Aortic Valve Replacement and Concomitant Procedures With the Perceval Valve: Results of European Trials

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Background. The Perceval (Sorin Group, Milan, Italy) is a self-anchoring sutureless aortic valve prosthesis. We report the short- to midterm results of combined aortic valve replacement (AVR) with concomitant procedures in elderly patients undergoing operation as part of 3 consecutive prospective multicenter European studies.

Methods. From April 2007 to February 2013, 243 patients (mean age, 79.7 ± 5.1 years; female patients, 61%; median EuroSCORE, 9%) underwent AVR with concomitant procedures. The concomitant procedures were coronary artery bypass grafting (CABG) (182 cases), septal myectomy (21 cases), CABG + other procedures (18 cases), and 22 other procedures. Primary and secondary end points included implant feasibility and safety (for mortality and morbidity) and efficacy (New York Heart Association [NYHA] class improvement and hemodynamic results) of the prosthesis at the different follow-up periods. Data were expressed as mean ± standard deviation. Kaplan-Meier analysis was performed for survival analysis.

Results. Mean aortic cross-clamp and extracorporeal circulation (ECC) times were 50.7 ± 22.8 minutes and 78.9 ± 32.3 minutes, respectively. Thirty-day mortality was 2.1%. Mean postoperative gradient and effective orifice area were 10.1 ± 4.7 mm Hg and 1.5 ± 0.4 cm² and 8.9 ± 5.6 mm Hg and 1.6 ± 0.4 cm², respectively, at 1 year. There were early explantations, 4 of which resulted from paravalvular leaks. One additional valve explantation resulted from aortic root bleeding, probably caused by excessively extensive decalcification. In the late period, there was 1 mild paravalvular leak and no intravalvular insufficiency. No migration, dislodgement, or degeneration of the valve occurred during follow-up. Median follow-up was 444 days.

Conclusions. These trials confirm the safety and efficacy of the Perceval sutureless aortic valve, especially in elderly patients requiring AVR + concomitant procedures. In this patient group, sutureless valves may be advantageous compared to transcatheter valve implantations as concomitant procedures other than percutaneous coronary artery angioplasty are not always possible in the latter.

Transapical or transfemoral aortic valve implantation (TAVI) has been proposed for high-risk patients, but these procedures are limited to patients with isolated aortic valve pathologic processes [3]. Hybrid approaches, combining transfemoral aortic valve implantation together with percutaneous coronary artery angioplasty, are feasible only in patients with limited coronary artery disease. Three consecutive European multicenter prospective nonrandomized clinical trials were designed to evaluate the sutureless Perceval aortic valve prosthesis (Sorin Group, Milan, Italy) in elderly patients.

In this study, we describe the results of AVR combined with concomitant procedures using the Perceval sutureless aortic valve prosthesis as a subgroup of these 3 consecutive prospective multicenter European clinical studies (Pilot, Pivotal, and CAVALIER) trials.

Patients and Methods

Study Design

This series comprises patients who underwent AVR together with concomitant procedures from 3 consecutive European prospective multicenter trials between 2007 and 2012. Approval for these studies was granted by the ethical committees of the hospitals involved (see the Appendix).

PERCEVAL Pilot Trial

The objective of the PERCEVAL Pilot Trial was to assess the safety of AVR with the sutureless Perceval valve in 30 symptomatic patients, aged 75 years and older. The primary end point was the assessment of the safety of the Perceval prosthesis regarding mortality and morbidity at 30 days correlated with prosthetic valve performance. Secondary end points were the evaluation of mortality and morbidity, the evaluation of the clinical status on the basis of the New York Heart Association (NYHA) functional classification, and the evaluation of the hemodynamic performance by echocardiographic examination at 1, 3, 6, and 12 months from implantation.

PERCEVAL Pivotal Trial

The primary objective of the PERCEVAL Pivotal Trial was to assess the performance of the Perceval valve at 3 to 6 months after implantation in 150 patients at high surgical risk, aged 75 years or older, and requiring surgical intervention to replace the aortic valve. The primary performance end point was the assessment of the Perceval prosthesis at 3 to 6 months after operation regarding improvement of clinical status and hemodynamic performance through echocardiography. The primary safety end point was the assessment of the Perceval prosthesis regarding mortality and morbidity at 3 to 6 months after implantation. Secondary end points included the evaluation of the Perceval valve regarding improvement of clinical status, hemodynamic performance by echocardiography, and assessment of mortality and morbidity rates at discharge and 12 months after implantation.

