Performance of stentless versus stented aortic valve bioprostheses in the elderly patient: a prospective randomized trial


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Abstract

Objectives: Although stentless aortic bioprostheses are believed to offer improved outcomes, benefits remain unsubstantiated. The aim of our study was to compare stentless with stented bioprostheses, with regard to postoperative changes in left ventricular mass and hemodynamic performance, in the elderly patient. Methods: Forty patients with aortic stenoses, over the age of 75 years, were randomized to receive either the stented Perimount \((n = 20)\) or the stentless Prima Plus \((n = 20)\) bioprosthesis. Left ventricular mass regression, effective orifice area, ejection fraction and mean gradients were evaluated at discharge, 6 months and 1 year after surgery. Results: Overall a significant decrease in left ventricular mass was found 1 year postoperatively. However, there was no significant difference in the rate of left ventricular mass regression between the groups. Furthermore, 1 year postoperatively, the hemodynamic performance of the valves and the change in the ejection fraction did not differ between the groups. Conclusions: Our study shows that in a randomized cohort of elderly patients with aortic stenosis, we were not able to detect significant differences, with regard to hemodynamic performance and regression of left ventricular mass, between the stentless and stented valve groups. To our surprise, previously reported findings of non-randomized trials that showed faster and more complete regression of left ventricular mass and hemodynamic benefits of stentless valves were not reproducible.

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Keywords: Aortic valve replacement; Stentless bioprosthesis

1. Introduction

The only definitive treatment of critical aortic valve stenosis is aortic valve replacement (AVR). Despite the excellent perioperative results, 10 year survival for all age groups still ranges from 50% to 66% [1,2]. In the elderly (age >75 years) the survival rate at 15 years after AVR decreases to 18% [3]. Evidence from hypertensive patient populations and unoperated patient cohorts with aortic valve stenosis suggests that these poor long-term results may be related to the incomplete regression of left ventricular (LV) hypertrophy [4,5].

Stented bioprosthetic valve substitutes are commonly employed in the elderly. In the age group 65 years and above they display an incidence of structural valve deterioration of 6% at 15 years postoperatively [2]. The obstructive nature of the stent and sewing ring or patient prosthesis mismatch have been held accountable for persistently elevated transvalvular gradients. In the late 1980s stentless bioprostheses were introduced to circumvent these problems by offering a maximal orifice area for flow and eliminating the valvular sewing ring and stent. Thus, stentless valves seem to be the optimal choice for patients eligible for biological AVR.

The following study was designed to determine the effects of valve type on clinical and hemodynamic outcome, by means of a randomized trial in an elderly patient population.

2. Methods

From September 1999 to January 2001, 40 consecutive patients, over the age of 75 years, were eligible for inclusion in this prospective randomized trial. Patients were randomized to receive either the Carpentier–Edwards Perimount, pericardial stented bioprosthesis or the Prima Plus, porcine stentless bioprosthesis (Edwards Life Sciences Inc, Irvine, CA).

All patients provided written informed consent before
inclusion in the study. The consent form was approved by our ethical committee.

2.1. Inclusion and exclusion criteria

Eligible patients included those with isolated aortic stenosis (maximum transvalvular gradient >50 mmHg or aortic valve area <0.8 cm²) in which preoperative evaluation indicated the need for an isolated AVR. Only patients expected to survive the surgery and expected to be available to return to the study site for all follow-up examinations were included in the study.

Patients who specifically chose to have a mechanical valve substitute were not suitable for enrolment. Patients that required repair or replacement of an additional heart valve and those that had prior implantation of a bioprosthetic, mechanical valve or annuloplasty device were excluded from the study. Other exclusion criteria included active endocarditis, emergency operation and a history of myocardial infarction. Intraoperatively patients were excluded from the study if their aortic root and surrounding tissues had severe calcifications that could not be completely removed surgically and if their valve anatomy indicated an abnormally dilated aortic root or would require excessive trimming of the bioprosthesis.

2.2. Echocardiography

At our institution, only two operators performed all the echocardiograms for the study. A single echo machine (Wing Med, System Five) was used. All data collected were entered in a central database.

Apart from the standard imaging views, preoperative echocardiography also included the measurement of the diameter of the annulus and the size of the native aorta at the level of the sinotubular junction. This was necessary to identify a possible mismatch between the annulus and the sinotubular junction, which in turn would make the patients unsuitable for the implantation of a stentless valve.

