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REVIEW

Clinical update

Mechanical versus bioprosthetic aortic valve replacement

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Mechanical valves used for aortic valve replacement (AVR) continue to be associated with bleeding risks because of anticoagulation therapy, while bioprosthetic valves are at risk of structural valve deterioration requiring reoperation. This risk/benefit ratio of mechanical and bioprosthetic valves has led American and European guidelines on valvular heart disease to be consistent in recommending the use of mechanical prostheses in patients younger than 60 years of age. Despite these recommendations, the use of bioprosthetic valves has significantly increased over the last decades in all age groups. A systematic review of manuscripts applying propensity-matching or multivariable analysis to compare the usage of mechanical vs. bioprosthetic valves found either similar outcomes between the two types of valves or favourable outcomes with mechanical prostheses, particularly in younger patients. The risk/benefit ratio and choice of valves will be impacted by developments in valve designs, anticoagulation therapy, reducing the required international normalized ratio, and transcatheter and minimally invasive procedures. However, there is currently no evidence to support lowering the age threshold for implanting a bioprosthesis. Physicians in the Heart Team and patients should be cautious in pursuing more bioprosthetic valve use until its benefit is clearly proven in middle-aged patients.

Keywords Heart valve • Aortic valve replacement • Mechanical • Bioprosthetic • Bioprosthesis • Biological • Tissue • Transcatheter aortic valve implantation • Sutureless • Tissue engineered heart valve • Anticoagulation • Review

Introduction

Aortic valve replacement (AVR) has been performed since the 1950s.[1] Since then, the surgical procedure has been optimized to reduce the risk of procedure-related complications. In addition, technical advances in the design of valves have significantly improved long-term prognosis. After the initial use of mechanical ball-caged valves, numerous monoleaflet and bileaflet valves have been introduced and evaluated.[2] Moreover, bioprosthetic valves came on the market in the 1960s as an alternative to mechanical valves.

Besides the overwhelming number of AVRs that are performed each year,[3] surgical techniques in which there is no need to implant a prosthetic valve have also been developed. In younger patients, the Ross operation is an alternative to mechanical valve replacement.[4,5] In selected patients with aortic valve regurgitation, isolated aortic valve repair or in combination with replacement of a dilated aortic root maintains the native aortic valve.[6–8] However, these highly specialized operations with specific indications are often only performed in selected centres. In Germany through 2015 there were 21120 aortic valve procedures, which included only 92 Ross procedures, 124 isolated aortic valve repairs, and 603 David or Yacoub valve-sparing aortic root procedures.[9]

The main question for patients that require AVR remains whether a mechanical or bioprosthetic valve should be implanted.[10] This review discusses (i) the risks and benefits of mechanical and bioprosthetic valves, (ii) data on the use of mechanical and bioprosthetic valves, (iii) results of studies comparing mechanical versus bioprosthetic valves, (iv) new developments in mechanical and bioprosthetic valves, and (v) alternatives to conventional surgical mechanical or bioprosthetic valve use.

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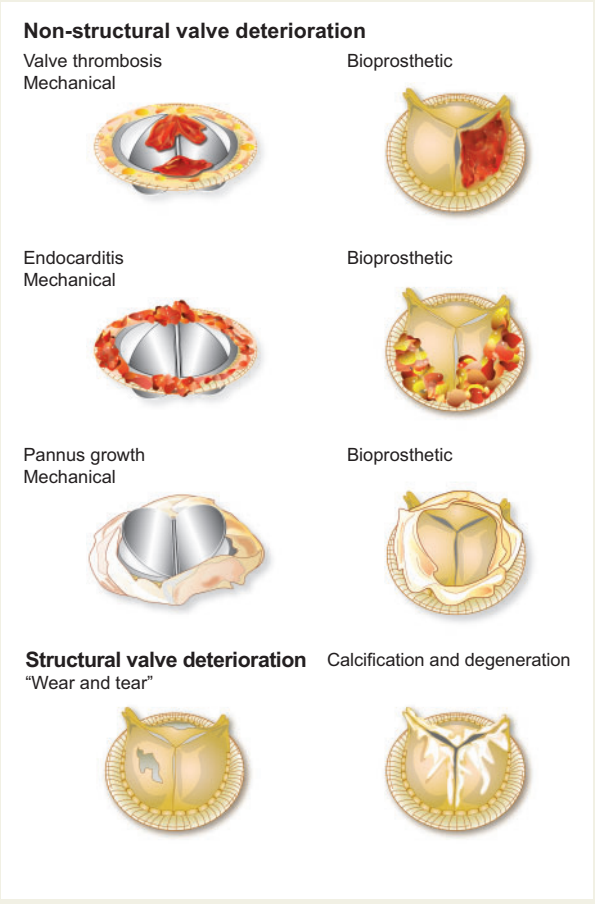

Figure 1 Examples of structural and non-structural valve deterioration.

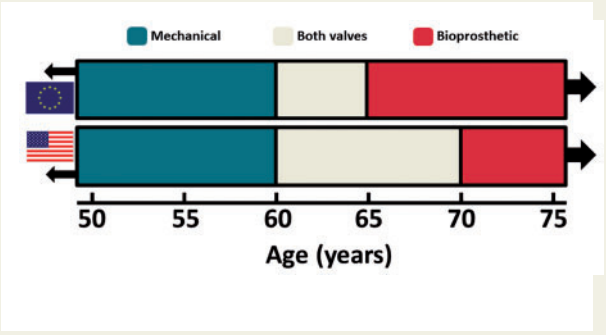

Figure 2 Guideline recommendations for the use of mechanical and bioprosthetic prostheses for aortic valve replacement. Recommendations from the North American AHA/ACC and European ESC/EACTS guidelines.[20,21]

Risks and benefits

Because of thrombogenicity of materials used in mechanical valves, high shear stress around the hinge points, and backflow jets that damage blood and activate clotting-pathways, patients require lifelong anticoagulation therapy to avoid blood clot formation. Bioprosthetic valves are generally made of either bovine pericardium or porcine aortic valves, but may also be produced from equine or porcine pericardium. The advantage of these bioprosthetic valves is that they do not require life-long anticoagulation. On the other hand, the use of tissue does introduce the possibility for 'wear and tear' and degeneration of the valve, which is virtually non-existent in mechanical valves.

