

## STATE-OF-THE-ART PAPER

# Choice of Prosthetic Heart Valve in Adults

## An Update

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In the last 7 years, more data have reconfirmed that patients' comorbid conditions are very important factors determining patient outcomes. Prosthetic heart valves (PHVs) that require aortic root replacement in the absence of aortic root disease are associated with poorer outcomes. For the vast majority of patients, the choice of PHV is between a mechanical valve and a stented bioprosthesis. The choice is largely dependent upon the age of the patient at the time of PHV implantation and on which complication the patient wants to avoid: specifically, anticoagulation therapy and its complications with the mechanical valve, and structural valve deterioration with a bioprosthesis. Data on the pros and cons of the choices and exceptions to the rules are discussed, and a new algorithm is developed. (J Am Coll Cardiol 2010;55:2413–26) © 2010 by the American College of Cardiology Foundation

*"Not all innovations represent progress."*

—Anonymous

*"The feasibility of an operation is not the best indication for its performance."*

—Lord Cohen of Birkenhead,  
at 1950 Moynihan Lecture,  
Royal College of Surgeons, England (1)

Determining the choice of a prosthetic heart valve (PHV) was published 7 years ago (2). In this update, a few issues are re-emphasized; however, the major thrust is on newer findings that have had an impact on the choice of PHV. Patients' survival after PHV has increased markedly; it is essential to consider the patient's point of view regarding the ideal PHV (Table 1), which should be the goal.

### Factors Determining Outcomes After PHV Replacement

The Department of Veterans Affairs (VA) randomized trial, the only randomized trial that determined adjudicated causes of death (3), showed that 43% to 63% of the deaths were not related to the PHV (Table 2). It was previously

emphasized that "patient-related factors," now called comorbid conditions, were very important in determining patient outcomes (4). Comprehensive lists of these are available (3–13); those useful in everyday practice are listed in Table 3.

**Conclusions.** When comparing outcomes with different PHVs, it is important to: 1) ensure that the baseline characteristics of the patients and their comorbid conditions are the same, or are at least very similar, which can be best determined by a good prospective randomized trial (14); and 2) determine cause of death when comparing survival after PHV replacement.

### Mechanical PHV

**Randomized trials.** The Starr-Edwards valve (Edwards Lifesciences, Irvine, California), a model in use since 1965, was compared with the St. Jude Medical valve (St. Jude Medical, St. Paul, Minnesota), first used in 1977. For aortic valve replacement (AVR) and mitral valve replacement (MVR), there were no significant differences in survival, event-free survival, and all outcomes (15) (Fig. 1). The Carbomedics valve (Carbomedics, Austin, Texas) was compared with the St. Jude Medical valve. Up to 10 years, there were no significant differences in survival and freedom from complications after AVR and MVR (16) (Fig. 2).

**Nonrandomized studies.** Very long-term studies have shown good outcomes with virtually no structural valve deterioration (SVD) with the Starr-Edwards valve up to 40 years (17), with the Medtronic-Hall valve (Medtronic, Minneapolis, Minnesota) up to 20 and 25 years (18,19), with the old Bjork-Shiley valve (Shiley, Irvine, California) which incorporated a Delrin ring (DuPont, Wilmington, Delaware), and with St. Jude Medical valves (2).

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**Abbreviations  
 and Acronyms**

- AVR** = aortic valve replacement
- C-E** = Carpentier Edwards
- CHADS<sub>2</sub>** = congestive heart failure, hypertension, age  $\geq$ 75 years, diabetes mellitus, prior stroke or transient ischemic attack
- CI** = confidence interval
- HR** = hazard ratio
- MVR** = mitral valve replacement
- PHV** = prosthetic heart valve
- SVD** = structural valve deterioration
- TSPV** = Toronto stentless porcine valve
- VA** = Veterans Administration
- VP-PM** = valve prosthesis-patient mismatch

**Conclusions.** Mechanical PHVs that are approved by the Food and Drug Administration (FDA) and have good and comparable outcomes at  $\geq$ 15 to 20 years of follow-up will likely have good outcomes on very long-term follow-up.

**Biological PHVs That Require Aortic Root Replacement**

Biological PHVs that require aortic root replacement include stentless and homograft PHV (both of which can sometimes be used without replacing the root), and the Ross principle (autograft).

**Operative mortality.** For isolated aortic valve disease without specific root pathology, using these 3 types of PHV that require aortic root replacement is associated with a higher opera-

tive mortality (9,20,21). Yacoub et al. (22), using selected low-risk patients (age  $>$ 16 years) from Harefield Hospital in the United Kingdom and Rotterdam, the Netherlands, reported a low operative mortality with the Ross principle. These 2 groups and others analyzed 268 studies of the Ross principle between 2000 and 2008. Of 39 that met entry criteria, 17 involved adult patients and comprised 1,749 adult patients  $>$ 18 years of age; their operative mortality was low (3.12%) (Table 4) (23). In comparison, David (24) has described 466 patients  $\leq$ 50 years of age who had isolated AVR over a period of 20 years with 1 operative death (0.2%) (Table 4).

**SVD.** The younger the patient at the time of PHV implantation, the higher the risk of SVD, and SVD of biological valves should be evaluated with  $>$ 10 years of follow-up (3). At 12 years, the rate of SVD for stentless porcine valve was  $31 \pm 4\%$  (25); for patients  $<$ 65 years of age, it was  $48 \pm 8\%$ ; and for patients  $\geq$ 65 years of age, it was  $15 \pm 4\%$ . The incidence of grade 2 or higher aortic regurgitation was  $52 \pm 5\%$ . David (25), arguably the father of the stentless valve, stated that the Toronto stentless porcine valve (TSPV) has provided "...suboptimal durability particularly in patients less than 65 years of age. We now use this valve mostly in older patients who have a small aortic annulus." The hemodynamics of the TSPV are also not better than those of the stented Carpentier-Edwards (C-E) pericardial Perimount valve (Edwards Lifesciences) (see the following text). The rate of SVD for homografts is similar to that for bioprostheses (26); at 10 and 15 years, it was  $30 \pm 3.8\%$  and  $59.7 \pm 5.1\%$  (27), and at 13 years in another study, it was  $31.2 \pm 6.3\%$  (28).

An updated report of the Ross principle in the earlier Rotterdam data on 146 patients with a mean follow-up of 8.7 years showed the reoperation rate of the autograft at 13 years was  $30.8 \pm 6.6\%$ , but for patients  $\geq$ 16 years of age, it was  $43.3 \pm 9.5\%$  (29); the reoperation rate of the homograft in the pulmonary position was  $12.9 \pm 5.5\%$  at 13 years (29). In another study of 91 younger patients (age  $27 \pm 10$  years; range 6 to 49 years), the incidence of autograft dysfunction at 7 years was  $25 \pm 8\%$  (30). In a meta-analysis of 39 studies, 17 studies in adults, the follow-up ranged from only 1.8 to 8.7 years and was  $<$ 5 years in 59% (23). The authors concluded, "The Ross procedure provides satisfactory results for . . . young adults," which is questionable. They also appropriately concluded, "Durability limitations become apparent by the end of the post-operative decade, in particular in younger patients" (23); reality sets in. For autografts (Ross principle), the rate of SVD at 13 years was  $31.2 \pm 6.3\%$  (28). Ross's own data, which have the longest follow-up, had reported operative mortality of 7% to 13% and reoperation rates of 15% to 52% up to 20 years (31-33). Yacoub et al. (22) have warned that reoperation of an autograft root "is not simply a reoperation. [It is] a risk-carrying and demanding procedure" because aneurysmatic ascending aorta may be attached to the sternum, the pulmonary homograft may be compressed by and attached to the dilated autograft root, and the coronary buttons may also pose problems when they are removed from the autograft and reimplanted in a new root. These procedures usually require removal of the coronary arteries and reimplanting them in the new root. One study reported a 6% incidence of perioperative myocardial infarction in patients who did not have associated coronary artery disease (34).

