreases the mitral valve area further.

J.1.3 Rationale for research recommendation

Importance to ‘patients’ or the population	1. Potential increase of valve durability and delay of need for redo intervention on the valve in biological surgical valves and transcatheter valves replacement/implantation 2. Avoid thrombo-embolic complications following mitral valve repair (surgical or transcatheter) or replacement with a biological surgical valve

Relevance to NICE guidance	The comparison between antithrombotic treatment (anticoagulation or antiplatelets, or a combination) and placebo following biological surgical valve replacement, transcatheter implantation and valve repair interventions was considered in this guideline but none of the included randomised controlled trials covered this comparison. This meant that there was no included evidence to determine whether antithrombotic therapy is required following these types of valve interventions. Answering this question may provide stronger evidence on which to base recommendations about whether or not any antithrombotic therapy is required following these procedures.
Relevance to the NHS	Answer to this clinical question would allow standardisation of clinical practice in the NHS in this regard and potential reduction in cost if need for redo intervention is delayed.
National priorities	It is relevant to the NHS long term plan “action on prevention” priority.
Current evidence base	No randomised controlled trials have been performed comparing antithrombotic treatment (anticoagulation or antiplatelets, or a combination) and placebo following biological surgical valve replacement, transcatheter implantation and valve repair interventions, with all of them instead comparing between different types of antithrombotic treatment rather than comparing to placebo. As there is a lack of information regarding whether or not any form of antithrombotic therapy is required for all patients undergoing these procedures, randomised controlled trials covering a comparison of antithrombotic therapy with placebo is required to be able to make strong recommendations.
Equality considerations	None known.

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J.124 Modified PICO table

3

Population	<u>Inclusion</u> Adults aged 18 years and over with repaired valves or biological prosthetic valves stratified by type of intervention: • transcatheter replacement • surgical replacement. • transcatheter repair • surgical repair <u>Exclusion</u> • Children (aged <18 years) • • Adults who have other indications for anticoagulant or dual antiplatelet treatment (e.g. have atrial fibrillation or a

	mechanical valve replacement or take dual antiplatelet therapy for an indication related to coronary disease)
Intervention	Oral anticoagulation therapy: • Vitamin K Antagonists (including: warfarin, acenocoumarol and phenindione) • Direct acting oral anticoagulants (DOACs) (including: dabigatran, rivaroxaban, apixaban and edoxaban) Oral antiplatelet therapy: • Single therapy (including aspirin, clopidogrel, ticagrelor and prasugrel) • Dual therapy (the combination of aspirin with either clopidogrel, ticagrelor or prasugrel). Combined oral anticoagulation and oral antiplatelet therapy
Comparator	Placebo Note that the focus of the question is to compare each specific type of antithrombotic therapy with a placebo group and comparisons between different types of antithrombotic treatment are not required. Separate comparisons are required for each of the specific antithrombotic groups to placebo, as follows: • Vitamin K antagonists vs. placebo • DOACs vs. placebo • Single antiplatelet therapy vs. placebo • Dual antiplatelet therapy vs. placebo Combined oral anticoagulation and oral antiplatelet therapy vs. placebo
Outcome	<u>Primary outcomes</u> All-cause mortality; Health-related quality of life; Major bleeding; Minor bleeding; Arterial thromboembolic events Primary outcomes should be reported at ≤12 months and >12 months. <u>Secondary outcomes</u> Hospital re-admission at 12 months; Withdrawal due to adverse events at 12 months; Thrombus on imaging at <12 months; Need for reintervention at medium term (6 months to 12 months) and long term (>12 months); Valve degeneration (mean transvalvular gradient) at ≥12 months.
Study design	Randomised controlled trial

Timeframe	Long term
Additional information	None

J.125 Research recommendation

In adults with biological valve replacement, what effect does anticoagulation or antiplatelet therapy have on long-term valve function and outcomes?

