Transcatheter Aortic Valve Implantation in Patients With Severe Left Ventricular Dysfunction
Immediate and Mid-Term Results, A Multicenter Study

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Background—Few data exist about transcatheter aortic valve implantation (TAVI) in patients with low ejection fraction. The aim of the study was to analyze safety, feasibility, and efficacy of TAVI in patients with severe left ventricular dysfunction.

Methods and Results—The study sample (384 patients) was divided into 2 groups: group A (50 patients) with left ventricular ejection fraction (LVEF) ≤35%, and group B (334 patients) with LVEF >35%. Clinical, anatomic, and hemodynamic variables, as well as procedural results and follow-up outcomes, were compared between the groups. Procedural success was reached in 88%, with no significant difference between the groups. The incidence of periprosthetic leak >2+/+ after TAVI was higher in group A. All other complications were similar between the 2 groups. Group A showed a significant and early improvement in LVEF (from 27.7±6.0–35.2±11.1 after TAVI; P=0.0001). Thirty-day mortality was 4%; however, this was higher in group A compared with group B (10% versus 3%; P=0.010). Predictors of the cumulative late mortality were congestive heart failure, logistic euroSCORE, and moderate-to-severe periprosthetic leakage after TAVI. Estimated survival by Kaplan Meier at 1 year was, respectively, 69% in group A and 87% in group B (log rank <0.0001).

Conclusions—Transcatheter aortic valve implantation is a safe and effective procedure, even in patients with severe left ventricular dysfunction, leading to a high procedural success rate with an acceptable rate of complications and 30-day mortality. Also in these critically ill patients, TAVI provides clinical amelioration, with early improvement in LVEF. (Circ Cardiovasc Interv. 2012;5:253-260.)

Key Words: transcatheter aortic valve implantation  ■ aortic stenosis  ■ left ventricular dysfunction
■ left ventricular ejection fraction  ■ 30-day mortality

Degenerative aortic valve stenosis is the most common valvular disease in industrialized countries; this disease typically is found in elderly patients, and its prevalence will increase with the progressive lengthening in life expectancy.1 The prognosis of symptomatic patients left untreated is poor, with about 75% of patients dying within 3 years of symptom onset.2 Medical therapy is only a palliative measure, as the left ventricular outflow obstruction must be removed mechanically. Although current guidelines recommend surgical valve replacement as the therapy of choice in all symptomatic patients with severe aortic stenosis and in asymptomatic patients, who have already developed left ventricular dysfunction (class I),3 in the real world about one third of patients are excluded or not considered for surgery because of inoperability or high surgical risk due to advanced age or multiple comorbidities.1

This clinical issue stimulated the research and development of alternative less invasive techniques. In 2002, Professor Alain Cribier and his collaborators4 developed a new interventional technique, transcatheter aortic valve implantation (TAVI). This procedure is currently the only therapeutic option in truly inoperable patients5–7 and may represent a viable alternative to traditional surgical aortic valve replacement in high surgical risk patients,8–12 as was recently presented in the results of Cohort A of the Partner trial.13 Among patients at increased operative risk, who are therefore often excluded from surgical intervention, there are those with severe left ventricular dysfunction.14 In these...
patients, the transvalvular aortic gradient often is reduced because of low cardiac output, and sometimes a differential diagnosis of “pseudostenosis” can be challenging.\textsuperscript{15,16}

Transcatheter aortic valve implantation now has demonstrated excellent immediate and long-term results.\textsuperscript{17–20} However, less is known about the safety and efficacy of this technique in patients with left ventricular dysfunction.\textsuperscript{21,22} The aim of this study is to assess the immediate procedural results and long-term outcomes after TAVI in patients with severe aortic stenosis and severe left ventricular dysfunction, and to compare these with those of patients with normal or only moderately depressed left ventricular function to obtain information on the safety, feasibility, and efficacy of TAVI in this particular clinical context.

**WHAT IS KNOWN**

- Transcatheter aortic valve implantation (TAVI) has demonstrated excellent results in inoperable and high risk patients affected by severe aortic stenosis.
- Impairment in left ventricular function increases the surgical risk for conventional aortic valve replacement.

