Is Tissue Valve the Preferred Option for Patients Aged 60 Years and Older?

Tissue Valve Is the Preferred Option for Patients Aged 60 and Older

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A 60-year-old man presents to your clinic. He has symptomatic severe Aortic stenosis with a bicuspid valve diagnosed by transthoracic echocardiogram. No coronary disease was found on cardiac catheterization. What would be the valve choice in this patient? To answer this question, we need to explore the myths surrounding heart valve prostheses, which include the following:

1. Patients with mechanical valves survive longer.
2. Patients with bioprostheses will never require anticoagulation.
3. Patients on warfarin therapy should get mechanical valve.
4. Patients with mechanical valve should receive mechanical valve at the time of reoperation.
5. Reoperation and structural valve deterioration (SVD) rates are the same.
6. Mechanical valves have better hemodynamics.

Response by Suri and Schaff on p 1371

Recently, there has been a monumental shift toward the use of bioprosthetic valves. From the Society of Thoracic Surgeons (STS) database, applications of mechanical valves have decreased from 49.9% in 1997 to 20.5% in 2006, whereas bioprosthetic valve usage increased from 43.6% in 1997 to 78.4% in the aortic position.1 A similar trend was documented in the mitral position; from the STS database, usage of mechanical valve has decreased from 68% in 2000 to 37% in 2007.2 Classic teaching recommends mechanical valve for younger patients because of its durability at the expense of lifetime anticoagulation. In contrast, bioprostheses will free patients from anticoagulation but exposes them to the risk of SVD, which increases with time. As the trend grows toward increased use of bioprostheses, age limit for bioprosthetic valve use versus mechanical valve is intensely debated.

According to the most updated American College of Cardiology/American Heart Association (ACC/AHA) guideline from 2008, patient age is no longer on the Class I recommendation for aortic valve replacements (AVR). There is class IIa recommendation to use mechanical valve in patients aged <65 years who do not have a contraindication to anticoagulation and bioprosthetic valve in patients either aged >65 years without risk of thromboembolism or aged <65 years who elect to receive this valve for lifestyle considerations after detailed discussions of the risks of anticoagulation versus the likelihood that a second AVR may be necessary in the future.3 Similarly for mitral valve replacement (MVR), Class I indication does not include age criteria (see Appendix I in the online-only Data Supplement). The European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) guideline recommends mechanical valve for age <60 in AVR and <65 in MVR.4 These age cutoffs are set at the point where the benefit of bioprostheses (no anticoagulation) outweighs the risk (reoperation because of SVD), because age at implantation is directly associated with SVD. The removal of cutoff age in the ACC/AHA guideline is supported by some surgeons for the following reasons. (1) Current bioprostheses appear to have lower rates...
of structural valve deterioration than those used during the randomized controlled trials (RCT) that involved first-generation bioprostheses. (2) The risks of reoperation have continued to decrease over time. (3) Young patients undergoing valve surgery are often reluctant to accept warfarin therapy and the activity constraints associated with anticoagulants. In addition, emergence of transcatheter valve-in-valve (VIV) replacement, which avoids reoperative sternotomy and cardiopulmonary bypass, is highly anticipated. Although evidence to support this new technique is still being documented, it may provide a safer alternative for replacing previously placed bioprosthetic valves.

The purpose of this article is to demonstrate evidence supporting the use of bioprostheses in patients aged >60 years.

**Survival**

There have been 3 randomized, controlled trials (RCTs) on this topic (Table). Two RCTs were performed in late 1970s with late outcomes available. The Edinburgh study was the first performed RCT. Between 1975 and 1979, 433 patients were randomized to receive either Bjork-Shiley or porcine bioprostheses. Mean age was 54.4 years in mechanical group and 53.4 year in biological group. The Veterans Affairs (VA) Randomized Trial was performed between 1977 and 1982; 575 men undergoing single AVR (n=394) or MVR (n=181) were randomized to receive either the Bjork-Shiley spherical disc mechanical prosthesis or a Hancock porcine bioprosthetic valve.

