

## NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

### Interventional procedure consultation document

# Transcatheter aortic valve implantation for aortic stenosis

Aortic stenosis occurs when the aortic valve becomes narrowed. This reduces the flow of blood out of the heart. Catheter insertion of a new aortic valve (a procedure called 'transcatheter aortic valve implantation' or TAVI for short) may be an alternative to surgical valve replacement in patients for whom conventional aortic valve replacement by open heart surgery is not suitable, or who are at high risk of serious complications. The aim is to insert the new valve through a thin tube, usually into a large blood vessel at the top of the leg, and to place it over the existing faulty valve.

The National Institute for Health and Care Excellence (NICE) is examining transcatheter aortic valve implantation for aortic stenosis and will publish guidance on its safety and efficacy to the NHS. NICE's interventional procedures advisory committee has considered the available evidence and the views of specialist advisers, who are consultants with knowledge of the procedure. The advisory committee has made draft recommendations about transcatheter aortic valve implantation for aortic stenosis.

This document summarises the procedure and sets out the draft recommendations made by the advisory committee. It has been prepared for public consultation. The advisory committee particularly welcomes:

- comments on the draft recommendations
- the identification of factual inaccuracies
- additional relevant evidence, with bibliographic references where possible.

**Note that this document is not NICE's formal guidance on this procedure. The recommendations are provisional and may change after consultation.**

The process that NICE will follow after the consultation period ends is as follows.

- The advisory committee will meet again to consider the original evidence and its draft recommendations in the light of the comments received during consultation.

- The advisory committee will then prepare draft guidance which will be the basis for NICE's guidance on the use of the procedure in the NHS.

For further details, see the [Interventional Procedures Programme process guide](#), which is available from the NICE website.

Through its guidance NICE is committed to promoting race and disability equality, equality between men and women, and to eliminating all forms of discrimination. One of the ways we do this is by trying to involve as wide a range of people and interest groups as possible in the development of our interventional procedures guidance. In particular, we aim to encourage people and organisations from groups who might not normally comment on our guidance to do so.

In order to help us promote equality through our guidance, we should be grateful if you would consider the following question:

Are there any issues that require special attention in light of NICE's duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity, and foster good relations between people with a characteristic protected by the equalities legislation and others?

Please note that NICE reserves the right to summarise and edit comments received during consultations or not to publish them at all where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would otherwise be inappropriate.

Closing date for comments: 27 April 2017

Target date for publication of guidance: July 2017

## 1 Draft recommendations

- 1.1 Current evidence on the safety and efficacy of transcatheter aortic valve implantation (TAVI) for aortic stenosis is adequate to support the use of this procedure provided that standard arrangements are in place for clinical governance, consent and audit.
- 1.2 Details of all patients should be entered into the [UK TAVI registry](#).
- 1.3 Patient selection should be carried out by an experienced multidisciplinary team, which must include interventional cardiologists experienced in the procedure, cardiac surgeons, a

cardiac anaesthetist and an expert in cardiac imaging. The multidisciplinary team should determine the risk level for each patient.

- 1.4 During the consent process patients should be told about all alternative treatment options and that there is currently a lack of information on the longer-term efficacy of TAVI.
- 1.5 TAVI is a technically challenging procedure that should only be done in specialised centres and only by clinicians and teams with special training and experience in complex endovascular interventions. Units doing this procedure should have both cardiac and vascular surgical support for the emergency treatment of complications.

## **2 Indications and current treatments**

- 2.1 Aortic stenosis causes impaired outflow of blood from the heart and is usually progressive. The increased cardiac workload leads to left ventricular hypertrophy and heart failure. Symptoms of aortic stenosis typically include shortness of breath and chest pain on exertion.
- 2.2 Surgical aortic valve replacement (SAVR) with an artificial (biological or mechanical) prosthesis is the conventional treatment for patients with severe symptomatic aortic stenosis who are well enough for surgery. Optimal medical care has traditionally been the only option for those whose condition is unsuitable for surgery. Aortic balloon valvuloplasty is occasionally used.
- 2.3 SAVR may not be suitable for patients because of medical comorbidities or technical considerations (for example, if the patient has a calcified aorta or scarring from previous cardiac surgery),

which mean that the risks of SAVR outweigh the potential benefits. Patients for whom SAVR is suitable range from those considered to be high risk (for example, as defined in the PARTNER 1A trial) to those for whom the benefits of surgery clearly outweigh the risks of surgery.

### **3 The procedure**

- 3.1 Transcatheter aortic valve implantation (TAVI) aims to provide a less invasive alternative to open cardiac surgery for treating aortic stenosis, avoiding the need for cardiopulmonary bypass.
- 3.2 TAVI may be done with the patient under general anaesthesia or using local anaesthesia with sedation. Access to the aortic valve may be transluminal, through a large artery (usually the femoral or subclavian artery; percutaneous or endovascular approach), or surgical, by a minithoracotomy with apical puncture of the left ventricle (transapical approach). The choice of access route (transluminal or transapical) depends on various patient-related factors including atherosclerotic disease in the arteries, which would make the transluminal approach impossible.
- 3.3 Initially the aortic valve ring is dilated using a balloon catheter, which is advanced over a guidewire. The new prosthetic valve is manipulated into position and used over the existing aortic valve.
- 3.4 Different devices are available for this procedure. Some may contain material derived from animal sources.

### **4 Efficacy**

This section describes efficacy outcomes from the published literature that the committee considered as part of the evidence about this procedure. For more

detailed information on the evidence, see the [interventional procedure overview](#) [add URL].

Evidence is based only on studies that reported outcomes by the risk level of the patients.