**Conclusions.** In 2000, Ross advised the terminology "Ross procedure" should not be used because what surgeons are doing is not what he described; instead, it should be called the "Ross principle" (35). These procedures are associated with a 2- to 3-fold increase of operative mortality (Table 4).

**Table 1** **Patient's Point of View of the Ideal Prosthetic Heart Valve**

The valve should:
Provide a cure
Have normal function
Provide normalization, or at least marked improvement of lifestyles and outcomes
Last a lifetime
PHV implantation should be:
Possible with very low mortality and morbidity
Nondestructive, that is, does not damage other parts of the cardiovascular system
Duration of hospitalization is short
Can be implanted at a cost that is affordable
Minimal needs for further:
Test(s) and procedure(s)
Therapy
Can be inserted percutaneously

**Table 2 Incidence of Prosthesis-Related Cause of Death**

Cause of Death	Aortic Valve Replacement		Mitral Valve Replacement	
	Mechanical	Bioprosthesis	Mechanical	Bioprosthesis
Valve related*	37%	41%	44%	57%
Bleeding†	24%	11%	25%	14%
Sudden death†	35%	38%	31%	26%

\*Percent of all deaths. †Percent of valve-related deaths. Data from Hammermeister et al. (3).

These PHVs are destructive to other cardiovascular structures and are associated with a significant rate of SVD that requires complicated reoperation procedures. The SVD rate is similar to that of porcine bioprostheses. The follow-up times were very short, <10 years. One should be very concerned about the very likely “high” rate of reoperation that will occur beyond 10 years of follow-up, as documented in the Rotterdam study (29). Moreover, it needs to be emphasized, 10 years is certainly not a lifetime (36), particularly for “young” people. These PHVs “should be reserved for specific root pathology” (9). If used for only aortic valve disease, pre-operatively one should explain to the patient: 1) what the procedure involves and that it is not just a valve replacement; 2) the risks involved; 3) that young people will need multiple reoperations in their lifetime; 4) the complexities and risks of reoperation; and 5) that there are simpler procedures (AVR with stented bioprosthesis) that are less destructive, less risky, and of more proven durability. Thus, currently for the overwhelming majority of adult patients age ≥60 to 65 years, the choice of a biological PHV is a stented bioprosthesis. However, there are exceptions; for example, for active infective endocarditis with an associated abscess or uncontrolled infection, a homograft valve may be chosen (37,38).

### Mechanical Valve Versus Stented Bioprosthesis

**Randomized trials.** Two large trials, the EHVT (Edinburgh Heart Valve Trial) (39) and the VA trial (3),

randomized the comparison of the old Bjork-Shiley (Delrin ring) valve to a porcine valve. The findings were similar. After AVR and MVR, there were no statistically significant differences up to 15 to 20 years after MVR and also after AVR between mechanical and bioprosthesis for systemic embolism, valve thrombosis, prosthetic endocarditis, any valve-relation complication, and also for survival (with 1 exception, discussed in following text). The bleeding rate was higher among patients with a mechanical valve. In both trials, there was no SVD with mechanical valves out to 18 to 20 years. In the VA trial, after AVR, use of a mechanical valve resulted in a lower mortality rate ( $66 \pm 3\%$  vs.  $79 \pm 3\%$ ,  $p = 0.02$ ) (Fig. 3) and a lower reoperation rate ( $10 \pm 3\%$  vs.  $25 \pm 5\%$ ,  $p = 0.004$ ).

The difference became apparent after 10 years. In the VA trial, SVD occurred mainly among patients <65 years of age. After AVR primary valve failure (which is now called SVD) among patients <65 years of age, the SVD was higher with bioprosthetic valves than with mechanical valves ( $26 \pm 6\%$  vs.  $0 \pm 0\%$ ,  $p = 0.001$ ) but not among patients ≥65 years of age ( $9 \pm 6\%$  vs.  $0 \pm 0\%$ ,  $p = 0.16$ ) (Table 5).

**Nonrandomized study of older patients. MEDICARE DATA.** Medicare data from 1,199 U.S. hospitals undergoing AVR identified 111,151 patients who received a bioprosthesis (age  $76.7 \pm 5.9$  years) and 195,903 who received a mechanical valve (age  $74.7 \pm 6.0$  years) from 1991 to 2003 (40). Patients who received bioprostheses had a lower hazard ratio (HR) for death (HR: 0.97; 95% confidence interval [CI]: 0.95 to 0.92), readmission for hemorrhage, stroke or embolism (HR: 0.90, 95% CI: 0.88 to 0.92), and death or reoperation (HR: 0.97, 95% CI: 0.96 to 0.98), but had a higher hazard ratio for reoperation (HR: 1.25, 95% CI: 1.16 to 1.35). Of importance, overall mortality and complication rates were >20 and >10 times higher, respectively, than the overall reoperation rate.

**Conclusions.** At present, the choice of PHV in most clinical situations is between a mechanical PHV and a stented bioprosthesis. An important determining factor in the choice between these 2 PHVs is which of the 2 complications, anticoagulation therapy or SVD, one wants to avoid.

### Complications of PHVs

Data from the 2 large randomized trials were discussed in preceding text.

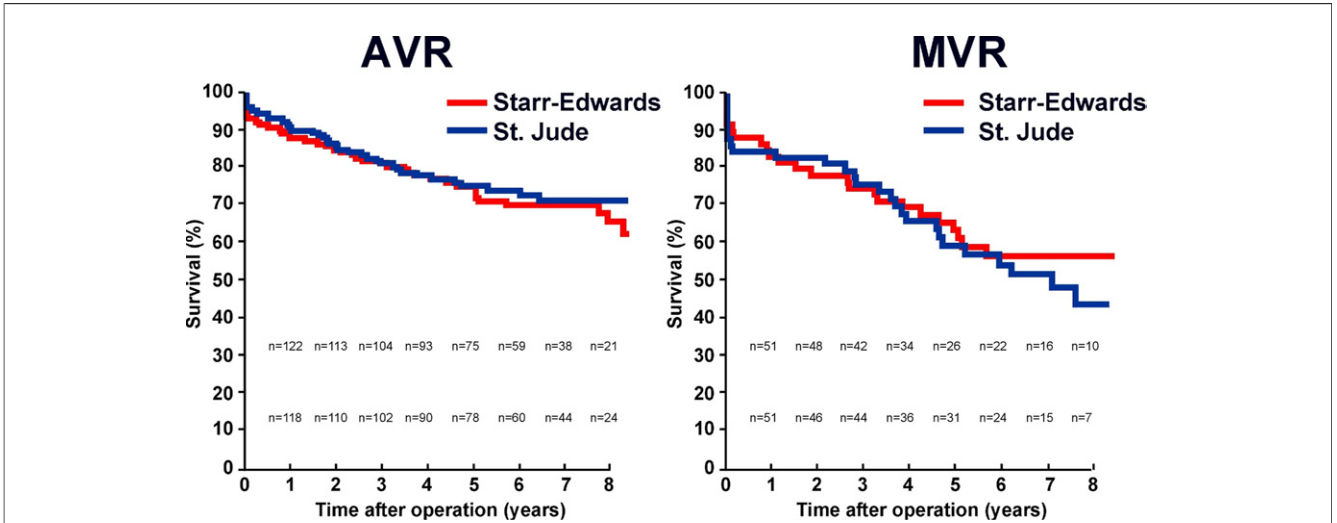
**Nonrandomized studies.** A review of 70 published series, 24,202 valves and 132,519 years of follow-up (26), showed

