Valvular Heart Disease

Percutaneous Transarterial Aortic Valve Replacement in Selected High-Risk Patients With Aortic Stenosis

John G. Webb, MD; Sanjeevan Pasupati, MBChB; Karin Humphries, PhD; Christopher Thompson, MD; Lukas Altwegg, MD; Robert Moss, MD; Ajay Sinhal, MD; Ronald G. Carere, MD; Brad Munt, MD; Donald Ricci, MD; Jian Ye, MD; Anson Cheung, MD; Sam V. Lichtenstein, MD, PhD

Background—Percutaneous aortic valve replacement represents an endovascular alternative to conventional open heart surgery without the need for sternotomy, aortotomy, or cardiopulmonary bypass.

Methods and Results—Transcatheter implantation of a balloon-expandable stent valve using a femoral arterial approach was attempted in 50 symptomatic patients with severe aortic stenosis in whom there was a consensus that the risks of conventional open heart surgery were very high. Valve implantation was successful in 86% of patients. Intraprocedural mortality was 2%. Discharge home occurred at a median of 5 days (interquartile range, 4 to 13). Mortality at 30 days was 12% in patients in whom the logistic European System for Cardiac Operative Risk Evaluation risk score was 28%. With experience, procedural success increased from 76% in the first 25 patients to 96% in the second 25 ($P = 0.10$), and 30-day mortality fell from 16% to 8% ($P = 0.67$). Successful valve replacement was associated with an increase in echocardiographic valve area from 0.6±0.2 to 1.7±0.4 cm$^2$. Mild paravalvular regurgitation was common but was well tolerated. After valve insertion, there was a significant improvement in left ventricular ejection fraction ($P < 0.0001$), mitral regurgitation ($P = 0.01$), and functional class ($P < 0.0001$). Improvement was maintained at 1 year. Structural valve deterioration was not observed with a median follow-up of 359 days.

Conclusion—Percutaneous valve replacement may be an alternative to conventional open heart surgery in selected high-risk patients with severe symptomatic aortic stenosis. (Circulation. 2007;116:755-763.)

Key Words: stenosis • stents • valves • valvuloplasty

When aortic stenosis progresses to the point of symptoms, the prognosis with medical management alone is poor.1,2 Unfortunately, many patients with severe aortic stenosis do not undergo surgical aortic valve replacement (AVR), despite the proven benefits of this therapy.2–7 Such patients frequently have comorbidities, in particular advanced age, that increase the morbidity and mortality associated with sternotomy, aortotomy, and cardiopulmonary bypass.4,5

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A percutaneous alternative was first explored in an animal model by Andersen et al.8,9 Subsequently, a number of groups pursued various approaches to transcatheter aortic valve implantation.8–16 It was not until a decade after initially proposed that the feasibility of percutaneous AVR was demonstrated in humans by Cribier et al17,18 using a transvenous, transseptal approach. Subsequently, we described a retrograde procedure using percutaneous femoral artery access.19 We report the early and late outcomes with this procedure in the initial 50 high-risk patients.

Methods

Patients

Percutaneous AVR was approved for compassionate clinical use by the Department of Health and Welfare (Ottawa, Canada) in symptomatic patients not considered candidates for open heart surgery. A team of cardiologists and cardiac surgeons accepted patients on the basis of a consensus that conventional surgery was excessively high risk in terms of anticipated mortality and morbidity. Patient or physician preference alone was not considered adequate.14 Written informed consent was obtained.

Patients underwent coronary and aortofemoral angiography. The diameter of the aortic annulus was measured from the echocardiographic parasternal long-axis view at the level of the leaflet attachments. Patients were excluded if the aortic annulus diameter was <18 or >26 mm, if there was severe iliofemoral arterial disease, or if a reasonable quality or duration of life was considered unlikely despite valve replacement because of comorbidities.

