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Original research

Formal consensus study on surgery to replace the aortic valve in adults aged 18–60 years

Serban Stoica ¹, Chloe Beard,¹ Johanna J M Takkenberg,² Mostafa M Mokhles,² Mark Turner,³ John Pepper,⁴ Noreen Hopewell-Kelly,⁵ Umberto Benedetto,⁶ Samer A M Nashef,⁷ Ismail El-Hamamsy,⁸ Peter Skillington,⁹ Mattia Glauber,¹⁰ Ruggero De Paulis,¹¹ Elaine Tseng,¹² Bart Meuris,¹³ Marta Sitges,¹⁴ Victoria Delgado,¹⁴ Markus Krane,¹⁵ Martin Kostolny,¹⁶ Maria Pufulete ¹⁷

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For numbered affiliations see end of article.

Correspondence to

Serban Stoica, Cardiothoracic Surgery, Bristol Heart Institute, Bristol, BS2 8ED, UK; serban.stoica@uhbw.nhs.uk

SS and MP contributed equally.

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ABSTRACT

Objective There is uncertainty about surgical procedures for adult patients aged 18–60 years undergoing aortic valve replacement (AVR). Options include conventional AVR (mechanical, mAVR; tissue, tAVR), the pulmonary autograft (Ross) and aortic valve neocuspidisation (Ozaki). Transcatheter treatment may be an option for selected patients. We used formal consensus methodology to make recommendations about the suitability of each procedure.

Methods A working group, supported by a patient advisory group, developed a list of clinical scenarios across seven domains (anatomy, presentation, cardiac/non-cardiac comorbidities, concurrent treatments, lifestyle, preferences). A consensus group of 12 clinicians rated the appropriateness of each surgical procedure for each scenario on a 9-point Likert scale on two separate occasions (before and after a 1-day meeting).

Results There was a consensus that each procedure was appropriate (A) or inappropriate (I) for all clinical scenarios as follows: mAVR: total 76% (57% A, 19% I); tAVR: total 68% (68% A, 0% I); Ross: total 66% (39% A, 27% I); Ozaki: total 31% (3% A, 28% I). The remainder of percentages to 100% reflects the degree of uncertainty. There was a consensus that transcatheter aortic valve implantation is appropriate for 5 of 68 (7%) of all clinical scenarios (including frailty, prohibitive surgical risk and very limited life span).

Conclusions Evidence-based expert opinion emerging from a formal consensus process indicates that besides conventional AVR options, there is a high degree of certainty about the suitability of the Ross procedure in patients aged 18–60 years. Future clinical guidelines should include the option of the Ross procedure in aortic prosthetic valve selection.

INTRODUCTION

Severe aortic valve disease in patients aged 16–60 years (adults aged 18–60 years) usually requires surgery to replace the valve.¹ In this manuscript, we focus on valves that are not amenable to repair. Patients in this age group can have conventional aortic valve replacement (AVR) with a tissue or a mechanical valve (tAVR, mAVR), or the pulmonary autograft (Ross) or aortic valve neocuspidisation (Ozaki) procedures.^{2–10} Transcatheter aortic valve implantation (TAVI) may also be an option for

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The choice of aortic valve substitute in adults aged 18–60 years remains a matter of debate. Patients are keen to be involved in shared decision-making, and alternative non-aortic valve replacement (AVR) options are being discussed.

WHAT THIS STUDY ADDS

⇒ Conventional AVR has the highest degree of indication consensus among experts based on patient and procedure-related variables. The Ross procedure is also agreed on in a comparatively high number of scenarios. The Ozaki procedure is a modern option but with uncertainty around indications and longer-term data.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Non-AVR options are increasingly available and recognised consensually by surgeons and cardiologists. The Ross procedure in particular deserves higher visibility in guidelines. More research is needed on refining indications and improving access to non-AVR options.

selected patients in this age group, including those with low-to-moderate surgical risk.¹¹ The choice of valve is influenced by cardiologists, surgeons and patients; it is value sensitive and influences both quantity and quality of life.

A mechanical valve is potentially permanent but requires lifelong anticoagulation and its attending complications, while a tissue valve degenerates over time and needs replacement every 10–15 years or sooner in younger patients.^{3,4} The Ross operation is technically complex and has been criticised for creating ‘double valve disease’, although meta-analyses of observational studies have shown excellent outcomes.^{1,2,5,10,12,13} The Ozaki procedure, which involves creating three new leaflets with hand-sewn pericardial patches (animal or autologous), has generally shown good mid-term results in young patients,^{6,7} although there have been issues



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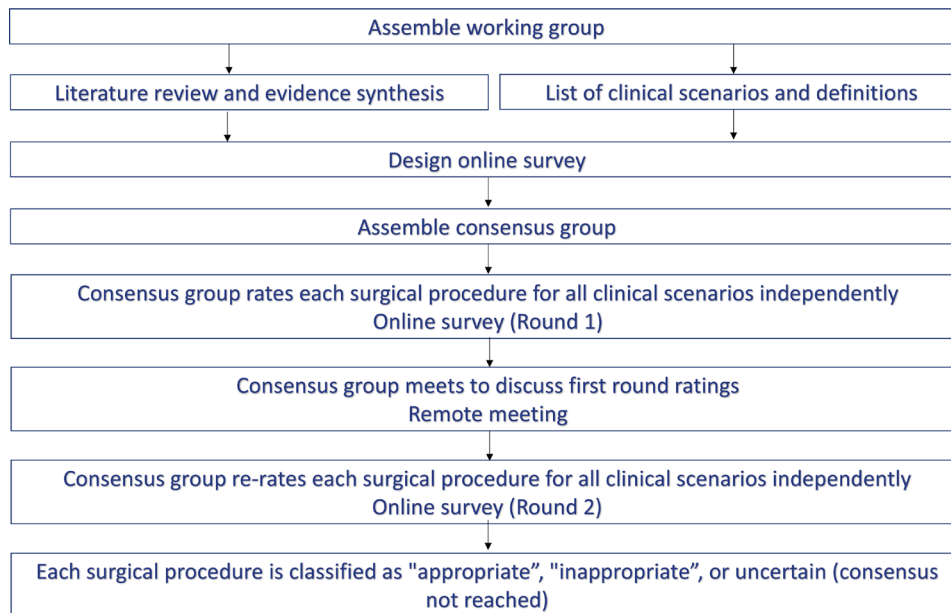


Figure 1 Flow chart showing the sequence of events in the formal consensus process.

related to the behaviour of the biomaterial used to reconstruct the leaflets.^{8,9}

There is uncertainty about which procedure should be considered in adults aged 18–60 years and which patient factors are relative contraindications.¹ Randomised controlled trials (RCTs) on AVR are difficult to conduct because randomisation removes patient choice to a great extent and the outcome curves separate late in time. In addition, in younger patients, outcome curves separate much later.^{10–14} We therefore conducted a formal consensus study using RAND Corporation/University of California Los Angeles (RAND/UCLA) methodology,¹⁵ which involves using the best available evidence and expert opinion to make recommendations about what type of intervention should be offered and for whom.

