Stentless vs. stented aortic valve bioprostheses: a prospective randomized controlled trial


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KEYWORDS
Aortic valve replacement; Thoracic surgery; Stentless valve; Mass regression

Aims We sought to assess the haemodynamic profile of the Freedom stentless aortic valve compared with a stented bioprosthesis in a randomized controlled trial using echocardiography.

Methods and results Sixty patients (mean age 73 years) undergoing bioprosthetic aortic valve replacement (AVR) were randomized to either Sorin Freedom stentless (n = 31) or Sorin More stented (n = 29) valves. The primary endpoints were left ventricular mass index (LVMI) reduction at 6 and 12-months. We also assessed post-operative effective orifice area index (EOAI), aortic gradient and operative time. There were no significant differences in baseline characteristics. The stentless valve was associated with a lower post-operative gradient [PG 17 (12) vs. 31 (13) mmHg, P < 0.0001] and greater EOAI [1.1 (0.3) vs. 0.8 (0.2) cm²/m², P < 0.0001]. A highly significant reduction in LVMI occurred by 6 months in both groups, but LVMI was significantly lower in the stentless group [LVMI 119 (39) vs. 135 (30) g/m², P = 0.05]. However, there was continued regression of left ventricular hypertrophy (LVH) in the stented but not in the stentless group, resulting in no significant difference in LVMI at 12 months [119 (36) vs. 126 (31) g/m², P = 0.42].

Conclusion The use of the Sorin Freedom stentless bioprosthesis for AVR results in lower PG and greater EOAI when compared with a Sorin More stented valve. This is associated with earlier regression of LVH.

Introduction
Severe aortic stenosis with congestive heart failure carries a 2-year mortality of over 90% with conservative treatment.¹ Aortic valve replacement (AVR) is the only definitive treatment for these patients. However, despite excellent peri-operative results, long-term results are less than optimal, with 15-year survival in the region of 18–50%.²⁻⁴ Evidence from long-term studies following-up hypertensive patients and patients with unoperated aortic valve stenosis suggest that a reason for these poor long-term results may be due to the incomplete regression of left ventricular hypertrophy (LVH).⁵⁻⁶ In addition, there is evidence that patient-prosthesis mismatch and the inherently stenotic nature of conventional bioprostheses contribute to this incomplete regression.⁷⁻⁸

Stentless aortic tissue valves were developed with the goal of maximizing the effective orifice area (EOA) and therefore facilitating left ventricular (LV) mass regression. Cohort studies following patients for up to 10 years have shown good results and improvements in ventricular hypertrophy with stentless valves,⁹⁻¹¹ but randomized controlled trials (RCTs) have shown more equivocal results.¹²⁻¹⁹

The Sorin Freedom stentless valve is a unique two-sheet bovine pericardial stentless valve and is entirely free of any fabric reinforcement. This allows it to be completely inverted during implantation, allowing more rapid suturing with superior visibility. However, its ability to provide significant improvements in the mean aortic gradient and rapid LV mass regression have not yet been assessed in an RCT.

Parameters of LV long-axis function have been demonstrated to be reduced in aortic stenosis, even in the presence of preserved LV ejection fraction (EF). Mitral annular longitudinal excursion has an inverse correlation with peak aortic gradient and may also predict symptoms in patients with unoperated aortic stenosis.²⁰ We have previously demonstrated recovery of mitral annular longitudinal velocity following AVR,²¹ but it is not clear whether this recovery is influenced by prosthetic valve type.

The aim of our study was to investigate whether the Sorin Freedom stentless valve would result in greater LV mass regression at 6 months and 1 year following AVR, compared with the Sorin More Pericarbon-stented valve. We also aimed to examine the effect of valve type on recovery of LV long-axis function.

Methods
This was a single blinded prospective RCT conducted over a two-and-a-half year period from January 2002 to July 2004. Consecutive patients over the age of 65 who had elected to receive a biological aortic valve were eligible for entry into the trial. The trial was conducted at a single centre (The James Cook University Hospital, Middlesbrough, UK) and for the first year all operations were conducted by a single surgeon (S.H.). From the second year,
a second surgeon joined the study (S.K.). Table 1 summarizes the pre-operative characteristics of the study participants.

### Eligibility criteria

Eligible patients included those patients with aortic stenosis who were referred for AVR and who for medical or lifestyle reasons required a bioprosthetic valve. In addition, patients with mixed aortic valve disease were eligible if their aortic gradient was above 50 mmHg or if the aortic valve area was <0.8 cm². Every patient was required to provide written informed consent prior to inclusion.