Prosthetic Valve Implantation

Procedures were performed in a catheterization laboratory, usually under general anesthetic with endotrachal intubation. Patients were premedicated with aspirin, clopidogrel, and vancomycin. Heparin was used to maintain activated clotting time >250 seconds. Vaso-
Data and Definitions
Clinical follow-up and transthoracic echocardiograms were obtained before discharge and at 1, 6, and 12 months. Patients in whom the procedure was not successful were followed up for 30 days. Procedural success was defined as implantation of a functioning prosthetic valve within the aortic annulus and without in-laboratory mortality. Structural valve deterioration was defined as any change in valve function resulting from an intrinsic abnormality causing stenosis or regurgitation. 23 Myocardial infarction was defined as elevation of troponin T above normal with ECG evidence of ischemia and a compatible clinical history. Severe lung disease was defined as any change in valve function resulting from an intrinsic abnormality causing stenosis or regurgitation. 22 Myocardial infarction was defined as elevation of troponin T above normal with ECG evidence of ischemia and a compatible clinical history. Severe lung disease was defined as any change in valve function resulting from an intrinsic abnormality causing stenosis or regurgitation. 23-24 Clinical follow-up was completed for all patients, and these data were used to plot survival. Echocardiograms were obtained in 98%, 100%, 86%, and 100% of patients reaching discharge and 1, 6, and 12 months, respectively.

Statistical Analysis
Categorical variables are presented as frequencies and continuous variables as means or medians as appropriate. Survival curves were generated with the Kaplan-Meier method (censored data). Survival rates in the first 25 patients and second 25 patients were compared by use of the log-rank test. Paired t test or Wilcoxon signed rank test was used for continuous variables, and the binomial test for ordinal variables was used to compare echocardiographic variables at baseline and after the procedure. The same parameters were evaluated for changes from postprocedure and 1, 6, and 12 months using a repeated-measures mixed model for continuous outcomes, and ordinal logistic regression, assuming proportional odds, was used for ordinal outcomes with adjustment for baseline values. General estimating equations (GEE) methodology was used to adjust for the correlation between multiple measurements from the same patient. A strength of the GEE methodology is that subjects contributed data up to their last scheduled visit. A 2-sided value of P<0.05 was considered statistically significant. All analyses were conducted with SPSS version 13.0 (SPSS Inc, Chicago, Ill) except for the time trend analyses, which were conducted with SAS version 9.1 (SAS Corp, Cary, NC).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results
Patients
Percutaneous transfemoral transarterial valve replacement was attempted in 50 high-risk severely symptomatic patients. Mean age was 82±7 years (range, 62 to 94 years). Logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) risk score was 28%. 25 Comorbidities included, among others, coronary artery disease (72%), moderate to severe mitral regurgitation (48%), severe lung disease (32%), prior thoracotomy (34%), porcelain aorta (16%), severe pulmonary hypertension (18%), prior cerebral ischemic events (12%), and severe debility (22%). Baseline characteristics are shown in Table 1. Study flow is shown in Figure 2.

Early Outcome
Procedural success was achieved in 43 patients (86%). Valve implantation was unsuccessful in 7 attempts. Reasons for

constrictor agents were used to maintain coronary perfusion pressure during periods of hemodynamic instability. Cardiopulmonary bypass was not used. A percutaneous sheath (22F or 24F) was placed in the femoral artery.

The balloon-expandable prosthesis (Cribier Edwards, Edwards Lifesciences Inc, Irvine, Calif) is a tubular slotted stainless steel stent with an attached equine pericardial trileaflet valve and fabric sealing cuff (Figure 1). Two sizes were available: 23- and 26-mm expanded diameter. The prosthetic stent valve was mechanically crimped onto a balloon catheter immediately before implantation.

With a steerable guiding catheter, the balloon-mounted valve was passed retrogradely through the aorta and positioned within the native aortic annulus as previously described. 20 Positioning was confirmed by fluoroscopy, aortography, and transesophageal echocardiographic imaging. 20 Transient partial cardiac standstill was induced with right ventricular burst pacing to minimize transvalvular flow and cardiac motion. 21 The delivery balloon was inflated to expand the valved stent, thereby excluding and compressing the native aortic valve. The femoral puncture site was closed surgically, followed by extubation in the catheterization laboratory and mobilization the next day. Aspirin was continued indefinitely; clopidogrel was continued for 1 to 3 months. Warfarin was substituted for clopidogrel in patients with atrial fibrillation.

