Are Stentless Valves Superior to Modern Stented Valves?
A Prospective Randomized Trial

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Background—It is presumed that stentless aortic bioprostheses are hemodynamically superior to stented bioprostheses. A prospective randomized controlled trial was undertaken to compare stentless versus modern stented valves.

Methods and Results—Patients with severe aortic valve stenosis (n=161) undergoing aortic valve replacement (AVR) were randomized intraoperatively to receive either the C-E Perimount stented bioprosthesis (n=81) or the Prima Plus stentless bioprosthesis (n=80). We assessed left ventricular mass (LVM) regression with transthoracic echocardiography (TTE) and magnetic resonance imaging (MRI). Transvalvular gradients were measured postoperatively by Doppler echocardiography to compare hemodynamic performance. There was no difference between groups with regard to age, symptom status, need for concomitant coronary artery bypass surgery, or baseline LVM. LVM regressed in both groups but with no significant difference between groups at 1 year. In a subset of 50 patients, MRI was also used to assess LVM regression, and again there was no significant difference between groups at 1 year. Hemodynamic performance of the 2 valves was similar with no difference in mean and peak systolic transvalvular gradients 1 year after surgery. In patients with reduced ventricular function (left ventricular ejection fraction [LVEF] <60%), there was a significantly greater improvement in LVEF from baseline to 1 year in stentless valve recipients.

Conclusions—Both stented and stentless bioprostheses are associated with excellent clinical and hemodynamic outcomes 1 year after AVR. Comparable hemodynamics and LVM regression can be achieved using a second-generation stented pericardial bioprosthesis. In patients with ventricular impairment, stentless bioprostheses may allow for greater improvement in left ventricular function postoperatively. (Circulation. 2006;114[suppl I]:I-535–I-540.)

Key Words: aortic stenosis ■ aortic valve ■ surgery ■ valve replacement ■ valves

Aortic valve replacement (AVR) is the treatment of choice for patients with significant aortic valve stenosis. This procedure is associated with a low perioperative mortality, minimal morbidity, and good long-term outcomes.1 To optimize the hemodynamic characteristics of prostheses, elimination of the sewing ring and stent of conventional bioprosthetic valves has been proposed. The intention with these “stentless valves” was to maximize the area for blood flow across the valve, which, in turn, might equate to superior hemodynamic performance through lower postoperative transvalvular gradients.2 Their design is postulated to impart characteristics which more closely emulate the normal physiology of the aortic valve and root. It has been further suggested that more favorable hemodynamic performance may lead to enhanced resolution of left ventricular hypertrophy (LVH),1 a known potent cause of premature mortality.4,5 However, in concert with the evolution of stentless valves, there have been important advances in the design of conventional stented valves. Modern stented valves have been shown to have excellent hemodynamic characteristics.6,7 Previous randomized controlled trials have used a variety of stented and stentless valves, several of which are currently outmoded.8,9 Furthermore, many of the trials were too small for meaningful conclusions to be drawn.10 Our aim was to conduct a randomized controlled trial to compare widely accepted state-of-the-art stentless and stented prostheses. Clinical outcomes, hemodynamic performance, and postoperative left ventricular mass (LVM) regression were the principal outcomes assessed.

Methods

Patients
Patient flow through the trial is summarized in Figure 1. The study was performed at 2 institutions (Papworth Hospital, Cambridge and Morriston Hospital, Swansea) by 3 surgeons, all experienced in the placement of both stented and stentless valves. Ethical approval of the study protocol was obtained from local research ethics committees and all patients gave signed consent.
Patients were eligible for the study if they were older than age 65 years and required AVR for aortic valve disease, in which stenosis was the dominant lesion, with a peak aortic transvalvular gradient >50 mm Hg at transthoracic echocardiography. The need for concomitant coronary artery bypass grafting did not preclude patients from entering the trial. Preoperative exclusion criteria were: active aortic valve infection, active malignant disease, renal failure requiring dialysis, AVR being performed primarily for aortic valve regurgitation, the requirement of additional cardiac procedures (other than coronary artery bypass grafting), emergency operations, or previous cardiac surgery. In addition, patients were excluded intraoperatively if the surgeon considered them unsuitable for the implantation of a stentless valve (abnormal coronary anatomy, root calcification, annular diameter >29 mm). Postoperatively patients received 150 mg of aspirin as prophylaxis against valvular thromboembolism. Patients were not formally anticoagulated with warfarin unless there was a specific indication such as paroxysmal or chronic atrial fibrillation.

