This review covers the period July 2003 to June 2004 with three exceptions.

AORTIC STENOSIS

Additional evidence of atherosclerosis and inflammation in aortic valve (AV) stenosis. Calcified stenotic AV were shown to have a prevalence of calcium nodules (Fig. 1) surrounded by markers for inflammation and neoangiogenesis that were not present in control valves. The presence of active inflammation correlated with an abundance of thin neovessels (p < 0.01) and heat shock protein (hsp)60 gene expression (p = 0.04). Neoangiogenesis correlated with inflammation (p = 0.04), calcium (p = 0.01), and hsp60 gene expression (p = 0.04). These findings “indicate an active immuno-mediated process in the final phase of the disease” (1).

The genotype distribution of patients with aortic stenosis (AS) differed significantly compared with patients without AS (p = 0.03), with increasing prevalence of the apolipoprotein E allele in those with AS (p = 0.01). In multivariate analysis, increasing age and apolipoprotein E allele were significant independent predictors of AS (p = 0.046) (2).

Twenty patients with calcific AS had elevated levels of C-reactive protein compared with control subjects (p = 0.013) (3).

Calcified AV stenosis compared with control valves showed an increase of messenger ribonucleic acid expression and activation of matrix metalloproteinases, which may be the result of insufficient inhibition of endogenous specific tissue inhibitors (4).

Echocardiography is superior to electron beam computed tomography (EBCT) for AV calcium. Of 327 subjects in the Framingham Heart Study, 14% had AV calcium deposits detected by EBCT. Compared with echocardiography, the AV could not be adequately scanned by EBCT in 18 subjects (6%), and the sensitivity and specificity of EBCT for the detection of “degenerative” AV disease were 24% and 94%, respectively (5).

Diagnostic techniques. MULTISLICE COMPUTED TOMOGRAPHY (CT). Three-dimensional aortic valve calcification volume showed a close non-linear relationship to echocardiographic parameters of severity of AS (6).

CARDIAC MAGNETIC RESONANCE IMAGING. In 24 patients, comparison of cardiac magnetic resonance imaging to echocardiography/Doppler (7) revealed that the r value for velocity time interval was 0.96 and for aortic valve area (AVA) was 0.83. Comparison for AVA showed that the methods agreed, exhibiting a mean difference of zero.

Comment: The clinical value of CT and cardiac magnetic resonance imaging were not studied. At present, for clinical practice the two techniques are not comparable to echocardiography/Doppler.

Importance of natriuretic peptides (NPs) in patients with AS. B-type natriuretic peptide (BNP), N-terminal BNP (NTBNP), and N-terminal atrial natriuretic peptide (NTANP) were determined in 130 patients with severe AS who were followed for 377 ± 150 days (8). The NP increased with increasing New York Heart Association (NYHA) functional classes and decreasing left ventricular ejection fraction (LVEF). Asymptomatic patients who later became symptomatic had higher levels of BNP and NTBNP at baseline.

In patients presenting with chest pain, AV sclerosis was not a predictor of cardiac death and myocardial infarction (MI). Of patients presenting in the emergency department, AV sclerosis was identified in 203 of 405 patients (49%) (9). On multivariate analysis, independent predictors of cardiac death or MI at one year were coronary artery disease (p = 0.003), MI at index admission (p = 0.008), ascending terciles of C-reactive protein (p = 0.001), congestive heart failure (HF) (p = 0.02), and age (p = 0.04).

Is “contractile reserve” of value in patients with low gradient AS? Yes and no. This prospective study enrolled 136 patients with severe AS, AVA 0.7 cm², and LVEF 0.31. Left ventricular (LV) “contractile reserve” was defined as an increase of LV stroke volume (obtained from echocardiography/Doppler) of ≥20% with intravenous dobutamine infused up to a maximal dose of 20 μg/kg/min (10). Group I was composed of 92 patients who had “contractile reserve,” and Group II was composed of 44 who had no “contractile reserve.” Decisions for surgery were made by individual clinicians. At three years, patients in both groups who had surgery had a better survival than those treated medically. An improvement in functional class occurred in 84% of Group I patients and in 45% of Group II patients (p = 0.002); medical treatment was “equally poor in both groups.”

Comment: Contractility was not determined. In both subgroups, survival and functional outcomes were better with surgery than no surgery; not a helpful study. Assess-
ment of myocardial viability may be of value in Group II patients (see “Mitral Regurgitation”).

AORTIC REGURGITATION (AR)

NPs are elevated in patients with AR. Compared with control subjects, NPs were elevated in asymptomatic patients with AR (p < 0.05); symptomatic patients had higher levels (11).

Patients with severe AR may have right ventricular (RV) diastolic dysfunction. Forty consecutive patients with AR, LVEF ≥0.55, LV end-diastolic pressure ≤15 mm Hg, RV systolic pressure ≤30 mm Hg, and normal coronary arteries had evidence of abnormal RV relaxation and filling as assessed by echocardiography/Doppler (12). There was no description of the septal movement or of the findings on clinical examination of the patient.