The risks of mechanical valves are related to anticoagulation therapy, and this is often the reason to refrain from choosing a mechanical prosthesis as reported by patients and physicians. Patients not taking anticoagulation have a high risk of developing valve thrombosis (*Figure 1*), and even with the use of anticoagulation this risk is apparent when the international normalized ratio (INR) is outside the range of the targeted 2.0–3.0 for valves in the aortic position. On the other hand, higher than normal INR ranges introduce the risk of spontaneous bleeding (e.g. gastrointestinal bleeding) or trauma-related bleedings (e.g. subdural hematoma), which cause considerable mortality and morbidity.[11] Even in patients dedicated to maintain an INR ratio in perfect range, severe fluctuations are observed that increase the risk of bleeding or thromboembolic events and even survival.[12,13] The major advantage of mechanical valves, however, is that structural valve deterioration (SVD) is rare. Cases of leaflet escape have been reported,[14] but since strut fractures occurred in Björk–Shiley valves in the 1980s that have since been taken of the market, they are extremely rare. There are reasons for reoperation beyond SVD, e.g. non-SVD, like pannus growth, endocarditis, and valve thrombosis, but the requirement for reoperations is low.[15]

The main risk with bioprosthetic valves is reoperation for SVD due to the limited durability of bioprosthetic valves (*Figure 1*). The average lifespan of a bioprosthetic valve is estimated at 15 years in elderly patients, but this risk is higher in younger patients in whom SVD is accelerated due to a more pronounced immunologic response to the valve and enhanced calcification of the valve.[16–18] In addition, elderly patients generally have a shorter life expectancy during which they are at risk for requiring replacement of a deteriorated bioprosthetic valve and thus less often require reoperation. The most common reason for reoperation is SVD. Risk of non-SVD is considered to be equally low to that of mechanical valves. Particularly important is the risk of prosthetic valve endocarditis (*Figure 1*) that has a similar incidence in mechanical and bioprosthetic valves and is a devastating diagnosis that often requires the need for reoperation. Rates of major bleeding, stroke and valve thrombosis are low with bioprosthetic valves, although recent reports have questioned previously reported low rates of thrombosis by showing that multislice computed tomography (MSCT) during follow-up identified 7% of patients after AVR to have reduced leaflet motion as the result of thrombosis.[19]

Clinical guidelines

The risk/benefit ratio of mechanical and bioprosthetic valves has led American and European guidelines on valvular heart disease to be consistent in recommending the use of mechanical aortic valve prostheses in patients younger than 60 years of age (*Figure 2*).[20,21] Recommendations for using a bioprosthetic valve are above the age of 65 in European guidelines and above the age of 70 in American guidelines. The span of 5–10 years in between represents an area of

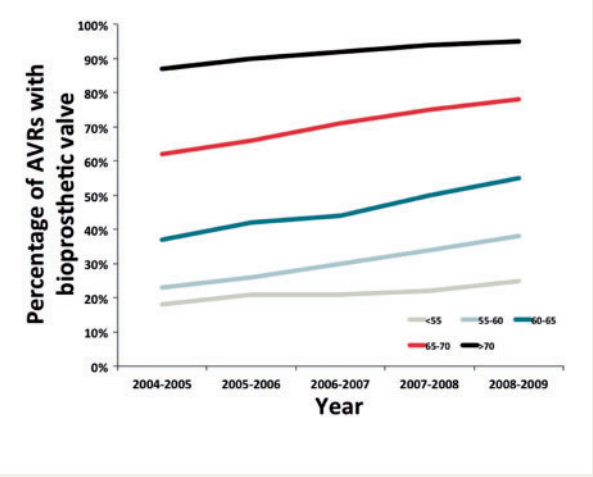

Figure 3 Percentage of aortic valve replacements with biological prostheses in Great Britain and Ireland. Data from Dunning and co-authors.[22]

uncertainty in which both mechanical or bioprosthetic valves can be used, depending on the surgeons' and patients' preference as well as certain patient characteristics. A class of recommendation and level of evidence IIa B and IIa C support these recommendations in, respectively, American and European guidelines.

The ESC/EACTS guidelines list the following reasons for choosing a specific valve: (i) life expectancy; (ii) the estimated risk of a potential reoperation in the future; (iii) bleeding risk, which may be higher because of specific comorbidities, compliance concerns, or geographic, lifestyle and occupational conditions; (iv) comorbidities, such as atrial fibrillation (AF), peripheral vascular disease, a hypercoagulable state, or other conditions that require use of oral anticoagulation; (v) the risk of SVD that may be accelerated in patients with hyperparathyroidism or renal failure; (vi) the wish of a patient to become pregnant; and (vii) patient preferences.[20] American guidelines add the expected haemodynamics for a specific valve type and size as an important factor when considering the type of prosthesis.[21]

Use of mechanical and biological valves

Despite guideline recommendations, the use of bioprosthetic valves has significantly increased over the last decades. Dunning and co-authors reported from the Great Britain and Ireland National Database that the use of bioprosthetic valves increased from 65.4 to 77.8% between 2004 and 2009.[22] Remarkably, patients in age categories of <55 and 55–60 years showed a similar increase to patients in older age categories (*Figure 3*). An analysis of the Netherlands Cardiac Surgery National Database showed an increase in bioprosthetic valve use between 1995 and 2010, particularly in age categories of patients 55–65, 65–70, and 70–100 years but not in patients aged 18–55 years.[23] The use of bioprostheses between 1999–2011 in the USA increased largest in patients aged 55–64 years.[24]

The change in use of bioprosthetic and mechanical valves is somewhat counterintuitive for two reasons. First, it is well recognized that bioprosthetic valve deterioration is accelerated in younger patients.[16] Second, a continuously improving life expectancy exposes patients to a higher risk of (multiple) reoperation(s), thus demanding long durability of valves.