**WHAT THE STUDY ADDS**

- The presence of severe left ventricular dysfunction is not infrequent, being 13% of our TAVI treated population.
- Despite the fact that patients with left ventricular dysfunction were sicker and had more comorbidities, TAVI seems to be a safe and effective procedure providing a prompt and sustained improvement in clinical and left ventricular ejection function.
- The presence of severe left ventricular dysfunction is not to be considered a contraindication to TAVI.

**Methods**

**Study Sample and Study Design**

This is a retrospective analysis of prospectively collected data within a dedicated database that includes all patients with symptomatic aortic valve stenosis (aortic valve area ≤0.6 cm\(^2\)/m\(^2\)), who underwent TAVI between June 2007, and December 2010, in 2 Italian hospitals, the Cardiology Clinic of the University of Padua and the Laboratory of Hemodynamics of the Scientific Institute San Raffaele in Milan. All patients were deemed inoperable or at high surgical risk for conventional surgery by a multidisciplinary team consisting of cardiothoracic surgeons, cardiologists, and anesthesiologists. All patients provided informed consent to undergo the procedure. The study sample included a total of 384 patients. Fifty of these had a severe impairment in left ventricular ejection fraction (LVEF) ≤35% (group A). This subgroup was compared with the remaining study sample (334 patients, group B), in terms of clinical, anatomic, and hemodynamic variables, as well as procedural results and follow-up outcomes.

**Procedural and Prosthesis Details**

The procedures were performed via a retrograde transfemoral, transsubclavian, or transaortic approach, or via an antegrade transapical approach. The transfemoral procedure was preferred when the ilio-femoral arteries were large enough to accommodate the delivery sheath. Transfemoral procedures were performed under local anes-
Table 1. Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total Sample n=384</th>
<th>Group A n=50</th>
<th>Group B n=334</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y, mean±SD</td>
<td>25.7±1.7</td>
<td>25.7±1.7</td>
<td>25.7±1.7</td>
<td>0.39</td>
</tr>
<tr>
<td>Weight (kg), mean±SD</td>
<td>80.7±5</td>
<td>78.6±6</td>
<td>81.7±7</td>
<td>0.08</td>
</tr>
<tr>
<td>Body surface area (m²), mean±SD</td>
<td>1.74±0.16</td>
<td>1.72±0.17</td>
<td>1.74±0.17</td>
<td>0.40</td>
</tr>
<tr>
<td>Body mass index, mean±SD</td>
<td>26.0±4.4</td>
<td>24.9±4.5</td>
<td>26.2±4.4</td>
<td>0.049</td>
</tr>
<tr>
<td>NYHA class III/IV</td>
<td>2.8±10.3</td>
<td>2.6±12.9</td>
<td>2.6±12.8</td>
<td>0.14</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>152 (40)</td>
<td>21 (42)</td>
<td>131 (39)</td>
<td>0.71</td>
</tr>
<tr>
<td>Hypertension</td>
<td>305 (79)</td>
<td>35 (70)</td>
<td>270 (81)</td>
<td>0.077</td>
</tr>
<tr>
<td>Diabetes</td>
<td>103 (27)</td>
<td>20 (40)</td>
<td>83 (25)</td>
<td>0.024</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>95 (25)</td>
<td>19 (38)</td>
<td>76 (23)</td>
<td>0.020</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>98 (26)</td>
<td>15 (30)</td>
<td>83 (25)</td>
<td>0.44</td>
</tr>
<tr>
<td>Previous CAGB</td>
<td>77 (20)</td>
<td>15 (30)</td>
<td>62 (19)</td>
<td>0.060</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>61 (16)</td>
<td>7 (14)</td>
<td>54 (16)</td>
<td>0.70</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>183 (48)</td>
<td>28 (56)</td>
<td>155 (46)</td>
<td>0.21</td>
</tr>
<tr>
<td>Dialysis</td>
<td>11 (3)</td>
<td>6 (12)</td>
<td>5 (2)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Pulmonary insufficiency</td>
<td>132 (34)</td>
<td>18 (36)</td>
<td>114 (34)</td>
<td>0.80</td>
</tr>
<tr>
<td>Peripheral vasculopathy</td>
<td>92 (24)</td>
<td>13 (26)</td>
<td>79 (24)</td>
<td>0.72</td>
</tr>
<tr>
<td>Pacemaker</td>
<td>32 (8)</td>
<td>11 (22)</td>
<td>21 (6)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Multivessels CAD</td>
<td>115 (30)</td>
<td>22 (44)</td>
<td>93 (28)</td>
<td>0.020</td>
</tr>
<tr>
<td>Bioprosthesis</td>
<td>13 (3)</td>
<td>1 (2)</td>
<td>12 (4)</td>
<td>0.56</td>
</tr>
<tr>
<td>Logistic euroSCORE (%)</td>
<td>24.0±15.6</td>
<td>39.6±19.4</td>
<td>21.6±13.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Standard euroSCORE (%)</td>
<td>10.6±2.6</td>
<td>12.9±2.8</td>
<td>10.3±2.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>STS score (%)</td>
<td>9.8±8.8</td>
<td>12.8±11.7</td>
<td>10.3±2.4</td>
<td>0.052</td>
</tr>
</tbody>
</table>