The Edinburgh study showed improved survival in mechanical valve at 12 years but showed no difference in mortality at 20 years between mechanical valve and biological valve (25.0% versus 22.6%, P=0.39). In the VA study, there were similar outcomes at 5 and 11 years, but after 15 years follow-up all-cause mortality after AVR was lower with the mechanical valve (66% versus 79%, P=0.02) but not after MVR (81% versus 79%, P=0.30).

In general, both RCTs showed similar mortality between the 2 groups. Although mechanical valve showed survival advantage at certain point of time in both RCTs, the following must be noted. These 2 studies examined older generation prostheses in heterogeneous patient populations. Also, there was no focus on specific age group and had high number of redo-thoracotomy/sternotomy patients as initial replacement surgery. Perioperative mortality is not acceptable for the current times (15.5% in MVR), thus direct application of these outcomes to our current practice should be done with extreme caution.

The most recent RCT was performed between 1995 and 2003. Three hundred ten patients between age 55 and 70 receiving AVR were randomized: 165 patients received a bioprosthetic valve, and 155 patients received a mechanical valve. New bioprostheses including Carpentier-Edwards porcine and bovine pericardial valve (Edwards Lifesciences, Irvine, CA) as well as newer mechanical valves (St. Jude Medical, Inc., St. Paul, MN) and 48 CarboMedics (Sorin SpA, Milan, Italy) were used. The mean age in this study was 64.0 years in mechanical versus 63.5 years in bioprostheses. At late follow-up, there was no difference in overall mortality (Biological versus Mechanical: 27.5% versus 30.6%), valve-related mortality (6.7% versus 8.1%), nor cardiac-related mortality (16.7% versus 21.7%) at 13-year follow up.

There are several retrospective studies which showed improved survival in mechanical valves, but more recent larger series indicate no difference in early and late mortality in both AVR and MVR. One of the largest retrospective series was published by van Geldorp et al which assessed 3934 patients who underwent AVR. After microsimulation, for a 60-year-old man, simulated life expectancy in years for biological versus mechanical prostheses were similar (11.9 years versus 12.2 years). Also in the largest meta-analysis of 32 articles with follow-up over 10 years with 17439 patients and 101819 patient-years receiving AVR, they did not find significant differences in mortality between mechanical and biological valves in all age groups. Even in the age group below age 60, no survival difference in either AVR or MVR was reported after 20-year follow-up.

One needs to keep in mind that in retrospective studies, there is a chance that critical patients were chosen to receive bioprostheses because of the risk of long-term anticoagulation, which may bias toward lower survival. Combining the outcome from RCT and large retrospective studies, long-term survival and mortality are similar between mechanical valve and tissue valve in patients aged >60 years. Therefore, the concept that patients with mechanical valves live longer is a myth.

**Bleeding and Anticoagulation**

Anticoagulation has been the Achilles heel of mechanical valves. Optimal anticoagulation in mechanical valves prevents

| Table. Three RCTs Comparing the Outcomes in Mechanical Versus Bioprosthetic Valves |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                 | n               | Valves Used     | Follow-Up       | Mortality       | Reop            | Bleeding        | Thromboembolism |
| Edinburgh study                | 1975–1979       | 514             | M: Bjork-Shiley | 20yr            | No dif          | B>M             | M>B             |
|                                 |                 | AVR +MVR        | B: Hancock      |                 |                 |                 |                 |
|                                 |                 | AVR +MVR        | B: Hancock      |                 | MVR: No dif     |                 |                 |
|                                 |                 | AVR only        | Medical CarboMedics |               |                 |                 | (P=0.08)        |
|                                 |                 |                 | B: CE SAV,     |                 |                 |                 |                 |
|                                 |                 |                 | CE pericardial  |                 |                 |                 |                 |

B indicates bioprosthetic valve; CE, Carpentier Edwards; and M, mechanical valve.
thromboembolic events but increases the risk of bleeding complication. Despite recent reports suggesting anticoagulation for initial 6 months for bioprostheses immediately after surgery, mechanical valves require lifetime anticoagulation, which is associated with an accumulative risk of bleeding especially if the valve was implanted at a young age.