Comment: This is probably the Bernheim syndrome/effect first described in 1910 (13). Paul Wood stated that it was a result of LV dilatation, and also of rapid dilatation of the LV in early diastole (e.g., from left-sided valve regurgitation) so that the septum bulges into the RV and interferes with proper filling of the RV; therefore, the RV is small and the right atrium is large (14). Clinical examination shows elevated jugular venous pressure, absence of RV heave, and because there is no increase in pulmonary vascular resistance the intensity of P2 is normal.

AV repair with good results is feasible in selected patients. Between 1986 and 2001, 1,410 patients had surgery for severe AR of whom 160 (11%) had valve repair (15). There was one operative death (0.6%), and two patients required early re-repair; at a mean interval of 2.8 years 10% had re-operation. At seven years, survival was 89% and re-operation on the AV was 15%.

BICUSPID AORTIC VALVE

Prevalence of bicuspid aortic valve (BAV) is high. In a prospective study of 817 children (400 males, 417 fe-

In a prospective study of 817 children (400 males, 417 fe-

males, age 10 years) attending primary school in a valley with 41,432 inhabitants (16), echocardiography of the children showed BAV in 0.5%; prevalence in males versus females was 0.75% versus 0.24%. The dimensions of the aortic root in patients with tricuspid aortic valve (TAV) versus BAV at the level of the annulus were 18.4 ± 2.6 mm versus 20.5 ± 2.6 mm, at the sinuses of Valsalva were 22.2 ± 2.4 versus 25.7 ± 2.0 (p = 0.02), and in the ascending aorta were 19.7 ± 2.3 versus 22.2 ± 4.4 (p < 0.001).

BAV is heritable. Of 309 probands and relatives, echocardiography showed BAV in 74 (prevalence 24% and a heritability [h2] of 89%); BAV and/or other cardiovascular malformation in 97 (prevalence 31%, h2 75%) (17).

Abnormalities in aneurysmal tissue of BAV and Marfan syndrome. Marfan syndrome is known to be a genetic disorder caused by a mutation in the fibrillin gene (18). Immunohistochemical study of cultured BAV and of Marfan syndrome vascular smooth muscle cell (VSMC) showed intracellular accumulation and reduction of extracellular distribution of fibrillin, fibronectin, and tenasin (18). The VSMC of both groups showed no increase in expression of fibrillin, fibronectin, or tenasin, and an increased expression of matrix metalloproteinase-2 in Marfan syndrome (Fig. 2). There was a four-fold increase in loss of cultured VSMC incubated in serum-free medium for 24 h of 32 (p = 0.02), and in the degree of AR increased in 17 patients (25%). Progression of aortic diameter dilation occurred irrespective of baseline BAV function.

The failure of BAV may relate to the different way it performs. Cryopreserved and then thawed human aortic roots containing BAV were studied in a left heart simulator.
using intravascular ultrasound and high-speed (500 frames/s) cinematography (23). The function of the clinically “normal” BAV was characterized by: 1) excessive folding and creasing, which (unlike in the TAV) persisted throughout the cardiac cycle; 2) extended areas of leaflet contact; 3) asymmetrical flow patterns and turbulence which subject the BAV to abnormal stresses; and 4) significant morphologic stenosis.

**Does aortic valve replacement (AVR) stabilize the ascending aortic dilation? Yes and no.**

**YES.** Follow-up (30.0 ± 23.4 months) in 185 patients undergoing AVR showed no increase in ascending aorta dimension (24), and progressive aortic dilation occurred in only 9.3%. No patient with baseline aortic dilation of 3.5 to 5.3 cm dilated beyond 5.5 cm.

*Comment:* Only 13 of 185 patients (7%) had “congenitally abnormal valve,” presumably BAV.

**NO.** In a study of 13 patients with BAV, and 14 with TAV before and after AVR, and of 18 BAV without AVR (25), the aortic dilation in BAV patients tended to be faster than with TAV; however, a statistically significant difference was found only at the proximal aorta (0.18 ± 0.08 vs. 0.08 ± 0.08 mm²/m² per year; p = 0.03). Patients with BAV showed similar progressive dilation with or without AVR. Patients in the AR dominant subgroup showed a tendency of more progressive dilation (p = NS). Patients with TAV did not show further dilation after AVR.

*Comment:* This study included small numbers of patients. After AVR, in patients with BAV the ascending aortic dilation is likely to be progressive but not in those with TAV.

### MITRAL STENOSIS

Non-invasive assessment of mitral valve area (MVA) is best by real-time three-dimensional echocardiography (RT3D). The MVA by pressure half time, two-dimensional echocardiography, proximal iso-velocity surface area, and RT3D were compared with MVA obtained within 24 h by using the Gorlin formula (simultaneous LV-left atrial pressures and cardiac output by thermodilution) in 80 patients (26). Compared with all other echocardiography/Doppler methods, MVA by RT3D had the best agreement with MVA obtained by the Gorlin formula (average difference with both methods was 0.08 cm², and the range of limits of agreement was −0.48 to 0.6). The RT3D showed the best interobserver and intraobserver variability with Kappa indexes of 0.84 and 0.96, respectively. The authors concluded that RT3D is “feasible, accurate and highly reproducible for assessing MVA” and “has the best agreement with high-quality invasive methods.”