2.3. Surgical technique

A total of four surgeons performed all operations. All patients had retrograde cold blood cardioplegia and carbon dioxide insufflation of the open thorax for organ protection. Access to the aortic valve was gained via a hockey stick aortotomy. After complete resection of the native aortic valve and debridement of the aortic annulus, accurate sizing was carried out using the respective CE sizers for the Prima Plus stentless and CE Perimount stented valves.

The Prima Plus stentless valves were implanted in the subcoronary position. The commissures were positioned 120° apart, with the muscular shelf corresponding to the right coronary sinus. Care was taken to suture the base of the valve subannularly, to ensure that the coaptation line of the leaflets was at the height of the native annulus. Single interrupted unpledged 4-0 Ethibond sutures were used for the proximal end, and the rims of the valve commissures were sutured to the native aorta using 4-0 Prolene running sutures. For the CE Perimount stented valve implantation, interrupted mattress pledgeted 2-0 Ethibond sutures were placed circumferentially from below the annulus. The valves were implanted in the supra-annular position, with the stent positioned so as not to interfere with the coronary ostia.

2.4. Anticoagulation regime

Our anticoagulation regime was the same for both groups. It included subcutaneous low molecular heparin for the first days and parallel oral anticoagulation with vitamin K antagonists. As soon as the International Normalized Ratio (INR) levels reached the therapeutic range of 2.5–3.5, heparin was stopped. Oral anticoagulation was continued for 3 months. INR levels were monitored by the patient’s general practitioner. After 3 months oral anticoagulation was stopped.

2.5. Follow-up

Follow-up examinations were scheduled for discharge from the hospital at 6 months and 12 months after operation. All patients had evaluation of their clinical status including New York Heart Association (NYHA) classification blood data including signs of hemolysis and coagulation profile, occurrence of early and late complications and echocardiographic data.

Our special emphasis was focused on the evaluation of LV mass regression. Both completeness and rate of LV mass regression were assessed. Additional endpoints were changes in LV function and hemodynamics including effective orifice area (EOA) and changes in postoperative transvalvular gradients.

2.6. Statistical methods

Data were compiled and analyzed using Microsoft Access, Microsoft Excel (Redmond, WA) and Stat view (Cary, NC). The baseline characteristics and hospital outcomes for the two groups were compared using chi-square or Fisher’s exact test for categorical data and unpaired t-tests for continuous variables. Results are reported as the mean ± standard deviation in text and tables. Statistical significance was defined as a P value less than 0.05.

3. Results

Preoperative clinical characteristics including age, gender, body surface area (BSA), ejection fraction (EF), NYHA functional class and hypertension were comparable in the two groups (Table 1).

Table 2 summarizes the intraoperative outcomes. Cross-
Table 1
Preoperative patient characteristics^

<table>
<thead>
<tr>
<th></th>
<th>Perimount (n = 20)</th>
<th>Prima Plus (n = 20)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>12</td>
<td>9</td>
<td>NS</td>
</tr>
<tr>
<td>Male</td>
<td>8</td>
<td>11</td>
<td>NS</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>79 ± 4.3</td>
<td>78 ± 3.8</td>
<td>NS</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.85 ± 0.8</td>
<td>1.79 ± 0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>9</td>
<td>10</td>
<td>NS</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Preop mean gradient</td>
<td>50.9 ± 14.8</td>
<td>58.1 ± 18.2</td>
<td>NS</td>
</tr>
<tr>
<td>Preop IVS thickness</td>
<td>1.91 ± 0.91</td>
<td>1.94 ± 1.90</td>
<td>NS</td>
</tr>
<tr>
<td>Preop LVW thickness</td>
<td>1.98 ± 0.20</td>
<td>1.93 ± 0.28</td>
<td>NS</td>
</tr>
<tr>
<td>LV end diastolic dimen.</td>
<td>4.6 ± 0.3</td>
<td>4.8 ± 0.4</td>
<td>NS</td>
</tr>
<tr>
<td>LV end systolic dimen.</td>
<td>3.5 ± 0.2</td>
<td>3.2 ± 0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Preop EF</td>
<td>66.6% ± 8.6</td>
<td>65.9% ± 7.4</td>
<td>NS</td>
</tr>
<tr>
<td>Preop NYHA III-IV</td>
<td>18</td>
<td>17</td>
<td>NS</td>
</tr>
<tr>
<td>Concomitant CABG</td>
<td>3</td>
<td>2</td>
<td>NS</td>
</tr>
</tbody>
</table>

^ BSA, body surface area; IVS, interventricular septal thickness; LVW, left ventricular posterior wall thickness; LV, left ventricular; EF, ejection fraction; NYHA, New York Heart Association; CABG, coronary artery bypass grafting.

clamp times and cardiopulmonary bypass times were significantly longer in the CE Prim Plus stentless valve group.