**Table 3 Factors Other Than PHV That Determine Outcomes After PHV\***

Decade of age
Other valve disease
Complications of PHV
Comorbid conditions
Cardiac
LV dysfunction (systolic and diastolic), heart failure, NYHA functional class III and IV, CAD, myocardial infarction, CABG, arrhythmias (e.g., atrial fibrillation), pulmonary hypertension, infective endocarditis
Noncardiac
Impaired renal function (creatinine clearance), renal dialysis, diabetes, hypertension, dyslipidemia, metabolic syndrome, smoking, liver disease, lung disease (e.g., COPD)

\*For operative (30-day mortality), additional factors include emergency surgery > urgent > elective, previous cardiac surgery, perioperative myocardial infarction, duration of the operation and of aortic cross-clamp time, and younger women.

CABG = coronary artery bypass graft; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; LV = left ventricle; NYHA = New York Heart Association; PHV = prosthetic heart valve.

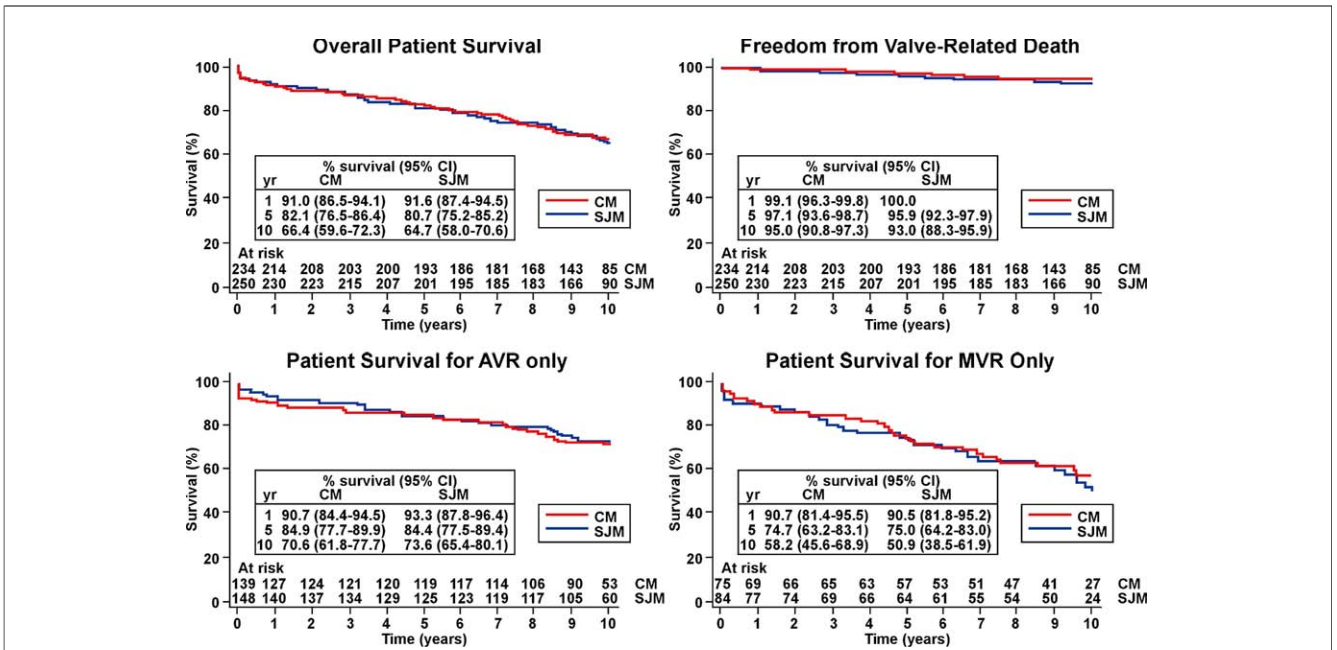


**Figure 1** Starr-Edwards Versus St. Jude Medical Mechanical Prosthetic Heart Valves

Data from a prospective randomized trial. Survival after aortic valve replacement (AVR) (left panel) and mitral valve replacement (MVR) (right panel) with Starr-Edwards (red line) and St. Jude Medical (blue line) mechanical prosthetic heart valve. There were also no differences in event-free survival between the 2 types of valves (not shown). Reprinted, with permission, from Murday et al. (15).

there were no significant differences among the various mechanical valves for thromboembolism and also among the various bioprosthesis. That was also true for bleeding rates. **Anticoagulation therapy.** Warfarin (the name comes from the organization that funded its original research, namely, Wisconsin Alumni Research Foundation) has had major

beneficial effects. It prevents or reduces the incidence of valve thrombosis and thromboembolism, especially with mechanical PHV. The disadvantages include lifetime needs for tests and therapy (Table 1). Moreover, difficulties are encountered during initiation of therapy and in maintaining an adequate international normalized ratio (INR) in the



**Figure 2** Carbomedics Versus St. Jude Medical Mechanical Prosthetic Heart Valve

Data from a prospective randomized trial. There were no significant differences between Carbomedics (CM) (red line) and St. Jude Medical (SJM) (blue line) with regard to overall patient survival (upper left panel), freedom from valve-related death (upper right panel), patient survival for aortic valve replacement (AVR) only (lower left panel), and patient survival for mitral valve replacement (MVR) only (lower right panel). Reprinted, with permission, from Bryan et al. (16). CI = confidence interval.



**Table 4** Operative Mortality for AVR in Isolated Aortic Valve Disease

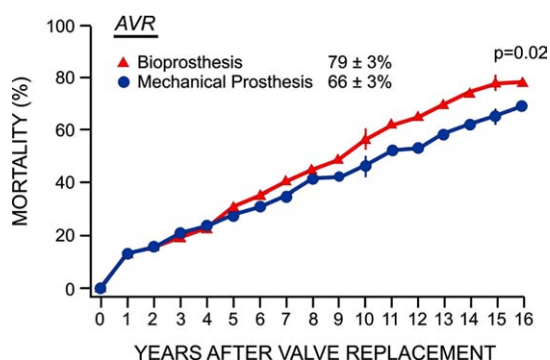
	Operative Mortality	
	Standard AVR	AVR + Root Reconstruction
STS database*	5.7%	9.2%
UK heart valve registry†	3.6%	10.7%
Single center‡	2.2%	14.2%
Low-risk patients:		
Age >16 yrs		
Meta-analysis of Ross principle§	—	3.12%
Age <55 yrs		
David	0.2%	—

\*The Society of Thoracic Surgeons (STS), n = 409,904 valve procedures (from Rankin et al. [9]). †United Kingdom (UK), n = 122,971 valve procedures (from Kalkat et al. [20]). ‡Single center, n = 215 (from Ali et al. [21]). §Meta-analysis = 17 studies from 2000 to 2008; see text (from Takkenberg et al. [23]). ||David = single center, 466 patients over a 20-year period (from David [24]).

AVR = aortic valve replacement.

therapeutic range. In the SPORTIF II (Stroke Prevention Using Oral Thrombin Inhibitor in Atrial Fibrillation) trial of atrial fibrillation (40,41), over the first 12 weeks, only 44% of the time was the patient's INR in the therapeutic range (INR: 2.0 to 3.0); 38% of the time, the INR was subtherapeutic; and 18% of the time, it was above the therapeutic range. In the Warfarin Compliance Trial (42), adherence to anticoagulation therapy was a problem. At a mean follow-up of 32 weeks, the INR was out of range 38% of the time in the adherent group and 50% of the time in the nonadherent group.