Surgical Technique, Intraoperative Assessment, and Randomization

After anesthesia was induced, the chest was opened through a median sternotomy. Cardiopulmonary bypass was established using a 24-Fr ascending aortic cannula and a single 2-stage venous cannula. Myocardial protection was achieved through the infusion of cold blood cardioplegia into the isolated aortic root. A transverse aortotomy was used to access the aortic valve. After excision of the aortic valve and annular debridement, the diameter of the aortic annulus was measured with precalibrated cylindrical sizers. Proprietary valve sizers were also used to determine the optimal sizes of both stented and stentless valves for each patient before randomization. Before proceeding, the surgeon had to be satisfied that it was safe to implant either a stented or a stentless valve. Participants were randomized on a 1:1 basis to receive either the Edwards Prima Plus stentless porcine bioprosthesis (Edwards Lifesciences, Irvine, Calif) or the Carpentier-Edwards (C-E) Perimount pericardial stented bioprosthesis (Edwards Lifesciences, Irvine, Calif). The trial statistician produced a computer-generated randomization list and allocations were contained in sequentially numbered and sealed envelopes. The group allocation was not revealed to the surgeon until all intraoperative measurements were recorded.

Valve Implantation Technique

The stentless prosthesis was implanted with the full subcoronary technique using a 2-layer suture line. Stented valves were implanted in a supra-annular position with interrupted annular sutures as described previously.

Echocardiographic Measurements

Two-dimensional transthoracic echocardiography was used to measure transvalvular gradients and LVM preoperatively, and at 1 week, 8 weeks, and 12 months postoperatively. Standard apical, long-axis, and short-axis views, together with Doppler flow measurements, were utilized.

Cardiac MRI

A consecutive subset of patients at one center (Papworth) also underwent cardiac magnetic resonance imaging (MRI) to allow for further quantification of LVM and function at baseline and 1 year after surgery. Because of cost restraints, we were unable to submit all trial participants to MRI evaluation. Two-chamber, 4-chamber, and left ventricular outflow tract images were obtained. Seven to 10 short-axis slices were used to image the entire left ventricle during alternate heartbeats for 40 acquisitions.

Objectives and Outcomes

The main objective of this study was to compare clinical and hemodynamic outcomes between the stented and stentless valve groups. The primary outcomes are peak and mean systolic transvalvular gradients and LVM regression at 12 months postoperatively. Secondary outcomes are operative characteristics, postoperative complications, 30-day mortality, and actuarial survival 1 year after operation. Postoperative complications were reported according to the joint guidelines of the Society of Thoracic Surgeons (STS) and American Association of Thoracic Surgery (AATS).13

Statistical Methods

For the purpose of the calculation, it was assumed that, at 12 months, mean (SD) peak and mean systolic gradient and effective orifice area index in the stented valve group would be 30 mm Hg (6), 15 mm Hg (3.5), and 0.8 cm²/m² (0.35), respectively. It was anticipated that a reduction of one-quarter in peak and mean gradient and an increase of one-third in effective orifice area index would be observed in the stentless valve group. No difference in LVM index was expected between the 2 groups. The required sample size was 130 participants (based on 90% and 5% significance) and the intention was to recruit 160 to allow for loss to follow-up. Data analysis was by intention-to-treat basis for those patients who had primary outcome measurements at 12 months. Baseline findings, operative characteristics, and outcomes were compared between the 2 groups using 2-sample t tests or Mann-Whitney U tests for continuous variables, and χ² or Fisher exact tests in the case of categorical variables. To compare outcomes, multivariate analysis of variance was used including valve as a fixed factor and baseline measurement as a covariate. Because there was no loss to follow-up before 30 days postoperatively, 30-day mortality was compared using Fisher exact test. Overall survival was estimated using Kaplan-Meier methods and compared using the log-rank test. Statistical significance refers to P<.05.