Two early RCTs (VA study and Edinburgh study) showed statistically significant increase in bleeding with mechanical valves. A recent RCT showed no statistically significant difference (mechanical versus bioprostheses: 1.47%/pt-yr versus 0.72%/pt-yr), but probability value of 0.08 indicating tendency to bleed in mechanical valves. Interestingly, 21.1% of bioprostheses group was receiving warfarin at the time of follow-up, and bleeding rate in patients with bioprostheses who were not receiving warfarin was less than mechanical with warfarin. The use of warfarin was dictated by the local treating physician in this study and the indication is unknown, which may be the reason why the difference in bleeding did not reach statistical significance.

Advocates of mechanical valves emphasize the finding above; bioprostheses will need anticoagulation if patient develops atrial fibrillation. However, for atrial fibrillation one can keep the international normalized ratio to lower level compared with mechanical prostheses, especially for mitral valve. Also, atrial fibrillation may be treated with surgical or catheter intervention and freedom from anticoagulation may be achieved, whereas mechanical valves will commit the patients to lifetime anticoagulation.

Retrospective studies show more tendency toward bleeding in the mechanical valve group. In microsimulation, simulated lifetime risk of bleeding was 12% in bioprostheses versus 41% in mechanical valve for a 60-year-old man. It cannot be ignored that overall observed mortality of a bleeding event was 22%, which is much higher than published reoperation AVR mortality (5% to 6%). The bleeding events reported in the literature are mainly major bleeding life-threatening events and thus must be accounted for seriously.

Difficulty controlling the therapeutic level with warfarin is often described using the term within therapeutic range. One RCT compared interventional patient education with patients starting warfarin versus control group in the first 6 months. Interventional group had time within therapeutic range of 56% and in control group only 32%. Patients who are not in time within therapeutic range are exposed to bleeding risk if international normalized ratio is higher or thromboembolism if international normalized ratio is lower. Bioprostheses will not expose patients to these risks.

Anticoagulation risk is higher in elderly patients and in patients with comorbidities. In a prospective study in 472 patients aged >65 years, major hemorrhage was 13.1% in age >80 versus 4.7% <80. When CHADS2 score (Congestive heart failure, Hypertension, Age >75, Diabetes mellitus, and stroke or transient ischemic attack) ≥3, both bleeding risk and rates taken off anticoagulation is markedly higher. More than 30% of patients were off warfarin when CHAD2 score is >3 in 1 year.

There are other benefits in avoiding warfarin that are not frequently discussed in the literature. Frequent blood draw, drug interaction, activity, and diet regulation for young active patients and cost of medication and monitoring are some of the issues associated with warfarin. Moreover, warfarin needs to be discontinued when bleeding episodes occur or when the patients have to undergo a surgical or dental procedure. This discontinuation predisposes patients under risk of thromboembolism and valve thrombosis in mechanical valves which may require emergency reoperation (Figure 1).

The recent introduction of oral direct thrombin inhibitors and factor Xa inhibitor for the treatment of atrial fibrillation as an alternative to warfarin needs to be mentioned. Currently, these agents are not approved for mechanical valves. On the other hand, patients who have received bioprostheses with atrial fibrillation may have a choice between warfarin and new oral anticoagulants that are easier to manage with no dietary restriction and no repeated blood test.

Therefore, the myth associated with the need for mechanical valve in patients already on anticoagulation or previous mechanical valve needs to be reconsidered.

**Structural Valve Degeneration and Reoperation**

All Bioprostheses are at risk for SVD, which may require reoperation. In the VA study, primary valve failure occurred mainly in patients <65 years of age (P=0.001 for AVR and P=0.0001 for MVR), which defined the importance of age at the time of implantation. SVR for porcine valve after MVR began at ≈5 years, and in AVR =8 years. Recent bovine pericardial valve has much longer durability of 12 years or more, which has inspired the enthusiasm for using bioprostheses in young patients. High rate of valve failure in the old 2 RCTs can be attributed to usage of porcine bioprostheses. However, a recent RCT using pericardial bioprostheses also showed valve failures and reoperations more frequent in the biological group. In retrospective studies, SVD in young patients (<65) are reported from 11% to 61%/20 years in AVR and 25%/17 years to 73%/20 years in MVR, certainly less with current pericardial valves.