Figure 1. Left, Photograph of the balloon-expandable stent from the aortic aspect showing leaflets in the closed position (top) and from the side showing the fabric sealing cuff (bottom). Middle, Fluoroscopic image of the implanted and fully expanded valve as seen from the aortic aspect (top). The aortic angiogram (bottom) shows the valve securely fixed in the annulus. The left main coronary artery can be seen to originate from the sinotubular junction above the valve adjacent to a transesophageal echo probe. Right, Transesophageal echocardiogram short axis (top) and long axis (bottom). Ao indicates aorta; LA, left atrium; LVOT, left ventricular outflow tract; and SV, sinus of Valsalva.
failure included inability to pass the iliac artery in 1 patient and cross the aortic valve in 3 patients, a defective prototype delivery catheter in 1 patient, and malpositioning in 2 patients.

Malpositioning of the prosthesis occurred in 2 patients very early in the experience (patients 4 and 9). In both cases, the prosthesis was incorrectly expanded above the level of the aortic annulus so that it was free in the ascending aorta, although constrained by the delivery catheter. The valves were withdrawn with the delivery catheter and further dilated and fixed within the transverse aorta in a location where major branch vessels would not be compromised. Both procedures were otherwise uncomplicated. One patient subsequently underwent elective conventional AVR at 103 days. A second patient continues on medical management for aortic stenosis. Both patients remain alive at 12 months after their procedures.

The initial 2 patients in the series (patients 1 and 2) suffered iliac injury requiring major vascular repair, with subsequent mortality in 1 patient. In a third patient, perforation of the abdominal aorta resulting in mortality occurred as a consequence of difficulty in advancing the bulky prosthesis across the stenotic aortic valve. A fourth patient with retroperitoneal bleeding from an iliac artery perforation was successfully treated with a covered stent. Two patients received antibiotics for access site infections after complex vascular closure. During the course of this experience, vascular access techniques, equipment, and screening evolved with a reduction in vascular complications.

Periprocedural stroke occurred in 2 patients, with complete recovery in 1 patient and mortality at day 29 in the second. Median hospital stay was 5 days (interquartile range, 4 to 13). By 30 days after successful valve replacement, 50% of patients had improved by ≥1 New York Heart Association functional classes (P<0.0001). Outcome events are listed in Table 2.

Mortality at 30 days was 12% in patients in whom the logistic EuroSCORE risk score was 28%25,26 There was 1 intraprocedural death caused by aortic injury (2%). The additional 5 postprocedural deaths occurring within 30 days of the procedure were a consequence of ventricular arrhythmia, left main occlusion, iliac injury, stroke, and multiorgan failure (each in 1 patient). No patient underwent conversion to open heart surgery within the initial 30-day follow-up period.

Late Outcome
All procedures were done >6 months and 30 were done >1 year before last follow-up contact. There were 3 deaths occurring after 30 days (days 56, 71, and 98 as a result of respiratory failure, myocardial infarction, and renal failure, respectively) but no subsequent deaths. Of the successfully implanted patients, 35 and 17 patients were alive at 6 and 12 months, respectively (Figure 2). At a median follow-up of 359 days (interquartile range, 60 to 371 days), 35 of 43 patients undergoing successful transcatheter AVR (81%) remained alive. Figure 3A illustrates the Kaplan-Meier survival after percutaneous valve implantation.

Subsequent valve procedures were performed in 3 patients. In each case, the reason was ongoing symptomatic aortic stenosis after an unsuccessful transcatheter procedure. Repeat valve procedures consisted of transcatheter AVR using direct left ventricular apical puncture at day 11, conventional surgical AVR at day 103 (as discussed above), and reattempted transfemoral transcatheter AVR at day 466. All 3 procedures were successful with all 3 patients remaining alive at the 30-day follow-up.

Structural valve deterioration was not observed during follow-up. The early improvement in functional class achieved after valve insertion was maintained at 6 months and 1 year (P=0.59, GEE for time trend) (Figure 4E).