METHODS

Systematic reviews

Several systematic reviews have been published recently comparing Ross and TAVI with conventional AVR.^{2,3,5,10,12} A systematic review of Ozaki versus conventional options was also available.⁸ Outcomes of interest were mortality, valve-related complications, need for reintervention and quality of life. The methodological quality of the included studies was assessed using the Newcastle–Ottawa scale.¹⁶ A summary of this body of evidence was made available to the expert panel.

Formal consensus working group

The formal consensus process is summarised in [figure 1](#). We assembled a working group comprising six experts (three surgeons, one cardiologist with imaging and TAVI expertise, one methodologist with expertise in formal consensus and one expert in clinical decision-making in cardiothoracic interventions). We held a 1-day meeting and developed a long list of potential factors for consideration when choosing a valve option using evidence from the systematic reviews and their expert knowledge of aortic valve disease and surgery. The long list was finalised after discussion through emails and teleconferences. The final list of factors was divided into eight subheadings (heart structure characteristics, presentation characteristics, existing

heart-related conditions, existing non-heart-related conditions, concurrent medications and treatments, lifestyle factors, personal preference). For each factor, statements describing categories relevant to that factor were developed. For example, for the factor ‘thromboembolic risk’, the categories were ‘high’ and ‘low’, each with a precise definition to avoid ambiguity, while for a factor like ‘aortic root dimension’, precise size thresholds were defined. The long list of potential factors underwent several iterations, in which factors were removed, combined or regrouped and categories redefined.

Survey (round 1)

The final list of factors and their categories was collated in an online questionnaire (SurveyMonkey) (online supplemental table 1). For each factor and within each category, respondents were asked to rate the appropriateness of each procedure on a 9-point scale where 9 indicated that the surgery is very appropriate in that clinical scenario, 1 that the procedure is very inappropriate (the harm outweighs any likely benefit) and 5 that benefit and harm were thought to be about equal or that the member was unable to make a judgement for the situation described. The online survey was piloted by three clinician colleagues of members of the working group and amended appropriately.

Consensus group

We assembled a consensus group comprising experts in management of patients with aortic valve disease—three Ross, two Ozaki, five conventional AVR surgical experts (including less invasive AVR) and two cardiologists. Most of these clinicians had expertise in more than one surgical intervention. The clinicians were chosen to ensure a diversity of views and expertise related to the management of patients with aortic valve disease. Two were congenital surgeons who operate on both children and adults, to reflect the transition of this problem from paediatric into adult practice and inherent clinical commonalities. Participants were identified by clinician members of the working group and were asked to complete the survey (round 1). The consensus was based on the distribution of responses for each factor/category/surgical procedure.

Criteria for consensus

Data for each statement were presented as median and IQR. A median score of ≥ 7 and IQR 6–9 were considered as agreement, or a consensus, that the surgery is appropriate in that clinical scenario. A median score of ≤ 3 and IQR 1–3 were considered to be in a consensus that the surgery is not appropriate. Scores in the 4–6 range indicated a consensus not reached. Data were analysed using Stata/IC (V.17.0, StataCorp, Texas, USA).

Remote meeting

We convened a 1-day meeting with the consensus group to discuss the responses. The meeting was conducted remotely using Zoom Video Communications because of COVID-19 restrictions on travel. Also present were an independent chair with expertise in patient and public involvement (PPI), two members of the working group, two project managers/administrators, a PPI facilitator and four patients who had had AVR and represented each procedure (Ross, Ozaki, mechanical and tissue valve). The anonymised survey responses were presented to the consensus group and discussed in turn, considering all the evidence. The discussion focused on factors/procedures which were not in consensus, that is, medians < 7 but > 3 .

Survey (round 2)

Following the consensus meeting, the survey was amended. Factors/categories within surgical options which were in consensus (that they are appropriate/not appropriate) in the first round of the survey were removed. Factors that were relevant to some surgical options but not others were only included under the relevant surgical options. We provided explanations within the survey for all the changes made. TAVI was removed from the individual clinical scenarios because there was a lot of uncertainty around it in the first round, little evidence in this age group and we did not expect to reach a consensus on the appropriateness of TAVI with respect to most clinical scenarios. However, the results of round 1 of the survey highlighted several scenarios in which TAVI may be appropriate; we grouped these scenarios in a TAVI-specific question so that respondents could rate the appropriateness of TAVI for each scenario.

The amended survey was completed in a second round of voting anonymously by all participants who attended the consensus group meeting. Consensus was defined as previously.

Patient and public involvement

We convened a patient advisory group specifically for the purpose of this study including four patients who had received the four surgical options (mAVR, tAVR, Ross and Ozaki). The PPI was facilitated by an experienced PPI researcher. The group participated in all aspects of the formal consensus process, except for voting in the two rounds of the survey. We held two preliminary meetings with the patient group to discuss the purpose of the formal consensus process, confirm the list of relevant factors, brief patients on their contribution to the formal consensus meeting and determine the group's preference for how to provide input during the consensus meeting itself (members decided on supportive communication through a WhatsApp group during the meeting, through which questions were posed and conveyed to the clinician members of the panel via the PPI facilitator). Members were provided with layman-friendly versions of all study documents, including a layman's version of the study survey itself. The consensus meeting was chaired by a professor of PPI who ensured the patient group

were able to provide input and that there was full integration of patient voices throughout the meeting.