### **Survival beyond 30 days**

- 4.1 A randomised controlled trial (RCT) of 358 patients (PARTNER 1B) for whom surgical aortic valve replacement (SAVR) was unsuitable compared transcatheter aortic valve implantation (TAVI; n=179) with medical management (n=179). Patients who had TAVI had significantly lower all-cause mortality and cardiovascular mortality compared with medical management at a follow-up of 1, 2 and 5 years (30% compared with 51% at 1 year, 43% compared with 68% at 2 years and 72% compared with 94% at 5 years for all-cause mortality and 20% compared with 45% at 1 year, 31% compared with 62% at 2 years and 58% compared with 86% at 5 years for cardiovascular mortality).
- 4.2 In an RCT of 797 patients for whom SAVR was suitable but high risk (the CoreValve trial), a Kaplan–Meier cumulative probability analysis for all-cause mortality at 3-year follow-up was 33% for TAVI compared with 39% for SAVR (p=0.068). In another RCT of 699 patients for whom SAVR was suitable but high risk (the PARTNER 1A trial), a Kaplan–Meier probability analysis for all-cause mortality up to 5 years of follow-up was 68% for TAVI compared with 62% for SAVR (p=0.76). When data were pooled for both RCTs (based on an intention-to-treat [ITT] analysis), the hazard ratios did not show statistically significant differences between TAVI and SAVR for hazard of death (pooled estimates were risk ratio [RR] 0.89; 95% confidence interval [CI] 0.73 to 1.09, p=0.26 at 1 year and RR 0.95; 95% CI 0.79 to 1.13, p=0.55 at
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2 years). There were no significant differences for cardiovascular mortality at 1 year (RR 1.05; 95% CI 0.79 to 1.39,  $p=0.73$ ) and 2 years (RR 0.92; 95% CI 0.67 to 1.28,  $p=0.79$ ).

- 4.3 In an RCT of 2,032 patients for whom SAVR was suitable but intermediate risk (the PARTNER 2A trial) there were no significant differences between TAVI and SAVR at 1- and 2-year follow-up for all-cause mortality and cardiovascular mortality (all-cause mortality: 12% compared with 13% [ $p=0.69$ ] at 1 year and 17% compared with 18% [ $p=0.45$ ] at 2 years; cardiovascular mortality: 7% compared with 8% [ $p=0.47$ ] at 1 year and 10% compared with 11% [ $p=0.38$ ] at 2 years). In an RCT of 276 patients for whom SAVR was suitable but low to intermediate risk (the NOTION study) there were no significant differences between TAVI and SAVR at 1- and 2-year follow-up for all-cause mortality and cardiovascular mortality (all-cause mortality: 5% compared with 8% [ $p=0.38$ ] at 1 year and 8% compared with 10% [ $p=0.54$ ] at 2 years; cardiovascular mortality: 4% compared with 8% [ $p=0.25$ ] at 1 year and 7% compared with 9% [ $p=0.40$ ] at 2 years). A systematic review including 2 RCTs and 6 observational studies representing 16,638 patients for whom SAVR was suitable and not high risk (comprising 6,875 patients in an analysis) showed a non-significant difference in all-cause mortality for TAVI compared with SAVR (odds ratio [OR] 0.67, 95% CI 0.42 to 1.07 at 30 days; OR 0.91, 95% CI 0.67 to 1.23 at 1 year; OR 0.06, 95% CI 0.59 to 1.91 at long-term follow-up [more than 1 year]). In a systematic review of patients at low and intermediate risk from surgery including 4 RCTs ( $n=3,179$  patients, including the CoreValve trial), in which patients had a mean STS risk score of 7%, TAVI was associated with a lower hazard of death at 2 years compared with SAVR when done by the transfemoral but not by the transapical route (transfemoral

route: hazard ratio [HR] 0.79, 95% CI 0.66 to 0.94, [risk difference -3.0, 95% CI -0.8 to -4.9]; transapical route: HR 1.34, 95% CI 0.91 to 1.97).

### **Symptomatic improvement**

- 4.4 The RCT of 358 patients (PARTNER 1B) for whom SAVR was unsuitable compared TAVI (n=179) with medical management (n=179). More patients were asymptomatic or had mild symptoms (New York Heart Association [NYHA] class I or II) in the TAVI group than those in the medical management group (at 2 years: 83% [79/95] compared with 42% [17/40],  $p<0.001$ ; at 3 years: 70% [49/50] compared with 50% [7/14],  $p=0.245$  and at 5 years: 85.7% [42/49] compared with 60% [3/5],  $p=0.531$ ; NYHA class was not significantly different at baseline among these groups).
- 4.5 In the RCT of 797 patients for whom SAVR was suitable but posed a high risk (CoreValve trial), a greater proportion of patients were in NYHA class I or II in the SAVR arm (79%; 72%) than in the TAVI arm (84%; 80%) ( $p<0.01$ ;  $p=0.04$ ) at 1 and 6 months. At 12 months, there were no statistically significant differences between the SAVR and TAVI groups (79% compared with 72%,  $p=0.10$ ). In the other RCT of 699 patients for whom SAVR was suitable but high risk (PARTNER 1A), the proportion of patients in NYHA class I or II was the same (64%) for TAVI and SAVR at 12 months.
- 4.6 In the RCT of 2,032 patients for whom SAVR was suitable but intermediate risk (PARTNER 2A) there were no significant differences between TAVI and SAVR in the proportion of patients in NYHA class I and II at 1- and 2-year follow-up. In an RCT of 276 patients for whom SAVR was suitable but low to intermediate risk (NOTION) there were no significant differences between TAVI and SAVR in NYHA class at 3-month and 2-year follow-up. The
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systematic review (4 studies; n=2,146) of patients for whom SAVR was suitable but low to intermediate risk found that TAVI was associated with an increased risk of heart failure symptoms (NYHA class II or more: OR 1.29; 95% CI 1.08 to 1.55) at 2-year follow-up compared with SAVR. The odds ratio for moderate or severe heart failure symptoms (NYHA class III or more) was 1.29 (95% CI 1.08 to 1.55).