Results

Patient Characteristics

Between November 2001 and August 2004, 188 patients were recruited to the study (Figure 1). Three percent (5/188) of patients who had been consented were withdrawn preoperatively for reasons previously reported.2 Twenty-two (12%) patients were excluded intraoperatively, leaving 161 patients for randomization. Reasons for intraoperative exclusion are
listed in Figure 1. The most common reason for exclusion was excessive splaying of the sinotubular junction secondary to ascending aortic dilatation. Eighty-one patients were randomized to receive a C-E Perimount stented valve and 80 patients to receive a Prima Plus stentless valve. All patients received the allocated valve and 147 patients completed the study, with the last follow-up assessment taking place in July 2005.

Demographics were similar for stentless and stented valve recipients (Table 1). Preoperative transthoracic echocardiography confirmed that the severity of aortic stenosis, baseline LVM, and LVEF were similar between both groups (Table 1).

Intraoperative and Perioperative Data
There was no significant difference in the mean absolute native aortic annular size, although patients in the stentless group received a larger valve prosthesis (25.3 ± 2.0 versus 23.2 ± 2.0 mm, P < 0.001). Myocardial ischemic and cardiopulmonary bypass times were significantly longer when implanting stentless valves (Table 1). This observation held true whether the patient required concomitant coronary artery bypass grafting.

There were no differences in Intensive Therapy Unit (ITU) stay (median 21 hours in both groups) or hospital stay (median 8 days in both groups).

Survival and Complications
The 30-day mortality was 2.5% (95% confidence interval [CI], 0% to 9.5%) in the stented group compared with 3.7% (95% CI, 0% to 10.5%) in the stentless group. This difference was not significant (P = 0.682). Overall there were 14 deaths in our study population, with 7 in each group. The mean (standard deviation) follow-up time for the entire cohort was 1.94 (0.91) years. No differences were noted between stented and stentless valves recipients in one year survival (92.5% versus 95.0%; P = 0.97). There was no difference in perioperative outcomes or the frequency of common postoperative complications, this has been described previously.12 One patient in each group experienced a cerebrovascular event within the 1-year follow-up period. Two patients who underwent stentless valve replacement developed prosthetic valve endocarditis on days 26 and 52; both patients died as a result of this complication.

Echocardiographic Evaluation of Transvalvular Gradient, LVEF, and LVM Regression
Transthoracic echocardiography was used to assess hemodynamic performance. In both groups there was a large and comparable reduction in both peak and mean systolic transvalvular gradients 1 week after surgery, this reduction was maintained at 1 year (Figures 2 and 3 and Table 2). There were no significant differences between groups in either peak or mean gradients at 1 week, 8 weeks, or 12 months after surgery. Similarly, effective orifice area (EOA) and its index increased in both groups from baseline (Figure 4 and Table 2).

Figure 2. Peak systolic transvalvular gradient (95% CI), with probability value from analysis of variance, adjusted for baseline measurements.

Figure 3. Mean systolic transvalvular gradient (95% CI), with probability value from analysis of variance, adjusted for baseline measurements.
2). There was a trend toward a continual increase in EOA in the stentless group. At 1 year the EOA was significantly greater in stentless valve recipients (Figure 4 and Table 2). There was a significant reduction in LVM from baseline to 1 year postoperatively in both groups (Figure 5). There was no difference in overall LVM or the rate of regression between groups at 1 week, 8 weeks, or 1 year postoperatively (Table 2).