**Dobutamine stress echo in predicting clinical events.** Dobutamine stress echo (DSE) was performed in 53 patients age 37.4 ± 11.3 years. During follow-up (60.5 ± 11.0 months), 29 patients presented with clinical events; the best performance of DSE for prediction of clinical events was at a cutoff value of 18 mm Hg DSE-mean gradient.

<table>
<thead>
<tr>
<th>Table 1. Size of Ascending Aorta in BAV and TAV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of Ascending Aorta</td>
</tr>
<tr>
<td>--------------------------</td>
</tr>
<tr>
<td>Aortic sinuses</td>
</tr>
<tr>
<td>Sino-tubular junction</td>
</tr>
<tr>
<td>Ascending aorta</td>
</tr>
</tbody>
</table>

p < 0.005 for all three values. From Morgan-Hughes GJ et al. (21).

BAV = bicuspid aortic valve; TAV = tricuspid aortic valve.
which had a sensitivity of 90%, specificity of 87%, and accuracy of 90%. The authors stated the addition of DSE to "conventional cardiology work-up would allow a 17% increment for detection of high-risk patients in the entire population and 40% increment in patients with presumed moderate disease." (27)

Comment: An accompanying editorial stated that the role of DSE is of value "in selecting those patients with symptoms out of proportion to the severity of their calculated mitral valve area who will most probably benefit from an intervention that may be either medical or invasive." (28)

Older patients have less good outcome with catheter balloon commissurotomy. Older patients had more co-morbid cardiac conditions; at five years, they had higher mortality and fewer patients were in NYHA functional classes I and II (Table 2). The echocardiographic score did not correlate well with age (29).

Successful catheter balloon commissurotomy does not prevent development of subsequent atrial fibrillation. Of 323 consecutive patients with catheter balloon commissurotomy, 181 had no history of atrial arrhythmias. Atrial fibrillation developed in 37 (20%) patients (30). Patients who developed atrial fibrillation were older (p < 0.001), had a higher echo score, and had a larger left atrial diameter (p = 0.004).

MITRAL REGURGITATION

Basic abnormalities of mitral valve (MV) leaflets and chordae in mitral valve prolapse (MVP). It has been known that the myxomatous degeneration seen in MVP has findings on gross and histologic examination that are identical to those seen in Marfan syndrome. Marfan syndrome results from mutation in the gene that codes for extracellular protein fibrillin, and fibrillin in MVP is not known (31). The leaflets of MV in areas of myxoid degeneration, examined by immunohistochemical staining, showed a more diffuse, weaker, and non-laminar pattern for fibrillin (31) (Fig. 3). Similar, but less severe abnormality of elastin, collagen I, and collagen III were also present. The abnormal fibrillin and altered protein matrix architecture may contribute to the development of myxomatous degeneration (also see section on BAV).

The MV leaflets and chordae in MVP had 3% to 9% higher water contents and 30% to 150% higher concentrations of glycosaminoglycans than normals when expressed in terms of dry weight (p < 0.005) (32). There are lower collagen concentrations in the leaflets compared with normals (p < 0.002). The biochemically measurable effects were more pronounced in chordae than in leaflets.

Different mechanisms responsible for exercise-induced increase of mitral regurgitation (MR). Seventy patients, in chronic post-MI phase and LVEF <0.45, showed a wide range of exercise-induced effective regurgitant orifice (ERO) that was not related to the degree of MR at rest (r = 0.20). On exercise, the independent predictors of ERO were changes in mitral deformation (i.e., differences in systolic mitral tenting area, systolic annular area, and coaptation height; p < 0.0001) and wall motion score in anterior and inferior MI groups. Larger changes in ERO in both infarct groups were associated with posterior displacement of the papillary muscles. Apical displacement of the mitral leaflets was important in patients with anterior MI. A decrease in ERO was seen in patients with inferior MI who had improvement in wall motion score. The changes in ERO "are related to those in LV remodeling and in mitral deformation but not those in global LV function." (33)

Comment: Echocardiography/Doppler must be performed during, and not after, peak exercise.

Table 2. Patient Outcomes After CBC for MS

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Patients (n)</th>
<th>NYHA Functional Class I/II (%)</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>19</td>
<td>87</td>
<td>0</td>
</tr>
<tr>
<td>40–54</td>
<td>101</td>
<td>63</td>
<td>5</td>
</tr>
<tr>
<td>55–69</td>
<td>173</td>
<td>36</td>
<td>31</td>
</tr>
<tr>
<td>≥70</td>
<td>112</td>
<td>19</td>
<td>59</td>
</tr>
</tbody>
</table>

From Shaw TRD et al. (29).

CBC = catheter balloon commissurotomy; MS = mitral stenosis; NYHA = New York Heart Association.
Increased extravascular norepinephrine (NE₂) release rate. The NE₂ increase after mitral valve repair (MVrep) (34) was directly proportional to the changes in LV end-systolic dimension (r = 0.01, p < 0.001) and inversely related to the changes in LV fractional shortening (r = −0.82, p < 0.001) and LVEF (r = 0.78, p < 0.001).