### **Haemodynamic improvement**

- 4.7 The RCT of 358 patients (PARTNER 1B) for whom SAVR was unsuitable compared TAVI (n=179) with medical management (n=179). There was a significantly higher mean aortic valve area in the TAVI group than in the medical management group at 1-year follow-up (1.6 cm<sup>2</sup> [SD 0.5] compared with 0.7 cm<sup>2</sup> [SD 0.3], p<0.001; baseline values were not significantly different). Mean pressure gradient improved from baseline (44.7 mmHg [SD 15.4]) to 13.2 (SD 11.2) for TAVI and from 43.2 (SD 15.4) to 44.3 (SD 16.1) for medical management (p values not reported). Left ventricular ejection fraction (LVEF) improved from 53.9 (SD 13.1) at baseline to 57.2 (SD 10.6) for TAVI and from 51.2 (SD 14.3) to 56.9 (SD 10.3) for medical management respectively.
- 4.8 In the RCT of 699 patients for whom SAVR was suitable but high risk (PARTNER 1A, TAVI [n=348] compared with SAVR [n=351]), there was a significantly higher mean aortic valve area in the TAVI group than in the SAVR group at 30-day, 6-month and 1-year follow-up respectively (1.7 m<sup>2</sup> [SD 0.5] compared with 0.5 cm<sup>2</sup> [SD 0.4], p=0.001 at 30 days; 1.7 cm<sup>2</sup> [SD 0.5] compared with 1.5 cm<sup>2</sup> [SD 0.5], p=0.01 at 6 months and 1.6 cm<sup>2</sup> [SD 0.5] compared with 1.4 cm<sup>2</sup> [SD 0.5], p=0.002 at 1 year). Mean pressure gradients improved but were not statistically significant (9.9 mmHg [SD 4.8]

compared with 10.8 mmHg [SD 5.0],  $p=0.04$  at 30 days; 10.2 mmHg [SD 4.3] compared with 10.8 mmHg [4.8],  $p=0.16$  at 6 months; and 10.2 mmHg [SD 4.3] compared with 11.5 mmHg [SD 5.4],  $p=0.008$  at 1 year). LVEFs improved but not statistically significantly (55.5 [SD 11.4] compared with 56.0 [SD 11.4],  $p=0.63$  at 30 days; 56.2 [SD 10.8] compared with 56.8 [SD 9.9],  $p=0.56$  at 6 months; and 56.6 [SD 10.5] compared with 57.1 [SD 10.3],  $p=0.64$  at 1 year). Baseline values were not significantly different for all the outcomes. In the other RCT of 797 patients for whom SAVR was suitable but high risk (CoreValve trial, TAVI [n=394] compared with SAVR [n=401]), there was a significantly higher mean aortic valve gradient in the TAVI group compared with the SAVR group (1.70 cm<sup>2</sup> [SD 0.49] compared with 1.55 cm<sup>2</sup> [SD 0.51],  $p<0.01$  at 1 year; and 1.79 cm<sup>2</sup> [SD 0.48] compared with 1.56 cm<sup>2</sup> [SD 0.52],  $p<0.0001$  at 3 years. Mean pressure gradients also improved significantly (8.90 mmHg [SD 3.73] compared with 12.17 mmHg [SD 7.10],  $p<0.0001$  at 1 year; and 7.62 mmHg [SD 3.57] and 11.40 mmHg [SD 6.8],  $p<0.0001$  at 3 years. Baseline values were not significantly different for all the outcomes.

- 4.9 In the RCT of 2,032 patients for whom SAVR was suitable but intermediate risk (PARTNER 2A) the mean aortic valve area was significantly higher in the TAVI group than in the SAVR group at 30 days (1.7 cm<sup>2</sup> [SD 0.5] compared with 1.5 cm<sup>2</sup> [SD 0.4],  $p<0.001$ ), and this persisted at 1 year (1.6 cm<sup>2</sup> [SD 0.4] compared with 1.4 cm<sup>2</sup> [SD 0.4],  $p<0.001$ ) and at 2 years (1.5 cm<sup>2</sup> [SD 0.4] compared with 1.4 cm<sup>2</sup> [SD 0.4],  $p<0.001$ ). Mean pressure gradients also improved significantly (9.7 mmHg [SD 3.5] compared with 10.9 mmHg [SD 4.3],  $p<0.001$ ) at 30 days and this persisted at 1 year (10.7 mmHg [SD 4.5] compared with 11.5 mmHg [SD 4.4],  $p=0.001$ ) and 2 years (10.8 mmHg [SD 4.6] compared with

11.7 mmHg [SD 4.8],  $p < 0.001$ ). LVEF was higher for the TAVI group than for the SAVR group (56.9 [SD 10.2] compared with 55.0 [SD 11.0],  $p = 0.04$ ) at 30 days but this was reversed at 1 year (55.9 [SD 11.2] compared with 57.2 [SD 9.9],  $p = 0.04$ ) and at 2 years (54.9 [SD 11.2] compared with 57.2 [SD 9.7],  $p = 0.005$ ). In the RCT of 276 patients for whom SAVR was suitable but low to intermediate risk (NOTION) there were significantly greater improvements in mean valve area in the TAVI group than in the SAVR group (1.7 cm<sup>2</sup> compared with 1.4 cm<sup>2</sup>,  $p < 0.001$  at 30 days; 1.7 cm<sup>2</sup> compared with 1.3 cm<sup>2</sup>,  $p < 0.001$  at 1 year; 1.6 cm<sup>2</sup> compared with 1.3 cm<sup>2</sup>,  $p < 0.001$  at 2 years). There were no significant differences from baseline for mean pressure gradient.

### Quality of life

4.10 In the RCT of 358 patients for whom SAVR was unsuitable (PARTNER 1B, TAVI compared with medical management) there were significant improvements in self-reported quality of life in patients in the TAVI group compared with those in the medical management group (Kansas City Cardiomyopathy Questionnaire [KCCQ] quality-of-life summary score for heart failure: mean difference [MD] 14, 95% CI 8.6 to 21.0,  $p < 0.001$  at 1 month and greater benefits at 6 months [MD 24.2, 95% CI 17.4 to 36.6,  $p < 0.001$ ] and at 12 months [MD 30.5, 95% CI 22.3 to 38.7;  $p < 0.001$ ]). At 12 months, the TAVI group also had higher SF-12 physical and mental health scores (MD 5.7 and 6.4, respectively ( $p < 0.001$ )).

