Randomized Comparison of Stentless Versus Stented Valves for Aortic Stenosis
Effects on Left Ventricular Mass

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Background—Aortic valve replacement (AVR) is the established treatment for severe aortic stenosis. In response to the long-term results of aortic homografts, stentless porcine valves were introduced as an alternative low-resistance valve. We conducted a randomized trial comparing a stentless with a stented porcine valve in adults with severe aortic stenosis.

Methods and Results—The primary outcome was change in left ventricular mass index (LVMI) measured by transthoracic echocardiography and, in a subset, by cardiovascular MR. Measurements were taken before valve replacement and at 6 and 12 months. Patients undergoing AVR with an aortic annulus ≤25 mm in diameter were randomly allocated to a stentless (n=93) or a stented supra-annular (n=97) valve. There were no significant differences in mean LVMI between the stentless versus stented groups at baseline (176±62 and 182±63 g/m², respectively) or at 6 months (142±49 and 131±45 g/m², respectively), although within-group changes from baseline to 6 months were highly significant. Changes in LVMI measured by cardiovascular MR (n=38) were consistent with the echo findings. There was a greater reduction in peak aortic velocity (P<0.001) and a greater increase in indexed effective orifice area (P<0.001) in the stentless group than in the stented group. There were no differences in clinical outcomes between the 2 valve groups.

Conclusions—Despite significant differences in indexed effective orifice area and peak flow velocity in favor of the stentless valve, there were similar reductions in left ventricular mass at 6 months with both stented and stentless valves, which persisted at 12 months. (Circulation. 2005;112:2696-2702.)

Key Words: echocardiography ■ hypertrophy ■ magnetic resonance imaging ■ stenosis ■ valves
ing longer cardiopulmonary bypass and ischemic times. Previous studies comparing the effect of stentless and stented valves on LV mass regression after AVR have shown conflicting results. Despite this, there is a general belief that greater relief of valve orifice narrowing relates to a more favorable outcome. Most of these studies were too small to provide a reliable comparison, and many were not randomized, thus introducing potential biases. To address this issue, we performed the Aortic Stentless versus Stented valve assessed by Echocardiography Randomized Trial (ASSERT) study. The aim of the study was to compare the effect of 2 similarly manufactured porcine valves (a stentless [Prestyled Freestyle, Medtronic Inc] valve and a stented [Mosaic, Medtronic Inc] valve) on LV mass regression in patients with aortic stenosis.

**Methods**

This was a prospective, multicenter randomized study. Patients were recruited from 10 hospitals in the United Kingdom, Norway, Belgium, and Poland (Appendix A in the online-only Data Supplement; http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.104.521161/DC1). Eligible patients were those with aortic stenosis scheduled for AVR. Clinical exclusion criteria were as follows: age <40 years, previous surgery on the aortic valve, need for aortic root replacement, need for additional valve repair or replacement, acute infective endocarditis, aortic valve disease with predominant aortic regurgitation, cerebrovascular accident within the previous 6 months, poor quality echocardiogram, or inability to comply with follow-up procedures. There were additional exclusion criteria based on assessment at the time of surgery (see below).

Criteria for the severity of aortic stenosis requiring AVR were left to the judgment of the individual cardiac surgeon. All study centers had appropriate local ethics approval for the trial. Written informed consent was obtained from all patients.

During the operation the annulus size was measured with the use of the Freestyle sizer. Patients with an annulus size ≤25 mm and without any other contraindication to implantation of either valve in the view of the surgeon (eg, extensive root calcification, coronary ostia opposed by 180°, presence of 2 coronary ostia very close to each other, or excessive disproportion between sinotubular junction and annulus [eg, sinotubular junction >2 mm or 10% greater than annulus diameter]) were randomized into the study.

The reason for selecting an annulus size of ≤25 mm was because any differences between valves would be more apparent in this range.

**Figure 1.** Consort diagram showing number of patients enrolled, randomized, and followed up. ITT indicates intention to treat.
Outcomes and Follow-Up

The primary outcome of the study was reduction in LV mass index (LVMI) at 6 months (Appendix B in the online-only Data Supplement). Secondary outcomes were LVMI at 12 months, LV function (fractional shortening and ejection fraction), NYHA class and 6-minute walk test, quality of life (Short Form–36 [SF-36] health survey), and clinical events up to 12 months.