Learning Curve
Characteristics and outcomes in the initial 25 patients and subsequent 25 patients were compared. Baseline characteristics were not significantly different with respective mean ages of 82±7 versus 82±8 years. However, rates of procedural success, malposition, and intraprocedural and peri-procedural mortality were more favorable in the later group. Procedural success increased from 76% to 96% (P=0.10), malposition fell from 8% to 0%, and intraprocedural mortality fell from 4% to 0%. Logistic EuroSCORE25,26 operative mortality

### TABLE 1. Baseline Characteristics of 50 High-Risk Patients Undergoing Percutaneous AVR

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Age, y, mean±SD</td>
<td>82±7</td>
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<tr>
<td>Female sex</td>
<td>20 (40)</td>
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<tr>
<td>New York Heart Association class</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>0 (0)</td>
</tr>
<tr>
<td>II</td>
<td>5 (10)</td>
</tr>
<tr>
<td>III</td>
<td>32 (64)</td>
</tr>
<tr>
<td>IV</td>
<td>13 (26)</td>
</tr>
<tr>
<td>Body mass index</td>
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<tr>
<td>&lt;20 kg/m²</td>
<td>4 (8)</td>
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<tr>
<td>20–24.9 kg/m²</td>
<td>19 (38)</td>
</tr>
<tr>
<td>25–29.9 kg/m²</td>
<td>16 (32)</td>
</tr>
<tr>
<td>&gt;30 kg/m²</td>
<td>11 (22)</td>
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<tr>
<td>Hypertension</td>
<td>31 (62)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>12 (24)</td>
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<tr>
<td>Coronary artery disease</td>
<td>36 (72)</td>
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<tr>
<td>Severe lung disease</td>
<td>16 (32)</td>
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<tr>
<td>Cerebral ischemic event</td>
<td>6 (12)</td>
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<tr>
<td>Peripheral vascular disease</td>
<td>10 (20)</td>
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<tr>
<td>Prior thoracotomy</td>
<td>17 (34)</td>
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<tr>
<td>Glomerular filtration rate &lt;60 mL/min</td>
<td>26 (52)</td>
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<tr>
<td>Ejection fraction &lt;50%</td>
<td>12 (24)</td>
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<tr>
<td>Mitral regurgitation (moderate or severe)</td>
<td>24 (48)</td>
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<tr>
<td>Pulmonary hypertension &gt;60 mm Hg</td>
<td>9 (18)</td>
</tr>
<tr>
<td>Porcelain aorta</td>
<td>8 (16)</td>
</tr>
<tr>
<td>Frail and poor mobility</td>
<td>11 (22)</td>
</tr>
<tr>
<td>Predicted 30-d surgical mortality, mean %†</td>
<td>28</td>
</tr>
</tbody>
</table>

†Logistic EuroSCORE

Values are expressed as n (%) unless otherwise noted.
estimation was 26% in the initial cohort and 30% in the later cohort. Actual 30-day mortality was 16% in the initial cohort, falling to 8% in the later cohort ($P=0.39$). Survival at 0, 1, and 6 months in the early and late cohorts was 96%, 84%, and 70% in the initial cohort and 100%, 92%, and 88% in the later cohort as illustrated in Figure 3B ($P=0.09$). There were no deaths between 6 and 12 months.

**Echocardiographic Evaluation**

Transthoracic echocardiography documented an immediate reduction in transaortic mean gradient from $46 \pm 17$ to $11 \pm 5$ mm Hg ($P<0.001$) and an increase in estimated aortic valve area from $0.6 \pm 0.2$ to $1.7 \pm 0.4$ cm$^2$ ($P<0.0001$). Time trend using the multiple linear regression models showed this improvement to be maintained up to 1 year (Figure 4A). Echocardiography documented prosthetic valve durability with no structural or significant hemodynamic deterioration at a median follow-up of 359 days extending to a maximum follow-up of 734 days.