There is no question that use of bioprostheses is associated with increased risk of SVD. Chance of SVD decreases with older age at implantation, therefore at a certain age, the risk of SVD and reoperation from bioprostheses will be lower than the risk of bleeding from mechanical valve. Microsimulation showed at 55 years of age, combined risk of subsequent

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**Figure 1.** Mechanical valve thrombosis, which presented with acute heart failure necessitating emergency valve replacement.
reoperation and bleeding with bioprostheses is equal to that of mechanical valve. In another words, at age >55 years, bioprostheses have lower risk of combined reoperation and bleeding compared with mechanical valve.

SVD does not equal reoperation. In the Edinburgh study after 15 year follow-up, of 29% in bioprosthetic AVR who received reoperation, 23% were from SVD. Similarly, in bioprosthetic MVR, 50% had reoperation and 44% were from SVD. It is important to realize that mechanical valve also has risk of reoperation; 0.3 to 1.2%/yr risk of reoperation for mechanical valve is reported in the literature. Therefore, the concept that reoperation and SVD is the same is a myth.

Not all patients will require reoperation with bioprostheses. Rahimtoola plotted age at biological aortic valve implantation versus % of SVD and obtained linear curve between the 2 (Figure 3). Cumulative 15- to 20-year risk for SVD at implantation age of 60 and 55 averages 25% and 34%. Therefore, if the patient is 60 at the time of implantation, the probability of not developing SVD at age of 75 to 80 years old is 75%. Fifteen-year survival after valve surgery at age 60 is 30.9% for AVR and 16.1% for MVR and SVD of 15 years in age 60 is about 25%; therefore, the numbers of patients who will need reoperation in 15 years are only 7.5% in AVR and 4% in MVR.

Even if reoperation is required, reoperative AVR can be performed safely. Initial reoperative mortality from RCT was up to 29.7%, but recent outcomes have improved dramatically with reduced mortality of 5% to 7% in reoperative AVR. Reoperation after previous minimally invasive AVR may make the reoperation easier.

In the future, VIV transcatheter aortic valve replacement (TAVR) may be an important treatment option for patients who receive bioprostheses with SVD. TAVR has shown improved outcome in nonsurgical patients and is noninferior to surgical treatment in high risk patients with aortic stenosis. VIV TAVR is currently performed off label on high-risk patients who are deemed inoperable. Large trials comparing reoperative AVR and VIV TAVR has not been performed, but promising outcomes are reported. The largest series to date is reported by the Global valve-in-valve registry with 202 patients who underwent VIV TAVR. Seventy-eight patients used Edwards SAPIEN (Edwards Lifesciences, Irvine, CA) and 124 used CoreValve (Medtronic, Minneapolis, MN). Procedural successes were in 93.1%; 2% required emergency surgery. Thirty-day mortality was 8.4% and calculated 1-year survival was 85.8%. These data must be interpreted with a background understanding that current VIV TAVR is mainly performed on patients who are not eligible for open heart surgery. Application to broader patient population may improve its outcome even further. The enthusiasm regarding the VIV-TAVR must be observed with caution. Operative mortality of 8.4% is higher than the recent reports of open reoperative AVR and the long-term durability of these percutaneous valves are unknown at this point. VIV procedure is also technically demanding. Global valve-in-valve registry warned in their article that “the VIV procedure is technically demanding and should be reserved for highly experienced centers.” However, patients who receive bioprosthetic valves now will likely develop SVD in the next 12 to 15 years, and with further advances in device (smaller device etc) and better patient selection (understanding of high risk group) VIV TAVR may be a safe procedure. It is uncertain whether VIV technique will have equal or better outcome compared with open procedure; only time will answer this question. It is important to add that with current technology, initially placed mechanical valve will not allow VIV TAVR at the time of reoperation.