Importance of magnitude of viable myocardium in determining postoperative survival. Fifty-four patients with LVEF of 0.27 ± 0.09 had viable myocardium identified by positron emission tomography (35). After MVrep, those with <5 segments of viable myocardium had a higher six-month mortality than those with ≥5 segments of viable myocardium, 43% versus 3.6% (p < 0.01).

TRICUSPID VALVE DISEASE

Results of tricuspid valve replacement with mechanical and bioprosthetic prosthetic heart valve (PHV) are similar. Data from 11 studies with 646 mechanical and 514 biologic valves, median age 50 years, were pooled (36). The hospital mortality for tricuspid valve replacement was 19%. There was no significant difference in late survival between the two types of prosthesis; mortality (excluding hospital mortality) at 1, 5, 10, and 15 years was approximately 14%, 26%, 40%, and 52%, respectively. There was a large variability in complication rates between the studies. There was no significant difference between valve types with regard to thrombosis or structural valve deterioration (SVD).

INFECTIVE ENDOCARDITIS (IE)

Antibiotic prophylaxis reduces the incidence of bacteremia. In this double blind, randomized, placebo-controlled trial, children were assigned to the American Heart Association-recommended dose of amoxicillin or to a placebo (37). Aerobic and anaerobic blood cultures were drawn at eight specific times before, during, and after the procedure in 100 children (mean age 3.5 years). At least one of the eight cultures was positive in the placebo group in 84% versus 33% (p < 0.001) in the amoxicillin group. Bacteremia occurrence rates were lower in the amoxicillin group (Table 3).

Comment: This is an early step in documenting the clinical benefit of antibiotic prophylaxis.

Elevated procalcitonin level for early diagnosis. Procalcitonin levels were higher in patients with IE than in those with other final diagnoses (p < 0.001). At a cutoff value of 2.3 ng/ml for diagnosis of IE, the sensitivity, specificity, negative and positive predictive values were 81%, 85%, 92%, and 72%, respectively (38).

Early clinical predictors of in-hospital death. In 267 consecutive patients, the in-hospital mortality was 20%. Eighty-two percent of patients had native valve IE. Independent predictors of death by logistic regression analysis were embolic event, diabetes mellitus, Staphylococcus aureus, and APACHE II score. APACHE II includes “acute physiology,” age, and chronic health evaluation (39).

Predictors for “major” embolic event. Overall, 75 symptomatic embolic events occurred in 43 of 94 patients (46%) (40). Seventy percent of patients had native valve IE. By multivariate logistic regression analysis, predictors of embolic event were young age (p = 0.006), vegetation size (p = 0.045), and C-reactive protein (p = 0.028).

Comment: A good transesophageal echocardiogram (TEE) is essential for clinical practice. It is of great value for the diagnosis of IE; the additional information it provides (e.g., vegetation size, abscess) is also of value in clinical decision-making. It must be performed urgently in such patients.

Aspirin does not reduce risk of an embolic event. In a multicenter double-blind, placebo-controlled, randomized trial of aspirin versus placebo, the embolism rate was 28.3% versus 20.0% (p = 0.29) and the bleeding rate was 28.8% versus 14.5% (p = 0.075) (41).

Valve surgery reduces six-month mortality. Of 513 adults with complicated, left-sided native IE treated with antibiotics, 45% underwent valve surgery and 55% received medical therapy alone. The six-month mortality in those with valve surgery versus no valve surgery was 16% versus 33%, p < 001 (42). Patients with moderate to severe heart failure (HF) showed the greatest reduction in mortality with surgery (14% vs. 51%, p = 0.001). Most of the deaths in the no surgery group occurred in the first two weeks.

MV_rep WAS FEASIBLE IN 63 OF 78 (81%) PATIENTS. Early complications were: two deaths (3.2%) and two reoperations, of which one was for severe MR and one for subsequent aortic IE. For all 78 patients, the seven-year survival was 78 ± 6%; multivariate predictors of event-free survival were hypertension (p < 0.006) and intervention for acute endocarditis (p < 0.020). Five-year survival after MVrep for acute endocarditis was 96 ± 4% and for healed endocarditis was 91 ± 5% (43).

PERCUTANEOUS VALVE AND RELATED SURGICAL PROCEDURES

Percutaneous pulmonary valve (PV) replacement. Since 2001, 23 of 24 patients have had successful PV replacement when the RV outflow tract did not exceed the maximum diameter of 22 mm. A larger stent developed for those with larger RV outflow tract was successfully implanted in 8 of 10 patients (44).

Percutaneous AV replacement. A PHV was successfully implanted in the subcoronary position in the first five of six “nonsurgical patients” with “end-stage” calcific AS; the sixth patient died shortly thereafter because the device was ejected to the ascending aorta. In the five patients, the AVA
Increased from 0.49 ± 0.08 to 1.66 ± 0.13 cm², LVEF increased from 24 ± 9.5 to 41 ± 12%; in two patients AR2+ increased to 3+; three of five patients died of non-cardiac causes at two, four, and eight weeks (45).