### Exclusion criteria

Patients were excluded if the surgeon anticipated concomitant cardiac procedures other than coronary arterial bypass grafting (i.e. mitral or tricuspid valve surgery, ascending aortic procedures, or operation for congenital defects) or if this was not the patient’s first cardiac operation. Patients undergoing AVR for endocarditis were also excluded. In addition, patients requiring urgent operation or unable to return for serial echocardiographic follow-up were excluded. No exclusions were applied to the size of the aortic annulus unless the surgeon considered that an aortic root enlargement might be required. The surgeons assessed the aortic annulus for suitability to implant a stentless valve prior to random allocation, but no patients were excluded as a result of this assessment (Figure 1).

### Randomization

The study protocol was approved by our institutional ethics committee. After patient eligibility was confirmed, they were entered into the trial. Randomization was performed using minimization by age, sex, and ejection fraction. This occurred in theatre after aortic annulus assessment, and was performed by a computer-generated randomization protocol (MINIM). All data was kept centrally in a secure database with complete anonymization.

### Surgical technique

The Freedom (stentless) and More (stented) valves are both manufactured by Sorin and are composed of similar bovine biological material. The stented bioprosthesis was inserted in a supra-annular position using interrupted 2.0 Ticron horizontal mattress sutures, either with or without pledgets at the surgeon’s discretion. Our position using interrupted 2.0 Ticron horizontal mattress sutures, material. The stented bioprosthesis was inserted in a supra-annular position, using continuous 4.0 prolene both for the proximal layer and for the distal layers, incorporating the commissural support sutures.

### Table 1 Demographic variables

<table>
<thead>
<tr>
<th></th>
<th>Stentless valve (n = 31)</th>
<th>Stented valve (n = 29)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>20 (65)</td>
<td>17 (59)</td>
<td>0.64</td>
</tr>
<tr>
<td>Age, years (SD)</td>
<td>73 (5)</td>
<td>73 (5)</td>
<td>0.70</td>
</tr>
<tr>
<td>BSA, m² (SD)</td>
<td>1.83 (0.20)</td>
<td>1.81 (0.19)</td>
<td>0.67</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>19 (61)</td>
<td>21 (72)</td>
<td>0.36</td>
</tr>
<tr>
<td>AS/AR/mixed (mmHg)</td>
<td>29/0/2</td>
<td>27/1/1</td>
<td>0.51</td>
</tr>
<tr>
<td>CAGB (%)</td>
<td>16 (52)</td>
<td>18 (62)</td>
<td>0.61</td>
</tr>
<tr>
<td>NYHA III and IV (%)</td>
<td>13 (42)</td>
<td>16 (55)</td>
<td>0.30</td>
</tr>
<tr>
<td>Euroscore (SD)</td>
<td>6.58 (1.77)</td>
<td>6.57 (1.95)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

### Echocardiography and outcome measures

Transthoracic echocardiographic studies were performed by two experienced operators (R.G. and J.T.) who assessed the patient pre-operatively, before discharge, at 6 and 12 months post-operatively. Patients were studied in the left lateral position using a Vivid-7 (General Electric Healthcare, London, UK) system equipped with a 2.5 MHz probe. Digital loops were acquired for later analysis by a single cardiologist (R.G.) using the onboard EchoPac software. He was not informed of the valve used although it is acknowledged that echocardiographically the valves may be distinguished. All measurements were averaged over three cardiac cycles in sinus rhythm and five cycles if in atrial fibrillation.

All measurements were performed in accordance with the recommendations of the American Society of Echocardiography. LVOT and LV dimensions were measured from M-mode images in the parasternal long-axis view with LV mass calculated using the modified formula of Devereux and indexed to body surface area. Aortic valve leaflets were measured using the modified Bernoulli formula from continuous wave Doppler profiles. EOA was calculated using the continuity equation, and was also indexed to body surface area.

LV long-axis function was assessed using tissue velocity imaging (TVI) to measure mitral annular longitudinal systolic velocity. This was obtained by activating the TVI preset and placing a pulsed-wave sample volume at the septal and lateral borders of the mitral annulus in the apical four-chamber view. Peak systolic (S) velocity was measured at each site and averaged between the two positions.

### Statistics and power calculation

The primary outcome measure was left ventricular mass index (LVMI). The study was powered to have an 80% chance of detecting a 20% superior improvement in LVMI at 12 months when compared with the improvement seen in the stented valve group using a P-value of 0.05. We used the largest available study by 2002 to report recurrent data to provide the initial estimations. They reported that the LVMI was 118 g/m² (SD 30) in the stented group. In order to demonstrate a 20% improvement of this with a
Freedom stentless valve, 25 patients would be required in each group. We aimed to recruit 30 for each group to allow for incomplete follow-up or premature adverse events precluding 12-month echocardiography.

Univariate analysis of binomial categorical variables was performed using the Fisher’s exact test, and other categorical variables were analysed using the $\chi^2$ test with a continuity correction when the cell count dropped to below 15. Continuous data was analysed using an unpaired $t$-test when a Kolmogorov–Smirnov test demonstrated normality or alternatively a Mann–Whitney $U$ test. A $P$-value of 0.05 was taken to indicate significance.