The risk of SVD in MVR is considered to be higher for 2 reasons: (1) SVD occurs faster in mitral position, and (2) porcine valves are used more commonly in mitral position. There are reports showing increased SVD with bioprostheses, but when all major prosthesis related events in the midage group (50–65 years old) is considered there is no difference between mechanical and bioprostheses. Reoperative MVR can be
performed safely. Recent literature reports mortality of 5% to 7%, which is much decreased compared with old reports.43–45

Previously placed bioprostheses will allow VIV transcatheter mitral valve replacement (TMVR) using the previous strut as an anchor. TMVR is currently not indicated for initial operation because of the lack of anchoring structure. Only small case series are reported regarding VIV TMVR, but the largest series to date, with 23 patients from Cheung et al,46 reports zero 30-day mortality and 90.4% survival after median follow-up of 753 days. Although the future of this technique seems promising, further reports are needed to assess its validity.

Life Expectancy
Life expectancy is an important aspect of valve choice. Bioprostheses should be considered in patients whose life expectancy is lower than the presumed durability of the bioprostheses. Patients with prosthetic heart valve have less life expectancy compared with the general population group, especially in the younger age groups.47,48 When compared with the general population, 60-year-olds undergoing AVR have 90% life expectancy compared with the general population if event free and 70% if valve-related events occur (Figure 4).49 Simulated models showed life expectancy of 60-year-olds being 11.9 in bioprostheses and 12.2 in mechanical,17 much shorter than life expectancy of 22.6 years in 60-year-olds from National census.48 In AVR, median time to reoperation for SVD with Carpentier-Edwards versus 9.3 for biological versus mechanical prostheses in AVR.17 a 60-year-old man, simulated event-free life expectancy was 9.8 years.49

This also favors bioprosthetic valve in this age group.

Valve Hemodynamics
Valve area in prostheses is important, because implantation of small valve in small annulus predisposes patients to patient prosthesis mismatch. Previous teaching was that mechanical valves have higher effective orifice areas compared with bioprostheses. The only direct comparison of mechanical versus bioprostheses in RCT showed no significant difference in valve areas between Bjork-Shiley valves and porcine valve after 6 months of implantation.50 In vivo measurement data show similar valve area index between the newer generation mechanical valves (23–24 mm St. Jude’s Regent valve: Area index 1.04±0.32 cm²/m²)51 and bioprostheses (Carpentier-Edwards Magna: Mean size 23.4±2.1 mm, Area index 1.07±0.4),52 although no study has compared the 2 under same circumstance. Therefore, a belief that mechanical valve has better hemodynamics is a myth.

Other Considerations
The rates of thromboembolism, valve thrombosis, and endocarditis are no different among mechanical and bioprosthetic valve groups in previously mentioned RCTs.5,6,10 However, with the current bioprostheses using pericardial valve, the incidence of valve thrombosis is close to zero without anticoagulation.53 Bioprostheses should be chosen if there is a risk of thrombosis or risk of interrupting anticoagulation.

In MVR, difficulty opening leaflets in mechanical valve sometimes necessitates resection of leaflet or subvalvular apparatus. In bioprostheses, it is easier to preserve both valve leaflets and subvalvular apparatus and theoretically aid the remodeling of the left ventricle postoperatively.

Quality of life issues and informed patient preferences must be taken into account. As mentioned previously, inconvenience of oral anticoagulation can be avoided by bioprostheses. Patients who are contraindicated for anticoagulation, do not wish to take anticoagulation medication, or patients at increased risk for bleeding with anticoagulation (hemorrhagic stroke, gastrointestinal bleeding, etc) should receive bioprostheses.

Patient Choice
In the case scenario presented in the introduction, after careful 30-minute consultation, the patient mentioned that he has already decided the valve type based on information he gathered on the Internet and discussion with the referring cardiologist. He has a lot of data on warfarin treatment and was informed regarding the likely possibility of future VIV TAVR. He received bioprostheses according to his wishes.