SD indicates standard deviation; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; CAGB, coronary artery bypass grafting; CAD, coronary artery disease; STS, Society of Thoracic Surgeons.

Results

Baseline Characteristics

Mean age of total sample was 80±7 years, and the majority were females (52%). Patients in group A included younger patients with a lower body mass index. Moreover, group A patients were more likely to be symptomatic with dyspnoea and presented with a higher prevalence of diabetes mellitus, previous myocardial infarction, end stage chronic kidney disease requiring hemodialysis, previous permanent pacemaker, and multivessels coronary artery disease. Procedural risk estimated using the logistic euroSCORE, standard euroSCORE, and Society of Thoracic Surgeons score, was significantly higher in group A. Baseline clinical characteristics are shown in Table 1.

Baseline Echocardiographic Data

Mean LVEF measured 52.8±12.8% (27.7±6.0 in group A versus 56.5±8.7 in group B, P<0.0001). Six percent of the sample presented with associated mitral regurgitation >2+/4, according to Sellers classification. The 2 groups differed significantly from each other in terms of peak and mean transvalvular aortic gradient, which were significantly lower in group A, and pulmonary artery systolic pressure, which was higher in group A. Finally, the mean aortic valve annulus diameter was significantly larger in group A. Baseline echocardiographic data are shown in Table 2.

Table 2. Baseline Echocardiographic Data

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total Sample n=384</th>
<th>Group A n=50</th>
<th>Group B n=334</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF (%), mean±SD</td>
<td>52.8±12.8</td>
<td>27.7±6.0</td>
<td>56.5±8.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Aortic annulus (mm), mean±SD</td>
<td>22.7±2.0</td>
<td>23.3±2.0</td>
<td>22.6±1.9</td>
<td>0.041</td>
</tr>
<tr>
<td>AVA (cm²), mean±SD</td>
<td>0.75±0.48</td>
<td>0.71±0.21</td>
<td>0.76±0.51</td>
<td>0.50</td>
</tr>
<tr>
<td>AVA (cm²/m²), mean±SD</td>
<td>0.43±0.25</td>
<td>0.41±0.12</td>
<td>0.44±0.27</td>
<td>0.56</td>
</tr>
<tr>
<td>Aortic peak gradient (mm Hg), mean±SD</td>
<td>81.3±25.5</td>
<td>67.4±23.2</td>
<td>83.3±25.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Aortic mean gradient (mm Hg), mean±SD</td>
<td>49.7±17.0</td>
<td>41.6±14.5</td>
<td>50.9±17.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RVSP (mm Hg), mean±SD</td>
<td>41.9±13.7</td>
<td>48.3±15.2</td>
<td>40.9±13.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Aortic regurgitation &gt;2+/4</td>
<td>39 (10)</td>
<td>5 (10)</td>
<td>34 (10)</td>
<td>0.96</td>
</tr>
<tr>
<td>Mitral regurgitation &gt;2+/4</td>
<td>23 (6)</td>
<td>5 (10)</td>
<td>18 (5)</td>
<td>0.20</td>
</tr>
</tbody>
</table>

LVEF indicates left ventricular ejection fraction; SD, standard deviation; AVA, aortic valve area; RVSP, right ventricular systolic pressure.