4.11 In both the PARTNER 1A and CoreValve trials (patients for whom SAVR was suitable but high risk), patients having TAVI using the transfemoral route reported a greater improvement in quality of life (measured using EQ-5D, where 0 equals dead and 1 perfect

health-related quality of life) than those having SAVR (PARTNER 1A: average change of 0.08 [SD 0.25] compared with 0.02 [SD 0.25] at 1 month, 0.1 [SD 0.3] compared with 0.09 [SD 0.27] at 6 months and 0.09 [SD 0.23] compared with 0.08 [SD 0.08] at 1 year; CoreValve study: average change of 0.055 [SD 0.23] compared with -0.073 [SD 0.26] at 1 month; 0.053 [SD 0.22] compared with 0.01 [SD 0.17] at 6 months and 0.043 [SD 0.2] compared with 0.0003 [SD 0.02] at 1 year). When data from these 2 trials were pooled for the transfemoral route, the overall estimates for EQ-5D showed statistically significant differences between the TAVI and SAVR groups at 1 month (RR 0.009, 95% CI 0.03 to 0.16; p=0.006). However, the differences were insignificant at 6 months (RR 0.01; 95% CI -0.02 to 0.05, p=0.47) and at 1 year (RR 0.03; 95% CI 0.00 to 0.06, p=0.09). When data were pooled for transapical TAVI compared with SAVR (from PARTNER 1A) and non-transfemoral TAVI compared with SAVR (from the CoreValve trial), the overall estimates for EQ-5D showed no statistically significant differences between the TAVI and SAVR groups (RR -0.03; 95% CI -0.09 to 0.04, p=0.44 at 1 month, RR -0.02; 95% CI -0.07 to 0.05, p=0.66 at 6 months and R -0.02; 95% -0.09 to 0.05, p=0.58 at 1 year). There was a greater improvement in SF-12 scores (both physical and mental) in the TAVI group than in the SAVR group at 1-month follow-up (MD for physical summary scores 2.0; 95% CI 0.1 to 3.9, p=0.4 in PARTNER 1A and MD 4.9; 95% CI 3.1 to 6.7, p<0.001 in the CoreValve trial; MD for mental summary scores 5.4; 95% CI 3.1 to 7.7, p<0.001 in PARTNER 1A and 6.1; 95% CI 3.8 to 8.5, p<0.001 in CoreValve trial). At 6 months the only statistically significant difference was reported in the CoreValve trial (MD 2.2, 95% CI 0.3 to 4.1; p=0.026). There were no statistically significant differences

using either the transfemoral or non-transfemoral route at 12 months for both physical and mental scores. Statistically significant differences in favour of TAVI were reported for KCCQ quality-of-life summary score at 1-month follow-up in both PARTNER 1A (MD 9.8, 95% CI 4.0 to 15.6;  $p=0.001$ ) and in CoreValve study (19.0, 95% CI 13.7 to 24.3;  $p<0.001$ ) but did not persist at 6- and 12-month follow-up. There were no statistically significant differences in KCCQ quality-of-life scores using either the transfemoral route in PARTNER 1A or the non-transfemoral routes in CoreValve study.

- 4.12 In the systematic review of patients for whom SAVR was suitable but low to intermediate risk ( $n=2,146$ , including data from 797 patients in 1 study [CoreValve study] with follow-up of 2 years), there was a non-significant difference in KCCQ quality-of-life summary score (22.2 compared with 18.7 points, MD 3.5; 95% CI 1.9 to 8.9).

### **Repeat hospitalisation**

- 4.13 The RCT of 358 patients for whom SAVR was unsuitable (PARTNER 1B) compared TAVI ( $n=179$ ) with medical management ( $n=179$ ). TAVI had a statistically significantly lower hazard rate of repeat hospitalisation because of aortic stenosis (including complications because of TAVI) than medical management at 2 years (HR 0.41; 95%CI 0.30 to 0.58,  $p<0.001$ ), 3 years ( $p<0.0001$ ) and 5-year follow-up ( $p<0.0001$ ).
- 4.14 In the RCT of 699 patients for whom SAVR was suitable but high risk (PARTNER 1A, TAVI compared with SAVR) there was a non-significant difference in repeat hospitalisation rates (59 [9%] compared with 45 [16%],  $p=0.38$  at 1 year; 74 [25%] compared with 60 [22%],  $p=0.41$  at 2 years; and 108 [42%] compared with 81

[34%],  $p=0.17$  at 5 years). In the RCT of 797 patients (CoreValve trial, [n=390 TAVI compared with n=357 SAVR]) for whom SAVR was suitable but high risk there was no significant difference in repeat hospitalisation rates (95 [27%] for TAVI compared with 64 [21.9%] for SAVR,  $p=0.087$ ) at 3 years. In the RCT of 2,032 patients for whom SAVR was suitable but intermediate risk (PARTNER 2A) there were no significant differences in re-hospitalisation rates between TAVI and SAVR.

- 4.15 The specialist advisers listed key efficacy outcomes as procedural success, satisfactory device positioning, shorter length of hospital stay, haemodynamic improvement, improvement in left ventricular function, improved quality of life, improved exercise capacity, symptom relief, prolonged survival, reduced mortality and morbidity and reduced re-hospitalisation.

## 5 Safety

This section describes safety outcomes from the published literature that the committee considered as part of the evidence about this procedure. For more detailed information on the evidence, see the [interventional procedure overview](#) [add URL].

Evidence is based only on studies that reported outcomes by the risk level of the patients.

### All-cause mortality and cardiovascular mortality within 30 days

- 5.1 An RCT of 358 patients for whom surgical aortic valve replacement (SAVR) was unsuitable (PARTNER 1B) compared transcatheter aortic valve implantation (TAVI; n=179) with medical management (n=179). There were no statistically significant differences in all-cause mortality (5% [9/179] compared with 3% [5/179],  $p=0.41$ ) and

cardiovascular mortality (5% [8/179] compared with 2% [3/179],  $p=0.22$ ) between TAVI and medical management at 30-day follow-up.

5.2 In an RCT of 699 patients for whom SAVR was suitable but high risk (PARTNER 1A,  $n=348$  TAVI compared with  $n=351$  SAVR) there were no statistically significant differences in all-cause mortality (3% [12/348] compared with 7% [22/351],  $p=0.07$ ) and cardiovascular mortality (3% [11/348] compared with 13% [10/251],  $p=0.90$ ) between the TAVI group and SAVR group at 30-day follow-up. In another RCT of 797 patients (the US CoreValve trial,  $n=394$  TAVI compared with  $n=401$  SAVR) there were also no statistically significant differences in all-cause mortality (3% [13/390] compared with 5% [16/357],  $p=0.43$ ) and cardiovascular mortality (3% [12/390] compared with 5% [16/357],  $p=0.32$ ) between the TAVI group and SAVR group at 30-day follow-up. When data were pooled for both studies the risk ratio (less than 1 favours TAVI) for all-cause mortality was 0.64 (95% CI 0.38 to 1.39,  $p=0.06$ ) and for cardiovascular mortality was 0.90 (95% CI 0.52 to 1.56,  $p=0.70$ ).