Bleeding is another disadvantage of anticoagulation therapy. In the randomized trials of anticoagulation therapy in atrial fibrillation, patients' average age ranged from 65 to 75 years in the placebo group, in whom the incidence of major bleeding ranged from 0% to 4.6% per year (2). The incidence of minor bleeding was as high as 10.5% per year,



**Figure 3** Veterans Administration Randomized Trial of Mechanical and Bioprosthetic Heart Valves

Data from the Veterans Administration randomized trial. Mortality after aortic valve replacement (AVR) in patients with mechanical valve (old Delrin ring Bjork-Shiley [blue line]) and a porcine bioprosthesis (Hancock or Carpentier-Edwards [red line]) was significantly different only after 10 years of follow-up. Reprinted, with permission, from Hammermeister et al. (3).

**Table 5** Primary Valve Failure\* After Aortic Valve Replacement at 15 Years

All patients			
Bioprosthetic valve	23 ± 5%		
Mechanical valve	0 ± 0%		p = 0.0001
Age <65 yrs			
Bioprosthetic valve	26 ± 6%		
Mechanical valve	0 ± 0%		p = 0.001
Age ≥65 yrs			
Bioprosthetic valve	9 ± 6%†		
Mechanical valve	0 ± 0%		p = 0.10

\*Primary valve failure is now called structural valve degeneration (SVD). †The 1 instance of primary valve failure was actually not due to SVD but was due to reoperation for another cause. Data from Department of Veterans Affairs randomized trial (from Hammermeister et al. [3]).

and there were some deaths from bleeding (2). The bleeding rates were obtained with follow-up times of about 2 years; thus, bleeding rates might be higher if obtained over longer follow-up times. Recent data of 13,559 adults with 66,000 person-years of follow-up in the ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) study of atrial fibrillation showed that the rate of intracranial hemorrhage with warfarin therapy offset the benefit of reduction of ischemia for patients <65 years of age and for patients 65 to 74 years of age, as well as for patients with CHADS<sub>2</sub> (an acronym for congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and prior stroke or transient ischemic attack) score of 0 and 1 (43). In another study of warfarin therapy for atrial fibrillation, 327 patients ≥80 years of age had a higher risk of major bleeding than 456 patients <80 years of age (2.5% vs. 0.9% per year; relative risk: 1.9, 95% CI: 1.2 to 2.8, p = 0.004) (44).

In patients with mechanical valves and the same level of anticoagulation therapy, at 7 years, patients >60 years of age had up to 7 times higher bleeding rates than patients <60 years of age (45). In the Stroke Prevention in Atrial Fibrillation III trial (46) with INR of 2.0 to 3.0, the incidence of bleeding was 1.5% per year, which is what one would expect with AVR in sinus rhythm according to clinical practice. With MVR, it will be somewhat higher because the INR after MVR is maintained at a higher level (3). Among patients >75 years of age, the bleeding rate is greatly increased in those with a mechanical valve compared with those who received a bioprosthesis, with odds ratio of 18.9 (95% CI: 2.2 to 163.0, p = 0.007) (47). In an initiation study of anticoagulation therapy in 472 patients with atrial fibrillation ≥65 years of age (48), in the first year, the bleeding rate ranged from 5.0% to 7.4% per year, intracranial bleed rate was 2.5% per year, and major hemorrhage among patients ≥80 years of age was 13.1% versus 4.7% among patients <80 years of age. Furthermore, both bleeding rates and need to be taken off therapy are markedly increased among patients with CHADS<sub>2</sub> score of ≥3 (Table 6).

**Conclusions.** Anticoagulants are essential with the use of mechanical valves, and can be instituted and maintained in

CHADS <sub>2</sub> Score	Major Bleed Rate/100 Person-Years (95% CI)	Taken Off Therapy Rate/100 Person-Years (95% CI)
0	3.12 (0.08–17.38)	15.59 (5.06–36.39)
1	4.28 (1.17–10.96)	17.12 (9.79–27.81)
2	2.04 (0.42–5.96)	12.92 (7.78–20.18)
3	19.54 (10.10–34.13)	32.56 (19.89–50.29)
≥4	23.24 (8.59–50.97)	35.12 (16.06–66.68)

Adapted from Hylek et al. (48).  
 CHADS<sub>2</sub> = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus (1 point for each), and prior stroke or transient ischemic attack (2 points); CI = confidence interval.

many patients with low risk. The disadvantages include lifetime needs of therapy and tests, difficulties in initiating and maintaining an adequate INR in many patients, and major risks of bleeding. The risks of bleeding are increased for patients ≥65 years of age, greatly so for those ≥75 years of age and for those with CHADS<sub>2</sub> score ≥3. For these patients, warfarin may have to be discontinued for at least a period of time because of bleeding, or because of the need for noncardiac surgical and nonsurgical procedures that expose the patients to the risks of thromboembolism and of mechanical PHV thrombosis, which is associated with heart failure, embolism, and mortality (49).

**Structural Valve Deterioration**

**Experimental study.** Valve tissue was implanted subcutaneously in rats, and calcium content was studied at 90 days (50). The C-E porcine and pericardial Perimount valves had the lowest calcium levels, 2.13 ± 5.99 μg/mg and 3.3 ± 8.4 μg/mg dry weight, respectively. Calcium content was much higher in the Mitroflow pericardial valve (214 ± 11.44, p < 0.01), the Medtronic Mosaic porcine valve (25.37 ± 57.68, p = 0.02), and the TSPV (244.43 ± 41.74, p = 0.01).

**Clinical studies.** There is considerable difficulty in obtaining good and comparable data with regard to SVD. The main reasons are as follows: 1) both of the large randomized trials (EHVT and VA) showed that SVD after MVR begins at about 5 years; and 2) after AVR it begins at about 8 years (3,39). The incidence increases after 10 years, and SVD after AVR begins to have a deleterious effect on survival after 10 years (3) (Fig. 3). A meta-analysis comprising 5,837 patients (31,874 patient-years of follow-up) with porcine bioprostheses for AVR showed SVD begins at 8 years and increases greatly after 10 years (Fig. 4) (51). Thus, data with ≤10 years of follow-up are of limited value for assessing the rate of SVD unless the rate of SVD between 5 and 10 years is already unacceptably high. Two, data are often presented as freedom from reoperation. Reoperation is a movable target because reoperation may be performed for causes other than SVD, indications for reoperation are often not provided, reoperation may not be performed in spite of presence of SVD, and unless careful follow-up with frequent echocardiographic/Doppler studies is available, SVD

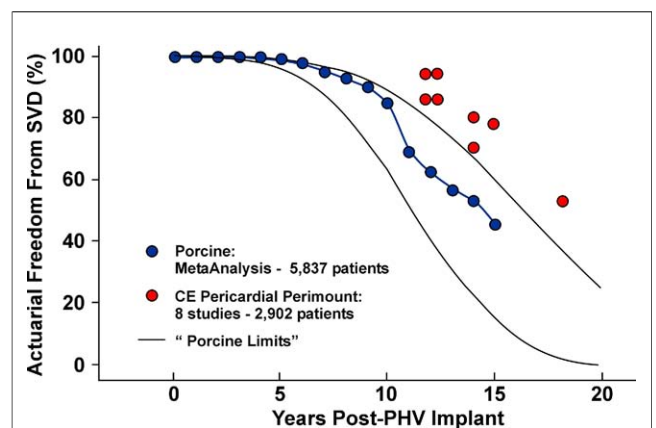
may not be diagnosed. The rate of SVD of bioprosthesis is also related to the site of PHV implantation.