RESULTS

The working group identified a long list of 65 factors for consideration when choosing a valve option. Several factors were combined to avoid duplication, resulting in 52 final factors. As many of these factors had subcategories, we ended up with 75 individual scenarios for scoring (table 1). These were grouped as follows: 8 cardiac anatomy (15 scenarios); 11 presentation characteristics (14 scenarios); 5 cardiac comorbidities (10 scenarios); 12 non-cardiac comorbidities (16 scenarios); 4 concurrent medications and treatments (5 scenarios); 6 lifestyle factors (10 scenarios); 5 personal preferences (5 scenarios). For cardiac anatomy, 7 of the 15 scenarios were only relevant to the Ross operation (cells with symbol † in table 1) and the denominator changed accordingly in reporting percentages (75 for Ross and 68 for the other procedures). All 12 members of the consensus group completed round 1 of the survey and 11 members completed round 2 of the survey.

mAVR and tAVR were considered appropriate for 39 (57%) and 46 (68%) scenarios, respectively. Ross was deemed appropriate for 29 (39%), while Ozaki was deemed appropriate for 2 (3%). There were no scenarios for which tAVR was regarded not appropriate. mAVR, Ross and Ozaki were deemed not appropriate for 13 (19%), 20 (27%) and 19 (28%) scenarios, respectively. There was most uncertainty with regard to Ozaki, where a consensus was not reached for 47 (69%) scenarios, and least uncertainty with regard to mAVR, where a consensus was not reached for 16 (23.5%) scenarios.

Table 2 shows a summary of situations in which mAVR, Ross and Ozaki were considered not appropriate. They were related as follows: mAVR—the need for anticoagulant medication; Ross—pulmonary valve abnormalities and surgical risk; Ozaki—anatomical and cardiac comorbidities. There were no such situations for tAVR.

Table 3 summarises the few specific indications for which TAVI was considered appropriate (high surgical risk, severe liver disease, previous stroke with neurological sequelae and reduced mobility, history of cancer with reduced life expectancy and severe frailty—representing 5 of 68 (7%) of all clinical scenarios).

DISCUSSION

The choice of aortic valve substitute in non-elderly individuals, who have a longer absolute life expectancy, is complex for patients and clinicians. This is reflected in many recent publications and the framework of shared decision-making.^{4 17 18} In this study, we identified five decision domains (demographic, lifestyle, preference, clinical and anatomical factors) that clinicians and patients take into account when choosing an aortic valve substitute. These factors were identified by both the clinicians in the working group and patients in our PPI group. In terms of valve choices, we went beyond the usual dichotomy of mAVR versus tAVR and reflected all contemporary treatments. We determined which valve substitute is appropriate for each of these domains using formal consensus methodology.

mAVR and tAVR were agreed to be appropriate for over half of these factors (57% and 68%, respectively) and uncertainty was reasonably low (24% and 32%, respectively). mAVR was agreed to be inappropriate for 19% of factors, mainly relating to the use of anticoagulation. There were no factors for which tAVR was deemed to be inappropriate. There was also high certainty with regard to the Ross procedure; it was deemed appropriate

Table 1 Suitability of mAVR, tAVR, Ross and Ozaki for adults aged 18–60 years based on 75 different clinical scenarios

		mAVR		tAVR		Ross		Ozaki		
		Median (IQR)		Median (IQR)		Median (IQR)		Median (IQR)		
Cardiac anatomy										
Root dimension	Small	7 (6–8)	A*	6 (5–7)	X	8 (7–9)	A	5 (3–7)	X	
	100%–125% of normal	9 (7–9)	A	7 (7–8)	A*	8 (7–8)	A	4 (4–7)	X	
	>125% of normal	9 (7–9)	A	7 (5–8)	A*	7 (5–8)	A	3 (3–4)	I	
Annulus dimension	Small	7 (5–7)	A*	6 (5–7)	X	8 (6–9)	A	5 (3–7)	X	
	Large	9 (8–9)	A	8 (7–9)	A	7 (7–8)	A	3 (2–5)	I	
Small left ventricular outflow tract dimension		7 (5–7)	A	5 (4–6)	X	8 (6–9)	A	5 (5–6)	X	
Size discrepancy between aortic valve (AV) and pulmonary valve (PV)	AV<PV	†	†	†	†	6 (4–8)	X	†	†	
	AV>PV					5 (3–7)	X			
Left anterior descending artery crosses the right ventricular outflow tract		†	†	†	†	2 (1–2)	I	†	†	
PV dysfunction	Bicuspid but otherwise fully functional	†	†	†	†	4 (1–5)	X	†	†	
	Preoperative mild regurgitation					3 (2–8)	X			
	Preoperative mild stenosis					2 (1–4)	I			
	Intraoperatively PV looks abnormal					2 (1–2)	I			
Bicuspid AV without symptomatic connective tissue phenotype or high-risk genotype		9 (7–9)	A	7 (5–7)	A*	7 (6–8)	A*	5 (3–7)	X	
Aneurysm of the ascending aorta		8 (5–9)	X	6 (5–9)	X	8 (6–9)	A	4 (3–7)	X	
Presentation										
Aortic stenosis (dominant lesion)		9 (7–9)	A	9 (6–9)	A*	9 (8–9)	A*	5 (5–8)	X	
Aortic regurgitation (dominant lesion)		9 (7–9)	A	9 (6–9)	A*	8 (7–8)	A	5 (4–5)	X	
Emergency presentation		9 (9–9)	A	9 (5–9)	X	4 (2–5)	X	4 (2–5)	X	
Left ventricular ejection fraction	Moderate (35%–55%)	8 (6–9)	A	8 (6–9)	A*	6 (4–7)	X	3 (2–5)	I*	
	Poor (<35%)	7 (6–9)	A	7 (6–8)	A	3 (2–4)	I	3 (3–4)	I	
High thromboembolic risk		2 (1–5)	X	7 (6–8)	A	9 (6–9)	A	6 (5–9)	X	
High bleeding risk		1 (1–2)	I	7 (7–8)	A	8 (6–9)	A*	5 (5–7)	X	
Surgical risk	Medium (EuroSCORE II 3%–6%)	8 (6–9)	A	8 (7–9)	A*	6 (5–7)	X	5 (3–8)	X	
	High (EuroSCORE II >6%)	7 (5–9)	X	6 (5–8)	X	3 (3–3)	I	2 (2–7)	X	
Active endocarditis		5 (5–7)	X	6 (5–7)	X	7 (6–7)	A	7 (4–7)	A	
Aortopathy	No connective tissue weakness	9 (7–9)	A	8 (7–9)	A*	7 (6–7)	A*	3 (3–5)	I*	
	Severe (eg, Marfan, Ehler-Danlos, etc)	9 (7–9)	A	8 (2)	A*	2 (1–4)	I	3 (2–5)	I	
Previous sternotomy		8 (7–9)	A	7 (5,8)	A	6 (5–7)	X	3 (3–5)	I*	
Previous thoracic radiotherapy		8 (8–9)	A	7 (3,8)	X	6 (3–7)	X	4 (3–8)	X	
Cardiac comorbidities										
Mitral valve (MV) disease which requires surgery as a secondary indication	MV amenable to repair	7 (6–9)	A*	8 (7–9)	A*	7 (5–8)	A*	3 (3–6)	I*	
	MV needs replacement	8 (7–9)	A	8 (6–9)	A	5 (3–6)	X	3 (3–6)	I	
Tricuspid valve (TV) disease which requires surgery as a secondary indication	TV amenable to repair	7 (7–9)	A	7 (6–9)	A	7 (4–8)	X	5 (3–7)	X	
	TV needs replacement	9 (8–9)	A	8 (7–9)	A	4 (2–5)	X	3 (2–4)	I	