5.3 In an RCT of 2,032 patients for whom SAVR was suitable but intermediate or low risk ( $n=1,011$  TAVI compared with  $n=1,021$  SAVR) there was a non-significant lower all-cause mortality (3% compared with 4%,  $p=0.24$ ) and cardiovascular mortality (2% compared with 3%,  $p=0.72$ ) for TAVI using the femoral route compared with SAVR at 30-day follow-up. For the transthoracic route all-cause mortality (6% compared with 4%,  $p=0.21$ ) and cardiovascular mortality (5% compared with 3%,  $p=0.47$ ) were not significantly different. In another RCT of 280 low and intermediate-risk patients ( $n=145$  TAVI compared with  $n=135$  SAVR), all-cause mortality (2% [3/142] compared with 3% [5/134],

p=0.43) and cardiovascular mortality (2% [3/142] compared with 4% [5/134], p=0.43) were not significantly different. A systematic review of 6,875 patients (2 RCTs and 6 observational studies) reported a non-significant lower all-cause mortality for TAVI compared with SAVR (odds ratio [OR] 0.67; 95% CI 0.42 to 1.07, p=0.08) at 30-day follow-up. Another systematic review of 3,179 patients (with risk scores of 8% or less in 4 RCTs) also reported a non-significant lower all-cause mortality for TAVI compared with SAVR (OR 0.67, 95% CI 0.42 to 1.07).

### **Cerebral complications**

- 5.4 In the RCT of 358 patients for whom SAVR was unsuitable (PARTNER 1B, TAVI compared with medical management) the hazard ratio of stroke or transient ischaemic attack (TIA) was significantly higher in the TAVI group (hazard ratio [HR] 2.81; 95% CI 1.26 to 6.26, p=0.004) at 2-year follow-up, whereas at 3-year follow-up there were no significant differences between the TAVI and medical management groups (HR 1.39; 95% CI 0.62 to 3.11, p=0.555).
- 5.5 In 2 RCTs (PARTNER 1A [n=699] and CoreValve [n=797] trials) in patients for whom SAVR was suitable but high risk the incidence of stroke and TIA was reported. Both pooled and individual risk ratios from PARTNER 1A and CoreValve trials showed no statistically significant differences in the incidence of all stroke in patients for whom SAVR was suitable but high risk at 30 days (relative risk [RR] 1.6; 95% CI 0.56 to 2.86, p=0.57), 1 year (RR 1.21; 95% CI 0.49 to 2.98, p=0.68), 2 years (RR 1.21; 95% CI 0.51 to 2.41, p=0.78), 3 years (RR 1.14; 95% CI 0.53 to 2.46, p=0.75) and 5 years (PARTNER 1A, ITT RR 1.13; 95% CI 0.68 to 1.87, p=0.65).

Both pooled and individual risk ratios for TIA from PARTNER 1A

and CoreValve trials also showed no statistically significant differences at 30 days (RR 3.04; 95% CI 0.62 to 15.01, p=0.107), 1 year (RR 1.46; 95% CI 0.63 to 3.41, p=0.38), 2 years (RR 1.92; 95% CI 0.90 to 4.11, p=0.09), 3 years (CoreValve, ITT RR 1.53; 95% CI 0.55 to 4.25, p=0.42) and 5 years (PARTNER 1A, ITT RR 1.77; 95% CI 0.75 to 4.15, p=0.19).

5.6 In the RCT of 2,032 patients for whom SAVR was suitable but intermediate risk (PARTNER 2A, TAVI compared with SAVR) there were no significant differences between groups in all strokes at 30 days (55 [6%] compared with 61 [6%], p=0.57), 1 year (78 [8%] compared with 79 [8%], p=0.88) and at 2 years (91 [10%] compared with 85 [9%], p=0.67). An RCT of 276 patients for whom SAVR was suitable but low to intermediate risk (the NOTION study, TAVI compared with SAVR) reported incidence of stroke and TIA at 30 days (4 [3%] compared with 4 [3%], p=0.94), 1 year (7 [5%] compared with 8 [6%], p=0.68) and at 2 years (13 [10%] compared with 10 [8%], p=0.67). The systematic review of 3,179 patients (based on data from 2,576 patients in 2 studies) reported a non-significant reduction in stroke rates (RR 0.80; 95% CI 0.63 to 1.01) for transfemoral TAVI compared with SAVR at 3-year follow-up. Comparing transapical TAVI with SAVR (based on data from 552 patients in 2 studies), the risk ratio was 1.67 (95% CI 0.97 to 2.87) at 2-year follow-up.

### **Aortic regurgitation**

5.7 In the RCT of 358 patients for whom SAVR was unsuitable (PARTNER 1B, TAVI compared with medical management) there were similar rates of moderate or severe aortic regurgitation in both groups at 30-day (15% compared with 17%) and 1-year (15% compared with 17%) follow-up.

- 5.8 In 2 RCTs (PARTNER 1A [n=699] and CoreValve [n=797] trials) the incidence of aortic regurgitation (paravalvular and transvalvular) in patients for whom SAVR was suitable but high risk was reported. Pooled data (RR 4.02; 95% CI 1.99 to 8.11, p=0.0001) at 1 year and individual study data favoured SAVR over TAVI at all follow-up points up to 3 years (PARTNER 1A: at 30 days RR 16.29; 95% CI 3.98 to 66.6, p=0.0001; at 6 months RR 30.26; 95% CI 4.16 to 220.01, p=0.0008; at 2 years p=0.008; CoreValve trial: at 3 years p=0.04).
- 5.9 In the RCT of 276 patients for whom SAVR was suitable but low to intermediate risk (NOTION, TAVI compared with SAVR) significant differences in moderate to severe aortic regurgitation at 3 months (15% compared with 22%, p<0.001) and at 1 year (16% compared with 1%, p=0.001) were reported. In the systematic review of 3,179 patients (based on data from 3 trials) moderate or severe aortic regurgitation occurred more often after TAVI than after SAVR at 2-year follow-up (RR 12.22; 95% CI 5.17 to 28.88).