Treatment and Procedures

Randomization

After checking the eligibility of subjects and obtaining informed consent, investigators registered patients by telephone contact with the coordinating center (Clinical Trials and Evaluation Unit, Royal Brompton Hospital, London, UK). Registration of patients and confirmation of eligibility criteria were required before release of the case report form and unique study identification number. Each case report form contained a randomization envelope. During the operation, the surgeon determined that the annulus size was ≤25 mm using the Freestyle valve sizer and assessed whether the patient was eligible for the study from a surgical point of view. If the patient was considered suitable for either valve, the envelope was opened, and the patient was randomized to one of the study valves. Randomization was stratified by center and by whether the patient required concomitant coronary artery bypass grafting (CABG).

Valves and Surgical Procedures

The Freestyle (stentless) and Mosaic (stented) valves are both manufactured by Medtronic Inc and are composed of similar porcine biological materials. Both valves are preserved in 0.2% glutaraldehyde, subjected to zero-pressure fixation, and treated with α-amino oleic acid to reduce calcification of the valve. The Mosaic bioprosthesis is mounted on a flexible acetal homopolymer stent covered with polyester fabric. As part of the study protocol, it was required that the Mosaic valve be inserted with the use of simple nonmatress, interrupted sutures ensuring fixation in a supra-annular position. The Freestyle stentless valve was inserted in the subcoronary position, and it was recommended that interrupted sutures be used for the proximal layer and continuous sutures for the distal layers and separate support for the 3 commissures. The non–coronary sinus was left unscalloped, similar to the subcoronary insertion of a homograft. It was recommended that patients receive aspirin 80 to 325 mg/d for the first 12 postoperative weeks.

Echocardiography

Echocardiographic examination was performed before the operation, before discharge, and at 6 and 12 months. Patients with an inadequate preoperative echocardiogram for M-mode assessment of LV mass were not enrolled into the study. The required echocardiographic views (parasternal long-axis, apical 4- and 5-chamber views) with prespecified 2D cineloops, M-mode, and Doppler were recorded on a super-VHS videotape. All tapes were sent to the echocardiography core laboratory at the Royal Brompton Hospital for analysis by an experienced echocardiographer blinded to the type of aortic valve substitute. The technical quality of the echocardiograms was also assessed by the core laboratory throughout the study. From M-mode recordings of the LV, end-systolic and end-diastolic dimensions were measured with leading-edge methodology. This assessment was always recorded on the first part of the tape separated from the recording of the rest of the views so that the echocardiographer was blinded to the type of aortic prosthesis when calculating LV mass.

Measurements were obtained for a mean of 3 consecutive beats when the patient was in sinus rhythm or 5 consecutive beats if the patient was in atrial fibrillation. All measurements were done in accordance with the recommendations of the American Society of Echocardiography. Valve EOA, fractional shortening, and ejection fraction were calculated as described in Appendix B in the online-only Data Supplement. LV mass was calculated by the Penn Convention formula (Appendix B in the online-only Data Supplement). Aortic flow velocities were assessed by the use of continuous-wave Doppler, and LV outflow velocities and LV filling were assessed by pulse-wave Doppler. The interobserver and intraobserver variabilities of LVMI by echocardiography were 0.71 and 0.81, respectively.

Cardiovascular Magnetic Resonance

Patients from 2 centers were enrolled for the cardiovascular magnetic resonance (CMR) substudy (Royal Brompton Hospital, London, UK, and Medical University of Silesia, Silesia, Poland) to assess LV mass and LV volumes. CMR can be used to tomographically section the entire heart, providing accurate 3D measurements of global and segmental LV volume and mass, independent of echocardiographic geometric assumptions. Patients were scanned while they were supine (1.5-T Sonata or 1-T Harmony, both Siemens). A phased-array radiofrequency receiver coil was placed on the chest. All images were obtained by repeated breath-holds and ECG gating. End-diastolic epicardial and endocardial borders were traced for calculation of LV mass and volumes. LV mass was estimated by semiautomatic software analysis (CMRTools, Cardiovascular Imaging Solutions). The interobserver and intraobserver variabilities of LVMI by CMR were 0.82 and 0.98, respectively.

Sample Size and Statistical Analysis

On the basis of a prior study, the ASSERT study was powered to detect a difference in LVMI (g/m²) between the stentless and stented groups of 15%, with an assumed SD of 42 g/m², an α of 0.01, and a power of 90%. This required a sample size of 208 patients, allowing for a 20% dropout rate. Comparisons between groups for LVMI (and other continuous variables) were performed with the use of mean differences from baseline compared by mixed-model ANCOVA for a 20% dropout rate. Comparisons between groups for LVMI by CMR were 0.82 and 0.98, respectively.