There were three deaths (two early and one late) in the CE Perimount group and no deaths in the Prima Plus group. Although this seems to be an important difference in outcome, none of the deaths were valve-related. One patient had a pneumonia, the other patient died of septicemia, and the third patient, a late complication, actually had a ruptured abdominal aortic aneurysm. The other intra- and postoperative outcomes were comparable between the groups. The overall rate of valve-related complications was low in both groups. There was one case of endocarditis with subsequent reoperation in each group. One patient in each group suffered a stroke and there was a case of anticoagulation-related bleeding in the Perimount group. Analyses of the implanted valve sizes showed that in both groups for any given annular diameter a slightly larger valve was implanted. Oversizing was 1.9 mm in the Perimount group and 1.6 mm in the Prima Plus group. LV mass regressed significantly in both groups over time. However, there were no differences in mass regression between the groups at either 6 or 12 months postoperatively.

EOAs improved significantly in both groups over time.

Again, there were no differences between the groups at 6 and 12 month postoperatively. However, no significant differences in mean gradients were noted between the groups at 6 and 12 month postoperatively.

Echocardiographically determined EF did not improve or increase significantly over time in both groups. Although there was a slight decrease in EF at 12 months in the Perimount group and a slight increase in the Prima Plus group, overall no significant differences were found in the groups at 6 and 12 months, respectively.

NYHA classification improved over time in all patients. Most patients were in NYHA class I and II at 6 months and remained in it at 12 months, regardless of which valve substitute they had received. All clinical results over time are summarized in Table 3.

Table 3
Echocardiographic findings^

<table>
<thead>
<tr>
<th></th>
<th>Preop</th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVW</td>
<td>PE</td>
<td>1.98 ± 0.20</td>
<td>1.66 ± 0.13</td>
</tr>
<tr>
<td></td>
<td>PP</td>
<td>1.93 ± 0.28</td>
<td>1.63 ± 0.22</td>
</tr>
<tr>
<td>P value</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>IVS</td>
<td>PE</td>
<td>1.91 ± 0.91</td>
<td>1.51 ± 0.21</td>
</tr>
<tr>
<td></td>
<td>PP</td>
<td>1.94 ± 1.90</td>
<td>1.54 ± 0.20</td>
</tr>
<tr>
<td>P value</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Mean gradient</td>
<td>PE</td>
<td>50.9 ± 14.8</td>
<td>7.28 ± 3.75</td>
</tr>
<tr>
<td></td>
<td>PP</td>
<td>58.1 ± 18.2</td>
<td>8.40 ± 3.56</td>
</tr>
<tr>
<td>P value</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>EOA</td>
<td>PE</td>
<td>0.76 ± 0.29</td>
<td>1.51 ± 0.63</td>
</tr>
<tr>
<td></td>
<td>PP</td>
<td>0.87 ± 0.41</td>
<td>1.63 ± 0.44</td>
</tr>
<tr>
<td>P value</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>PE</td>
<td>66.6 ± 8.6</td>
<td>66.2 ± 10.5</td>
</tr>
<tr>
<td></td>
<td>PP</td>
<td>65.9 ± 7.4</td>
<td>67.6 ± 8.7</td>
</tr>
<tr>
<td>P value</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

^ LVW, left ventricular posterior wall thickness; IVS, interventricular septal thickness; EOA, effective orifice area; PE, CE Perimount stented bioprosthesis; PP, CE Prima Plus stentless bioprosthesis.

Table 2
Intraoperative outcomes

<table>
<thead>
<tr>
<th></th>
<th>Perimount</th>
<th>Prima Plus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross-clamp time (min)</td>
<td>79 (±17)</td>
<td>108 (±25)</td>
</tr>
<tr>
<td>CPB time (min)^</td>
<td>105 (±23)</td>
<td>130 (±27)</td>
</tr>
<tr>
<td>Implantation technique</td>
<td>Supra-annular</td>
<td>Subcoronary</td>
</tr>
<tr>
<td>Valve size (mm)</td>
<td>21 6 4</td>
<td>23 10 9</td>
</tr>
<tr>
<td></td>
<td>25 4 6</td>
<td>27 – 1</td>
</tr>
</tbody>
</table>