#### **Aortic valve reintervention**

- 5.10 In the systematic review of 3,179 patients for whom SAVR was suitable but low to intermediate risk (based on data from 3,058 patients in 3 studies) the risk for aortic valve reintervention was significantly higher after TAVI than after SAVR (RR 3.25; 95% CI 1.29 to 8.14).

#### **Prosthesis-patient mismatch**

- 5.11 In the RCT of 699 patients (PARTNER 1A) for whom SAVR was suitable but high risk, the overall incidence and severity of prosthesis-patient mismatch was significantly better in the TAVI group than in the SAVR group (first echocardiogram: 46%, severe

20% compared with 60%, severe 28%;  $p < 0.001$  and 42% compared with 57%,  $p < 0.001$  at 30 days).

### **Myocardial infarction**

- 5.12 In the RCT of 358 patients for whom SAVR was unsuitable (PARTNER 1B, comparing TAVI with medical management) there were no significant differences in the occurrence of myocardial infarction (MI) at 2-year ( $p = 0.069$ ) and 3-year ( $p = 0.59$ ) follow-up.
- 5.13 In 2 RCTs (PARTNER 1A [ $n = 699$ ] and CoreValve [ $n = 797$ ] trials, comparing TAVI with SAVR) the incidence of MI for patients for whom SAVR was suitable but high risk was reported. Pooled data (at 30 days RR 0.72; 95% CI 0.47 to 2.94,  $p = 0.64$ ; at 1 year RR 1.18; 95% CI 0.42 to 3.29,  $p = 0.76$ ; at 2 years RR 0.51; 95% CI 0.06 to 4.05,  $p = 0.52$ ) and individual study data (3-year CoreValve ITT, RR 1.14; 95% CI 0.45 to 2.94,  $p = 0.78$  or 5-year PARTNER 1A ITT, RR 0.46; 95% CI 0.16 to 1.31,  $p = 0.14$ ) showed no statistically significant differences between the treatment groups.
- 5.14 In 2 RCTs (PARTNER 2A and NOTION, comparing TAVI with SAVR) with 2,032 and 276 patients for whom SAVR was suitable but intermediate risk there were no significant differences in incidence of MI between TAVI and SAVR. The systematic review of 3,179 patients for whom SAVR was suitable but intermediate to low risk (based on data from 3,128 patients in 4 studies) found no difference between the treatment groups for MI (RR 0.87; 95% CI 0.59 to 1.29) at 2-year follow-up.

### **Endocarditis**

- 5.15 In the RCT of 358 patients for whom SAVR was unsuitable (PARTNER 1B, comparing TAVI with medical management) there

were no significant differences between the groups in endocarditis at 2-year (2% compared with 1%,  $p=0.32$ ) and 3-year (2% compared with 1%,  $p=0.32$ ) follow-up.

- 5.16 In 2 RCTs (PARTNER 1A [ $n=699$ ] and CoreValve [ $n=797$ ] trials, comparing TAVI with SAVR) in patients for whom SAVR was suitable but high risk there were no significant differences between groups in endocarditis (PARTNER 1A: at 1 month 0% compared with less than 1%,  $p=0.32$ ; at 1 year 2 [1%] compared with 3 [1%],  $p=0.63$ ; at 2 years 4 [2%] compared with 3 [1%],  $p=0.61$ ; and at 5 years 5 [2%] compared with 6 [2%],  $p=0.65$ ; CoreValve study: 3 [1%] compared with 5 [2%],  $p=0.346$ ).
- 5.17 In 2 RCTs (PARTNER 2A study and NOTION, comparing TAVI with SAVR) with 2,032 and 276 patients, for whom SAVR was suitable but intermediate risk there were no significant differences in endocarditis between TAVI and SAVR (RCT of 276 patients: at 30 days 1 [1%] compared with 0,  $p=0.33$ ; at 1 year 4 [3%] compared with 2 [2%],  $p=0.47$ ; RCT of 2,032 patients: transfemoral route at 1 year 6 [1%] compared with 6 [1%],  $p=0.92$ ; at 2 years 10 [2%] compared with 6 [1%],  $p=0.33$ ; transthoracic route 1 compared with 0,  $p=0.32$ ).

### **Atrial fibrillation**

- 5.18 In the RCT of 358 patients for whom SAVR was unsuitable (PARTNER 1B, TAVI compared with medical management) there were no significant differences in the incidence of new atrial fibrillation between the treatment groups (at 30 days less than 1% compared with 1%,  $p=1.00$ ; at 1 year less than 1% compared with 2%,  $p=0.62$ ).

- 5.19 In 2 RCTs (PARTNER 1A [n=699] and CoreValve [n=797] trials, comparing TAVI with SAVR) in patients for whom SAVR was suitable but high risk there were significant differences in the incidence of atrial fibrillation (PARTNER 1A: at 1 year 12% compared with 17%,  $p=0.07$ ; CoreValve study: 12% [45] compared with 31% [108],  $p<0.001$  at 30 days, 15% [60] compared with 33% [115],  $p<0.001$  at 1 year).
- 5.20 In 2 RCTs (PARTNER 2A and NOTION, comparing TAVI with SAVR) with 2,032 and 276 patients, for whom SAVR was suitable but intermediate risk there were significant differences in the incidence of new atrial fibrillation between the treatment groups. In the RCT of 2,032 patients for transfemoral TAVI compared with SAVR at 30 days the incidence was 38 (5%) compared with 204 (27%),  $p<0.001$ ; at 1 year 45 (6%) compared with 210 (28%),  $p<0.001$  and at 2 years 55 (7%) compared with 211 (28%)  $p<0.001$ . In the same RCT for transthoracic TAVI compared with SAVR at 30 days the incidence was 53 (23%) compared with 61 (26%),  $p=0.50$ ; at 1 year 55 (24%) compared with 62 (26%),  $p=0.60$ ; and at 2 years 55 (24%) compared with 62 [26%],  $p=0.60$ ; in the RCT of 276 patients: at 30 days 24 [17%] compared with 77 [58%],  $p<0.001$ ; at 1 year 51 [38%] compared with 79 [60%]  $p<0.001$ ; at 2 years 32 [23%] compared with 80 [60%],  $<0.001$ ). The systematic review of 3,179 patients (based on data from 3,058 patients in 3 studies) found that the RR for new onset atrial fibrillation at 2-year follow-up was 0.43 (0.35 to 0.52) for TAVI compared with SAVR.