Percutaneous mitral annular reduction for MR. In nine adult sheep, HF and MR were produced by rapid ventricular pacing. A mitral annular constraint device (Fig. 4) was implanted through the right internal jugular vein in the coronary sinus and the great cardiac vein to create a short-term stable reduction (24.9 ± 2.5%) in the mitral annular septal-lateral dimensions (46). The MR, quantitated echocardiographically and expressed as ratio of left atrial area (MR/LAA), was reduced from 42 ± 6% to 4 ± 3%. Mean pulmonary artery wedge pressure fell from 26 ± 3 to 18 ± 3 mm Hg (p < 0.01) and cardiac output increased from 3.4 ± 0.3 to 4.3 ± 0.4 l/min (p = 0.01).

Percutaneous endovascular end-to-edge MVrep. This procedure was successfully performed in 12 of 14 adult pigs (Fig. 5); in 2 animals the clip released from the anterior leaflet. In the remaining 12 animals, the clip successfully approximated the middle scallops of the anterior and posterior leaflets to produce double orifice mitral valves (47), which is similar to the Alfieri repair in humans.

Surgical edge-to-edge MVrep. Alfieri presented data on 81 patients who underwent this procedure without annuloplasty from 1993 to 2001 (48). There were three hospital deaths and four late deaths. At four years, the survival was 85 ± 6.7%; 61 patients were in NYHA functional classes I or II, 9 were in classes III or IV; 9 patients required re-operation (freedom from re-operation was 89 ± 3.9%). Only 1 of 42 patients required re-operation when annular calcification, rheumatic disease, or rescue procedure were not present as risk factors. The authors concluded that overall results of the edge-to-edge technique are suboptimal when annuloplasty is not added to the repair.

A cohort of 224 patients underwent the Alfieri MVrep from 1997 to 2001 of whom 188 (84%) also underwent concomitant ring annuloplasty. Preoperative MR was 4+ in 109 patients (50%) and 3+ in 65 (30%). Hospital mortality was 2%. At three months, MR was present in 60% and was 3+ in 14%, the incidence of which rose “slowly thereafter” (49). The authors concluded: “In ischemic MR, steadily increasing prevalence of moderately severe and severe regurgitation after edge-to-edge repair suggests other techniques are needed.”

Comment: Tests for viability were not described in the last study (49) (see another article from the same institution in the section on MR). Mitral valve repair by percutaneous techniques is promising but needs further development and refinement. For MVrep, by percutaneous or surgical techniques, a combination of procedures and appropriate patient selection are likely to be needed.

**PROSTHETIC HEART VALVES**

Mechanical PHV. Starr-Edwards and St. Jude valves have similar outcomes. A prospective randomized trial of the Starr-Edwards valve (a model in use since 1965) and the St. Jude valve (first used in 1977) was performed at St. Thomas Hospital, London, United Kingdom (50). For AVR and for mitral valve replacement (MVR) there were no significant differences in survival, event-free survival, and all outcomes (Fig. 6, Table 4). Survival after AVR was related to LV function. Only 10% of all the deaths in the whole trial were related to the PHV. The average reduction in NYHA functional classes from preoperative levels to five years for Starr-Edwards and St. Jude for AVR was 1.4 and 1.5, respectively, and for MVR was 1.8 and 1.6, respectively.

Comment: This study is the only randomized trial comparing patient outcomes with different mechanical PHVs.

LONG-TERM RISK OF STROKE AND THE BENEFIT OF THE MAZE PROCEDURE AFTER MVR. Of 812 patients (age 18 to 79 years, median 58 years) who underwent MVR with a
mechanical prosthesis, the 15-year survival was 85.4 ± 3.2% (51). Risk factors for late mortality by multivariate analysis were preoperative NYHA functional class IV (p = 0.0032) and age >65 years (p = 0.0001). At 15 years, the freedom from stroke was 90.7 ± 6.5% in patients with regular rhythm compared with 73.8 ± 6.9% in patients with chronic atrial fibrillation (p < 0.0001). The risk factors for stroke on multivariate analysis were: history of stroke (p = 0.0003), chronic atrial fibrillation (p = 0.0004), no Maze procedure (p = 0.03), and year of operation (p = 0.05). The late incidence of atrial fibrillation was much lower in those who had a concomitant Maze procedure (Fig. 7).

INTERNATIONAL NORMALIZED RATIO (INR) SELF-MANAGEMENT. The Early Self Controlled Anticoagulation Trial II (ESCAT II) (52) randomized multicenter trial began in 1998 and compared a “conventional” group (INR 2.5 to 4.5) with a “low-dose” group (AVR: INR 1.8 to 2.8; MVR/double valve replacement (DVR) INR 2.5 to 3.5). The INR was within therapeutic range in 74% in the conventional group and 72% in the low-dose group. The linearized thromboembolic rate was 0.21% per year and for bleeding in the low-dose group versus the conventional group was 0.56% versus 0.91% per year (p = NS).