**Aortic valve replacement.** The incidence of SVD with stentless porcine valve, homografts, and autografts are presented in the previous text; their SVD rate is similar to that of stented porcine valves (see the following text).

The rate of SVD is not significantly different for various porcine valves (standard Hancock, Hancock MO, and C-E porcine valves), including newer valves, and are within the expected range of the older porcine valves (51–55) (Fig. 4). More recently, very early SVD was documented in 4 of 122 patients at 3, 14, 19, and 44 months after implantation of Medtronic Mosaic porcine bioprostheses, all of whom were >68 years of age at the time of PHV implantation (56). The C-E pericardial Perimount valves have a much lower rate of SVD than the porcine valves (57–64) (Fig. 4).

The VA randomized trial documented that patients ≥65 years of age have a significantly lower rate of SVD (Table 5) (2). Studies of homograft, porcine, and pericardial valves have confirmed this finding (25–32,51–54,57–66) (Table 7). With the Bior porcine St. Jude Medical valve in patients age 70.8 ± 10.9 years, the reoperation rate for SVD at <20 years was 38.1 ± 8.5% (67).

With the Mitroflow A12 pericardial bioprosthesis study, in which 87.5% of 1,513 patients were ≥65 years of age, SVD at 20 years was 37.7 ± 5.0%, but there was only 1 patient at risk at that time (68). However, at 15 years, SVD in patients age 50 to 59 years and 60 to 69 years was >40% (value determined from their Fig. 2) (68). In another study, the SVD of the Mitroflow valve began at about 5 years and then increased rapidly among patients <70 years of age and



**Figure 4** Actuarial Freedom From SVD of Porcine and Pericardial PHV

Actuarial freedom from structural valve deterioration (SVD) after aortic prosthetic heart valve (PHV) implantation. "Porcine limits" (black line) are the limits of SVD of earlier model stented porcine bioprostheses, from Grunkemeier et al. (55). "Porcine" (blue circles) is from a meta-analysis of later-model stented porcine bioprostheses, from Puvimanasinghe et al. (51). Carpentier-Edwards (C-E) is from studies of C-E pericardial Perimount valve (red circles), from Nakajima et al. (60), Banbury et al. (61), Dellgren et al. (62), Neville et al. (63), Banbury et al. (64), Poirier et al. (58), and Frater et al. (56). The incidence of SVD is lower with C-E pericardial Perimount valves than with porcine valves.

**Table 7 SVD of Bioprosthesis in Younger and Older Patients**

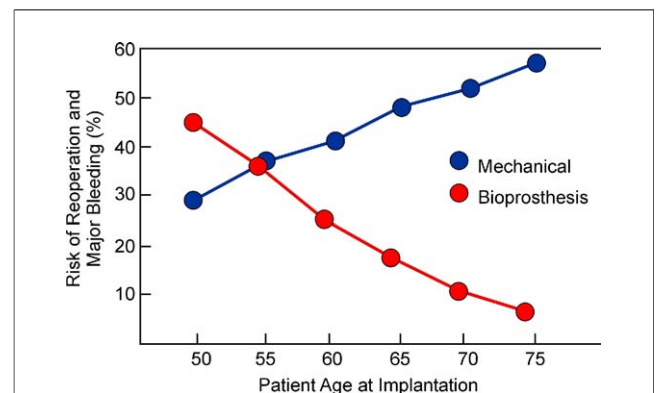
No.	First Author (Ref. #)	No. of Patients	Mean Age, yrs	SVD			
				At Time, yrs	Total	Age <65 yrs	Age ≥65 yrs
<b>After AVR</b>							
1	Banbury et al. (61)	310	64	12	18%	24%	7%
2	Neville et al. (63)	787	69	12	6%	11%	2%
3	Frater et al. (57)	267	65	14	20%	24%	4%
4	Banbury et al. (64)	267	65	15	23%	—	10%
5	Biglioli et al. (59)	298	67	18	47%	64%	16%
6	Borger et al. (65)	1,010	67	20	—	61%	27%
7	Myken and Bech-Hansen (67)	1,518	70	<20	26%	73%	41%
<b>After MVR</b>							
8	Neville et al. (63)	182	64	12	22%	48%	0%
9	Myken and Bech-Hansen (67)	194	64	17	19%	25%	12%
10	Borger et al. (65)	559	69	20	—	73%	41%

Note: Numbers and percentages are rounded. Numbers 1 to 5 and 8 are with use of Carpentier-Edwards pericardial Perimount valve. Numbers 6 and 10 are with use of Hancock II (Medtronic) porcine valve. Numbers 7 and 9 are with use of Bicor St. Jude porcine valve.  
AVR = aortic valve replacement; MVR = mitral valve replacement; SVD = structural valve deterioration.

70 to 74 years of age. The SVD at 15 years was  $37.2 \pm 5.8\%$ , but there were few patients at risk (69). With the Mitroflow A12 pericardial valve, SVD begins very early. 1) In 1 study, it began at about 5 years and then increased rapidly among patients <70 and 70 to 74 years of age. The SVD at 15 years was  $37.2 \pm 5.8\%$ , but there were few patients at risk (69). 2) In another study of patients  $79.5 \pm 3.1$  years of age, SVD began at about 3 to 4 years, and at 10 years was  $18.1 \pm 5.4\%$  (70). 3) Among patients >70 years of age, SVD began at 4 years and was  $44.2 \pm 2\%$  at 10 years (71). 4) Among patients age  $66.5 \pm 13.8$  years, SVD began at about 4 to 5 years, was  $44.4 \pm 6.8\%$  at 10 years, and was 95% at 15 years, but there were few at risk (72). The latter study compared SVD of the Mitroflow valve to the C-E Perimount valve; at 10 years, SVD of the Mitroflow valve was  $44.4 \pm 6.8\%$  versus  $13.3 \pm 4.7\%$  for the C-E Perimount valve (72).

**MVR.** The rate of SVD after MVR is greater than after AVR (26). There is much less information for SVD after MVR than for after AVR. With the Hancock II (Medtronic) porcine valve, the rate of SVD at 20 years for patients ≥65 years of age was  $41 \pm 11\%$  versus  $73 \pm 9\%$  for patients <65 years of age (65). SVD was diagnosed as clinically relevant valvular stenosis or insufficiency by Doppler echocardiography, reoperation, or autopsy (65). SVD with the Bicor porcine bioprosthesis at 13 years was  $35.2 \pm 5.3\%$ , and at 17 years, it was  $20.7\%$  (73). With the C-E Perimount valve after MVR, the SVD rate at 10 years for patients <60 years, 60 to 70 years, and >70 years of age was 21.9%, 10.6%, and 0%, respectively (74). After MVR for patients <60 years of age, SVD at 10 years with the C-E pericardial valve was  $16 \pm 3.7\%$  versus the C-E porcine valve, which was  $35.3 \pm 3.3\%$  ( $p < 0.05$ ); and SVD at 10 years for patients 61 to 70 years of age with the C-E pericardial valve was  $4.8 \pm 2.1\%$  versus  $24.8 \pm 3.7\%$  ( $p < 0.05$ ) for the C-E porcine valve (75).