PERCEVAL CAVALIER Trial

The ongoing CAVALIER trial was designed to assess the safety and effectiveness of the Perceval valve at 12 months after implantation when used to replace a diseased or dysfunctional aortic valve or aortic valve prosthesis in patients older than 65 years. The primary end point of the clinical investigation is the evaluation of the safety and effectiveness of the Perceval valve at 12 months after implantation. The safety of the Perceval valve is assessed regarding mortality and morbidity at 12 months after implantation. The effectiveness of the Perceval valve is assessed regarding improvement of clinical status as well as hemodynamic performance through echocardiographic measurements at 12 months after implantation. The secondary end points of the clinical investigation are the assessment of mortality and morbidity rates, the evaluation of the effectiveness of the Perceval valve for improvement of clinical status, and the evaluation of the effectiveness of the Perceval valve for hemodynamic performance through echocardiography at discharge and 3 to 6 months after operation and yearly thereafter.

Inclusion criteria for this study included all patients from these 3 studies who were undergoing combined AVR along with any concomitant cardiac procedure. A total of 243 patients (14 from the Pilot trial, 49 from the Pivotal trial, and 180 from the CAVALIER trial) from 23 different centers in 8 European countries were thus included for this study.

Perceval Sutureless Valve

Perceval is a valve prosthesis consisting of a bovine pericardium valve fixed in a metal frame of nitinol (equiatomic alloy of nickel and titanium). The design features 2 ring segments on the proximal and distal ends and connecting elements designed to support the valve and allow the prosthesis to anchor to the aortic root and the sinuses of Valsalva. In correspondence with each valve sinus, the proximal ring has 3 loops through which temporary guiding threads are passed to aid prosthetic positioning (Fig 1). Nitinol can undergo strong deformation and return to its original shape after the source of force is removed. Therefore the stent can be compressed for implantation and is then released to reach its final diameter. Before implantation, the prosthesis is collapsed and loaded onto a holder. The Perceval valve is then positioned and released into the aortic root, where the stent self-anchoring design allows stable sitting of the device.

For this study, 3 valve sizes (S, M, and L) were available.

Surgical Procedure

The patients were operated on either through a standard median sternotomy or an upper ministernotomy. After systemic heparinization, the ascending aorta and either the right femoral vein or the right atrium were cannulated and ECC started. After cross-clamping and attaining cardioplegia, a transverse aortotomy was performed 1 cm
Once the prosthesis was completely deployed, the guiding sutures were removed.

Concomitant coronary artery bypass grafting (CABG) was performed in patients with coronary artery disease. This was usually done during the time when the study valve was being collapsed to keep the aortic cross-clamp time as short as possible.

After closure of the aortotomy in the usual fashion, release of the aortic cross clamp, and thorough removal of air, valve function was investigated by transesophageal echocardiography in all patients.

After the procedure, the patients received anticoagulation treatment according to the standard protocol in use for bioprostheses at each center.

**Reporting on Adverse Events and Statistical Analysis**

Adverse events were reported according to current guidelines [4]. SAS software, version 9.2 (SAS Institute, Cary, NC) was used for descriptive statistics. All data are expressed as mean ± standard deviation or as median and quartiles if not normally deviated. Kaplan-Meier analysis was performed for medium-term survival.

**Results**

Overall, between April 2007 and February 2013, a total of 770 patients underwent AVR with the Perceval sutureless valve. Twenty-five centers in 8 European countries took part in the 3 studies. Of those patients, 243 underwent AVR with a Perceval valve together with concomitant procedures (Table 1).