Mechanical versus biological valves

Initial randomized trial data

Two large randomized trials in the 1970s and '80s compared mechanical versus bioprosthetic valves.[25,26] The veterans affairs (VA) trial in the USA randomly assigned 394 male patients undergoing AVR who were followed to a 15-year endpoint, and showed a better survival in patients receiving a mechanical prosthesis compared to a bioprosthesis (34% vs. 21%, respectively; $P = 0.02$).[25] As expected, reoperation rates were higher with a bioprosthesis (10% vs. 29%, respectively; $P = 0.004$) but bleeding complications were higher with a mechanical valve (51% vs. 30%, respectively, $P = 0.0001$). Stroke, endocarditis, and valve thrombosis occurred at similar rates.

The Edinburgh trial randomly assigned 211 patients who were followed for 20 years.[26] Survival was 31.3% for patients with a bioprosthesis vs. 28.4% for patients with a mechanical valve ($P = 0.57$). Secondary endpoints showed similar results as those of the VA trial: reoperation rates were higher with a bioprosthesis (56.2% vs. 7.4%, respectively; $P < 0.0001$); major bleeding events occurred more often with a mechanical valve (32.0% vs. 37.8%, respectively; $P = 0.021$); and rates of thromboembolisms and endocarditis were comparable between the groups.

Recent randomized trial data

After the initial large randomized trials, only a single trial has been performed to compare long-term outcomes.[27] Stassano and co-authors randomly assigned 310 patients aged 55–70 to either a mechanical or bioprosthetic valve. In a patient population that averaged 64 years-of-age, survival was comparable between the groups after a mean follow-up of nearly 9 years. A multivariable model identified that the type of valve was not an independent predictor of late mortality: hazard ratio (HR) associated with a mechanical valve = 0.73, 95% confidence interval (CI) 0.45–1.20 ($P = 0.2$). Bioprostheses had a higher linearized rate of valve failure ($P = 0.0001$) and higher rates of reoperation ($P = 0.0003$), while there was a trend towards higher rates of bleeding with mechanical valves ($P = 0.08$).

Data from observational studies

There are no randomized trials with contemporary valves. However, numerous observational studies have been performed comparing mechanical and bioprosthetic valves. A PubMed search (*Appendix*) was performed in September 2016 to systematically identify studies that included multivariable analysis to adjust for baseline differences or applied propensity-matching to allow for a more substantiated comparison between mechanical and bioprosthetic valves. A check of reference lists was also completed to identify articles missed with

Table 1 Long-term survival from observational studies applying propensity matching or performing multivariable analysis comparing mechanical with bioprosthetic aortic valve replacement

Author, year	Design	Patient inclusion	Number of patients	Patient age inclusion	Mean age (Mech. vs. Bio.)	Mean follow-up (Mech. vs. Bio.)	Outcome	Survival rates (Mech. vs. Bio.) HR associated with mechanical valve
Studies with propensity matching								
Sakamoto *et al.*, 2016[28]	Retrospective	1995–2014	*n* = 56	60–70 years	64 vs. 65 (*P* = 0.11)	7.0 vs. 7.8 years (*P* = 0.60)	15-year survival	88% vs. 85% (*P* = 0.73)
Okamoto *et al.*, 2016[29]	Retrospective	2001–2004	*n* = 104	≥75 years	79 vs. 79 (*P* = 0.82)	4.8 vs. 4.0 years (*P* = 0.22)	8-year survival	73% vs. 73% (*P* = 0.47)
Wang *et al.*, 2015[30]	Retrospective	2002–2009	*n* = 224	<60 years	49 vs. 50 (*P*=0.65)	Overall 8.6 years (no comparison)	10-year survival	88% vs. 89% (*P* = 0.86)
Glaser *et al.*, 2015[31]	Retrospective	1997–2013	*n* = 2198	50–69 years	62 vs. 62 (*P* = 0.44)	6.7 vs. 6.6 years (no *P*-value)	15-year survival	59% vs. 50% (*P* = 0.006) HR = 0.75, 95% CI 0.60–0.92
Roumieh *et al.*, 2015[32]	Retrospective	1996–2008	*n* = 120	55–65 years	62 vs. 61 (*P* = 0.4)	10.7 vs. 8.8 years (no *P*-value)	15-year survival	53% vs. 54% (*P* = 0.95)
Chiang *et al.*, 2014[33]	Retrospective	1997–2004	*n* = 2002	50–69 years	62 vs. 62 (*P*=0.94)	10.9 vs. 10.6 years[b] (no *P*-value)	15-year survival	62% vs. 61% (*P* = 0.74) HR = 0.97, 95% CI 0.83–1.14
McClure *et al.*, 2014[34]	Retrospective	1992–2011	*n* = 722	Adults <65 years	53 vs. 54 (*P*=0.30)	6 vs. 7 years[b](no *P*-value)	15-year survival	75% vs. 65% (*P* = 0.75)
Badhwar *et al.*, 2012[35]	Retrospective	2003–2007	*n* = 98	≤65 years	Not provided	Not provided	8-year survival	100% vs. ±83% (*P* = 0.04)[a]
Weber *et al.*, 2012[36]	Retrospective	2000–2009	*n* = 206	<60 years	50 vs. 55[b] (*P* = 0.03)	Overall 2.8 years (no comparison)	Survival during follow-up	98% vs. 90% (*P* = 0.04) HR = 0.24, 95% CI 0.05–0.92
Ashikhmina *et al.*, 2011[37]	Retrospective	1993–2007	*n* = 458	≥70 years	Not provided	Not provided	15-year survival	19% vs. 7% (*P* = 0.81)
Brown *et al.*, 2008[38]	Retrospective	1991–2000	*n* = 440	50–70 years	66 vs. 67 (*P*<0.01)	8.6 vs. 6.3 years (no *P*-value)	10-year survival	68% vs. 50% (*P* < 0.01) HR = 0.48, 95% 0.35–0.67
Studies with multivariable analysis								
Polomsky *et al.*, 2014[39]	Retrospective	2002–2011	*n* = 909	Adults	50 vs. 69[c] (*P*<0.001)	Not provided	Propensity-score adjusted 10-year survival	HR = 0.76, 95% CI 0.49–1.20
Brennan *et al.*, 2013[40]	Retrospective	1991–1999	*n* = 39199	>65 years	73 vs. 73 (*P* = 0.94)	13.0 vs. 12.4[c] (*P* < 0.0001)	Propensity-score adjusted 12-year survival	HR = 0.96, 95% CI 0.93–0.99
Gaca *et al.*, 2013[41]	Retrospective	1986–2009	*n* = 2148	>16 years	61 vs. 73[b] (no *P*-value)	Overall 7 years[c] (no comparison)	Multivariable adjusted 10-year survival	Valve type was not a significant predictor (*P* = 0.44)
Ruel *et al.*, 2007[42]	Retrospective	1969–2004	*n* = 314	Adults <60 years	48 vs. 48	Overall 13.4 years[c] (no comparison)	Multivariable analysis of survival beyond 20 years	HR = 1.05, 95% CI 0.77–1.43
Carrier *et al.*, 2001[43]	Prospective	1982–1999	*n* = 526	55–65 years	61 vs. 61[c] (*P*=0.1)	4 vs. 7 years[c] (*P* = 0.01)	Multivariable analysis of 10-year survival	Type of prosthesis was not associated with long-term mortality.
Khan *et al.*, 2001[44]	Retrospective	1976–. . ..	*n* = 1389	>18 years	65 vs. 72[c] (*P*=0.001)	5.8 vs. 4.7 years[c] (no *P*-value)	Multivariable adjusted 10-year survival	Valve type was not a significant predictor.
Petersheim *et al.*, 1999[45]	Retrospective	1976–1996	*n* = 841	>18 years	62 vs. 64 (*P* = NS)	Not provided	Multivariable adjusted 10-year survival	Valve type was not a significant predictor (*P* = 0.4).
Jamieson *et al.*, 1995[46]	Retrospective	1982–1993	*n* = 1929	None	59 vs. 67[d] (no *P*-value)	2.9 vs. 5 years[c] (no *P*-value)	Multivariable adjusted 8-year survival	HR = 1.32 (*P* = NS)