**Conclusions.** All biological valves are at risk for SVD. The age of the patient at the time of PHV implantation is the most important determinant of SVD (3,51,53,54,66) (Table 7). The risks of major bleeding with mechanical valves and of reoperation for patients 60 years of age at time of PHV implantation were equal at a follow-up time of 12 years (76). This was confirmed in a more recent review of 3,934 patients (26,467 patient-years of follow-up) (Fig. 5) (77). Data with the Bicor porcine valve (St. Jude Medical) are conflicting, and more studies are needed. Data with the Mitroflow A12 pericardial valve show that among older patients, and even among elderly patients, SVD begins very early at about 4 to 5 years, and its incidence at 10 years is high. The rate of SVD with the C-E Perimount is “low” even at long-term follow-up of >15 years, which is a significant advantage of the C-E Perimount valve. An

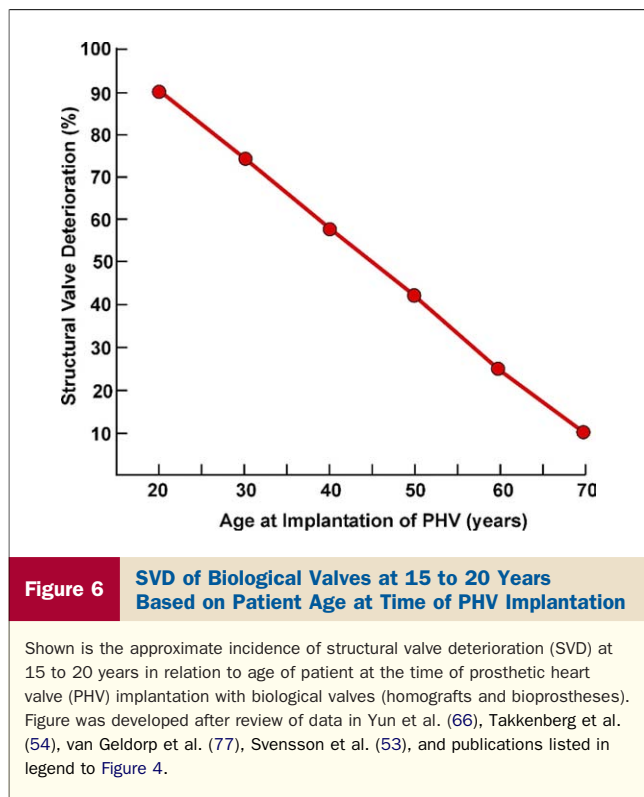


**Figure 5**

**Comparison of Risks of Reoperation and Major Bleeding Between Mechanical and Bioprosthetic Heart Valves Based on Patient Age at Valve Implantation**

A plot of the lifetime risks of major bleeding with mechanical valve (blue) and of reoperation with bioprosthesis (red) depending on age of patient at time of prosthetic heart valve implantation. Major bleeding was defined as bleeding requiring hospitalization or blood transfusions. Data from van Geldorp et al. (77).





approximate incidence of SVD after AVR at 15 to 20 years with homografts and bioprosthesis depending on the age at the time of implantation is shown in Figure 6. In “young” people, use of a biological valve will result in reoperation, probably in multiple reoperations.

**Actuarial versus actual.** Many studies including some cited above have cited only data by “actual” method of analysis or both actuarial and “actual” method of analysis. These 2 methods are very different.

**ACTUARIAL.** The Kaplan-Meier method estimates survival by censoring patients who have died and assuming the lifetime span of the survivors will be the same as for those who have already died. The Kaplan-Meier method estimates rates of nonfatal events, for example, SVD, by censoring patients who have died without SVD. It assumes patients without SVD (whether alive or dead currently) will have SVD in the future at the same rate as those who have already had SVD.

**ACTUAL.** The “actual” analysis first described by Starr and Grunkemeier (78) censors only patients who are alive without SVD (78,79). It estimates the percentage of patients who will experience an event.

**Consequences.** Survival estimates (curves) by the Kaplan-Meier and “actual” methods give “identical results” (79). For nonfatal events, for example, SVD, the Kaplan-Meier method estimates the cumulative incidence of SVD and the actual method only provides an estimate of the risk in the future for patients who are alive, which should be labeled “actual risk” for SVD. Unfortunately, in many publications,

it has been and is being incorrectly labeled as “actual freedom from SVD.” “Actual freedom” is not a statistical term (80). The definition of actual in English is “existing in fact; real” (81,82), and the actual method provides a value that neither exists in fact nor is real. The statistical aspects of the actual method have been discussed in an editorial and letters to the editors by statisticians and their colleagues (80,83,84). Two journals have stated they will no longer publish “actual freedom” results in articles reporting long-term intrinsic performance of PHV (80).

Many comorbid conditions listed in Table 3 contribute to, or are a cause of, both death and nonfatal events, and thus contribute to both of the “competing risks” (death and nonfatal events), but very few publications provide data on these comorbid conditions. Clinicians and clinical investigators must also recognize another major problem is accurate determination of the cause of death. With the actual method, all patients who had died are excluded; therefore, one has to be sure deaths that occurred were not due to SVD, and/or that SVD did not significantly contribute to the death. For example, SVD may lead to heart failure that caused death, but the death may be attributed to heart failure and not to SVD. Furthermore, even if the patient died of another cause, he or she could also have had SVD, which would not be detected unless the patient had an appropriate imaging technique shortly before demise or had a careful autopsy performed. In the Butchart et al. (18) study, autopsies were performed for 48% of all deaths and for 70% of sudden or unwitnessed death. At present, autopsy rates have declined to abysmally low rates. Diagnosis of causes of death is a moving target and potentially subject to considerable, even if unintentional, bias. In the VA randomized trial (3), causes of death were determined by an independent blinded committee (adjudicated), which may be the best that is possible at the present time.

**Conclusions.** 1) Studies showing better survival by the actual method than by actuarial method have problems in the calculations. 2) To obtain values of event rates for SVD, the Kaplan-Meier method should be used, and even if the manuscript states “actual freedom from SVD,” the actual method does not provide this information. 3) If one is certain about the absence of nonfatal events including SVD among patients who died, then the actual method provides an estimate of the “actual risk” in the future but not “freedom from.” 4) The concept of actual risk is still relevant but its misuse and difficulties of an accurate estimate suggests it should not be used. 5) Reoperation for SVD most likely underestimates SVD rates.

**Size of PHV**

Does size matter? Yes, provided the PHV size is measured after endothelialization and tissue in-growth is more or less complete; that is, at 6 months and 12 months after PHV implantation (85,86). After AVR, valve prosthesis-patient mismatch (VP-PM) (87), if mild, usually has no impact on



**Table 8** Severity of VP-PM

Severity of VP-PM after AVR	PHV area, cm <sup>2</sup> /m <sup>2</sup> *
Mild	>0.9
Moderate	>0.6 to 0.9
Severe	≤0.6
Severity of VP-PM after MVR	PHV area, cm <sup>2</sup> *
Very mild	>2.0
Mild	>1.5 to 2.0
Moderate	1.1 to 1.5
Severe	≤1.0

\*Reprinted with permission from Rahimtoola (2).

PHV = prosthetic heart valve; VP-PM = valve prosthesis-patient mismatch; other abbreviations as in Table 7.

patient outcomes; if moderate, usually the patient is asymptomatic or is symptomatic with associated conditions or it becomes severe due to thrombus and/or pannus; and if severe, is associated with significant limitations (86) and reduced survival (88). For definition of severity of VP-PM, see Table 8. Severe VP-PM should be avoided, and that is particularly important if pre-operative LV function is reduced. In such patients, aortic root enlargement can be performed at comparatively low risk by experienced and skilled cardiovascular surgeons.