Left ventricular ejection fraction increased after AVR from a mean of $53 \pm 15\%$ to $57 \pm 13\%$ ($P<0.0001$) within days. This improvement in ejection fraction was sustained up to 1 year ($P=0.80$, GEE for time trend). For the most part, this increase was due to an improvement in patients with moderate to severe left ventricular dysfunction. A left ventricular ejection fraction $<40\%$ at baseline was documented in 21% of patients before successful valve implantation, falling to 12%, 13%, 0%, and 6% at discharge and 1, 6, and 12 months, respectively (Figure 4B). Figure 5A shows the time trend in left ventricular ejection fraction in the 30 patients in whom left ventricular function was assessed at 6 months. This shows a trend to further improvement in ejection fraction after the time of discharge not resulting from patient selection, although this trend was not significant on the basis of GEE evaluation for time trend.

Mitrail regurgitation grade decreased from a median grade 2 (moderate) to grade 1 (mild) at discharge ($P=0.01$). Moderate to severe mitral regurgitation at baseline was present in 53% of successfully implanted patients, falling to 33%, 31%, 25%, and 24% at discharge and 1, 6, and 12 months, respectively (Figure 4C). The improvement in mitral regurgitation after valve insertion was maintained up to 1 year ($P=0.52$, GEE for time trend). Figure 5B examines the 29 patients who had mitral regurgitation assessed at 6 months.
There was a trend toward ongoing improvement in mitral regurgitation up to 6 months. Most of this improvement occurred in patients with moderate or severe mitral regurgitation.

Most patients had some degree of aortic insufficiency at baseline (Figure 4D). After AVR, aortic regurgitation increased from a median grade 0 (none/trivial) to grade 1 (mild) (P = 0.57) as determined by transthoracic echocardiography. Aortic regurgitation grade after valve implantation was unchanged in 24%, worsened in 44%, and improved in 32%. Postprocedural aortic insufficiency was determined by transesophageal echocardiography to be valvular (through the valve) or paravalvular (around the valve). In no patient was prosthetic valvular insufficiency more than mild. Most patients did have some degree of paravalvular insufficiency. When paravalvular insufficiency was judged excessive by transesophageal echocardiography, the prosthesis was sometimes redilated at the discretion of the operator, often with the addition of a very small amount of fluid to the semicompliant valvuloplasty balloon to achieve more complete and symmetrical expansion of the valve. Cautious redilation was not observed to result in leaflet damage or displacement of the prosthetic valve. No patient was left with severe paravalvular insufficiency. Moderate paravalvular insufficiency was observed in 3 patients, all of whom remained stable at follow-up. Clinical hemolysis was not observed.

**Discussion**

**Mortality Risk**

Prognosis in patients with symptomatic aortic stenosis is poor, and surgical AVR can be performed in good candidates at very low risk. However, large surgical series report a 5% to 15% operative mortality for isolated AVR in patients >70 years of age, and benchmark Medicare data document an operative mortality of 8.8% for patients >65 years of age. Surgical mortality rates escalate in the presence of comorbidities or the need for additional cardiac procedures. The factors that have a major impact on the risk of thoracotomy, aortotomy, or cardiopulmonary bypass (such as porcelain aorta, lung disease, or debility) may differ from those factors that determine the risk associated with a transarterial procedure such as iliofemoral disease. Better understanding of the risks associated with transcatheter procedures may allow improved patient selection.

Our experience suggests that percutaneous AVR can be performed with a mortality that compares favorably with that of open heart surgery in selected high-risk patients. Intraprocedural mortality was 2%, and 30-day mortality was 12%. In the latter half of this first-in-man percutaneous retrograde transarterial balloon-expandable valve experience, 30-day...
mortality fell further to 8% compared with a logistic EuroSCORE of 30%. Admittedly, the accuracy of this and other available objective predictors of surgical mortality is controversial, sometimes underestimating risk but perhaps more commonly overestimating risk.14,25,35,36 However, patients in the present series also were considered excessively high risk for surgery according to a consensus of senior surgeons and cardiologists representative of clinical practice in a high-volume center. It seems likely that with further incremental improvements in patient selection, techniques, and equipment, mortality rates with transcatheter valve implantation can decline further.