J.136 Why this is important

Cusp thrombosis is known to potentially occur occasionally in biological surgical valves and more often in transcatheter valves. It usually occurs in the first 3-6 months after valve replacement/implantation are in most cases it is subclinical at this stage, being identified on valve imaging by detecting thrombus on the affected valve cusp and reduced mobility of it. An immediate effect on valve function at the time of this diagnosis is rare and it manifests primarily through abrupt significant increase in transvalvular gradient and consequent decrease in calculated valve area, mainly in aortic valves. Commencement of anticoagulation at this stage has been found to result in gradual normalisation of valve function, as the thrombus resolves. Anticoagulation is only given as treatment in these rare cases of significant haemodynamic consequences of cusp thrombosis. However, there is concern that this cusp thrombosis even when undetected or subclinical may contribute to earlier degeneration of biological surgical and transcatheter valves. Consequently, it is thought that maybe preventive anticoagulation or dual antiplatelet therapy should be offered to prevent cusp thrombosis, to avoid early degeneration of the valve and premature need for redo intervention.

J.147 Rationale for research recommendation

Importance to ‘patients’ or the population	1. Potential increase of valve durability and delay of need for redo intervention on the valve in biological surgical valves and transcatheter valves replacement/implantation 2. Avoid thrombo-embolic complications following mitral valve repair (surgical or transcatheter) or replacement with a biological surgical valve
Relevance to NICE guidance	The comparison between antithrombotic treatment (anticoagulation or antiplatelets, or a combination) and placebo following biological surgical valve replacement, transcatheter implantation and valve repair interventions was considered in this guideline but none of the included randomised controlled trials covered this comparison. This meant that there was no included evidence to determine whether antithrombotic therapy is required following these types of valve interventions. Answering this question may provide stronger evidence on which to base recommendations about whether or not any antithrombotic therapy is required following these procedures.
Relevance to the NHS	Answer to this clinical question would allow standardisation of clinical practice in the NHS in this regard and potential reduction in cost if need for redo intervention is delayed.

National priorities	It is relevant to the NHS long term plan “action on prevention” priority.
Current evidence base	No randomised controlled trials have been performed comparing antithrombotic treatment (anticoagulation or antiplatelets, or a combination) and placebo following biological surgical valve replacement, transcatheter implantation and valve repair interventions, with all of them instead comparing between different types of antithrombotic treatment rather than comparing to placebo. As there is a lack of information regarding whether or not any form of antithrombotic therapy is required for all patients undergoing these procedures, randomised controlled trials covering a comparison of antithrombotic therapy with placebo is required to be able to make strong recommendations.
Equality considerations	None known.

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J.13 Modified PICO table

Population	<u>Inclusion</u> Adults aged 18 years and over with biological prosthetic valves stratified by type of intervention: • transcatheter replacement • surgical replacement. • transcatheter repair • surgical repair <u>Exclusion</u> • Children (aged <18 years) • Adults with congenital heart disease (other than bicuspid aortic valves) • Tricuspid stenosis or pulmonary valve disease interventions • Adults who have had a mechanical valve replacement
Intervention	Oral anticoagulation therapy: • Vitamin K antagonists (including: warfarin, acenocoumarol and phenindione) • Direct acting oral anticoagulants (DOACs) (including: dabigatran, rivaroxaban, apixaban and edoxaban) Oral antiplatelet therapy: • Single therapy (including aspirin, clopidogrel, ticagrelor and prasugrel)

	• Dual therapy (the combination of aspirin with either clopidogrel, ticagrelor or prasugrel). Combined oral anticoagulation and oral antiplatelet therapy
Comparator	Placebo
Outcome	<u>Primary outcomes</u> All-cause mortality; Health-related quality of life; Major bleeding; Minor bleeding; Arterial thromboembolic events Primary outcomes should be reported at ≤12 months and >12 months. <u>Secondary outcomes</u> Hospital re-admission at 12 months; Withdrawal due to adverse events at 12 months; Thrombus on imaging at <12 months; Need for reintervention at medium term (6 months to 12 months) and long term (>12 months); Valve degeneration (mean transvalvular gradient) at ≥12 months.
Study design	Cohort study, sufficiently powered and adjusted for key confounders.
Timeframe	Long term
Additional information	None