Continued

Table 1 Continued

		mAVR		tAVR		Ross		Ozaki	
		Median (IQR)		Median (IQR)		Median (IQR)		Median (IQR)	
History of endocarditis (AV affected, PV not affected, no active infection)		7 (6–9)	A	7 (6–8)	A*	7 (6–9)	A	5 (3–7)	X
History of rheumatic heart disease	PV looks abnormal on echo	9 (8–9)	A	8 (5–9)	X	1 (1–2)	I	5 (4–7)	X
	PV looks normal on echo and intraoperatively	9 (8–9)	A	7 (5–9)	X	7 (5–8)	A	5 (5–8)	X
Needs revascularisation	CABG	9 (7–9)	A	8 (7–9)	A	3 (2–5)	I	4 (3–5)	X
	PCI	6 (4–8)	X	9 (7–9)	A*	5 (3–7)	X	4 (3–9)	X
	Either CABG or PCI	6 (6–9)	X	7 (6–9)	A	3 (2–7)	X	5 (4–7)	X
Non-cardiac comorbidities									
Pulmonary hypertension (systolic PA pressure >60 mm Hg)		8 (6–9)	A	7 (5–8)	A	2 (1–3)	I	5 (3–6)	X
Poorly controlled hypertension		9 (7–9)	A	8 (5–9)	X	6 (5–6)	X	5 (3–5)	X
Significant lung disease		7 (5–8)	A*	9 (8–9)	A*	2 (1–3)	I	3 (2–4)	I
Significant liver disease		2 (1–3)	I	9 (8–9)	A*	2 (1–3)	I	1 (1–5)	X
Significant kidney disease		7 (5–8)	A*	8 (7–9)	A*	3 (3–4)	I	3 (2–5)	I
Diabetes	Uncomplicated	8 (7–9)	A*	8 (8–9)	A	8 (6–9)	A*	5 (3–9)	X
	Complicated (life expectancy <10 years)	6 (5–7)	X	8 (7–9)	A	3 (2–5)	I	5 (2–9)	X
Stroke	Minor, resolved	6 (4–8)	X	7 (6–8)	A	6 (4–8)	X	5 (3–9)	X
	Major, sequelae present/reduced mobility	3 (1–5)	X	8 (5–8)	A	2 (1–4)	I	3 (2–3)	I*
History of cancer (life expectancy less than 5 years)		2 (1–3)	I	8 (4–9)	X	1 (1–3)	I	2 (1–5)	X
Body mass index	Low (<18 kg/m ²)	8 (6–8)	A*	7 (6–9)	A*	7 (5–8)	A*	5 (4–9)	X
	High (>30 kg/m ²)	9 (6–9)	A	7 (5–9)	X	5 (5–8)	X	5 (2–9)	X
Anorexia or intestinal absorption disorder		3 (2–5)	I*	9 (7–9)	A*	7 (5–8)	A	5 (5–9)	X
Frailty	Moderate	5 (4–6)	X	7 (7–8)	A	3 (3–5)	I*	3 (2–8)	X
	Severe	6 (2–8)	X	5 (4–8)	X	1 (1–2)	I	2 (2–4)	I
Comorbidities that influence adherence to medication		2 (1–4)	I	7 (5–8)	A	7 (5–8)	A	5 (5–7)	X
Concurrent medications and treatments									
Already on anticoagulation	With warfarin	9 (8–9)	A	4 (3–8)	X	3 (3–6)	I	3 (2–3)	I
	With novel oral anticoagulant or antiplatelet therapy	8 (6–9)	A	6 (5–9)	X	5 (3–5)	X	4 (3–7)	X
Chemotherapy (current or within the last 6 months)		5 (5–7)	X	7 (6–8)	A	4 (2–6)	X	3 (2–6)	X
Radiotherapy (current or within the last 6 months)		5 (5–7)	X	7 (5–9)	X	3 (2–5)	I	3 (2–5)	I
High-dose oral steroids as replacement therapy		7 (6–9)	A	7 (6–7)	A	5 (4–7)	X	4 (3–8)	X
Lifestyle									
Physical activity	Sedentary with minimal activity	7 (6–9)	A	7 (5–9)	X	5 (2–8)	X	4 (3–5)	X
	Moderate to highly active	5 (4–9)	X	7 (5–9)	X	8 (7–9)	A	6 (5–8)	X
	Highly active (amateur or professional athlete)	4 (2–9)	X	7 (5–9)	X	9 (–9)	A	6 (5–9)	X