Comment: The low-dose group had an INR range almost identical to the recommendations in the 1998 American College of Cardiology/American Heart Association Guidelines, which were INR 2.0 to 3.0 for AVR and 2.5 to 3.5 for MVR (53).

Bioprosthetic PHV. MORE GOOD NEWS ABOUT THE CARPENTIER-EDWARDS PERICARDIAL VALVE (CE-PV). A prospective randomized trial compared CE-PV to the Toronto Stentless Porcine Valve (T-SPV). The primary end point was regression of LV mass determined by echocardiography indexed to body surface area (LVMI); the secondary outcome was the Duke Activity Status Index (54). Overall LVMI at 12 months for CE-PV and T-SPV was 22.3 g/m² versus 23.8 g/m² (p = 0.39). The Duke Activity Status Index scores improved significantly over time in both groups (p = 0.001); there was no significant difference between the two types of PHV (p = 0.10). Other findings are also of interest: Cardiopulmonary bypass times were longer for the T-SPV versus CE-PV (148.5 ± 30.9 min vs. 118.6 ± 36.3 min, p = 0.0001), and also for aortic cross-clamp times T-SPV versus CE-PV (123.6 ± 24.1 min vs. 95.4 ± 28.6 min, p = 0.0001). The AVA improved over time in both groups but was not statistically significant.

Table 4. Outcomes at 8 Years After Randomization

<table>
<thead>
<tr>
<th>At 8 Years</th>
<th>AVR</th>
<th>MVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
<td>65 ± 5%</td>
<td>71 ± 4%</td>
</tr>
<tr>
<td>Freedom from thromboembolism</td>
<td>86%</td>
<td>88%</td>
</tr>
<tr>
<td>Event-free survival</td>
<td>43%</td>
<td>45%</td>
</tr>
</tbody>
</table>

From Murday AJ et al. (50).
AVR = aortic valve replacement; MVR = mitral valve replacement.
in the T-SPV (p = 0.66), whereas the AVA in the CE-PV improved from 3 to 12 months from 1.53 ± 0.45 to 1.91 ± 0.9 cm² (p = 0.005). However, at 12 months the difference between the two was not significant: T-SPV versus CE-PV, 1.74 versus 1.91 cm² (p = 0.34).

**Comment:** This study is the only randomized trial comparing valve areas of two bioprosthetic valves at 12 months after AVR. The stentless valve is more difficult to insert, which accounts for the longer bypass and cross-clamp times. All readings of echocardiograms were performed at the core site by two experienced echocardiographers who were blinded to patient and prosthesis. The manufacturer’s labeled valve size was much bigger for the T-SPV (26.3 ± 2.0 mm vs. CE-PV 22.9 ± 2.0 mm, p = 0.0001). The reason the AVA at 12 months was not different was because the actual manually measured internal diameters before implantation were not significantly different (CE-PV 21.9 ± 2.0 mm vs. T-SPV 22.3 ± 2.0 mm, p = 0.29). The implication is to rely on the information of the effective internal diameter of PHV, and not on the manufacturer’s stated valve sizes (55). The Magna CE-PV, recently approved by the Food and Drug Administration, has an even larger effective internal diameter for any stated valve size.

**LV Mass Regression Is Similar for Three Different Valve Sizes.** The LV mass regression was evaluated 12 months after CE-PV insertion with 19-mm valves in 34 patients, 21-mm valves in 29 patients, and 23-mm valves in 25 patients (56). At follow-up after 2.3 ± 1 years, the AVA index (cm²/m²) in the three groups was 0.74 ± 0.12, 0.82 ± 0.15, 0.86 ± 0.13, respectively (p < 0.05 for 19 mm vs. 21 mm and vs. 23 mm). The relative LVMI regression (g/m²; mean ± SD) in the three groups was −20.7 ± 18.9, −19.3 ± 17.8, and −21.9 ± 15.7 (p = 0.86) (Fig. 8).

**Comment:** Inserting a small PHV in smaller people will have beneficial effects; the AVA index at ≥6 to 12 months after PHV insertion is also an important determinant of patient outcomes. (Also see the preceding text and valve prosthesis-patient mismatch).

At 10 years, the freedom from SVD for the CE-PV (n = 1,021) was 98.5 ± 1% versus 92 ± 2% (p = 0.04) for CE-porcine valve (n = 518) (57). In patients >70 years of age at the time of implantation of CE porcine valve, the rate of SVD was low at 15 to 18 years (57).

The CE-PV have a lower rate of SVD deterioration than porcine valves, including the T-SPV and Hancock II valve. The latter two PHV had SVD rates similar to earlier stented valves (58).

In an experimental study in rats, PHV were examined 90 days after implantation (59). The mean calcium content (µg/mg dry weight) of CE-PV was 3.30, which was significantly lower than that of another pericardial valve, Mitroflow (214.60; p < 0.01). The mean calcium content of the CE-PV was also lower than that of porcine valves, the Medtronic Mosaic (25.37; p = 0.02) and the Toronto SPV (244.43; p = 0.01) but not that of other CE-porcine valves.