Procedural Technical Details

The majority of patients (75%) were treated using the transfemoral approach, 17% via the transapical approach, and 7% via the trans-subclavian approach, and only 2 patients required usage of the transaortic approach, with no statistically significant difference between groups A and B. The use of self-expandable and balloon expandable prostheses was well balanced in the general sample (47% and 53%, respectively) and between the groups. General anesthesia was necessary in less than one third of cases (32%), with no statistically significant difference between groups A and B (P=0.49). The only procedural parameter that varied between the 2 groups was the rate of aortic predilation, which was lower in group A than group B (84% versus 94%; P=0.015). On the other side, the need of postdilatation was similar between groups (22% in group A versus 17% in group B; P=0.39).

Intra- and Periprocedural Outcome

Procedural success was reached in 88% of the total sample, with no significant difference between the 2 groups. Device success rates were not different between the 2 groups, although there was a trend toward higher device success rates in group B (82% in group A versus 91% in group B, P=0.060). The incidence of periprosthetic leak >2+/4 following the procedure was higher in group A (10% in group A...
between the groups. The incidence of vascular complications was quite low (1%), but similar between the groups. The rate of permanent pacemaker implantation (3%) was already evident, with 94% of patients in NYHA I/II class. Moreover, out of 50 patients in group A, 22 (44%, group A2) had a mean gradient <40 mm Hg. LVEF increased significantly in both groups (linear mixed model time effect, P<0.0001). In contrast, the patients who had a better LVEF at baseline (group B) did not show any significant improvement at the time of their first postoperative echocardiogram (their ejection fraction changed from 56.5±8.7% to 55.9±9.2%, P=0.24). Although group B had a persistently higher LVEF than group A at each time point during follow-up, the absolute difference between the groups was reduced at 1 year follow-up, due to a trend to progressive improvement in LVEF over time among the patients of the group A. Restricting the analysis only to those patients who had LVEF measured at 1 year (116 patients), we still observed that LVEF increased significantly in both groups (linear mixed model time effect, P<0.0001), and the magnitude of change was significant between groups (linear mixed model group effect, P<0.0001, and linear mixed model by time effect, P=0.001).

Moreover, out of 50 patients in group A, 22 (44%, group A1) had low-flow, low-gradient aortic stenosis (mean gradient <40 mm Hg), and 28 (56%, Group A2) had a mean gradient ≥40 mm Hg. LVEF increased significantly in both subgroups (linear mixed model time effect, P<0.0001), but the magnitude of change was not significant between subgroups (linear mixed model group effect P=0.004, and linear mixed model group by time effect, P=0.089; Figure 1, panel B). However, although not statistically significant, patients with low-flow, low-gradient aortic stenosis showed almost a 2-fold increase in the in hospital mortality rate compared with patients without low gradient aortic stenosis (18% versus 11%). Finally, in our analysis, permanent pacemaker implantation after TAVI and completeness of coronary revascularization before TAVI had no significant effect on the change in LVEF before and after TAVI.

Follow-Up
Mean follow-up length was 9±8 months (limits 1–36 months), with no significant difference between the 2 groups (8±7 months in group A; 9±8 months in group B, P=0.40). At 30 days a significant improvement in NYHA functional class was already evident, with 94% of patients in NYHA I/II at 30-day follow up (P<0.0001 versus baseline value).
At 1-year follow-up (for the 278 eligible patients), all cause death was 14% (40 patients; 29% in group A versus 12% in group B, \( P < 0.012 \)). Cardiovascular death was similar between the 2 groups (10% in group A versus 6% in group B; \( P = 0.434 \)). Estimated total survival by Kaplan Meier at 1- and 2-year follow-up was 84% and 73%, respectively, in total sample, 69% and 52% in group A and 87% and 76% in group B (log rank \( P = 0.012 \); Figure 2, panels A and B).

**Predictors of Mortality**

The major independent predictors of the cumulative late mortality were congestive heart failure (\( P < 0.0001 \); HR 2.69; 95% CI, 1.64–4.40), logistic euroSCORE (\( P = 0.002 \); HR 1.02; 95% CI, 1.01–1.04), and moderate-to-severe periprosthetic leakage after TAVI (\( P = 0.043 \); HR 2.19; 95% CI, 1.02–4.67).