Continued

Table 1 Continued

		mAVR		tAVR		Ross		Ozaki	
		Median (IQR)		Median (IQR)		Median (IQR)		Median (IQR)	
Heavy drinking (exceeds recommended safe limit guidelines)		3 (1–4)	I	7 (7–8)	A	6 (4–8)	X	4 (3–9)	X
Reduced mobility (eg, wheelchair users, Parkinson's disease)		5 (2–7)	X	7 (5–8)	A	3 (1–4)	I	3 (2–5)	I
Working or living in a remote area with no easy access to healthcare		3 (2–5)	I	7 (7–9)	A	8 (7–9)	A	7 (3–9)	X
Patient considered unlikely to comply with anticoagulant medication		1 (1–1)	I	7 (6–9)	A	8 (7–9)	A	6 (5–8)	X
Women of childbearing age	Currently considering pregnancy	2 (1–3)	I	7 (5–8)	A	9 (7–9)	A	7 (3–9)	X
	Considering pregnancy in the future	2 (1–2)	I	7 (5–8)	A	9 (7–9)	A	7 (3–9)	X
	Does not wish to have children	8 (7–9)	A	5 (4–7)	X	6 (5–9)	X	5 (5–7)	X
Personal preference									
Thinks mechanical valve sound will be disturbing		2 (1–4)	I	8 (7–9)	A	9 (7–9)	A	7 (4–9)	X
Prefers not to have further surgical intervention		9 (8–9)	A	4 (2–7)	X	6 (5–8)	X	1 (1–4)	I
Prefers not to have warfarin anticoagulation		1 (1–2)	I	8 (7–9)	A	9 (7–9)	A	7 (5–8)	A
Prefers a small surgical incision for cosmetic reasons		7 (6–9)	A	7 (7–9)	A	1 (1–5)	X	3 (3–5)	I
Refuses transfusion on religious grounds		3 (2–4)	I*	8 (7–9)	A	6 (5–7)	X	6 (3–7)	X
The scores refer to the average score given by 12 experts on a scale of 1–9.									
*Consensus was reached after the remote meeting (round 2 of the survey); if no asterisk then a consensus was reached in round 1 of the survey. X indicates that a consensus was not reached in either round of the survey.									
†Anatomical scenarios are not relevant to those surgical procedures.									
A, appropriate for the indication; CABG, coronary artery bypass grafting; I, inappropriate for the indication; mAVR, aortic valve replacement with a mechanical valve; PA, pulmonary artery; PCI, percutaneous coronary intervention; tAVR, aortic valve replacement with a tissue valve.									

for 39% of factors and not appropriate for 27% of factors, with uncertainty for only 34% of factors. These results highlight the fact that these three procedures are well established in this population group, backed by evidence and, for AVR, in keeping with current guidelines.^{17 18}

There was substantial uncertainty for the Ozaki procedure; it was deemed appropriate for just 3% of factors and not appropriate for 28%, with uncertainty for 69% of factors. This highlights the lack of evidence and familiarity with this procedure among clinicians. The Ozaki procedure is a relatively recent development (currently not part of valve guidelines) which aims to offer a solution that is free from heavy anticoagulation, while combining other advantages of tAVR and Ross.^{8 9} It is seen as technically less demanding than Ross, but its track record in adults aged 18–60 years is relatively short compared with the other clinical options, which may explain the uncertainty around its role.

TAVI was agreed to be appropriate for few scenarios (9%), largely related to the inability to withstand open heart surgery or reduced life expectancy, also in keeping with current recommendations.^{17 18} The European Society of Cardiology (ESC)/

European Society of Cardiothoracic Surgery (EACTS) guidelines suggest the age of 75 years as a guide for surgical AVR versus TAVI, whereas according to the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines, shared decision-making on this can take place from 65 years of age. Both these indicative ages are above the age of our target population. A recent systematic review and meta-analysis showed that TAVI was associated with lower risk of death and stroke compared with open surgery for up to 2 years, although there was a higher risk of major vascular complications and pacemaker implantation.¹⁹ However, there are no long-term follow-up data. The mean age in the comparative studies examined by Siontis *et al* was between 73 and 85 years, so these results cannot be extrapolated to our target patients. For the time being, surgical risk and life expectancy remain the deciding factors in considering a non-surgical intervention in younger patients.

Because the vast majority of patients who require AVR are elderly, there are limited opportunities for generating high-quality research data in patients younger than 60 years of age. Regardless of the initial intervention, the early mortality and morbidity are generally low. Investigators must plan for many

Table 2 Situations in which mAVR, tAVR, Ross and Ozaki were considered not appropriate in patients aged 16–60 years

mAVR	Median (IQR)
High bleeding risk	1 (1–2)
Significant liver disease	2 (1–3)
History of cancer with reduced life expectancy	2 (1–3)
Anorexia or intestinal absorption disorder	3 (2–5)
Comorbidities that influence adherence to medication*	2 (1–4)
Heavy drinker	3 (1–4)
Works or lives in a remote area with no easy access to healthcare	3 (2–5)
Considered unlikely to comply with anticoagulant medication	1 (1–1)
Woman considering pregnancy (now/in the future)	2 (1–3)/2 (1–2)
Finds mechanical valve sound disturbing	2 (1–4)
Prefers not to have warfarin anticoagulation	1 (1–2)
Refuses transfusion on religious ground	3 (2–4)
tAVR	
No contraindications	
Ross	
Left anterior descending artery crosses the right ventricular outflow tract	2 (1–2)
Pulmonary valve dysfunction (preoperative mild stenosis/ intraoperative findings of abnormalities)	2 (1–4)/2 (1–2)
Poor left ventricular function (ejection fraction <35%)	3 (2–4)
High surgical risk (EuroSCORE II >6%)	3 (3–3)
Severe aortopathy	2 (1–4)
History of rheumatic heart disease with abnormal pulmonary valve	1 (1–2)
Needs coronary artery bypass grafting	3 (2–5)
Pulmonary hypertension	2 (1–3)
Severe lung/liver/kidney disease	2 (1–3)/2 (1–3)/3 (3–4)
Complicated diabetes	3 (2–5)
History of stroke with major sequelae	2 (1–4)
History of cancer with reduced life expectancy	1 (1–3)
Frailty (moderate/severe)	3 (3–5)/1 (1–2)
Already taking warfarin anticoagulation	3 (3–6)
Radiotherapy (current or within 6 months)	3 (2–5)
Reduced mobility†	3 (1–4)
Ozaki	
Aortic root >125% of normal	3 (3–4)
Large annulus dimension	3 (2–5)
Moderate (35%–55%)/poor left ventricular function (<35%)	3 (2–5)/3 (3–4)
Aortopathy (mild/severe)	3 (3–5)/3 (2–5)
Previous sternotomy	3 (3–5)
Mitral valve disease (repair/replacement)	3 (3–6)/3 (3–6)
Tricuspid valve disease that needs replacement	3 (2–4)
Significant lung/kidney disease	3 (2–4)/3 (2–5)
Major stroke	3 (2–3)
Severe frailty	2 (2–4)
Already taking warfarin anticoagulation	3 (2–3)
Radiotherapy (current or within 6 months)	3 (2–5)
Reduced mobility†	3 (2–5)
Prefers not to have surgical reintervention at any point in the future	1 (1–4)
Prefers a small surgical incision for cosmetic reasons	3 (3–5)

*Cognitive impairment, psychosis, severe anxiety or depression.