Since 1992, CE-PV and CE-porcine valve are treated with XenoLogix (containing alcohol and Tween-80) during valve preparation. This experimental study provides one possible explanation for the lower rate of SVD with CE-PV.

**Re-Operative Mortality for SVD of Porcine Mitral PHV Is Lower in the Recent Era.** There were 34 deaths in 463 patients (7.3%) (60). The mortality from 1975 to 1986 was 9.8%, from 1987 to 1992 was 10.8%, and from 1993 to 2000 was 3.4% (p value for third vs. first time period was 0.05 and vs. second time period was 0.0005). The mortality for elective/urgent re-operation was 6% versus 17.8% for emergent (p = 0.0009). The mortality for patients in NYHA functional classes I and II was 0% (0 of 37), III was 5.1% (14 of 273), and IV was 11.7% (20 of 171) (p = 0.007). In the third time period, independent predictors of mortality by multivariate regression analysis were age at implant and at explant.

**Comment:** In this study there was a small number of patients in NYHA functional classes I and II.
Early autograft dysfunction after the Ross principle operation is not infrequent. Ninety-one patients, age 27 ± 10 years, underwent pulmonary autograft for AVR and cryopreserved homograft in the pulmonary position. Follow-up was 4.0 ± 1.9 years (range 1 to 8 years) (61). At seven years, freedom from aortic dilation was 42 ± 8%, freedom from regurgitation was 75 ± 8%, and freedom from re-operation was 85 ± 10%.

**Thrombosed PHV: Importance of Thrombus Size Diagnosed by TEE.** From 1985 to 2001, 107 patients (71 females; age 24 to 86 years) from 14 centers, all of whom had good definition of thrombus size by TEE, were identified (62). The mitral valve was affected in 73.8%, aortic in 12.2%, and tricuspid valve in 14%. A definite mass was seen in 86.2%; the largest area was 14.7 cm². The inability to visualize a mass on an obstructed valve was usually associated with a small thrombus or pannus affecting the lineage of prosthesis. Thrombi without significant hemodynamic obstruction were observed in 14 patients. After thrombolytic therapy, complete hemodynamic success (defined as return of gradient to “normal” levels) was achieved in 76.3% of the 93 obstructed valves, and partial success was seen in 8.6%. Thrombus with a soft mass was associated with a success rate of 91.5%, and a hard mass with a 75% success rate. A soft mass by TEE was the single best predictor of success (p = 0.029). Clinical success (defined as hemodynamic success without clinical complications) was achieved in 73.8%; for aortic, mitral, and tricuspid valves the success rates were 63.6%, 74.6%, and 93.3% (p = NS). In a logistic regression model, independent predictors of success were smaller thrombus area by TEE and lack of previous history of stroke (Table 5). Complications occurred in 17.8% (Table 6).

**Comment:** A good TEE is essential for clinical decision-making; it must be performed urgently in such patients because they are at high risk. The method used to calculate the thrombus area was not described; assuming the shape of the thrombus is a circle, a thrombus size of 0.8 cm² calculates to a diameter of 1 cm.

**Early Thrombosis After Mitral PHV and Outcome Related to Thrombus Size.** A cohort of 680 patients underwent TEE on day 9 after mechanical PHV. Early thrombi were detected in 64 (9.4%) (63). Maximum thrombus size <5 mm was observed in 29 (45%) patients (Group A) and ≥5 mm was observed in 35 (55%) patients (Group B). During early follow-up, complications occurred in 3.4% in Group A versus 22.9% in Group B patients (p = 0.027). In the long-term survey, complications occurred in 10.3% Group A patients and 31.4% Group B patients (p = 0.04).

**Comment:** The adequacy of anticoagulant therapy (early and late) was not described. Issues that need to be resolved are: Should all patients have early TEE after MVR, and if thrombus is found how should it be treated?

**Table 5. Outcome With Thrombolytic Therapy in Patients With Thrombosed PHV**

<table>
<thead>
<tr>
<th>Complication</th>
<th>Rate</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA FC I–II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombus &lt;0.8 cm²</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thrombus ≥0.8 cm²</td>
<td>41%</td>
<td>0</td>
</tr>
<tr>
<td>p value</td>
<td>0.003</td>
<td>—</td>
</tr>
<tr>
<td>NYHA FC III–IV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombus &lt;0.8 cm²</td>
<td>10.8%</td>
<td>5.4%</td>
</tr>
<tr>
<td>Thrombus ≥0.8 cm²</td>
<td>32.3%</td>
<td>12.9%</td>
</tr>
<tr>
<td>p value</td>
<td>0.03</td>
<td>—</td>
</tr>
<tr>
<td>Thrombus Area</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.8 cm²</td>
<td>6.25%</td>
<td>3.1%</td>
</tr>
<tr>
<td>0.8–1.5 cm²</td>
<td>28.6%</td>
<td>3.6%</td>
</tr>
<tr>
<td>p value</td>
<td>0.003</td>
<td>—</td>
</tr>
<tr>
<td>≥1.6 cm²</td>
<td>46.7%</td>
<td>20%</td>
</tr>
<tr>
<td>p values vs. &lt;0.8 cm² vs. 0.8–1.5 cm²</td>
<td>0.0001</td>
<td>0.016</td>
</tr>
<tr>
<td>Risk Factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombus area ≥0.8 cm²</td>
<td>34.9%</td>
<td>9.3%</td>
</tr>
<tr>
<td>History of stroke</td>
<td>42.3%</td>
<td>11.5%</td>
</tr>
<tr>
<td>Both risk factors</td>
<td>78.6%</td>
<td>21.4%</td>
</tr>
<tr>
<td>None of the two risk factors</td>
<td>7.7%</td>
<td>3.9%</td>
</tr>
</tbody>
</table>