### **Need for permanent pacemaker**

- 5.21 In the RCT of 358 patients for whom SAVR was unsuitable (PARTNER 1B, TAVI compared with medical management) the proportion of patients with permanent pacemaker implantation

(PPI) was lower in the TAVI group at 2 years (7% compared with 9%,  $p=0.047$ ) although no significant differences were seen at 3 years (8% compared with 9%,  $p=0.75$ ).

5.22 In 2 RCTs (PARTNER 1A [ $n=699$ ] and CoreValve [ $n=797$ ] trials, comparing TAVI with SAVR) in patients for whom SAVR was suitable but high risk the need for PPI was reported. Pooled data tended to favour the SAVR group, however the differences were not statistically significant at 30 days (RR 1.94; 95% CI 0.70 to 5.34,  $p=0.20$ ), at 1 year (RR 1.75; 95% CI 0.94 to 3.25,  $p=0.08$ ) and at 2 years (RR 1.77; 95% CI 0.95 to 3.30,  $p=0.07$ ). At 3-year follow-up (CoreValve trial:  $n=394$  TAVI,  $n=401$  SAVR) there were statistically fewer PPI in the SAVR group than in the TAVI group (14.5% compared with 28%,  $p<0.001$ ). At 5 years (PARTNER 1A) there were no statistically significant differences between the treatment groups (9.7% compared with 9.1%,  $p=0.64$ ).

5.23 In 2 RCTs (PARTNER 2A and NOTION, comparing TAVI with SAVR) with 2,032 and 276 patients, for whom SAVR was suitable but intermediate risk the need for PPI was reported. In the RCT of 2,032 patients there were no significant differences between the groups (9% compared with 7%,  $p=0.17$  at 30 days; 10% compared with 9%,  $p=0.43$  at 1 year; 12% compared with 10%,  $p=0.29$  at 2 years) but in the RCT of 276 patients the need for PPI was higher in the TAVI group than in the SAVR group (at 30 days 46 [34%] compared with 2 [2%],  $p<0.001$ ; at 1 year 51 [38%] compared with 3 [2%],  $p<0.001$ ; and at 2 years 55 [41%] compared with 5 [4%],  $p<0.001$ ). The systematic review of 3,179 patients (based on data from 3,128 patients in 4 studies) reported an increased risk of PPI (RR 2.46; 95%CI 1.17 to 5.15) for TAVI compared with SAVR.

### **Acute kidney injury and renal failure**

- 5.24 In the RCT of 358 patients for whom SAVR was unsuitable (PARTNER 1B, TAVI compared with medical management) there were no significant differences in the occurrence of acute kidney injury (AKI) between the treatment groups at 2-year (3% compared with 8%,  $p=0.15$ ) and 3-year (3% compared with 11%,  $p=0.08$ ) follow-up.
- 5.25 In 2 RCTs (PARTNER 1A [ $n=699$ ] and CoreValve [ $n=797$ ] trials, comparing TAVI with SAVR) in patients for whom SAVR was suitable but high risk, occurrence of AKI was reported. Pooled data (at 30 days RR 0.51; 95% CI 0.27 to 0.98,  $p=0.04$ ) and data from CoreValve study at 3 years (RR 0.45, 95% CI 0.29 to 0.72,  $p=0.0007$ ) significantly favoured the TAVI group, whereas there were no statistically significant differences in the pooled estimates at 1 year and 2 years (RR 0.76; 95% CI 0.23 to 2.59 at 1 year; RR 0.64; 95% CI 0.31 to 1.34,  $p=0.24$  at 2 years) and from PARTNER 1A at 5 years (RR 1.01; 95% CI 0.58 to 1.74).
- 5.26 In 2 RCTs (PARTNER 2A and NOTION, comparing TAVI with SAVR) with 2,032 and 276 patients, for whom SAVR was suitable but intermediate risk occurrence of AKI was reported. The RCT of 2,032 patients reported a lower incidence of AKI in TAVI than SAVR at 30 days (13 [1.3%] compared with 31 [3%],  $p=0.0006$ ). Incidence rates were similar for transthoracic TAVI and SAVR (4% compared with 3%). The incidence rates were significantly lower for transfemoral TAVI than SAVR (2.2% compared with 5%,  $p=0.002$  at 1 year; 3% compared with 7%,  $p<0.001$  at 2 years) and higher for transthoracic TAVI (7% compared with 4.4%,  $p=0.18$  at 1 year, 8% compared with 6%,  $p=0.23$  at 2 years). The RCT of

276 patients reported a higher occurrence of AKI in SAVR than in

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TAVI (9 [7%]) compared with 1[0.7%],  $p=0.01$ ) at 30 days. The systematic review of 3,179 patients (based on data from 2,576 patients in 3 studies) reported that the risk ratio of AKI at 2-year follow-up was 0.38 (95% CI 0.27 to 0.54) for transfemoral TAVI and 1.5 (95% CI 0.77 to 3.07) for transapical TAVI compared with SAVR.