The mean age of these 243 patients was 79.7 ± 5.1 years, and 48.1% of patients were 80 years or older; only 4.1% were younger than 70 years. One hundred forty-eight patients were women (60.9%). The median logistic EuroScore was 9. Concomitant procedures included CABG in 200 patients (82.3%), septal myectomy for severe septal hypertrophy resulting in subvalvular stenosis in 27 patients (11.1%), and other procedures such as tricuspid annuloplasty, atrial ablation, closure of a patent foramen ovale, and replacement of the ascending aorta in a total of 34 patients (14.0%). Mean aortic cross-clamp and ECC times were 50.7 ± 22.8 minutes and 78.9 ± 32.3 minutes, respectively.

The intraoperative and postoperative courses were uneventful in all patients except 3 patients who required mild inotropic support because of postoperative left ventricular dysfunction, with recovery in all patients. Intraoperative echocardiography confirmed regular position of the valve prosthesis in all cases and unrestricted movement of all leaflets. There was no sign of relevant transvalvular regurgitation or any paravalvular regurgitation in all patients during the operation. Early mortality was 2.1% (n = 5) and lower than the expected mortality of 9% according to the logistic EuroScore (Table 2). One patient had postoperative endocarditis (0.4%) and underwent reoperation 8 days after the initial implantation. The primary cause was identified as a recent pulmonary infection. However, the patient died 13 days after implantation. Study valve replacement was
also necessary in 1 case of aortic root bleeding. This extreme complication occurred because of an aortic wall tear 2 cm below the right coronary ostium. It was probably caused by excessively extensive decalcification of the annulus. The valve was explanted and an aortic root replacement (Bentall procedure) was performed with a biological valved conduit. Valve replacement was also necessary in 4 additional patients because of paravalvular leak (1.69%), all occurring during the early phase (learning curve). Replacement was necessary after 2 days in 2 patients and after 4 and 7 days, in 2 other patients, respectively. The further course of the patients was uneventful in all cases.

Mean follow-up was 444 days. At the time of the reported analysis, the follow-up was 86.6% complete at 1 year (Table 3) and 34.7% at 2 years, because follow-up of more than 1 year was not initially planned in the study designs for the Pilot and Pivotal trials and the 1- and 2-year follow-up of patients in the CAVALIER trial was still ongoing (follow-up window had not yet been reached by all patients). Overall survival of the patients was 86.4% at 2 years (Fig 2). There were 4 late explantations (1.35/ patient-years) all of them resulting from endocarditis (84, 169, 291, and 425 days after implantation, respectively). No cases of valve thrombosis, valve dislodgement, valve migration or structural valve deterioration were observed during follow-up.

Hemodynamics improved significantly after the operation (Table 4), despite the fact that two thirds of the patients received a valve sized S or M (Table 1) and 90% of the patients had an annulus of less than 23 mm after decalcification. Low gradients and high effective orifice area indices remained stable over up to 2 years. There was no sign of patient-prosthesis mismatch in any patient. In 1 patient, a mild paravalvular leak, which was not present in the intraoperative echocardiograms, occurred without any sign of hemodynamic relevance. There was no transvalvular leakage or any sign of nonstructural deterioration during follow-up. Most patients were in NYHA class I or II after the operation (Table 5), and no patients were in NYHA class IV.

### Table 1. Patients Characteristics (Mean ± Standard Deviation)

<table>
<thead>
<tr>
<th>Study</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female/male sex</td>
<td>148/95 (61%/39%)</td>
</tr>
<tr>
<td>Age at operation (y)</td>
<td>79.9 ± 5.1</td>
</tr>
<tr>
<td>Mean logistic EuroScore</td>
<td>12.1%</td>
</tr>
<tr>
<td>Median logistic EuroScore</td>
<td>9.0%</td>
</tr>
<tr>
<td>Patients with EuroScore &gt; 10</td>
<td>110</td>
</tr>
<tr>
<td>Patients with EuroScore &gt; 20</td>
<td>37</td>
</tr>
</tbody>
</table>