Future Direction
Despite the early hype of new anticoagulants, warfarin is unlikely to go away anytime soon and the need of anticoagulation under monitoring will continue. VIV procedure may become the mainstream of reoperation in bioprostheses failure. Patient awareness and easily accessed information may drive the choice of valve selection before physician visit.

Conclusion
Current-era bioprosthetic valves carry long durability with good hemodynamics. The survival between mechanical valve and bioprosthetic valves are similar, and one does not have an advantage
over the other. In patients aged >60 years, use of bioprostheses lowers the chance of major bleeding event. SVD is a risk associated with bioprostheses, but because of low life expectancy after valve surgery, average patients do not outlive the durability of bioprostheses at the age of 60. Combined risk of bleeding and reoperation is higher in mechanical valves compared to bioprostheses at the age of 60. Risk of reoperation has decreased over the years, and with future IVIV, TA, VR and TMVR this may improve even further. Bioprostheses will avoid frequent tests and monitoring and is indicated for patients who have contraindication or does not wish to take oral anticoagulation drugs. It is critical for physicians to provide good information to aid the understanding of true risks and benefits. In conclusion, the current literature supports the use of bioprosthetic valves in patients aged >60 years.

Disclosures

None.

References


Response to Kaneko et al

Rakesh M. Suri, MD, DPhil; Hartzell V. Schaff, MD

We have several comments in response to the manuscript by Kaneko et al. The authors contend that survival is equivalent after mechanical versus biological aortic valve replacement (AVR) in nonelderly patients. The weight of available evidence does not support this conclusion. The large retrospective series described in our review, along with contemporary reports and mechanical prostheses assessed by composites of valve-related complications to 15 years after mitral valve replacement. J Thorac Cardiovasc Surg. 2005;129:1301–1308.


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SUPPLEMENTAL MATERIAL

Appendix: ACC/AHA 2008 Guideline for valve selection

Major Criteria for Aortic Valve Selection

Class I

1. A mechanical prosthesis is recommended for AVR in patients with a mechanical valve in the mitral or tricuspid position. (Level of Evidence: C)

2. A bioprosthesis is recommended for AVR in patients of any age who will not take warfarin or who have major medical contraindications to warfarin therapy. (Level of Evidence: C)

Class IIa

1. Patient preference is a reasonable consideration in the selection of aortic valve operation and valve prosthesis. A mechanical prosthesis is reasonable for AVR in patients under 65 years of age who do not have a contraindication to anticoagulation. A bioprosthesis is reasonable for AVR in patients under 65 years of age who elect to receive this valve for lifestyle considerations after detailed discussions of the risks of anticoagulation versus the likelihood that a second AVR may be necessary in the future. (Level of Evidence: C)

2. A bioprosthesis is reasonable for AVR in patients aged 65 years or older without risk factors for thromboembolism. (Level of Evidence: C)

3. Aortic valve re-replacement with a homograft is reasonable for patients with active prosthetic valve endocarditis. (Level of Evidence: C)

Class IIb
1. A bioprosthesis might be considered for AVR in a woman of childbearing age (see Sections 5.7 and 5.8). (Level of Evidence: C)

Selection of a Mitral Valve Prosthesis

Class I

1. A bioprosthesis is indicated for MV replacement in a patient who will not take warfarin, is incapable of taking warfarin, or has a clear contraindication to warfarin therapy. (Level of Evidence: C)

Class IIa

1. A mechanical prosthesis is reasonable for MV replacement in patients under 65 years of age with longstanding atrial fibrillation. (Level of Evidence: C)

2. A bioprosthesis is reasonable for MV replacement in patients 65 years of age or older. (Level of Evidence: C)

3. A bioprosthesis is reasonable for MV replacement in patients under 65 years of age in sinus rhythm who elect to receive this valve for lifestyle considerations after detailed discussions of the risks of anticoagulation versus the likelihood that a second MV replacement may be necessary in the future. (Level of Evidence: C)