Results

Two hundred thirty-four patients were registered for the study, but 1 patient died before surgery, and 43 were considered unsuitable at the time of surgery. The main reason for patients not being included was an annulus size >25 mm, and most of the other reasons were surgical in nature (Figure 1). Therefore, 190 patients were randomized (envelope opened), 93 patients to stentless (Freestyle) and 97 to stented (Mosaic) bioprosthetic valves. Baseline characteristics were similar between both groups (Table 1).

| Table 1. Patient Characteristics and Operative Data |
|-----------------------------------------|----------------|--------------------|
|                                       | Stented       | Stentless          |
|                                       | (n=97)        | (n=93)             |
| Age, mean±SD, y                       | 70.9±8.3      | 70.1±9.2           |
| Male sex, n (%)                       | 47 (49)       | 58 (62)            |
| Body surface area, mean±SD, m²        | 1.86±0.19     | 1.85±0.21          |
| Prior myocardial infarction, n (%)    | 5 (5)         | 6 (7)              |
| NYHA class III-IV, n (%)              | 46 (47)       | 40 (43)            |
| Fractional shortening, mean±SD, %     | 35±10         | 35±10              |
| Annulus size, mean±SD, mm             | 23.2±1.7      | 23.6±1.7           |
| Valve size, mean±SD, mm               | 22.7±1.5      | 23.8±1.8           |
| CPB time, mean±SD, min                | 99±41         | 133±37*            |
| Cross-clamp time, mean±SD, min        | 70±28         | 100±30*            |
| CABG, n (%)                           | 36 (37)       | 38 (41)            |

*P<0.001 stented vs stentless group.
Operative Findings
The mean annulus size was 23.4 ± 1.7 mm, without significant differences between groups (Table 1). The average valve size was 23.8 ± 1.8 mm in the stentless group and 22.7 ± 1.5 mm in the stented group. Cardiopulmonary bypass time and cross-clamp time were significantly greater in the stentless group than in the stented group. Concomitant CABG surgery was performed in 39% of the patients.

LV Mass, Valve Orifice Area, and Valve Hemodynamics
LVMI decreased at 6 months in both valve groups, but there were no significant differences in mean LVMI between the 2 groups (P=0.11) (Table 2 and Figure 2). There were also no differences between groups in those with smaller root sizes (≤21 mm; P=0.28) or in younger patients (≤60 years; P=0.15). Peak aortic velocity and peak aortic gradient showed a greater decrease in the stentless than in the stented group (P<0.001) (Table 2), and indexed EOA showed a greater increase in the stentless group than in the stented group (P<0.001) (Table 2).

Cardiovascular Magnetic Resonance
A subgroup of 38 patients participated in the CMR substudy, of whom 15 patients received a stentless valve and 23 patients a stented valve. LVMI decreased in both valve groups at 6 months (P=0.05) (Figure 2). There were no significant differences in LVMI between the 2 groups at 12 months (P=0.11).

### Table 2. Echocardiographic Data

<table>
<thead>
<tr>
<th></th>
<th>Stented</th>
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<th></th>
<th>Stentless</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preoperative</td>
<td>Postoperative</td>
<td>6 Months</td>
<td>12 Months</td>
<td>Preoperative</td>
<td>Postoperative</td>
</tr>
<tr>
<td>LVMI, g/m² (all patients)</td>
<td>182±63</td>
<td>168±47</td>
<td>131±45</td>
<td>123±41</td>
<td>176±62</td>
<td>163±49</td>
</tr>
<tr>
<td>LV mass, g</td>
<td>338±126</td>
<td>308±126</td>
<td>244±92</td>
<td>228±79</td>
<td>325±120</td>
<td>298±99</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>70±14</td>
<td>67±16</td>
<td>71±14</td>
<td>70±15</td>
<td>71±13</td>
<td>70±13</td>
</tr>
<tr>
<td>EOA index, cm²/m²</td>
<td>0.39±0.19</td>
<td>0.74±0.26</td>
<td>0.78±0.27</td>
<td>0.72±0.21</td>
<td>0.42±0.17</td>
<td>0.93±0.35</td>
</tr>
<tr>
<td>Peak velocity change, mean±SE</td>
<td>1.6±0.1</td>
<td>1.8±0.1</td>
<td>1.7±0.1</td>
<td>1.9±0.1</td>
<td>2.2±0.1†</td>
<td>2.3±0.1†</td>
</tr>
<tr>
<td>Peak aortic gradient, mm Hg</td>
<td>80±25</td>
<td>48±22</td>
<td>28±11</td>
<td>31±10</td>
<td>77±24</td>
<td>24±11</td>
</tr>
</tbody>
</table>

Values are mean±SD unless indicated otherwise.
*One patient allocated to the stented valve group did not have evaluable preoperative echocardiographic measurements, and 2 patients allocated to the stentless valve group did not have evaluable preoperative echocardiographic measurements.
†P<0.001, stented vs stentless.