### Table 2. Early Clinical Results (< 30 Days)

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Logistic EuroScore (median)</td>
<td>. . .</td>
<td>9.0</td>
</tr>
<tr>
<td>30-day mortality</td>
<td>5</td>
<td>2.1</td>
</tr>
<tr>
<td>Stroke</td>
<td>3</td>
<td>1.3</td>
</tr>
<tr>
<td>Reexploration for bleeding</td>
<td>9</td>
<td>3.8</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>1</td>
<td>0.4</td>
</tr>
<tr>
<td>Third-degree atrioventricular block</td>
<td>8</td>
<td>3.4</td>
</tr>
<tr>
<td>Pacemaker implantation</td>
<td>14</td>
<td>5.9</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>2</td>
<td>0.8</td>
</tr>
<tr>
<td>Heart failure</td>
<td>3</td>
<td>1.3</td>
</tr>
<tr>
<td>Explantation</td>
<td>5</td>
<td>2.1</td>
</tr>
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</table>

### Table 3. Completeness of Follow-Up

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients at Risk</th>
<th>Number of Visits</th>
<th>Completeness of Follow-Up (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative</td>
<td>243</td>
<td>243</td>
<td>100.0</td>
</tr>
<tr>
<td>30 d</td>
<td>222</td>
<td>221</td>
<td>99.6</td>
</tr>
<tr>
<td>3–6 mo</td>
<td>198</td>
<td>179</td>
<td>91.5</td>
</tr>
<tr>
<td>12 mo</td>
<td>186</td>
<td>161</td>
<td>86.6</td>
</tr>
<tr>
<td>2 y</td>
<td>176</td>
<td>61</td>
<td>34.7</td>
</tr>
</tbody>
</table>

Fig 2. Kaplan-Meier curve of survival up to 2 years.
Comment

Aortic valve replacement has been widely accepted as the gold standard for the treatment of patients with aortic valve stenosis [6]. The age of patients presenting for AVR is increasing along with demographic changes. The database of the German Society of Cardithoracic and Vascular Surgery shows that more than 50% of the patients presenting for cardiac operations in Germany are older than 70 years, and more than 10% are older than 80 years. It is projected that this percentage will increase further.\(^1\) The situation is similar in other industrialized countries. The Society of Thoracic Surgeons (STS) database shows that the number of patients older than 80 years has increased from 12% to 24% over the past 20 years [7]. At the same time, the percentage of candidates requiring AVR as well as concomitant coronary bypass operations has increased from 5% to 25%. In addition, older patients often have significant comorbidities and pose a high perioperative risk [2].

Percutaneous aortic valve implantation has been proposed as an alternative to surgical aortic valve implantation. However, this approach does not allow the treatment of combined pathologic processes of the aortic valve and the coronary arteries.

Since interventional therapy of coronary artery disease is not possible in all patients, and even if possible, it has to be staged, an advantage of the technique described earlier is that CABG can be performed along with AVR within safe cross-clamp time limits.

In the late 1960s, a historical series of the Magovern-Cromie prosthesis, a cage ball mechanical prosthesis with spikes instead of a sewing ring [8], was performed, and reports on long-term follow-up of more than 40 years were recently published [9]. However, because of disappointing overall clinical results and parallel improvements in cardioplegic techniques, this sutureless valve concept was abandoned for conventional AVR with sutured valve prostheses.

With modern technology, new sutureless prostheses combine the benefits of biological stentless valves for hemodynamics and left ventricular remodeling. The technical benefits of modern sutureless valves include the following:

- Safe and complete decalcification of the annulus under direct vision to create a smooth annulus, thus preventing paravalvular leakage by proper fitting of the prosthesis into the annulus
- Avoidance of valve migration as a result of a unique valve design along with optimal sizing during implantation
- Absence of suturing ring present in conventional prostheses, resulting in increased functional valvular diameter
- Possibility of performing necessary concomitant procedures, such as CABG, further valve procedures, atrial ablation therapy and other procedures
- Safe use even in redo cases [10, 11]
- No need for anchoring sutures reducing the cross-clamp times and consequently ECC times

In this study, these potential advantages were observed. The aortic cross-clamp and ECC times were significantly lower than the ones in the Society of Thoracic Surgeons database.

No valve dislodgement or migration was observed even after a follow-up of more than 4 years. Even though the majority of patients had a short stature with small aortic annuli and received smaller prostheses, the postoperative transvalvular gradients were low and remained so during follow-up. No significant paravalvular leakage was observed either in the immediate perioperative period or in the follow-up [12–16].