[a]Read from Kaplan–Meier curve.
[b]Median instead of mean.
[c]Unadjusted analysis.
[d]Includes patients that underwent mitral valve replacement.
CI, confidence interval; Bio, bioprosthetic; HR, hazard ratio; Mech, mechanical; NS, not significant.

the PubMed search. A total of 11 studies reported results from propensity-matched cohorts, and an additional eight studies reported results from multivariable analysis (*Table 1*).

Two recent large, propensity-matched studies have reported conflicting results. Chiang and co-authors in a state-wide analysis out of New York found that among 1001 matched pairs, aged 50–69 years, survival at 15-year follow-up was 60.6% in the bioprosthetic vs. 62.1% in the mechanical valve group ($P = 0.74$).[33] Glaser and co-authors performed a similar analysis with data from the Swedish national registry. They were able to propensity-match 2198 patients aged 50–69 years and reported that 15-year survival was significantly improved in patients with a mechanical prosthesis (59% vs. 50% with a bioprosthesis; $P = 0.006$).[31] An important subgroup analysis according to age showed that the benefit of a mechanical over a bioprosthetic valve was only evident in patients aged 50–59 ($P = 0.03$) but not in those aged 60–69 ($P = 0.54$). Chiang and co-authors in an additional analysis were unable to confirm these findings and reported similar adjusted survival in age groups 50–59 and 60–69 between prosthesis types.[11,47]

Data from the society of thoracic surgeon's database in the USA recently confirmed the importance of age in the prediction of long-term survival with different prostheses. Brennan and co-authors analysed nearly 40 000 patients aged ≥65 years out of 605 hospitals.[48] Survival was significantly improved with mechanical vs. bioprosthetic valves in a propensity-score adjusted analysis, although the difference was only marginal (HR associated with bioprosthesis = 1.04, 95% CI 1.01–1.07). There was, however, a significant interaction between age and prosthesis type that showed a stepwise increase in the risk of mortality associated with a bioprosthesis in younger age groups. The hazard ratio associated with a bioprosthesis was 1.23 (95% CI 1.16–1.31) in patients aged 65–69, 1.04 (95% CI 0.99–1.09) in patients aged 70–74, and 0.95 (95% CI 0.90–0.99) in patients aged 75–79.

It should be noted that none of the analyses reported a significantly improved survival rate with bioprosthetic over mechanical prostheses. However, there were several studies, specifically those that included younger patients, which found a significant benefit of mechanical over bioprosthetic valves. Based on the currently available data, there does not seem to be sufficient evidence to support lowering the age cut-off for implanting bioprosthetic valves below the age of 60 years to improve long-term survival. In terms of quality of life, numerous studies have reported comparable scores with mechanical and bioprosthetic valves, although results have also been conflicting.[48–53]

Selected patient cohorts

The presence of specific comorbidities or risk factors may alter the decision-making process between mechanical and bioprosthetic valves. These patient characteristics should be considered when determining which prosthesis should be favoured (*Table 2*). Nevertheless, no single factor should be decisive and the risk/benefit of both valves should be established for each particular patient to select the most appropriate prosthesis.