There was no significant difference between groups in LVEF adjusted for baseline, as measured by echocardiography during follow-up (Table 3). However, for patients who had LVEF/110H1102160% at baseline, LVEF increased by 7% (SD 14%) at 1 week and 13% (SD 11%) at 12 months in the stented valve group compared with 14% (SD 14%) and 21% (SD 14%) in the stentless group. The difference between the groups in improvement was significant at 12 months (P/110H110210.032). Otherwise, in this subgroup there were no differences between stentless and stented recipients in peak or mean systolic gradient, effective orifice area, or left ventricular mass 1 year postoperatively. Baseline demographics, including preoperative LVEF in this subgroup were comparable.

Cardiac MRI Evaluation of LVM Regression
The stented and stentless valve recipients in the subgroup who had cardiac MRI had similar baseline characteristics. Preoperative LVM was measured in 50 patients (27 stented, 23 stentless). Because of death, contraindications, and patient refusal, only 39 patients (20 stented, 19 stentless) returned for measurement of LVM 1 year postoperatively. There was a significant reduction in LVM in both groups from baseline to 1 year (Table 3 and Figure 5). However, there was no difference between groups in overall LVM, adjusted for baseline, at 1 year postoperatively (Figure 5).

Discussion
In population studies, LVH has been associated with an increased incidence of sudden death, myocardial infarction, congestive heart failure, and consequently poorer long-term survival than age-matched controls.4 The majority of these studies are observational in design, in patients with hypertension, and not specifically from patients with LVH secondary to aortic valve disease.5 It has been suggested that enhanced regression of LVH after AVR may translate into clinical benefits. As yet, this hypothesis has not been confirmed by specific studies to determine whether survival after AVR is related to the rate and degree of resolution of LVH. Although AVR is associated with a low perioperative mortality and an acceptable long-term outcome, the 10-year survival is only 60%.14 More complete resolution of LVH may lead to improvements in long-term survival. Observational studies

### Table 2. Hemodynamic Outcomes at 1 Year

<table>
<thead>
<tr>
<th></th>
<th>All Study Patients</th>
<th>Stented n=81</th>
<th>Stentless n=80</th>
<th>Stented-Stentless Difference (95% CI)*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak systolic gradient, mm Hg (SD)</td>
<td>21 (8)</td>
<td>19 (9)</td>
<td>2.44 (–0.41, 5.28)</td>
<td>0.092</td>
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<tr>
<td>Mean systolic gradient, mm Hg (SD)</td>
<td>10 (4)</td>
<td>9 (5)</td>
<td>1.24 (–0.23, 2.71)</td>
<td>0.099</td>
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<td>Effective orifice area, cm² (SD)</td>
<td>1.44 (0.5)</td>
<td>1.66 (0.4)</td>
<td>–0.19 (–0.35, –0.03)</td>
<td>0.017</td>
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<tr>
<td>Effective orifice area index, cm²/m² (SD)</td>
<td>0.79 (0.3)</td>
<td>0.92 (0.3)</td>
<td>–0.12 (–0.20, –0.03)</td>
<td>0.010</td>
<td></td>
</tr>
<tr>
<td>LV mass, grams (SD)</td>
<td>198 (62)</td>
<td>211 (77)</td>
<td>–11.6 (–33.5, 10.4)</td>
<td>0.300</td>
<td></td>
</tr>
<tr>
<td>LV mass index, g/m² (SD)</td>
<td>107 (30)</td>
<td>116 (42)</td>
<td>7.2 (–19.5, 5.0)</td>
<td>0.246</td>
<td></td>
</tr>
<tr>
<td>Patients Having Cardiac MRI  n</td>
<td>20</td>
<td>19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV mass (MRI), grams (SD)</td>
<td>149 (50)</td>
<td>177 (50)</td>
<td>–15.4 (–35.0, 4.3)</td>
<td>0.122</td>
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</tr>
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</table>