^ CPB, cardiopulmonary bypass.
4. Discussion

In the elderly patients (age >75 years) with aortic valve stenosis, biological AVR is the treatment of choice. From the available bioprostheses, stented and stentless valves are suitable and commonly used in the group of this age. In non-randomized trials, stented aortic valve prostheses have demonstrated better hemodynamic performances than stented valve prostheses [6]. Due to their design features, they appear to have hemodynamic characteristics similar to those of homograft valves. In the literature these optimized hemodynamics are held accountable for faster and more complete regression of LV hypertrophy, which if persistent is known to be associated with increased morbidity and mortality [7]. LV hypertrophy is a reflection of the severity of aortic stenosis and has been well correlated to peak aortic valve gradients [8,9]. Even moderate LV hypertrophy often causes arrhythmias, congestive heart failure or sudden death [10]. Therefore, the extent and rate of regression in LV hypertrophy after AVR is an important determinant of long-term survival. The beneficial effects of a less obstructive valve have also been demonstrated by Pibarot et al. [11]. They used a stress echocardiography to compare stented with stentless aortic valves and found an increase in mean pressure gradients of almost 100% from the resting values in the stented valves and less than 20% in the stentless valves.

Nonetheless despite such promising findings, few randomized comparative trials exist with which to confirm the favorable results associated with stentless valve implantation. Especially in the elderly, where exercise-related gradients do not play a predominant role, due to their reduced physical activity, it would be helpful to have reliable randomized data.

Our study compared the performance of the CE Perimount stented with the CE Prima Plus stentless bioprosthesis in a prospective randomized setting. From our understanding of the pathophysiology of aortic valve stenosis, we would expect a significant difference in the regression of LV mass between bioprostheses, if their implantation results in significant differences in transvalvular gradients.

Jin et al. [12] evaluated the regression of LV mass in a large number of patients after AVR with different types of valve substitutes (the mean age of their patients was 76 ± 16 years). They found that patients with stentless valves or homografts had a greater reduction of LV mass than patients who received a stented bioprosthesis or mechanical valve. They also found that LV mass regression had been completed at 6 months postoperatively in patients with stentless valves, whereas LV mass regression had not been completed after 12 months in patients with stented valves.

We found that all our patients operated on for aortic stenosis had a significant reduction in LV mass, irrespective of the valve substitute they received. The rate of LV mass regression was similar in both groups at 6 and 12 months, respectively. Unlike most other studies our patients were randomized to receive a specific valve. Cohen et al. [13] also conducted a prospective randomized trial. Ninety-nine patients were randomly assigned to receive a Toronto stented porcine valve or a CE pericardial valve. The mean age was 71.8 ± 7.1 years.

Interestingly they shared our findings and reported no difference in the rate and completeness of LV mass regression after 3 and 12 months, respectively. Furthermore, they compared the transvalvular gradients based on the actual valvular internal diameters and found no statistically or clinically significant differences between the groups. Similarly there were no statistically significant differences between stented and stentless valves in our study. To explain these results, which are somewhat different to what we expected, from our knowledge of current literature, we first of all inquired whether 1 year of follow-up is sufficient to assess the regression of LV hypertrophy in patients after AVR. Jin et al. [12] found no differences in LV mass or ventricular function between 6 months and 3 years of follow-up. Monrad et al. [14] demonstrated that regression of LV hypertrophy is maximal within the first year of follow-up and that more than 8 years are necessary to detect a further reduction in ventricular mass.

We therefore assume that our follow-up period of 12 months should be suffice to detect all relevant changes in LV mass.

Apart from the changes in transaortic pressure gradients there are a number of additional independent factors influencing the rate of LV mass regression. Patients with advanced severe aortic stenosis often present with a specifically altered collagen matrix, which does not show remodeling within the first postoperative years despite relief of LV pressure overload due to AVR [15].

Furthermore, age is known to be an independent factor of LV hypertrophy [16]. Lindroos et al. [17] who evaluated the amount of LV hypertrophy in an old patient population found that the increase of LV mass is due partly to age-related disease but also partly to an independent effect of age. The LV mass was often found to exceed 70% of the standard limits in the oldest patient cohort (85 years old). As all of our patients were 75 years and older age in itself could not influence outcome significantly between the groups. Gender is also worth consideration, as LV mass, when indexed to BSA, has been found to be greater in men than woman [18]. However, female patients show greater increase in LV mass with advanced age. As our patients were well comparable with regards to gender, this again could not influence the outcome significantly between the groups.