Is there a perfect method to predict VP-PM pre-operatively? No. A study of 383 patients with echocardiography at 6 months after AVR (89) showed the best method to predict it pre-operatively was by PHV areas obtained in “normal” PHV from echocardiography at 6 months after PHV replacement in their own laboratory. It had a sensitivity of 53% and specificity of 83%, and it reduced the incidence of VP-PM from 8.7% to 0.8% ( $p = 0.003$ ). It was better than other methods based on in vitro data, manufacturer charts, and reference echocardiographic data in the literature. After MVR, severe VP-PM is associated with a worse outcome (90–92).

## Valve Areas With Use of Various PHV

### Mechanical Versus Bioprosthesis

**Randomized trial.** In the VA randomized trial, cardiac catheterization data 6 months after PHV implantation (85) showed there were no significant differences in PHV areas between the Bjork-Shiley valve and porcine valves in valve sizes 21 to 29 mm.

### Bioprosthesis Versus Bioprosthesis

**In vitro hydrodynamics.** The C-E Perimount valve was compared with 7 other bioprosthetic valves. At a flow rate of 5 l/min and a heart rate of 70 beats/min, the C-E had lower pressure drop (gradient) and larger valve areas in valve sizes 19 to 29 mm (93). With a bileaflet mechanical PHV valve size 21 mm at a flow rate of >4 l/min, the St. Jude Medical Regent-19 and the Sorin Bicarbon Slimline had larger effective valve orifice areas than the ATS 18 mm, On-X 19 mm, and Carbomedics Top Hat ( $p < 0.005$ ) (94). The C-E

Perimount valve was compared with the Medtronic Mosaic valve in sizes 21, 23, and 25 mm. At cardiac outputs of 2 and 3 l/min, the C-E valve had higher transvalvular resistance. However, at cardiac output of 4.1 to 9.0 l/min (at normal cardiac indexes), the C-E Perimount valves had very much lower resistances than the Medtronic Mosaic valves (95,96). **In vivo hemodynamics.** “Normal” Doppler echocardiographic values of prosthetic aortic valves have been listed (97).

**Randomized trials.** Data are shown in Table 9 (98–102).

**Conclusions.** There is no significant difference in valve areas at 6 months between a bileaflet mechanical valve and porcine bioprosthesis for valves with the same valve size. The stented C-E Perimount valve has similar PHV area as the TSPV. The C-E Perimount valve has a lower rate of SVD up to 15 to 20 years of follow-up and has larger PHV area than other bioprostheses. The C-E Perimount magna has an even larger valve area than the C-E Perimount valve.

## Choosing a PHV for an Individual Patient

The physicians involved in the decision-making process should be very knowledgeable about the patient outcomes with the use of the various PHV discussed above and also previously (2), and they should be completely discussed with the patient. The final choice of PHV should be a joint decision by patient, cardiologist, and cardiac surgeon.

Patients with a PHV have a less than normal life expectancy, especially the young (76,77,102–105). Several issues should be kept in mind while choosing a PHV for an individual patient (Table 10). A very important factor is the age of the patient. The older patients ( $\geq 55$  to 60 years of age for AVR and probably  $\geq 60$  to 65 years of age for MVR) have a shorter life expectancy, higher or very high risk of

**Table 9** PHV Areas From Randomized In Vivo Trials

	PHV Size (mm)	PHV Area Index (cm <sup>2</sup> /m <sup>2</sup> )	p Value
(A) Medtronic Mosaic	23	0.74 ± 0.06	
C-E Perimount	23	0.79 ± 0.08	<0.05
Medtronic Mosaic	25	0.80 ± 0.09	
C-E Perimount	25	0.85 ± 0.09	<0.05
(B) C-E Perimount Magna		1.17 ± 0.27	
C-E Perimount		0.94 ± 0.36	0.01
Medtronic Mosaic porcine		0.83 ± 0.23	<0.001
Soprano valve		0.87 ± 0.20	<0.004
(C) C-E Perimount	22.9 ± 2.0	1.9 ± 0.09	
Toronto stentless porcine	26.3 ± 2.0	1.74 ± 0.66	NS
	( $p = 0.0001$ )		
(D) C-E Perimount	24.8 ± 2.17	0.9 ± 0.2	NS
Toronto stentless porcine	24.8 ± 2.51	0.88 ± 0.22	
(E) C-E Perimount Magna	23.4 ± 2.1	1.07 ± 0.4	
C-E Perimount	22.4 ± 1.8	0.80 ± 0.2	
C-E Prima plus	24.3 ± 1.7	0.87 ± 0.3	0.028

(A) From Walther et al. (98). (B) Supraannular position in patients with small aortic annulus (21 to 23 mm); from Botzenhardt et al. (99). (C) From Cohen et al. (100). (D) From Chambers et al. (101). (E) From Totaro et al. (102).

C-E = Carpentier-Edwards; NS = not significant; PHV = prosthetic heart valve.

**Table 10** **Factors to be Considered in the Decision for Choice of PHV**

Age of the patient
Comorbid conditions: cardiac and noncardiac
Expected life span of patient
Use of a PHV
That does not require "root replacement" for isolated aortic valve disease
With long-term follow-up outcomes that are at least as "good" as the best of the available PHV
With which individual physicians and medical centers have the necessary skill and experience
Probability of adherence and compliance with warfarin therapy
Patient's wishes and expectations
Other extenuating circumstances

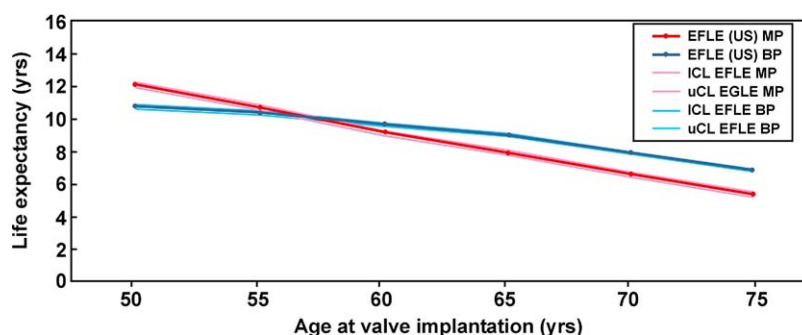
PHV = prosthetic heart valve.

bleeding with anticoagulant therapy, but fortunately, a lower incidence of SVD. At age 55 years with AVR, risks of bleeding with mechanical valves and of reoperation with bioprosthetic valves are equal (77) (Fig. 5). Furthermore, with AVR, patients  $\geq 60$  years of age have a better life expectancy with a bioprosthesis than with a mechanical valve (Fig. 7) (40,77). Thus, a stented bioprosthesis is the PHV of first choice for older patients. The younger the patient, the greater the risk of SVD (Fig. 6) and of reoperation; there is also a possibility of the need for multiple reoperations with a biological valve. Thus, a mechanical valve is a PHV of first choice for younger patients. However, certain subgroups of young patients with very low expected survival, for example, continuing intravenous drug abusers and patients on dialysis, who have a 45% and 85% mortality rate by 1 and 5 years, respectively (12), one may choose a bioprosthetic valve. Other factors, for example, patient wishes and expectations, are also very important in choice of PHV, and are listed in Table 10.

The issue of choice of PHV for young women who desire to be pregnant was reviewed in 2003 (106) and was updated in 2007 (107). It is a complex issue associated with multiple factors and is beyond the scope of this manuscript.