Atrial fibrillation or other conditions requiring anticoagulation therapy

There are no studies that evaluated outcomes explicitly of patients already on oral anticoagulation because of AF or vascular conditions, but in theory the benefit of bioprostheses in such patients may be diminished because the risk for complications related to anticoagulation use already exists. Surgeons should therefore consider favouring a mechanical valve even at an older age. However, an argument for

Table 2 Considerations for implanting a mechanical or bioprosthetic aortic valve

Patient characteristic	Consider favouring mechanical valve	Consider favouring bioprosthetic valve
Age <60	X	
Age 60–70	**Unclear**	**Unclear**
Age >70 years		X
Age <60 but life expectancy <10 years		X
Age <60 but pregnancy wish		X
Age <60 but hazardous occupation (e.g. sports, mining, stunt(wo)man, etc)		X
Preoperative lifelong anticoagulation indication (e.g. AF, PVD, hypercoagulable state)	X	
Reoperations for valve thrombosis because of compliance failure or inadequate INR regulation		X
High bleeding risk		X
Contra-indication for anticoagulation treatment		X
End-stage renal failure on dialysis		X
Metabolic syndrome	X	
Hyperparathyroidism	X	
Small aortic annulus	X	

These factors should be weighted and could potentially lean towards performing mechanical or bioprosthetic valve implantation. Presence of any of these factors does not exclude the opportunity to perform valve replacement with another type of valve.
AF, atrial fibrillation; INR, International normalized ratio; PVD, peripheral vascular disease.

bioprostheses is that patients on non-vitamin K antagonist anticoagulation (NOAC) agents can continue such treatment with a bioprosthesis but not a mechanical prosthesis. Non-vitamin K antagonist anticoagulation's are now recommended over vitamin K antagonists for stroke prevention in AF but are not recommended as anticoagulation for mechanical prostheses.[54]

End-stage renal disease including dialysis

Patients with end-stage renal disease have long been considered not to be candidates for bioprostheses because of assumed progression of calcification causing SVD. Indeed, a meta-analysis of early studies reported a trend towards improved survival with mechanical over bioprosthetic valves (HR = 1.34, 95% CI 0.96–1.86; $P = 0.086$), although this analysis consisted mainly of small studies and did not selectively include patients undergoing AVR.[55] The largest study to date from Herzog and co-authors included 5858 dialysis patients undergoing heart valve replacement of whom 3415 underwent isolated AVR; survival was only 39% at 2-year follow-up without a difference between mechanical and bioprosthetic valves.[56] Even in more recent reports, survival of patients on dialysis was generally short and therefore patients are not expected to outlive their bioprosthesis.[57] As a result, a bioprosthesis may be favoured to avoid the use of anticoagulation. No data exists on differences between valve types in patients with mild or moderate renal failure who also have increased calcium metabolism but a longer life expectancy.

Atherosclerotic risk

Although contradictory results have been reported, evidence supporting accelerated bioprosthetic SVD in patients with a less healthy lifestyle prone to atherosclerotic risk is available from several studies: (i) smoking has been identified as an independent predictor of reoperation for SVD[58,59]; (ii) different measures of cholesterol levels have been linked with valve calcification[60] and failure[61]; (iii) an Italian multicentre study reported that diabetes was the strongest predictor of bioprosthetic valve degeneration in a propensity-matched study including 2226 patients[62]; and (iv) metabolic syndrome accelerated SVD during annual echocardiographic follow-up of 217 patients who underwent AVR in a study by Briand and co-authors.[63] Because of the increased risk of SVD, a mechanical valve may be favoured in patients at high risk of atherosclerosis.

Coronary artery disease

Approximately 40% of patients who undergo AVR require concomitant CABG, which has a significant impact on long-term prognosis.[64] Only little evidence is available from studies comparing valve types in patients undergoing combined procedures. In a microsimulation study, differences in life-expectancy and event-free life-expectancy between mechanical and bioprosthetic valves were comparable whether male patients underwent isolated AVR or AVR + CABG, with a cut-off for implanting a bioprosthesis around 60 years of age.[65] The decision to opt for a mechanical or bioprosthetic valve in patients requiring a combined AVR + CABG procedure should not be different than for patients undergoing isolated AVR.

Small aortic annulus

Prosthesis-patient mismatch (PPM) occurs when the effective orifice area (EAO) of a prosthetic valve is too small for the body surface area of the patient.[66] Although its impact on long-term outcomes has long been debated, a meta-analysis found that survival was significantly improved in patients with no PPM as compared with moderate PPM (HR = 1.19, 95% CI 1.07–1.33) or severe PPM (HR = 1.84, 95% CI 1.38–2.45).[67] For patients with a small aortic annulus the EOA is crucial to optimize hemodynamic performance of the valve and thus avoid PPM. Small-size mechanical valves generally have larger EOAs than small-size bioprosthetic valves.[68] In some instances, patients with a small annulus may therefore benefit from a mechanical valve. However, a root enlargement to allow implantation of a larger bioprosthesis may also be an option to avoid PPM.[69,70]

Root replacement procedures

A number of studies have compared outcomes after bioprosthetic and mechanical composite grafts among patients requiring AVR with root replacement because of bicuspid valves or root aneurysms.[71] Conflicting results have been reported from studies applying various methods of adjustment for baseline differences, although generalizibility of these results is limited because only small number of patients were included in single-centre studies.[71–74] Therefore, if valve-sparing operations cannot be performed,[74] the indication for a bioprosthetic or mechanical composite graft is similar to that of isolated AVR procedures with respect to age cut-offs.

Aortic and mitral valve replacement/repair

In patients with a mechanical mitral valve already in place, implanting a mechanical aortic valve that has a lower INR target range than the mitral valve (2.0–3.0 vs. 2.5–3.5, respectively) would not add significant long-term risks. However, for the 5–10% of patients that require combined aortic and mitral valve operations, the most appropriate strategy remains a matter of debate. Studies have been controversial on whether mitral valve repair should be preferred over valve replacement in combination with AVR.[75,76] Leavitt and co-authors reported that survival of patients younger than 70 years was comparable between those with two mechanical valves and those with a bioprosthetic aortic valve and mitral repair but significantly lower among those with two bioprosthetic valves.[77] These studies and the differences in oral anticoagulation regimens after valve procedures impact on the decision to use a mechanical or bioprosthetic valve in the aortic position: (i) no long-term oral anticoagulation is mandatory after mitral valve repair and thus the choice of valve in the aortic position should depend on recommendations for isolated AVR; (ii) if the mitral valve requires replacement, clinical guidelines recommend the use of a mechanical valve in the mitral position up to the age of 65 and thus a mechanical aortic valve is advisable; (iii) a mechanical aortic valve is recommended if primary a mechanical mitral valve is chosen because of the INR target ranges.