*Adjusted for baseline.
have reported that stentless bioprostheses confer hemodynamic advantages after AVR, which may allow for superior regression of LVH and more favorable long-term outcomes in patients operated for aortic valve disease.3,15

An advantage of the stentless design, confirmed in this study, is that it provides a larger EOA for transvalvular blood flow. AVR led to a substantial increase in EOA from baseline values in both groups. No significant difference was noted in the EOA between groups in the early postoperative period. There was however a trend toward a continual increase in EOA in recipients of a stentless valve and, in fact, the EOA in this group was noted to be significantly greater than the stented group at 1 year. One of the proposed benefits of stentless prostheses is that they can continue to remodel within the aortic root. Other investigators have commented that there may be potential for the effective orifice area to increase progressively over time as the normal dynamic nature and distensibility of the aortic root is maintained.15 However, despite a larger cross-sectional area for blood flow across the stentless aortic valve, this did not confer superior hemodynamics in terms of lower transvalvular gradients at rest. In our analysis, we were unable to document any important difference in either peak or mean systolic transvalvular gradients between the 2 groups at 1 year after surgery. The transaortic gradient decreased in both groups to a very similar extent. Finally, LVM as measured by echocardiography decreased significantly in both groups from baseline values. There was, however, no statistically significant difference between the 2 groups in the extent of LVM reduction from baseline at 1 week, 8 weeks, or 1 year postoperatively. There was also no difference between groups in absolute values of LVM at 1 year or any of the earlier postoperative time points.

Cardiac MRI is a more recent modality used for the measurement of LVM. It may confer benefits over 2-dimensional echocardiography, which is operator-dependent, relies on satisfactory acoustic windows, and is associated with larger error. Using MRI, the entire left ventricle can be imaged using contiguous short-axis slices allowing precise calculations of left ventricular mass, volume, and function. This results in accurate and highly reproducible measurements. In a subgroup of our trial cohort, we further analyzed LVM using MRI. There was a significant reduction in overall LVM from baseline in recipients of both a stented and a stentless valve. However, we again failed to document any significant difference in absolute LVM or its regression between groups 1 year after AVR.

Our inability to document any hemodynamic advantages or superior LVM regression after stentless AVR parallels the findings of other recent randomized trials.10,16 Furthermore, in our trial we used 2 modalities to measure LVM and its subsequent regression after AVR, both failed to reveal any significant difference between groups in resolution of LVH. This is in contrast with earlier reports.8,9 These findings may reflect the progressive refinement and improvement in the design of modern stented bioprostheses. Newer generation stented valves have lower profile stents and more narrow sewing rings, which produce less impedance to transvalvular flow than older designs. Excellent hemodynamic performance of stented prostheses in the aortic position has been documented by a number of investigators.6,7 Second-generation stented pericardial bioprostheses, such as the C-E perimount valve used in our study, have, in particular, been demonstrated to confer excellent hemodynamics.6

It has been inferred that the use of stentless bioprostheses may be particularly advantageous in the setting of preoperative ventricular impairment. This is based on the findings of a few investigators who suggest that stentless valves may allow for greater improvement in left ventricular function postoperatively.17 It is has been demonstrated that early after AVR, stentless prostheses allow for greater and more immediate reduction in left ventricular systolic wall stress. This observation has been correlated with improved ventricular function in the early postoperative period.17 Our randomized study seems to substantiate this observation. There was a trend toward greater increase in ejection fraction from baseline at 1 week after stentless valve implantation in the group with reduced LVEF. At 1 year, this finding was statistically significant. In patients with reduced ventricular function, this