Results

Sixty patients were randomized to either stentless or conventional AVR. A total of 62% of patients were male and the mean age was 73. The patient demographics are shown in Table 1 and baseline echocardiographic data is given in Table 2. There were no significant differences in any variable including symptoms, Euroscore, degree of stenosis, LVMI, LVEF, mitral annular systolic velocity, or medications.

Intraoperatively, the prosthesis size of the implanted valve was significantly greater in the stentless group [stentless valve group 25.7 mm (SD 2.7) vs. stented valve group 22.9 mm (SD 2.5)]. This was a highly significant result. The bypass time and cross-clamp times were about 10 min longer in the stentless valve group, although this did not reach statistical significance.

The in-hospital morbidity and mortality was very low in both groups. One patient died (stentless valve group), and there were three cerebrovascular events (one stentless valve patient, two stented valve patients). Perioperative results are given in Table 3 and Figure 2.

Fifty-five patients attended echocardiographic follow-up at 6 months. Both peak and mean aortic valve gradients were significantly lower in the stentless valve group when compared with the stented group [mean gradient 9 (SD 5) vs. 17 mmHg (SD 6), $P < 0.0005$, Figure 3]. In addition, the effective orifice area index (EOAI) was significantly greater in the stentless valve group [1.09 (SD 0.30) vs. 0.78 cm$^2$ (SD 0.21), $P < 0.0005$]. LVMI was also significantly lower in the stentless AVR group when compared with the stented valves [119 (SD 30) vs. 134 g/m$^2$ (SD 31), $P = 0.04$, Figure 4]. Mitral annular systolic velocity was significantly greater in the stentless when compared with the stented group [7.6 (SD 1.7) vs. 6.7 cm/s (SD 1.7), $P = 0.04$].

Fifty-four patients attended echocardiographic follow-up at 12 months. Peak and mean aortic valve gradients...
remained significantly lower in the stentless valve group, and the EOAI remained significantly larger in the stentless group. There was no further change in left ventricular mass index in the stentless valve group [118 g/m² (SD 36)] but the reduction in mass index in the stented valve group continued to decline [126 g/m² (SD 31)]. The differences between the two groups at 12 months were therefore no longer significantly different. Similarly, there was no longer a significant difference in mitral annular systolic velocity (Table 4). There were no significant differences in the incidence of ACE-inhibition, beta-blocker usage, or statin therapy between the two groups in the 12 months of follow-up.

**Discussion**

LVH correlates well with mortality and morbidity in patients with aortic stenosis, increasing the risk of congestive cardiac failure, myocardial infarction, and sudden death. Furthermore, incomplete regression of LVH after AVR is associated with an increased mortality.26

We have demonstrated that implantation of the Sorin Freedom stentless valve results in a significantly reduced aortic valve gradient and a significantly increased EOAI when compared with a traditional stented valve and that this haemodynamic improvement results in significantly greater LV mass regression at 6 months. Our data suggest that regression of LVH is complete at 6 months following implantation of the Freedom stentless valve, with LVMI returning to the normal range. However, there is continued reduction in LV mass with the More stented valve between 6 and 12 months, such that the stented group has almost returned to a normal LV mass by 12 months post-operatively. Thus, while ultimately a similar degree of regression in LVH is seen with both types of bioprosthesis, there is earlier normalization of LV mass seen with the Sorin Freedom stentless valve.

In addition, this study suggests that the effect of prosthesis type on recovery of LV long-axis function following AVR mirrors the effect on LV mass regression. A significant difference in mitral annular long-axis velocity was evident between the stented and stentless groups at 6 months, but this difference was no longer significant by 12 months. This finding, in a group of patients with normal LVEF, supports that of Collinson et al.27 In a retrospective study of patients with poor LV function undergoing AVR, they demonstrated a significantly greater early improvement in LV function (both fractional shortening and long-axis function) in patients receiving a stentless when compared with a stented valve.

We have also demonstrated that implantation of the Sorin Freedom valve only requires an additional 10 min of cross-clamp time when compared with implantation of a traditional stented valve, with no effect on perioperative complications.

Ali et al.28 have recently performed a multicentre RCT comparing the Edwards Prima Plus Stentless valve with the Carpentier-Edwards Perimount stented valve. One hundred and sixty-one patients were randomized and assessed by echocardiography at 1 week, 8 weeks and 12 months. In addition, 50 patients underwent pre-operative and 1 year post-operative magnetic resonance image (MRI) scanning. However, in contrast to our own study they found no differences in the aortic valve gradient, EOAI, or LVMI either by echo or MRI, despite patients receiving a stentless when compared with a stented valve.