Endocarditis

The presence of active infection poses the risk of early recurrent endocarditis because a foreign body is implanted in an infected area. It has been suggested that a bioprosthesis may be favoured because it is less susceptible to reinfection and better to treat when reinfection does occur.[78] Indeed, the use of bioprostheses has increased also in active endocarditis.[79] However, mechanical valves have shown

excellent performance and low rates of recurrent endocarditis similar to that of bioprosheses.[80,81] In fact, adjusted 5-year mortality has been found to be significantly lower with mechanical valves among patients younger than 65 years old with active endocarditis (HR = 4.14, 95% CI 1.27–13.45), while survival was similar in patients older than 65 years (HR = 1.45, 95% CI 0.35–5.97).[82] Most recent data from the International Collaboration on Endocarditis Prospective Cohort Study (ICE-PCS) reported that implantation of a bioprosthesis independently predicted one-year mortality.[83] Therefore, there is no evidence to specifically support use of bioprostheses in all patients, irrespective of age, with active endocarditis.

Developments in favour of mechanical valves

Non-vitamin K antagonist anticoagulation with mechanical valves

Numerous NOAC agents have been developed to replace vitamin K antagonists. In studies of patients with AF, rivaroxaban, apixaban, edoxaban, and dabigatran showed to be non-inferior for stroke prevention with significantly lower rates of bleeding.[54] Translation of these results to NOAC use in patients with a mechanical prosthesis would show a drastic improvement in outcomes. In the RE-ALIGN trial, however, the use of dabigatran as compared with warfarin was associated with an increase in the composite of death, stroke, systemic embolism, and myocardial infarction (8% vs. 2%, respectively; $P = 0.11$), as well as bleeding complications (27% vs. 12%, respectively; $P = 0.01$), which is why the trial was stopped prematurely.[84] The small, pilot, phase 2 CATHAR trial investigated the safety and efficacy of rivaroxaban use in mechanical prostheses but had to suspend enrolment (clinicaltrials.gov number: NCT02128841). No large randomized trials on the use of NOACs in mechanical valves are currently ongoing.

Lower INR ranges and self-control and self-management with mechanical valves

Before positive results from NOAC trials are available, patients are still sentenced to vitamin K antagonist anticoagulation therapy, which has several disadvantages that result in INR values outside the targeted range: (i) food interactions, (ii) drug interactions, and (iii) regular laboratory monitoring. However, the risk of bleeding events can be significantly reduced with vitamin K antagonists if the targeted INR could be lowered. Koertke and co-authors performed a randomized trial in which 2673 patients undergoing AVR were randomized to anticoagulation with a target INR of 1.8–2.8 vs. 2.5–4.5.[85] After 2-year follow-up, the rate of thromboembolic events in the low-dose vs. conventional dose groups was not significantly different at 0.24 vs. 0.46% per patient-year, respectively, while the rate of bleeding was 1.42 vs. 1.78% per patient-year, respectively. In a more recent randomized trial among 33 centres in North America investigating the On-X mechanical valve (On-X Life Technologies, Austin, Texas, USA), 375 high-risk patients were randomized at 3 months post-AVR to receive aspirin with anticoagulation for a targeted INR of 1.5–2.0 or 2.0–3.0.[86] Over the course of 5-year follow-up, rates of bleeding were significantly lower for patients in the low INR group ($P = 0.002$), without significant increases in thromboembolic events ($P = 0.13$). Although it is evident that lower INR ranges are beneficial in terms of bleeding events, it remains unclear to what extend the INR target can be lowered to be considered safe for the prevention of valve thrombosis and stroke.

Even if vitamin K antagonists remain necessary, the inconvenience associated with regular outpatient INR checks can safely be avoided. In a meta-analysis of 11 randomized trials comparing self-monitoring and self-management of anticoagulation with outpatient management in primary care or anticoagulation clinics found that among 6417 participants with 12800 patient-years of follow-up, there was a significant decline in the self-monitoring group in the rate of thromboembolic events (HR = 0.51, 95% CI 0.31–0.85; $P = 0.01$) with similar rates of bleeding (HR = 0.88, 95% CI 0.74–1.06; $P = 0.18$) and death (HR = 0.82, 95% CI 0.62–1.09; $P = 0.18$).[87] Subgroup analyses found that the reduction of thromboembolic events with self-monitoring was seen particularly in patients with a mechanical valve as opposed to those with AF (P for interaction = 0.032), and in patients that not only self-tested but also self-managed anticoagulation dosing (P for interaction = 0.002).

A recent randomized trial attempted to combine the benefits of low-dose INR and self-management, by randomizing 1571 patients, of which 1304 had AVR, to low-dose INR self-control with a target range of 1.8–2.8 and weekly INR checks, very low-dose INR with a target range of 1.5–2.1 and weekly INR checks, and very low-dose INR with a target range of 1.5–2.1 and twice weekly INR checks over the course of 2 years.[13] Even though patients in the very low-dose INR groups were significantly more often outside the targeted INR range, a risk-adjusted analysis with the low-dose INR group as reference showed that major bleeding rates were significantly lower in patients in the very low-dose twice-weekly INR check (HR = 0.27, 95% CI 0.09–0.84; $P = 0.02$) as well as for those with a very low-dose weekly INR check (HR = 0.38, 95% CI 0.15–0.99; $P = 0.046$). There were comparable rates of major thrombotic events in the very low-dose INR twice-weekly (HR = 1.22, 95% CI 0.32–4.61; $P = 0.77$) and weekly checks (HR = 0.24, 95% CI 0.03–2.18; $P = 0.21$). Remarkably, even though death rates were low in all groups (range 1.1–2.9%), as compared with the low-dose INR group there was a significantly higher risk-adjusted mortality rate in the very low-dose INR group with twice-weekly checks (HR = 3.15, 95% CI 1.20–8.29; $P = 0.02$) but not in the very low-dose INR group with weekly checks (HR = 1.36, 95% CI 0.46–4.12; $P = 0.58$). These data still need to be replicated since the trial was stopped prematurely.