Consequently various “sutureless valve” prototypes have been in clinical use in Europe in recent years. So far, there is clinical experience with 3 different sutureless pericardial prostheses: the ATS 3f Enable Sutureless

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Table 4. Hemodynamic Performance (Up to 2 Years)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Preoperatively (n = 243)</th>
<th>30 Days (n = 221)</th>
<th>3–6 Months (n = 161)</th>
<th>1 Year (n = 161)</th>
<th>2 Years (n = 61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean gradient (mm Hg)</td>
<td>40.6 ± 16.6</td>
<td>10.1 ± 4.7</td>
<td>8.9 ± 4.2</td>
<td>8.9 ± 50.4.6</td>
<td>9.0 ± 3.4</td>
</tr>
<tr>
<td>Peak gradient (mm Hg)</td>
<td>70.0 ± 25.8</td>
<td>20.3 ± 9.9</td>
<td>18.0 ± 7.6</td>
<td>17.5 ± 8.2</td>
<td>18.3 ± 5.6</td>
</tr>
<tr>
<td>Effective orifice area (cm²)</td>
<td>0.8 ± 0.2</td>
<td>1.5 ± 0.4</td>
<td>1.5 ± 0.4</td>
<td>1.6 ± 0.4</td>
<td>1.7 ± 0.5</td>
</tr>
<tr>
<td>Effective orifice area index (cm²/m²)</td>
<td>0.4 ± 0.1</td>
<td>0.8 ± 0.2</td>
<td>0.9 ± 0.2</td>
<td>0.9 ± 0.2</td>
<td>1.0 ± 0.3</td>
</tr>
</tbody>
</table>

Table 5. Postoperative Symptoms According to NYHA Class

<table>
<thead>
<tr>
<th>Classification</th>
<th>Preoperative (n = 243)</th>
<th>3–6 Months (n = 179)</th>
<th>1 Year (n = 161)</th>
<th>2 Years (n = 61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA I</td>
<td>3 (1.3%)</td>
<td>102 (56.9%)</td>
<td>80 (49.7%)</td>
<td>28 (45.9%)</td>
</tr>
<tr>
<td>NYHA II</td>
<td>57 (23.5%)</td>
<td>64 (35.6%)</td>
<td>68 (42.2%)</td>
<td>28 (45.9%)</td>
</tr>
<tr>
<td>NYHA III</td>
<td>164 (67.5%)</td>
<td>13 (7.5%)</td>
<td>13 (8.1%)</td>
<td>5 (8.2%)</td>
</tr>
<tr>
<td>NYHA IV</td>
<td>19 (7.7%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

NYHA = New York Heart Association.
Bioprosthesis (ATS, Minneapolis MN), the Perceval sutureless aortic valve prosthesis (Sorin Group, Milan, Italy), and the EDWARDS INTUITY valve (Edwards Lifesciences, Irvine, CA) [5, 17, 18].

Our results confirm the safety and efficacy of the Perceval sutureless aortic valve even in complex aortic valve disease with additional cardiac procedures. The valve implantation resulted in significant improvement of patient symptoms as well as reduction of transvalvular pressure gradients, which proved to be stable over time. In patients requiring AVR plus concomitant procedures, shortening the aortic cross-clamp time and ECC time may help to reduce mortality and morbidity. Ranucci and coworkers [19] reported that the aortic cross-clamp time is an independent predictor of severe cardiovascular morbidity, with an increased risk of 1.4% per 1-minute increase. Therefore, sutureless valves may be advantageous in these cases, because the total cross-clamp times are potentially shorter because of the absence of sutures. The results in these complex cohorts reflect the overall good outcome of the whole cohort of 770 patients.

In summary, this study highlights the advantages of the Perceval sutureless valve even in an elderly high-risk population. Although we do not have a control group, the Perceval sutureless valve even in an elderly high-risk population. Although we do not have a control group, the Perceval sutureless aortic valve prosthesis may provide a good outcome of the whole cohort of 770 patients.

References


Appendix. Physicians and Surgical Sites Involved in the Study

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