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**Figure 2.** Mean±SD LVMI (g/m²) assessed by echocardiography at each time point.
months, but there was no significant difference between valves \((P=0.95)\), confirming the findings from the echocardiographic studies (Table 3). There were no differences between valves in ejection fraction or LV end-diastolic or end-systolic volumes.

### Functional and Clinical Outcomes

Proportions of patients in NYHA functional class III and IV decreased in both the stentless and stented groups from 43% and 47%, respectively, at baseline to 5% and 4%, respectively, at 6 months \((P=0.0001)\) but with no significant differences between groups. The 6-minute walk test improved significantly in both the stentless and the stented groups from baseline \((299\pm115\text{ and } 271\pm130\text{ m})\) to 6 months \((351\pm115\text{ and } 346\pm128\text{ m})\,\text{respectively}\) \((P=0.01)\), but again there were no significant differences between groups. Quality of life measured by the SF-36 questionnaire also improved significantly in both valve groups, but again there were no differences between valves. Thirty-day mortality was 3.2% \((3/93\text{ deaths})\) in the stentless group and 2.1% \((2/97\text{ deaths})\) in the stented group \((P=0.95)\), confirming the findings from the echocardiographic studies (Table 3). There were no differences between valves in ejection fraction or LV end-diastolic or end-systolic volumes.

### Discussion

Our study shows that the use of stentless valves for AVR in patients with aortic stenosis is associated with a similar degree of LV mass regression to a stented valve. Both valves provide regression of LV mass to within the normal range, but AVR with a stentless valve is associated with a significantly greater increase in EOA index and lower transvalvular velocities than a stented valve.

Nonrandomized studies have reported greater LVMI regression with stentless rather than stented valves.\(^6\)\(^-\)\(^7\) Previous randomized controlled studies comparing the effect of stentless and stented valves on LV mass regression showed mixed results.\(^8\)\(^-\)\(^12\) In a prospective randomized trial of 180 patients, Walther et al\(^8\) compared LV mass regression after stentless (Freestyle, \(n=49\); Toronto, \(n=57\)) versus intra-annular stented (Carpentier Edwards, \(n=74\)) AVR. At 6-month follow-up, hemodynamic and LV mass measurements were in favor of stentless valves. LVMI after 6 months was 141 g/m\(^2\) in the stentless group versus 170 g/m\(^2\) in the stented group \((P<0.05)\). Although this was a randomized study, there were imbalances in the numbers of patients and in patient characteristics, including age. Other studies have reported that the LV mass regression is independent of the type of valve,\(^9\)\(^-\)\(^12\) but 3 of these studies were underpowered to detect a difference in LVMI between valves.\(^9\)\(^-\)\(^11\)

We found that the use of a stentless valve resulted in a greater EOA index and lower transvalvular gradients compared with stented valves, similar to previous studies.\(^8\)\(^-\)\(^12\) A stentless valve resembles the native aortic valve more closely than a stented valve by providing a greater EOA index for a given valve size. Fries et al\(^17\) showed that transvalvular flow gradients at rest and at exercise were significantly lower in patients with stentless valves than in those with stented valves (peak gradient at rest, 11±4 stentless versus 21±10 stented; peak gradient at maximal exercise, 18±6 stentless versus 40±11 stented). In contrast, Chambers et al\(^18\) found no significant differences in peak velocity, mean pressure difference, or EOA either at rest or on exercise between the Perimount bovine pericardial stented valve and the Toronto porcine stentless valve. Pibarot and Dumesnil\(^19\) suggested that after AVR, patients have substantial pressure recovery downstream from their prosthesis, which allows an improve-