Mechanical valve design

At the moment, 3-D printed mechanical valves are being used to test new valve designs in prototypes to optimize design and materials associated with less thrombogenicity and better flow patterns. Studies with the use of a 3-D printed mechanical valve found a much lower thrombogenicity potential index when compared with other mechanical valves and which was similar to that of bioprosthetic valves.[88] In theory, such valves would be able to function without the need for anticoagulation. To our knowledge, currently no 3-D valve is being developed for use in the near future.

The On-X valve was designed to be safe with only antiplatelet therapy in some low-risk patients.[86] Its design with a smoother surface of pure carbon without silicon, 90-degree opening leaflets, a flared valve inlet, and stasis-free pivots reduce turbulence and

thrombogenicity. Data on the use of aspirin and/or clopidogrel instead of anticoagulation treatment with the On-X valve are underway from the PROACT trial (clinicaltrials.gov number: NCT00291525).

The Lapeyre-Triflo FURTIVA valve (Triflo Medical Switzerland, Neuchâtel, Switzerland) is a trileaflet instead of bileaflet mechanical valve which combines the haemodynamic excellence of trileaflet native or bioprosthetic aortic valves but with mechanical valve durability. Oral anticoagulation may potentially be omitted because the design reduces high-velocity backflow jets that damage blood and activate thrombus formation, eliminates low flow areas, and lowers shear stress and turbulence through pivots.[89]

Anticoagulation with bioprosthetic valves

The incidence of leaflet thrombosis with surgical bioprostheses regained interest after findings of reduced leaflet motion on MSCT following transcatheter aortic valve implantation (TAVI).[19,90] These data have triggered further analyses of bioprosthetic valve thrombosis.[91] Although it is not easy to derive the true incidence from these small studies, the risk factors they had in common were no or inadequate anticoagulation therapy, while initiation of anticoagulation resolved valve thrombosis in the majority of cases. Indeed, evidence supporting a recommendation for routine anticoagulation therapy after AVR with a bioprosthesis has been conflicting.[92,93] Early reports showed no difference between warfarin and aspirin treatment.[94] However, two recent studies found an indication for warfarin treatment. In elderly patients, Brennan and co-authors showed in a propensity-score adjusted analysis that warfarin in addition to aspirin treatment within the first 3 months after receiving a bioprosthesis significantly reduced rates of death (RR = 0.80, 95% CI 0.66–0.96) and embolic events (RR = 0.52, 95% CI 0.35–0.76) when compared to aspirin treatment alone, although at the cost of higher rates of bleeding (RR = 2.80, 95% CI 2.18–3.60).[95] A Danish nation-wide study investigated whether anticoagulation beyond the first 3 months was associated with improved outcomes by identifying 4075 patients that underwent AVR between 1997 and 2009 and were discharged with warfarin treatment. Continuing warfarin during follow-up produced favourable outcomes of stroke and cardiovascular death. Remarkably, rates of bleeding events were also reduced significantly; although from the data it is not clear whether patients discontinued warfarin before bleeding occurred or as a result of bleeding, and therefore these results should be interpreted with caution.[96]

At the moment, there is not enough evidence to support recommendations for routine anticoagulation therapy after bioprosthetic valve implantation, but future studies on this topic may significantly impact the debate on mechanical vs. bioprosthetic valves. It will be crucial to determine whether (i) anticoagulation indeed improves outcomes with bioprosthetic valves, (ii) the duration that anticoagulation therapy is necessary, and (iii) how outcomes of bioprosthetic valves with concomitant anticoagulation therapy compare with patients with a mechanical valve.

Developments in favour of biological valves

Bovine or pericardial bioprosthetic surgical valves

At short-term, several small randomized trials and prospective studies have found bovine valves to have significantly better hemodynamic results with lower valve gradients and larger aortic valve areas than porcine valves.[97–100] Whether these results translate into improved survival remains conflicted. The largest study to date from Hickey and co-authors included nearly 40 000 patients and found that the 10-year survival rate was comparable between the bovine and porcine valves (49.0% vs. 50.3%, respectively; $P = 0.77$), which was confirmed by several recent smaller studies.[101–104] Moreover, the authors of an overview on porcine vs. bovine studies clearly summarized that 'variability between valve manufacturers, study designs, study period and patient population in studies impose limitations to the comparisons of valve types.'[100]

Because of the assumed improved outcomes with bovine pericardial valves, newer bioprostheses generally contain bovine tissue leaflets. Newer bioprostheses may lead to improved outcomes because of state-of-the-art designs with better haemodynamic performance.[3] For example, the Trifecta valve (St. Jude Medical, Saint Paul, Minnesota, USA) established superiority over Objective Performance Criteria (OPC) and showed excellent haemodynamic performance with lower gradients and higher aortic valve areas.[105–108] Registry data on the Perigon (Medtronic Inc, Minneapolis, Minnesota, USA, clinicaltrials.gov number: NCT02088554) and Inspiris Resilia (Edwards Lifesciences, Irvine, California, USA, clinicaltrials.gov number: NCT01757665) valves are currently underway. Before these valves lead to even more implantation of bioprosthetic valves in younger patients, they should be compared to mechanical prostheses in such specific age groups.

Transcatheter valves

Over the last decade since the introduction of transcatheter heart valves (THVs), numerous randomized trials have shown TAVI to be non-inferior if not superior to AVR in selected patients that are at intermediate- or high-risk for surgical mortality or morbidity.[109–113] Numerous THVs have been produced, all of which are bioprosthetic valves; there is a need to crimp the valve to fit a sheath for a predominant transfemoral approach of implantation. Some concerns have been raised about crimping, since this can damage the leaflet tissue.