†Wheelchair users, Parkinson's disease.

mAVR, aortic valve replacement with a mechanical valve; tAVR, aortic valve replacement with a tissue valve.

Table 3 Indications for TAVI in adults aged 18–60 years (aged 16–60 years)

	Median (IQR)
High surgical risk (EuroSCORE II >6%)	9 (8–9)
Severe liver disease	8 (7–9)
Previous stroke—neurological sequelae and reduced mobility	8 (8–9)
History of cancer with reduced life expectancy	9 (8–9)
Severe frailty	8 (8–9)

TAVI, transcatheter aortic valve implantation.

years of follow-up in large cohorts before outcome curves separate in this age group. Such prospective studies are difficult to design, fund and deliver, and we enter a vicious cycle of 'not enough evidence'. This is particularly evident for the Ross procedure. There is only one important trial of Ross and the comparison arm was another biological root replacement in the form of homograft, against which Ross was superior.²⁰ A recent attempt to examine Ross versus conventional AVR in a multicentre prospective trial was abandoned due to the pilot study failing to recruit to target during the pandemic.¹⁴ Large retrospective studies^{2–5 10 12 21 22} show a clear superiority of the Ross procedure against conventional AVR in adults aged 18–60 years. The survival advantage disappears at around 60 years of age and is naturally more marked in younger patients.²¹ Despite this evidence, the Ross operation is not commonly performed and it receives minimal visibility in current guidelines.^{17 18} Yet, our study shows that there is sufficient clarity around which type of patients are suitable for Ross, with uncertainty for just over one-third of the factors, to justify more widespread use. In view of recent evidence, some authors describe the underuse of the Ross procedure as a lost opportunity and call for better training and proctoring arrangements so that more patients can benefit from it.^{23 24}

Our study has several strengths. It is the first to identify systematically the main factors which need to be taken into consideration when making a decision about choice of AVR in this age group. These factors were identified with the input of patients who had AVR. It is also the first study to use formal consensus methods to decide appropriateness of all existing valve options for all factors identified. Formal consensus methods are increasingly used in healthcare as a rigorous way of determining a consensus for complex clinical problems for which evidence from RCTs is lacking. The RAND/UCLA method was initially developed to evaluate the overuse/underuse of medical or surgical options¹⁵ and was therefore deemed appropriate for our study. We actively included patients in the entire process, from identifying the relevant factors to participating in the consensus discussion. This ensured that the clinical scenarios were relevant and representative of the 'lived-in' experience and allowed the most important aspects from the patients' point of view to be identified and considered during discussions. The involvement has also assisted in developing a template for best practice for PPI in a formal consensus process (https://cdn.eventsforce.net/files/ef-wqdbqri56uui/website/174/working_with_patients_and_the_public.pdf).

The study has limitations. We could not carry out a literature review specific to the current project as we originally intended. This was partly because of the large number of factors we identified, which would have necessitated a review that could not be conducted within our existing time and resources. However, there were already several recent systematic reviews and meta-analyses examining the various procedures included.

The face-to-face meeting was conducted virtually because of COVID-19 restrictions, which prevented the more subtle interactions/discussion between panellists and more in-depth discussion. Nevertheless, the outcome of the consensus process was largely as expected, with many factors that did not attain a consensus in the first round of the survey reaching a consensus in the second round. We did not examine less-invasive surgical AVR options in our study, as we felt that they are not applicable to all valve replacement choices and have less bearing on long-term outcomes. This excluded questions related to cosmesis and a possible earlier return to full activities, factors which were deemed important to members of our PPI group. We also had no options for considering patient factors together and trade-offs between factors. Finally, our results ideally require validation in a larger clinical cohort.

In summary, we identified 52 factors that need to be considered when deciding on AVR choice. There was a consensus for appropriateness/inappropriateness for almost two-thirds of these factors for mAVR, tAVR and Ross, indicating clinician certainty with regard to the suitability of these procedures in different situations. Therefore, the Ross procedure should be considered as an option for AVR in adults aged 18–60 years in future guidelines. Clinicians and patients should work together to find the best compromise in individual cases. New trial designs embedded in registries or routinely collected data on clinical and patient-centred outcomes, and using uniform outcome definitions may be able to overcome methodological difficulties and offer a finer separation of these options in coming years.²⁵

Author affiliations

¹Cardiothoracic Surgery, Bristol Heart Institute, Bristol, UK

²Cardiothoracic Surgery, Erasmus University Medical Center, Rotterdam, The Netherlands

³Department of Cardiology, University Hospitals Bristol and Weston NHS Foundation Trust, Bristol, UK

⁴Surgery, Royal Brompton Hospital, London, UK

⁵Health and Social Sciences, University of the West of England-Frenchay Campus, Bristol, UK

⁶School of Clinical Sciences, University of Bristol, Bristol, UK

⁷Cardiac Surgery, Papworth Hospital NHS Foundation Trust, Cambridge, UK

⁸Mount Sinai Hospital, Los Angeles, California, USA

⁹The Royal Melbourne Hospital, Parkville, Victoria, Australia

¹⁰Istituto Clinico Sant' Ambrogio, Milan, Italy

¹¹European Hospital, Rome, Italy

¹²University of California San Francisco School of Medicine, San Francisco, California, USA

¹³Cardiac Surgery, KU Leuven University Hospitals Leuven, Leuven, Belgium

¹⁴Cardiology, Hospital Clinic de Barcelona, Barcelona, Spain

¹⁵Yale School of Medicine, New Haven, Connecticut, USA

¹⁶Cardiothoracic Unit, Great Ormond Street Hospital and Institute of Cardiovascular Science, University College London, London, UK

¹⁷Bristol Heart Institute, Bristol Medical School, University of Bristol, Bristol, UK

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Contributors SS identified the clinical problem, obtained funding, conducted the study and co-wrote the manuscript. CB conducted the study and contributed to the PPI element. JJMT and MMM conducted the evidence synthesis and provided methodological expertise. NH-K designed and conducted the PPI element. MP conceived and designed the study, conducted the data analysis, co-wrote the manuscript and is the guarantor for the study. All other authors contributed expertise to the working group or the consensus group.