### **Vascular complications**

- 5.27 In the RCT of 358 patients for whom SAVR was unsuitable (PARTNER 1B, TAVI compared with medical management) the hazard ratio of major vascular complications at 3-year follow-up was statistically significantly higher with TAVI than with medical management (HR 8.27; 95% CI 2.92 to 23.44,  $p<0.0001$ ).
- 5.28 In 2 RCTs (PARTNER 1A [n=699] and CoreValve [n=797] trials, comparing TAVI with SAVR) in patients for whom SAVR was suitable but high risk there were no statistically significant differences between the treatment groups in the incidence of major vascular complications in either pooled data at 30-day ( $p=0.17$ ), 1-year ( $p=0.38$ ) or 2-year ( $p=0.09$ ) follow-up, or in the individual studies at 3-year (CoreValve study  $p=0.42$ ) or 5-year (PARTNER 1A : $p=0.19$ ) follow-up.
- 5.29 In 2 RCTs (PARTNER 2A and NOTION, comparing TAVI with SAVR) with 2,032 and 276 patients, for whom SAVR was suitable but intermediate risk, major vascular complications were reported. In the RCT of 2,032 patients there was a higher incidence of major complications in the TAVI group than in the SAVR group (7.9% compared with 5%,  $p=0.008$  at 30 days; 8% compared with 5.3%,  $p=0.007$  at 1 year and 9% compared with 6%,  $p=0.006$  at 2 years). The incidence rate was lower for transfemoral and transthoracic

TAVI than for SAVR. The RCT of 276 patients reported more major vascular complications in the TAVI group than in the SAVR group (6% compared with 2%,  $p=0.10$ ).

### **Major bleeding inoperable patients**

- 5.30 In the RCT of 358 patients for whom SAVR was unsuitable (PARTNER 1B, TAVI compared with medical management), the risk of major bleeding was statistically significantly higher for TAVI than for medical management (29% compared with 20%,  $p=0.04$ ) at 2 years, but not statistically significant different (32% compared with 33%,  $p=0.92$ ) at 3-year follow-up.
- 5.31 In 2 RCTs (PARTNER 1A [ $n=699$ ] and CoreValve [ $n=797$ ] trials, comparing TAVI with SAVR) in patients for whom SAVR was suitable but high risk there no statistically significant differences between the treatment groups in the risk of major bleeding in either pooled data at 30-day (RR 0.67; 95% CI 0.36 to 1.25,  $p=0.21$ ), 1-year (RR 0.73; 95% CI 0.48 to 1.12) and 2-year follow-up (RR 0.78; 95% CI 0.54 to 1.13,  $p=0.19$ ) or in the individual study at 3-year (RR 0.92; 95% CI 0.75 to 1.12,  $p=0.38$ ) follow-up. However, major bleeding was significantly lower in the TAVI group than in the SAVR group in the individual study at 5-year follow-up (RR 0.73; 95% CI 0.57 to 0.95,  $p=0.02$ ).
- 5.32 In 2 RCTs (PARTNER 2A and NOTION, comparing TAVI with SAVR) with 2,032 and 276 patients, for whom SAVR was suitable but intermediate risk, the risk of major bleeding was reported. In the RCT of 2,032 patients there was significantly lower life threatening or disabling bleeding in patients who had TAVI than those who had SAVR at 30-day (10% [105/1011] compared with 43% [442/1021],  $p<0.001$ ), 1-year (15% [151] compared with 46% [460] and 2-year

follow-up (17% [169] compared with 47% [471],  $p < 0.001$ ). The rates were also significantly lower in patients who had transthoracic TAVI than SAVR (23% compared with 50%,  $p < 0.001$  at 30-day, 29% compared with 52%,  $p < 0.001$  at 1-year and 30% compared with 54%,  $p < 0.001$  at 2-year follow-up). The RCT of 276 patients reported significantly lower bleeding in the TAVI group than in the SAVR group at 30 days (11% [16] compared with 21% [28],  $p = 0.03$ ). The systematic review of 3,179 patients (data from 2,576 patients in 3 studies) reported that transfemoral TAVI was associated with a significant reduction in major bleeding compared with SAVR (RR 0.39; 95% CI 0.29 to 0.54). Transapical TAVI (based on data from 552 patients in 2 studies) also had a reduced risk of bleeding, RR 0.53; 95% CI 0.42 to 0.67.

### **Rare safety events**

5.33 A number of observational studies reported rare safety events with TAVI for severe aortic stenosis including: acute myocardial infarction, acute myocardial injury from damage to apical epicardial collateral circulation, acute occlusion of right coronary artery, acute severe occlusion of the left main coronary artery, aortic arch rupture, aortic dissection, aorta perforation, aortic rupture (abdominal), aorto-right ventricular defect (lethal), apical left ventricular thrombus, apical tear, balloon rupture, catheter-induced ventricular septum defect, circumflex artery occlusion, cutaneo-pericardial fistula, delayed ventricular apical bleed, distal coronary embolisation, early valve degeneration, elliptic distortion of the aortic prosthesis, false left ventricular apical aneurysm, guide wire thrombus formation, iatrogenic chordal rupture, iliac artery rupture, intercostal artery pseudoaneurysm, interventricular septum rupture, late prosthesis migration and rotation, left ventricular

pseudoaneurysm, major bleeding from the apex, mitral valve destruction by wire entrapment, multivessel coronary artery spasm, papillary muscle rupture, perforation of the medial circumflex branch of the common femoral artery, pseudoaneurysm at the left ventricular apical access site, pseudoaneurysm of the apex, ruptured pseudoaneurysm of a renal artery, Takotsubo syndrome and valve embolisation.

- 5.34 In addition to safety outcomes reported in the literature, specialist advisers are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never done so). For this procedure, specialist advisers listed the following anecdotal adverse events: valve migration, embolisation, thrombosis, valve or annular trauma during TAVI implants leading to late 'fistulous' connections to adjacent cardiac structures. They considered that the following were theoretical adverse events: haemolytic anaemia, infective endocarditis, structural valve failure, reduced leaflet movement and longer-term problems with device durability requiring re-intervention by either sAVR or 'valve-in-valve' TAVI.

## **6 Committee comments**

- 6.1 The risk of needing a permanent pacemaker implanted after the procedure is influenced by the technique and by the type of valve used.
- 6.2 There is a move towards using sedation rather than general anaesthesia for this procedure.

- 6.3 The transfemoral approach is most commonly used but a transapical approach may be considered when arterial access is difficult.
- 6.4 There is a lack of evidence after 5 years' follow-up and this should be taken into account by the multidisciplinary team.

## **7 Further information**

- 7.1 For related NICE guidance, see the [NICE website](#).
- 7.2 Patient commentary was sought but none was received.
- 7.3 This guidance is a review of NICE's interventional procedure guidance on transcatheter aortic valve implantation for aortic stenosis: <http://www.nice.org.uk/IPG421>.

Tom Clutton-Brock

Chairman, interventional procedures advisory committee

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