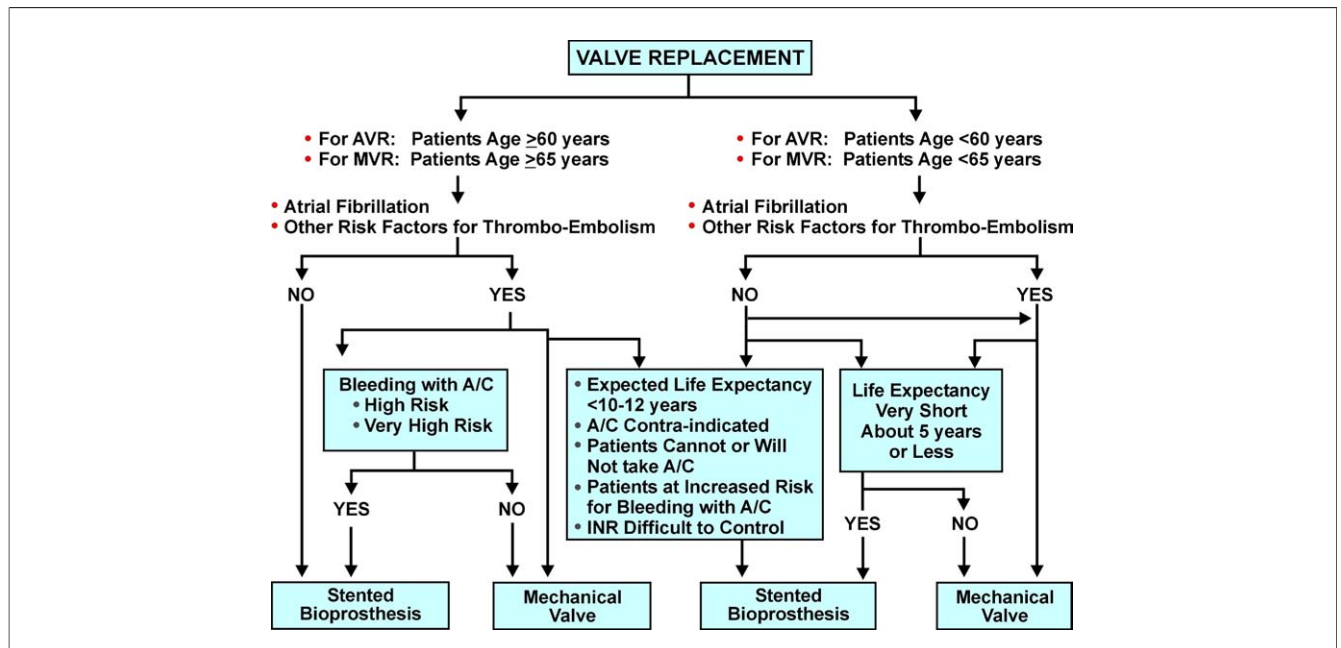
A suggested algorithm for choice of PHV for AVR and MVR is shown in Figure 8. The choice between the 2 types of PHV (mechanical or biological) is dependent upon which complication one wants to avoid or reduce to a minimum. Any mechanical PHV approved by the authorized agency of each country (FDA in the U.S.) and with documented good outcomes to  $\geq 15$  to 20 years of follow-up is acceptable for that country. Biological valves that need aortic root replacement (stentless, homograft, Ross principle) should not be used unless aortic root replacement is necessary for root disease. An exception is the homograft for active infective endocarditis with abscess or uncontrolled infection. Stented bioprostheses (porcine or pericardial) are the biological valve of choice. SVD with the Mitroflow A12 pericardial valve begins very early even in older patients, and at 10 years is high and greater than with the C-E Perimount valve. At present, the C-E Perimount valve has a documented "low" rate of SVD with follow-up of  $>10$  years (Fig. 4). It also has a more favorable hemodynamic profile, which is best with the C-E Perimount magna.

Some circumstances that would be exceptions to this algorithm include the following. 1) Bioprosthetic SVD is not reduced suddenly at 60 years for AVR and 65 years for MVR. Thus, if the patient is willing to accept a "small" increased risk of SVD (Fig. 6) if a bioprosthetic PHV were to be implanted 5 years earlier for benefit of not needing anticoagulant treatment with use of mechanical PHV, then the decision to insert a bioprosthetic PHV at that age may be reasonable. 2) In certain circumstances, even though the patient needs anticoagulant therapy for other indications such as atrial fibrillation, it may still be preferable to insert a bioprosthetic valve. For example, a patient 65 to 75 years of age who has atrial fibrillation is at an increased risk of thromboembolism but may also be at increased or greatly increased risk of bleeding with anticoagulant therapy. If bleeding requires discontinuing warfarin therapy for an extended period, then this puts the mechanical valve at serious risk of thrombosis and thromboembolism; therefore,



**Figure 7** **EFLE After AVR Based on Patient Age at Valve Implantation**

Event-free life expectancy (EFLE) after aortic valve replacement (AVR) in the U.S. with mechanical prosthesis (MP) (red) and bioprosthesis (BP) (blue) depending on age of patient at time of valve implantation. Included are 68% upper (u) and lower (l) confidence limits (CL). The EFLE is better with bioprosthesis for patients  $\geq 60$  years of age, and probably so for patients 55 years of age (see also Fig. 5). Reprinted, with permission, from van Geldorp et al. (77).



**Figure 8** Algorithm for Choice of Prosthetic Heart Valve

An algorithm for choice of prosthetic heart valve. Adapted and modified from Rahimtoola (2).  
A/C = anticoagulation; AVR = aortic valve replacement; INR = international normalized ratio; MVR = mitral valve replacement.

one should consider insertion of a bioprosthetic PHV. This probably also applies to the patient who already has a mechanical valve at another site, especially if the other site needs a lower INR level. Any reduction of risks of PHV thrombosis and thromboembolism is reasonable; also note the shorter life expectancy of these patients. 3) The need for reoperation in older patients for SVD must be kept in perspective. Life expectancy after aortic PHV implantation at age 60, 65, 70, and 75 years are 15, 12, 10, and 7 years, respectively; the risks of SVD at these times is 25%, 18%, 10%, and 5%, respectively (77). Thus, if 100 patients had PHV initially, the number of patients who will need reoperation in these age groups will be 4, 3, 1, and <1, respectively. 4) The survival of patients after MVR is lower than that after AVR (108). For patients 65 years of age who need MVR and anticoagulation therapy for another reason, the necessity of reoperation on these patients at age 80 years is small. For patients who had AVR or MVR at age 61 to 70 years, the probability of being alive at 15 years was 30.9% after AVR and 16.1% after MVR (108). The probability of SVD at this age is <20% (105). If initially 100 patients had AVR with a bioprosthesis, of the initial 100 patients who had AVR, only 6 will need reoperation. If initially 100 patients had MVR with a bioprosthesis, of the initial 100 patients, only 3 will need reoperation. With AVR or MVR at age >70 years, the probability of being alive 15 years later is 16.1% and 2.8%, respectively (108). If the rate of SVD is <10% in this age group (77), then of the initial 100 patients who had AVR or MVR, <2 and ≤1, respectively, will need reoperation.

Implantation of PHV has had greatly beneficial effects for patients with valvular heart disease and has had an enormous positive impact over the last century on the management of these patients (109). However, it is not a curative procedure and is associated with complications. The patient has to understand and accept the risks, which should be carefully and patiently explained to them because the patient is taking all the risks, and not the physicians.

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**Key Words:** aortic valve replacement ■ mitral valve replacement ■ mechanical heart valve ■ bioprosthesis ■ homograft ■ autograft.