Hypertension is often present in elderly patient populations and might significantly influence the rate of LV mass regression [19]. In our study the hypertensive patient distribution was even between the groups and could therefore not influence outcome significantly.
All these considerations indicate that in an elderly population with reduced physical activity that often has hypertension and has had aortic stenosis for a great number of years, it might be difficult to observe a complete regression of LV mass and ascribe it to the type of valve substitute. Furthermore, we were not able to detect significant hemodynamic differences between the stented and stentless valve groups.

Therefore, as no significant differences in transvalvular gradients were detected it is not surprising that no differences in the rate and completeness of LV mass regression resulted. Overall, the complexity of stentless valve implantation with its prolonged cross-clamping times might under these circumstances not be justifiable if, as we found, the same results can be achieved with a standard stented bioprosthesis. Our findings were obtained from evaluating valves of sizes 21–27 mm. As we did not implant valves of size 19 mm, we cannot extend our conclusions to patients with small aortic annuli.

References


Appendix A. Conference discussion

Dr H. Oelert (Mainz, Germany): You mentioned the influence of systemic hypertension in left ventricular hypertrophy regression postoperatively. Did you look into your results in your series? What was the systemic hypertension at the end of the follow-up during aortic valve replacement in both series? That is one question for you. The comment is that I think that postoperative gradients on your valves most probably will be done by echocardiography, which is often somewhat unreliable in artificial valves.

Dr Doss: Number one, we looked at the hypertensive population in our study, and, as I showed in the slide, there were about four hypertensive patients in one and five in the other group, and also postoperatively when patients came for follow-up, these hypertensive patients tended still to have slight hypertension, with systolic gradients of up to 150. But as the percentage was matched in both groups we didn’t find it as a significant factor to influence the overall results. And when you say echocardiography is unreliable, that is, unfortunately, the way everybody did it in all these studies, so that’s how we did it as well.

Dr W.-P. Kloevekorn (Bad Nauheim, Germany): Did you do a septal resorption prior to valve implantation?

Dr Doss: We looked at whether there was septal hypertrophy in the patients, that was part of the standard protocol, and all patients that would have any, let’s say, subannular stenosis were actually excluded from the study. So in these patients there was no septal resection done.

Dr C. Yankah (Berlin, Germany): My question relates to the left ventricular function of these patients. You didn’t measure any functional parameters like systolic and diastolic function by echo which I believe are useful and important parameters to predict postoperative cardiac morbidity and mortality. Did you have any figures or data on these patients to predict their outcome? Both valves, the stented or stentless, are differently designed and are hemodynamically different in behavior. However, in this age group valve-related risk factor and the effect on the cardiac performance is insignificant.

Dr Doss: Yes, I agree. First of all, in this group of patients, all patients that had a myocardial infarction preoperatively were excluded. That means we did not have patients with a low ejection fraction in this group. Secondly, we did not look at the diastolic cardiac function. We didn’t look at the systolic. We looked at fractional shortening, and that actually
matched the results of the ejection fraction that I had shown, which showed no differences between the groups.

**Dr G. Luciani (Verona, Italy):** We have been involved with stentless surgery for 10 years now, and I am a bit disturbed by several findings in your report. The first one, how do you go about randomizing stented and stentless bioprostheses? There are certain anatomical contraindications with stentless surgery and how do you exclude these patients? A second question, I noticed all your patients had normal ventricular function, but you have a mortality in the stented group which is 10%. Could you comment on that mortality estimate, which is quite high?

And the third question is, did you correct for effective orifice area after the implant of the valves to compare the functional performance?

**Dr Doss:** Well, the first question, how do we randomize the patients regarding anatomical implant considerations, we had a protocol, and if you had a patient that was not suitable for implantation of a stentless valve, then he was also not included in the study and he did not also receive a stented valve, number one.

Number two, we had a 10% mortality in the stented group, but, as I said, it was not valve-related. Actually one patient had a pneumonia, the other patient died of septicemia, and the third patient, which was a late complication, actually had a ruptured aortic aneurysm which was not treated and they found it in the long run. So it was not actually valve-related. I cannot say it was valve-related.

**Dr Luciani:** And did you match for effective orifice area after the operation to compare the regression of LV mass?

**Dr Doss:** We looked at the effective orifice area and we found no significant difference between effective orifice area. Actually these are also findings that were found by the other randomized trial that I had mentioned from the Cleveland Clinic. So, again, there we didn’t have any differences I have to say.