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ORCID iDs

Serban Stoica <http://orcid.org/0000-0002-0456-1249>

Maria Pufulete <http://orcid.org/0000-0002-1775-1949>

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Supplementary material

Table S1. Definitions

		Survey definitions
Cardiac anatomy		
Root dimension	Small 100-125% of normal >125% of normal	<p>Root dimension</p> <p><i>The annulus is normal or at least big enough to allow the insertion of a conventional AVR without causing patient-prosthesis mismatch (PPM). The aorta above the annulus up to the level of the sino-tubular junction is abnormal.</i></p> <p><i>Small root: TAVI may be contraindicated as a small root is associated with low coronary arteries. Ozaki may require technical modifications.</i></p> <p><i>Large root: Ozaki may be contraindicated. Ross may require technical modifications (interposition tube or externally supported root). AVR can be done as part of the root replacement if clinically indicated</i></p>
Annulus dimension	Small Large	<p>Annulus dimension</p> <p><i>Assume pulmonary valve (PV) is normal in size.</i></p> <p><i>Small annulus: Conventional AVR would result in severe patient-prosthesis mismatch (PPM) without annular enlargement. Ross would require a Konno or mini-Konno incision (fibrous annulus only).</i></p> <p><i>Large annulus: A Ross is technically possible only with AV annular reduction. Contraindication to Ozaki/TAVI if annulus is outside the treatable range (i.e. sizes and devices not available in bigger sizes).</i></p>
Small left ventricular outflow tract (LVOT) dimension		<p>Left ventricular outflow tract (LVOT) dimension</p> <p><i>Normal LVOT: LVOT is not a factor in valve choice.</i></p> <p><i>Small LVOT: There is tunnel-like obstruction which needs fixing by Konno-type surgery in addition to valve replacement</i></p>
Size discrepancy between aortic valve (AV) and pulmonary valve (PV)	AV < PV AV > PV	<p>Size discrepancy between aortic valve (AV) and pulmonary valve (PV)</p> <p><i>If size discrepancy is significant annular reduction or enlargement is needed for Ross, but Ross is technically feasible.</i></p>
Left anterior descending artery (LAD) crosses the		Left anterior descending artery (LAD) crosses the right ventricular outflow tract (RVOT)

	Survey definitions
right ventricular outflow tract (RVOT)	<i>The autograft cannot be safely lifted for Ross</i>
Pulmonary valve (PV) dysfunction Bicuspid but otherwise fully functional Preoperative mild regurgitation Preoperative mild stenosis Intraoperatively PV is thin looking with fenestrations, dysplastic or doming	Pulmonary valve (PV) dysfunction Bicuspid but otherwise fully functional Preoperative mild regurgitation Preoperative mild stenosis Intraoperatively PV is thin looking with fenestrations, dysplastic or doming
Bicuspid aortic valve (AV) without symptomatic connective tissue phenotype or high-risk genotype	Bicuspid aortic valve without symptomatic connective tissue phenotype or high-risk genotype <i>Both Ross and Ozaki possible</i>
Aneurysm of the ascending aorta	Aneurysm of the ascending aorta <i>The root is within reasonable limits, the abnormal dilatation of the aorta is in the ascending part, above the root. Ozaki and TAVI may have relative contraindications if the sino-tubular junction is borderline dilated.</i>
Presentation	
Aortic stenosis (dominant lesion)	Aortic stenosis (dominant lesion)
Aortic regurgitation (dominant lesion)	Aortic regurgitation (dominant lesion)
Emergency presentation	<i>The operation has to be performed within 24 hrs.</i>
Left ventricular function	Good (>55%) Moderate (35-55%) Poor (<35%)
High thromboembolic risk	Thromboembolic risk (history of embolism, clotting disorder, poor compliance with anti-thrombotic medication)

	Survey definitions
High bleeding risk	Bleeding risk (any history of severe bleeding, bleeding disorder, end-organ lesion prone to bleeding, e.g brain aneurysm, severe inflammatory bowel disease)
Surgical risk	Low (EuroSCORE II 0-3%) Medium (EuroSCORE II 3-6%) High (EuroSCORE II >6%)
Active endocarditis	Active endocarditis
Aortopathy No connective tissue weakness Severe (e.g. Marfan, Ehler-Danlos, etc.)	Mild/moderate (bicuspid aortopathy without evidence of connective tissue weakness) Severe (syndromic / severe connective tissue disease, e.g. Marfan, Ehler-Danlos, Loeys-Dietz or malignant connective tissue mutations)
Previous sternotomy	Previous sternotomy
Previous thoracic radiotherapy	Previous thoracic radiotherapy (everything looks reasonable when opening the chest)
Cardiac comorbidities	
Mitral valve (MV) disease which requires surgery as a secondary indication MV amenable to repair MV needs replacement	Moderate or severe mitral valve (MV) disease which requires surgery as a secondary indication MV amenable to repair MV needs replacement
Tricuspid valve (TV) disease which requires surgery as a secondary indication TV amenable to repair TV needs replacement	Moderate or severe tricuspid valve (TV) disease which requires surgery as a secondary indication TV amenable to repair TV needs replacement

	Survey definitions
History of endocarditis (aortic valve affected, pulmonary valve not affected, no active infection)	History of endocarditis (AV affected, PV not affected, no active infection)
History of rheumatic heart disease PV looks abnormal on echo PV looks normal on echo and intraoperatively	History of rheumatic heart disease PV looks abnormal on echo PV looks normal on echo and intraoperatively
Needs revascularisation Coronary artery bypass grafting (CABG) Percutaneous coronary intervention (PCI) Either CABG or PCI	Patient requires revascularisation for coronary artery disease Coronary artery bypass grafting (CABG) Percutaneous coronary intervention (PCI) Either CABG or PCI
Non-cardiac comorbidities	
Pulmonary hypertension (systolic PA pressure >60mm Hg)	Pulmonary hypertension (systolic PA pressure >60mm Hg)
Poorly controlled hypertension	Poorly controlled hypertension <i>Medically resistant forms or poor compliance with medication.</i>
Significant lung disease	Severe lung disease (AV surgery possible but a long operation ideally avoided)
Significant liver disease	Significant liver disease <i>Clinical and laboratory evidence of severe coagulopathy, liver dysfunction or consideration of future liver transplant</i>
Significant kidney disease	Significant renal disease <i>Clinical and laboratory evidence of significant kidney dysfunction, need for dialysis or consideration of future kidney transplant</i>
Diabetes Uncomplicated	Diabetes <i>Complicated if accompanied by microvascular</i>