**Comment:** The incidence of PHV thrombosis is low, but it is potentially a life-threatening complication.

**Table 6. Complications of Thrombolytic Therapy of Prosthetic Valve Thrombosis in 107 Patients**

<table>
<thead>
<tr>
<th>Complication</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral emboli</td>
<td>4 (3.7)</td>
</tr>
<tr>
<td>Central nervous system bleeding</td>
<td>2 (1.9)</td>
</tr>
<tr>
<td>Stroke</td>
<td>3 (2.8)</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>3 (2.8)</td>
</tr>
<tr>
<td>Coronary emboli</td>
<td>3 (2.8)</td>
</tr>
<tr>
<td>Bleeding requiring transfusion</td>
<td>4 (3.7)</td>
</tr>
<tr>
<td>Death</td>
<td>6 (5.6)</td>
</tr>
<tr>
<td>All embolic complications</td>
<td>15 (14.0)</td>
</tr>
<tr>
<td>Any complication</td>
<td>19 (17.8)</td>
</tr>
</tbody>
</table>

From Tong AT et al. (62).
sonography, counts of high-intensity transient signals in 39 patients with obstructed PHV were 8.3 ± 10.8 versus 2.2 ± 4.4 (p = 0.0002) in patients with normal PHV function (67).

Scoring system for prediction of risks for thromboembolism (TE). A total of 370 patients (249 AVR, 93 MVR, 28 DVR) were studied prospectively with a mean follow-up of 4.4 years (maximum 6.6). On multivariate analysis, 13 independent predictors for TE were identified. The authors stated, “These risk factors were additive when present in the same patient, enabled a scoring system to be developed that accurately predicted risk of TE based on number of risk factors” (68).

Short- and long-term impact of valve prosthesis-patient mismatch (VP-PM). SHORT-TERM INCREASED MORTALITY WITH SEVERE VP-PM. Thirty-day mortality was assessed in 1,266 consecutive patients undergoing AVR (69). In those with “severe” VP-PM (AVA ≤0.65 cm²/m²), the mortality was 7 of 27 patients (25.9%); with “moderate” (AVA ≤0.85 cm²/m²) and “mild” VP-PM (AVA >0.85 cm²/m²) the mortality was 27 of 447 (6.0%) and 23/769 (3.0%), respectively. Patients with severe VP-PM compared with moderate VP-PM had a much higher incidence of women, coronary artery disease, hypertension, diabetes, emergency/salvage operation, and concomitant coronary artery bypass graft surgery. The risk ratio for mortality for severe versus moderate was 7.2 (95% confidence interval of 2.5 to 20.9).

In analysis of predictors of mortality, the authors have combined the moderate and severe subgroups.

Comment: Although the body surface area of those in the severe VP-PM was larger than those in the moderate and mild subgroups, a very much higher percentage of these patients received PHV size ≤21 mm (77.8% in the severe group vs. 31.1% in the moderate group and 9.5% in the mild group). There was no separate analysis of risk predictors in only the subgroup of severe VP-PM, and thus, one cannot be certain whether co-morbid conditions, rather than severe VP-PM, were the major causes of the increased mortality. In this regard, small prosthesis size (≤21 mm) was an important predictor of operative mortality for AVR in critically ill patients (70). It is not possible clinically to calculate valve area with any degree of precision to hundreds of a centimeter, and thus, severe VP-PM should be ≥0.6 cm²/m², moderate >0.6 cm² to <0.9 cm²/m², and mild should be ≥0.9 cm²/m² (58).

LATE RESULTS OF VP-PM: INCREASED HF AND HF DEATHS. In a study of 1,563 patients undergoing AVR with follow-up of 4.3 ± 3.3 years (range 60 days to 17.1 years) (71), the adjusted hazard ratio (95% confidence interval) at five years for HF with mismatch (≤0.75 cm²/m²) was 1.64 (1.01 to 2.56), p = 0.047, and for HF deaths was 2.09 (1.03 to 4.27), p = 0.043.

REFERENCES


Reprint requests and correspondence: Dr. Shahbudin H. Rahimtoola, Distinguished Professor, University of Southern California, 2025 Zonal Avenue, Los Angeles, California 90033.

Year in Valvular Heart Disease

JACC Vol. 45, No. 1, 2005
January 4, 2005:111-22