### Table 3. CMR Data

<table>
<thead>
<tr>
<th></th>
<th>Stented (n=23)</th>
<th>Stentless (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVMI, g/m(^2)</td>
<td>129±46</td>
<td>134±41</td>
</tr>
<tr>
<td>LV mass, g</td>
<td>244±94</td>
<td>244±76</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>68±15</td>
<td>69±19</td>
</tr>
<tr>
<td>LV end-diastolic volume, median (interquartile range), mL</td>
<td>129 (100, 197)</td>
<td>134 (95, 194)</td>
</tr>
<tr>
<td>LV end-systolic volume, median (interquartile range), mL</td>
<td>35 (23, 69)</td>
<td>29 (15, 113)</td>
</tr>
</tbody>
</table>

*Values are mean±SD unless indicated otherwise.*

### Table 4. Adjudicated Clinical Outcomes at 12 Months

<table>
<thead>
<tr>
<th>Clinical Outcome</th>
<th>Stented (n=97)</th>
<th>Stentless (n=93)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>4 (4)</td>
<td>7 (8)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0 (0)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Stroke</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Valve dysfunction*</td>
<td>3 (3)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>0 (0)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Major bleed</td>
<td>7 (7)</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>8 (8)</td>
<td>8 (9)</td>
</tr>
<tr>
<td>Permanent pacemaker</td>
<td>2 (2)</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>

*Defined as any abnormality of valve function (stenosis, regurgitation, thrombus formation, vegetation, pannus, or valve displacement).*
ment in their maximal exercise capacity independent of the valve substitute.

We performed the CMR substudy to assess changes independently of echocardiographic geometric assumptions. It has been proposed that with the use of CMR, smaller sample sizes are sufficient to observe changes in ventricular remodeling. The findings in our sample of 38 patients included in the CMR substudy supported the 2D echocardiographic findings. Implantation of a stentless valve is more demanding than a stented valve, and this is reflected by longer cardiopulmonary bypass and cross-clamp times. Some reports have shown higher hospital mortality with stentless valves than with stented valves, but long-term mortality may be lower with stentless valves. Although prolonged bypass and cross-clamp times have been associated with higher mortality after AVR, we did not detect any difference in mortality and morbidity between valve groups, although our study was underpowered for this comparison. Both valves improved functional capacity as measured by NYHA class and quality of life, but there was no difference between the 2 valve types. Similarly, 6-minute walking distance was significantly improved in both groups, and there were no differences between valve types. This is the first study, to our knowledge, that has shown improvements in walking distance after AVR.

Our study of 190 patients is the largest randomized trial to date comparing stentless versus stented valves for patients with severe aortic stenosis. The 2 types of valves studied are manufactured with the use of similar high-quality materials and quality standards, supporting the validity of a direct comparison. At the time that we designed the study, echocardiography was the accepted standard for estimating LV mass. We addressed the issue of potential bias caused by measurement error in baseline values by reanalyzing the LV mass data using the method recommended by Chambless and Roeback. After correction for measurement error in LVMI values, there was still no significant differences in change in LVMI from baseline between valves, and our conclusions remained valid. We also used a MR method in a substudy to help validate the echocardiographic results. The main outcome of LV mass was also considered to be the most important measure of the efficacy of AVR and a reflection of favorable remodeling. However, when modern low-profile stentless and stented valves are compared, more sensitive measures may need to be used. Such as detailed imaging, to detect subtle changes in LV remodeling, natriuretic peptides, and coronary flow dynamics. Longer follow-up is also important.

In a case-matched study, Casali et al showed a lower risk of cardiac death (77±7% versus 90±4% [P=0.02]) and freedom from valve-related death (78±7% versus 91±4% [P=0.02]) after 3 years in stentless versus stented patients, respectively.

Our study has shown that stentless and stented aortic valves have similar effects on LV mass. We have confirmed that stentless valves have a significantly better hemodynamic profile, but their insertion is more demanding. These factors may influence the choice of valve for an individual patient. The stentless valve would theoretically be more advantageous in patients with impaired LV function and in those with very severe LV hypertrophy, particularly if out of proportion to the degree of aortic stenosis, as typically seen in elderly women. In repeat procedures, in which myocardial protection in an earlier era may have been less effective, stentless valves may also offer a real advantage. Furthermore, in the freestanding root format, a stentless valve provides greater technical flexibility. Further studies comparing stented with stentless valves are needed with longer follow-up and more sensitive measures to differentiate the effects of the valve design.

Acknowledgment

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Disclosure

Study coordination and data analysis were carried out independently of Medtronic. Dr Pennell has served as a consultant to Siemens. Professor Pepper has served on the Medical Advisory Board of Medtronic.

References


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