		Survey definitions
Complicated (life expectancy <10 years)		<i>disease, arteriopathy, ulcers, amputation, reduced mobility, life expectancy less than 10 years.</i>
Stroke	Minor, resolved Major, sequelae present and reduce mobility	History of stroke/transient ischaemic attack Minor, resolved Major, sequelae present and reduce mobility
History of cancer (life expectancy less than 5 years)		History of cancer (life expectancy less than 5 years)
Body mass index	Low (<18 kg/m ²) High (>30 kg/m ²)	Body mass index
Anorexia or intestinal absorption disorder		Anorexia or intestinal absorption disorder <i>The patient is not cachectic or severely frail and a longer operation is possible. Intestinal problems suggest unpredictable absorption of warfarin and other nutrients which may affect INR stability.</i>
Frailty	Moderate Severe	Frailty (defined using accepted criteria) Moderate (a long operation possible) Severe (a long operation ideally avoided)
Comorbidities that influence adherence to medication		Comorbidities that influence adherence to medication <i>For example, cognitive impairment, psychosis, severe anxiety or depression.</i>
Concurrent medications and treatments		
Already on anticoagulation	With warfarin With novel oral anticoagulant (NOAC) or antiplatelet therapy	Already on anticoagulation With warfarin (e.g. mechanical mitral valve) With novel oral anticoagulant (NOAC) (e.g. atrial fibrillation with moderate risk) or antiplatelet therapy

		Survey definitions
Chemotherapy (current or within the last 6 months)		Chemotherapy (current or within the last 6 months) <i>Life expectancy is more than 5 years.</i>
Radiotherapy (current or within the last 6 months)		Radiotherapy (current or within the last 6 months) <i>Life expectancy is more than 5 years.</i>
High dose oral steroids as replacement therapy		Oral steroids <i>High dose, at a level that requires perioperative replacement and raises some concerns about wound healing.</i>
Lifestyle		
Physical activity	Sedentary with minimal activity Moderate to highly active Highly active (amateur or professional athlete)	Physical activity Inactive (sedentary lifestyle with minimal activity) Moderate to highly active (engages in and values regular activities, some of which can be strenuous) Athlete (pursues strenuous activities at amateur or professional level)
Heavy drinking (exceeds recommended safe limits guidelines)		Heavy drinking (exceeds recommended safe limits guidelines) and unwilling or unable to restrict alcohol intake
Reduced mobility (e.g. wheelchair bound, Parkinson's disease)		Reduced mobility (e.g. wheelchair bound, Parkinson's disease)
Working or living in a remote area with no easy access to healthcare		Working or living in a remote area with no easy access to healthcare
Patient considered unlikely to comply with anticoagulant medication		Patient considered unlikely to comply with anticoagulant medication (e.g. mental health problems, homelessness) or refuses it

	Survey definitions
Women of childbearing age	<p>Currently considering pregnancy</p> <p>Considering pregnancy in the future</p> <p>Does not wish to have children</p>
Personal preference	Women of childbearing age (16-year old to menopause)
Thinks mechanical valve sound will be disturbing	Currently considering pregnancy
Prefers not to have further surgical intervention	Considering pregnancy in the future
Prefers not to have warfarin anticoagulation	Does not wish to have children
Prefers a small surgical incision for cosmetic reasons	
Refuses transfusion on religious grounds	

Supplementary material

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History of cancer (life expectancy less than 5 years)		History of cancer (life expectancy less than 5 years)
Body mass index	Low (<18 kg/m ²) High (>30 kg/m ²)	Body mass index
Anorexia or intestinal absorption disorder		Anorexia or intestinal absorption disorder <i>The patient is not cachectic or severely frail and a longer operation is possible. Intestinal problems suggest unpredictable absorption of warfarin and other nutrients which may affect INR stability.</i>
Frailty	Moderate Severe	Frailty (defined using accepted criteria) Moderate (a long operation possible) Severe (a long operation ideally avoided)
Comorbidities that influence adherence to medication		Comorbidities that influence adherence to medication <i>For example, cognitive impairment, psychosis, severe anxiety or depression.</i>
Concurrent medications and treatments		
Already on anticoagulation	With warfarin With novel oral anticoagulant (NOAC) or antiplatelet therapy	Already on anticoagulation With warfarin (e.g. mechanical mitral valve) With novel oral anticoagulant (NOAC) (e.g. atrial fibrillation with moderate risk) or antiplatelet therapy

		Survey definitions
Chemotherapy (current or within the last 6 months)		Chemotherapy (current or within the last 6 months) <i>Life expectancy is more than 5 years.</i>
Radiotherapy (current or within the last 6 months)		Radiotherapy (current or within the last 6 months) <i>Life expectancy is more than 5 years.</i>
High dose oral steroids as replacement therapy		Oral steroids <i>High dose, at a level that requires perioperative replacement and raises some concerns about wound healing.</i>
Lifestyle		
Physical activity	Sedentary with minimal activity Moderate to highly active Highly active (amateur or professional athlete)	Physical activity Inactive (sedentary lifestyle with minimal activity) Moderate to highly active (engages in and values regular activities, some of which can be strenuous) Athlete (pursues strenuous activities at amateur or professional level)
Heavy drinking (exceeds recommended safe limits guidelines)		Heavy drinking (exceeds recommended safe limits guidelines) and unwilling or unable to restrict alcohol intake
Reduced mobility (e.g. wheelchair bound, Parkinson's disease)		Reduced mobility (e.g. wheelchair bound, Parkinson's disease)
Working or living in a remote area with no easy access to healthcare		Working or living in a remote area with no easy access to healthcare
Patient considered unlikely to comply with anticoagulant medication		Patient considered unlikely to comply with anticoagulant medication (e.g. mental health problems, homelessness) or refuses it

	Survey definitions
Women of childbearing age	<p>Currently considering pregnancy</p> <p>Considering pregnancy in the future</p> <p>Does not wish to have children</p>
Personal preference	Women of childbearing age (16-year old to menopause)
Thinks mechanical valve sound will be disturbing	Currently considering pregnancy
Prefers not to have further surgical intervention	Considering pregnancy in the future
Prefers not to have warfarin anticoagulation	Does not wish to have children
Prefers a small surgical incision for cosmetic reasons	
Refuses transfusion on religious grounds	