The ASSERT trial12 randomized 190 patients to either the Medtronic Freestyle stentless valve or the Medtronic Mosaic stented valve. They assessed LVMI at 6 and 12 months and also 38 patients were assessed by MRI. Again they found no significant differences between the two groups in LVMI either by echocardiography or MRI, despite a significantly greater EOAI in the stentless group.

In contrast to these two large RCTs, the third published RCT of over 100 patients by Walther et al.14 did find a clinically significant difference. They randomized 180 patients to

**Table 4 Echocardiographic findings at 6 and 12 months**

<table>
<thead>
<tr>
<th>Findings at 6 months</th>
<th>Stentless valve group (n = 29)</th>
<th>Stented valve group (n = 26)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak gradient, mmHg (SD)</td>
<td>22.1 (13)</td>
<td>35.5 (11)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Mean gradient, mmHg (SD)</td>
<td>9 (5)</td>
<td>17 (6)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>EOAI, cm² (SD)</td>
<td>2.00 (0.61)</td>
<td>1.40 (0.39)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>LVMi, g/m² (SD)</td>
<td>1.09 (0.30)</td>
<td>0.78 (0.21)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>65 (11)</td>
<td>65 (10)</td>
<td>0.98</td>
</tr>
<tr>
<td>S’ (cm/s)</td>
<td>7.6 (1.7)</td>
<td>6.7 (1.7)</td>
<td>0.04</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Findings at 12 months</th>
<th>Stentless valve group (n = 28)</th>
<th>Stented valve group (n = 26)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak gradient, mmHg (SD)</td>
<td>17 (10)</td>
<td>31 (13)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Mean gradient, mmHg (SD)</td>
<td>7 (5)</td>
<td>15 (6)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>EOAI, cm² (SD)</td>
<td>2.1 (0.7)</td>
<td>1.4 (0.4)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>EOAI, cm² (SD)</td>
<td>1.1 (0.3)</td>
<td>0.8 (0.2)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>LVMi, g/m² at 12 months (SD)</td>
<td>118 (36)</td>
<td>126 (31)</td>
<td>0.42</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>67 (7)</td>
<td>63 (10)</td>
<td>0.12</td>
</tr>
<tr>
<td>S’ (cm/s)</td>
<td>7.8 (1.6)</td>
<td>7.0 (1.7)</td>
<td>0.08</td>
</tr>
</tbody>
</table>
Medtronic Freestyle stentless valve, the St Jude Toronto stentless valve, or the Carpentier-Edwards perimount stented valve. They found a statistically significant increased reduction in LV posterior wall thickness in the stentless valve groups.

Combining our own study with these three large RCTs and also six smaller RCTs in a meta-analysis we found that the combined results in over 900 patients were compatible with the findings from our study.\textsuperscript{29} We demonstrated that across all studies, implantation of a stentless valve replacement results in a reduced aortic valve gradient, greater EOAI, and that there is also an increased reduction in LVMl at 6 months.

Again, in agreement with our own study, the pooled data across the 10 studies demonstrate that this improvement in LVMl disappears after 1 year. We hypothesize that stentless aortic valves allow the myocardium to recover more rapidly from LVH due to the reduced residual gradient in the aortic annulus. However, the myocardium of patients who receive a stented valve will eventually fully recover, but this recovery is delayed rather than prevented by the raised aortic valve gradients found in stented valves.

Comparing our results to the meta-analysis,\textsuperscript{29} we found that while the Sorin Freedom stentless aortic valve took us an additional 10 min to implant, the mean increase in cross-clamp time across 10 RCTS was 27 min. We hypothesize that this may be due to the easy implantation technique that is possible with this valve, including only two continuous suture lines and the ability to invert the valve fully for the first suture line.

Finally, we have recently published a cohort study of 102 consecutive patients receiving the Sorin Freedom valve either alone or combined with grafts or other operations, including the patients from this study.\textsuperscript{30} We found that in follow-up, the 5-year survival was 89%, 5-year freedom from thrombo-embolism was 96%, and freedom from reoperation was 100%. No further mass regression was found after 6 months.

Our study has weaknesses. Our randomized trial is relatively small, although it was adequately powered to detect significant differences in all of our primary outcome variables. We did not perform MRI scanning although previous studies that have performed this, find that results are similar when compared with modern echocardiography. We have also not demonstrated any clinical benefits for patients in terms of morbidity or mortality, although this was not the aim of our study due to its size.

**Conclusion**

Our RCT of the Sorin Freedom stentless valve has demonstrated significant benefits to the aortic valve gradient, the EOAI, and the LVMl at 6 months when compared with conventional bioprostheses. The benefit of a stentless valve is in allowing a rapid reduction in LVMl, although patients receiving a conventional valve will eventually improve to the same level after 1 year.

**Acknowledgements**

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**Conflict of Interest:** We declare that none of the authors currently have any financial relationships with Sorin, or any other company relevant to this study.

**References**