Although TAVI is currently mostly reserved for elderly patients, the low complication rate of the procedure opens the door to implanting THVs in younger patients. The reduced invasiveness and faster recovery time as compared with AVR could tip the scale in favour of TAVI with a bioprosthetic valve as opposed to AVR with a mechanical valve, if long-term results are at least non-inferior.[114] Especially now that valve-in-valve procedures have emerged as a valuable option in patients with degenerated (surgical) bioprostheses.[115,116] Particularly in patients aged 60–70 in which both mechanical and bioprosthetic valves are valuable options according to clinical guidelines, implanting a bioprosthesis with a subsequent valve-in-valve in prospect may influence the decision to implant a mechanical or bioprosthetic valve in this age group. However, experience

with valve-in-valve procedures remains relatively limited, is selectively used in high-risk patients, and long-term follow-up is scarce.[117] Moreover, PPM is not infrequent after valve-in-valve procedures and has a detrimental impact on long-term outcomes.[67,117,118]

Sutureless valves

Transcatheter heart valve technology has been paralleled by similar developments in surgical AVR with the advent of sutureless, also named rapid-deployment, valves. Comparable to THVs, sutureless technology includes only bioprosthetic valves as these are compressed to a certain degree, although attempts have been made to develop sutureless mechanical valves that were tested in pigs.[119] The patient population that can benefit from sutureless valves is yet unclear, particularly considering the excellent results with TAVI in the intermediate- to high-risk patient population and its potential expansion to an all-comers population that includes those at low-risk.[120] However, with a growing interest in minimally invasive procedures, sutureless technology could be adopted more now that such procedures are considerably less technically challenging with a sutureless technique. Upcoming trials randomizing patients between sutureless or conventional AVR, like the PERSIST-AVR trial (clinicaltrials.gov number: NCT02673697), are underway.

Tissue-engineered valves

The need for mechanical and bioprosthetic valves could potentially be omitted in the future with the development of tissue-engineered heart valves. Constructed valves disrupt, although only marginally, the native size and shape of the aortic annulus, alternate haemodynamic flow, and are susceptible to cloth formation and endocarditis due to the presence of a foreign body. In contrast, tissue-engineered valves mimic natural blood flow through the left ventricular outflow tract and coronary arteries due to their natural structure, may have the possibility for self-repair and remodelling as opposed to degeneration of bioprosthetic valves, and provide no additional risk related to a triggered reaction as the result of a foreign body. Moreover, tissue-engineered valves have the potential to grow, allowing them to be implanted in paediatric patients without the obvious need for a reoperation when they would have outgrown their prosthesis.

Early concepts of tissue-engineering technology have focused on developing valves with the use of a matrix that is *in vitro* seeded with harvested cells. Since then, many methods have been tested to overcome technical, logistical and financial hurdles and potentially introduce an 'off-the-shelf' valve for routine use.[121] At the moment, these different concepts are being tested in sheep.[122,123] Their clinical application still requires additional feasibility studies and a first-in-man application, but it remains a promising prospect.[124]

Heart team

Multidisciplinary Heart Team decision-making is becoming more important for the treatment of aortic valve disease because of an increasing overlap of indications for AVR and TAVI. Clinical guidelines therefore recommended regular, formal Heart Team meetings. If a patient is a better candidate for AVR, these meetings furthermore provide the opportunity to discuss in a Heart Team whether a mechanical or bioprosthetic valve should be preferred based on the patient profile. Given the complex decision-making that relies on numerous comorbidities, expected hemodynamic performance of a prosthetic valve, and long-term secondary prevention that is directed by the cardiologist, these decisions may be more appropriate than when made by surgeons alone.

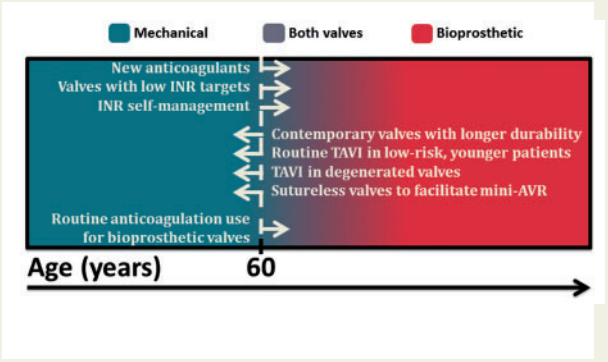

Figure 4 Advancements in therapy related to mechanical and bioprosthetic valves that may change the cut-off for implanting a bioprosthesis. Adapted from Head and co-authors.[10] AVR, aortic valve replacement; INR, international normalized ratio; TAVI, transcatheter aortic valve implantation.

Conclusions

The main reason to opt for a bioprosthesis is to avoid the indication for lifelong anticoagulation, which has resulted in a clear increase in the use of bioprosthetic as opposed to mechanical valves, particularly in middle-aged patients of 50–70 years old. However, there is currently no evidence to support lowering the age threshold below 60 years for implanting a bioprosthesis. New developments related to mechanical and bioprosthetic valves can potentially significantly alter the risk/benefit ratio associated with either prosthesis and thereby change the decision-making process (*Figure 4*). Future randomized studies should investigate these developments. Until then, physicians and patients should be cautious in pursuing more bioprosthetic valve use until its benefit is clearly proven in middle-aged patients.

Conflict of interest: SJH and APK report including patients for the PERIGON trial.

Appendix

PubMed search

'aortic valve replacement AND mechanical [tiab] AND (biologic [tiab] OR biological [tiab] OR bioprosthetic [tiab] OR bioprosthesis [tiab] OR tissue [tiab]) AND (propensity [tiab] OR multivariate [tiab] OR multivariable [tiab] OR random* [tiab] OR adjust* [tiab] OR independent [tiab])'.

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