<table>
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<th>All Study Patients</th>
<th>Stented (n=81)</th>
<th>Stentless (n=80)</th>
<th>Stentless-Stented difference (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) baseline LVEF, (%)</td>
<td>63 (14)</td>
<td>62 (14)</td>
<td>1.1 (−3.3, 5.6)</td>
<td>0.613</td>
</tr>
<tr>
<td>Mean (SD) LVEF at 1 week, (%)</td>
<td>60 (11)</td>
<td>61 (14)</td>
<td>−1.8 (−5.8, 2.1)</td>
<td>0.362</td>
</tr>
<tr>
<td>Mean (SD) LVEF at 1 year, (%)</td>
<td>64 (12)</td>
<td>65 (12)</td>
<td>−1.4 (−5.2, 2.4)</td>
<td>0.470</td>
</tr>
<tr>
<td>Low LVEF (&lt;60%)</td>
<td>n=31</td>
<td>n=25</td>
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<tr>
<td>Mean (SD) baseline LVEF, (%)</td>
<td>49 (9)</td>
<td>44 (10)</td>
<td>4.8 (−0.5, 10.1)</td>
<td>0.076</td>
</tr>
<tr>
<td>Mean (SD) LVEF at 1 week, (%)</td>
<td>56 (13)</td>
<td>58 (14)</td>
<td>−4.3 (−11.7, 3.2)</td>
<td>0.254</td>
</tr>
<tr>
<td>Mean (SD) LVEF at 1 year, (%)</td>
<td>63 (12)</td>
<td>65 (11)</td>
<td>−4.4 (−10.9, 2.1)</td>
<td>0.176</td>
</tr>
<tr>
<td>Peak systolic gradient, mm Hg (SD)</td>
<td>21 (10)</td>
<td>18 (7)</td>
<td>3.7 (−1.1, 8.6)</td>
<td>0.126</td>
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<tr>
<td>Mean systolic gradient, mm Hg (SD)</td>
<td>10 (5)</td>
<td>8 (4)</td>
<td>1.9 (−0.5, 4.3)</td>
<td>0.111</td>
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<tr>
<td>Effective orifice area, cm² (SD)</td>
<td>1.5 (0.6)</td>
<td>1.7 (0.3)</td>
<td>−0.14 (−0.41, 0.12)</td>
<td>0.291</td>
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<tr>
<td>LV mass (TTE), grams (SD)</td>
<td>209 (64)</td>
<td>210 (65)</td>
<td>−3.1 (−36.1, 29.9)</td>
<td>0.851</td>
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</tbody>
</table>

*Adjusted for baseline.
finding may have important implications for long-term outcome.

Our observations suggest that the routine use of stentless bioprostheses over stented valves in all patients, on the presumption that they confer hemodynamic advantages, is unlikely to be justified. However, in specific patient groups undergoing AVR, stentless valves may provide important benefits. We noted a trend toward improved hemodynamic performance of stentless valves in patients with smaller aortic annuli. In patients with an annular diameter of 21 mm or less, the mean systolic gradient was significantly lower in stentless valve recipients. However, this patient group comprised only a small proportion of our entire study cohort (the mode implanted valve size was 25 mm in both groups). Larger randomized studies in patients with smaller annular diameters are required to substantiate these findings as irrespective of the valve type implanted, a patient with a 25-mm aortic annular diameter should possess sufficient cross-sectional area to avoid any important obstruction to transvalvular flow.

As our intraoperative data indicate, one of the benefits of a stentless prosthesis is that a larger valve size can be implanted into a given sized aortic annulus. This is likely to be most beneficial in patients with smaller annular dimensions, as it may avoid patient–prosthesis mismatch, which can adversely affect hemodynamic outcomes and prognosis.18 In our study, patients receiving stentless valves had a significantly greater effective orifice area and effective orifice area index compared with those with stented valves 1 year after AVR. The long-term hemodynamic and prognostic implications of this finding need to be investigated during further follow-up.

In conclusion, both stented and stentless bioprostheses are associated with excellent clinical and hemodynamic outcomes 1 year after AVR. Comparable hemodynamics and LVM regression can be achieved using a second-generation stented pericardial bioprosthesis. In patients with ventricular impairment, stentless bioprostheses may allow for greater improvement in left ventricular function postoperatively.

Acknowledgments

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Disclosures

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References

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