**Discussion**

The most important findings of this study are (1) in a subgroup of patients with severe impairment in left ventricular function, procedural success rates are high and statistically similar to that of patients with normal or only a moderate reduction in LVEF, and (2) the intra- and periprocedural complications recorded between the 2 groups of patients were similar.

The device success rate of 90% reported in our total sample might appear lower than other published series, such as the Italian registry (98%),\(^\text{25}\) the French registry (92.6%),\(^\text{18}\) the Belgian registry (97%),\(^\text{26}\) the German registry (98.4%),\(^\text{17}\) the European SOURCE registry (93.8%),\(^\text{19}\) and the Canadian experience (93.3%).\(^\text{20}\) However, this apparent difference probably is due, at least in part, to differential definitions of procedural success between these published results;\(^\text{27}\) in our study, we followed the recommendations proposed by the VARG Committee.\(^\text{24}\) Despite similar procedural success rates between the 2 groups of our study, the device success rate tended to be significantly lower in group A because of a higher incidence of significant residual periprosthetic leak postprocedure. This phenomenon may be explained by the presence of larger mean annulus size and less frequent use of balloon predilation in group A; the combination of these 2 factors may have caused inadequate expansion and sealing of the prosthesis to the native aortic valve apparatus in this group. In our series, the strategy of no balloon aortic...
between 8% and 21%, and it depends on the presence of mitral regurgitation, impact significantly on the clinical outcome of these patients at late follow-up.

It is also important to note that a significant early and sustained improvement in LVEF was recorded in group A, with a trend toward a reduction in the absolute difference between the 2 groups at 1-year follow-up. Few studies in the literature have documented improvements in LVEF after TAVI, and even fewer have focused on outcomes in patients with severe left ventricular dysfunction at baseline. The improvement in LVEF obtained after TAVI seems even better than that observed after surgical aortic valve replacement; this may be due, at least in part, to a superior hemodynamic performance of transcatheter prosthesis in terms of the effective orifice area, transprosthetic gradients, and reduction of pressure overload on the left ventricle. In addition, we must consider that TAVI, with the exception of the transapical approach, allows for better protection and ensures an improved recovery of myocardial function, while avoiding (or at least minimizing) ischemic and ischemia/reperfusion injury, inflammatory response, cardioplegia, surgical trauma, and oxidative stress, which can lead to apoptosis and contractile dysfunction of survivor myocytes.

With regards to the follow-up data in our series, the estimated overall survival rate at 1 year for the total sample was 84%, which included both inoperable and high surgical risk patients. In the cohort A of PARTNER trial (high risk patients), this Figure was 75.8%, while in cohort B (inoperable patients) it was 69.3%, significantly better than those patients who were left untreated (49.3%). Moreover, in our study, the estimated overall survival rate at follow-up was significantly lower in group A than in group B, with an early divergence between the 2 curves.

In conclusion, TAVI is a safe and effective procedure, even in patients with severe left ventricular dysfunction, as it leads to procedural success rates that are similar to those of patients with normal or only moderately reduced LVEF, and also leads to clinical improvement in these patients and, in particular, rapid partial recovery of their left ventricular function. Although these results are encouraging, randomized trials data are needed to determine whether this therapeutic approach is able also to improve long-term survival rates in this subgroup of patients.

**Study Limitations**

This study has all the limitations inherent to a relatively small, nonrandomized, retrospective analysis. To this regard, the sample size for low LVEF is unpowered for comparisons of binary data between groups A and B, especially related to the procedural success and adverse events. Another important aspect is the absence of a systematic evaluation of myocardial viability and contractile reserve by low-dose dobutamine.
echocardiography before consideration of TAVI. Thus, we cannot make inferences on potential predictors of LV EF improvement after TAVI or on specific criteria defining the subset of patients who may benefit most from selection of a specific prosthesis type. Finally, no evaluation of the patient using a “frailty index” was performed, and it is possible that this may have affected the outcomes.

Disclosures
Gino Gerosa and Giambattista Isabella are physician proctors for Medtronic, Abbott, and ValtechCardio.

References


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