Morbidity
As important as mortality risk may be, procedural morbidity may weigh as heavily in the decisions made by elderly patients and their physicians.37 Hospital stay in this percutaneous high-risk group of largely elderly patients was relatively short at a median of 5 days and as little as 2 days. Although morbidity is difficult to further quantify, a procedural stroke rate of 4% and a sustained improvement in functional class are encouraging.

Learning Curve
Femoral transarterial valve implantation shares much in common with other percutaneous cardiac procedures.19 Nevertheless, a learning curve was apparent, likely attributable to incremental improvements in technique, equipment, and patient selection. Procedural success increased from 76% in the first half of this experience to 96% in the latter half. Malposition occurred very early in the experience and did not recur later in this experience as a consequence of improvements in understanding of the requirements of accurate positioning at the time of deployment and improvements in imaging. Major arterial complications declined with improvements in sheaths, angiographic screening, and technique. Left main occlusion, which occurred early in the experience, has not recurred after the application of routine fluoroscopic, angiographic, and echocardiographic screening for the presence of excessively bulky aortic valve leaflets, although the potential for it requires further study.

Valve and Cardiac Function
A prosthetic valve area of 1.7 cm² compares favorably with currently available surgical valves. Neither structural valve deterioration nor inadequate fixation of the prosthesis was observed at a mean follow-up of almost 1 year or in individual patients out to 2 years. Paravalvular insufficiency was common but generally mild, stable, and less of a concern than anticipated.18 However, paravalvular insufficiency does remain a concern, and further evaluation, including the potential for low-grade hemolysis and other hematological abnormalities, is required.38,39

In the present series, 48% of patients had moderate to severe mitral regurgitation, and 72% had coronary disease possibly sufficient to warrant the additional potential increased mortality risk with mitral valve replacement or coronary bypass had these patients undergone conventional AVR.27,29–33 Mitral regurgitation and coronary disease were generally well tolerated in these mostly elderly patients once aortic stenosis was relieved. Successful percutaneous aortic valve implantation was associated with a significant improvement in left ventricular function, mitral regurgitation, and functional class. Improvements were sustained at 1 year. Importantly, lack of late valve failure during clinical and serial echocardiographic with a median follow-up of almost 1 year suggests durability sufficient to offer significant benefit.

Study Limitations
Contraindications specific to transcatheter aortic valve implantation include an annulus too small or too large to accommodate the currently available prostheses or a partic-
ularly bulky aortic valve so that the prosthetic valve might displace an enlarged leaflet and obstruct a coronary ostium. Left ventricular dysfunction with nonrevascularized coronary disease and the potential for global ischemia during the procedure are relative contraindications. Arterial disease severe enough to prevent safe introduction of the prosthesis is a contraindication to a transarterial procedure. Vascular access injury, atheroembolism, and paravalvular insufficiency remain concerns and require further improvements in equipment and technique. In vivo durability of transcatheter valves equivalent to conventional surgical valves remains to be demonstrated. The presence of a learning curve requires careful dissemination of knowledge gained during development of this procedure. Early favorable experience with percutaneous AVR will need to be cautiously replicated in other centers, with larger numbers of patients, longer follow-up, and randomized evaluation.

Conclusions

Conventional open heart surgery remains first-line therapy for symptomatic aortic stenosis. However, percutaneous valve replacement is a viable alternative to conventional open heart surgery in selected high-risk patients with severe symptomatic aortic stenosis.

Disclosures

Drs Munt and Webb are consultants to Edwards Lifesciences Inc. The remaining authors report no conflicts.
CLINICAL PERSPECTIVE

Transcatheter aortic valve replacement represents an endovascular alternative to conventional open heart surgery without the need for sternotomy, aortotomy, or cardiopulmonary bypass. Percutaneous implantation of a balloon-expandable stent valve using a femoral arterial approach was attempted in 50 high-risk patients with severe symptomatic aortic stenosis. Mortality at 30 days was 12% in patients in whom the logistic European System for Cardiac Operative Risk Evaluation risk estimate was 28%. With experience, procedural success increased from 76% in the first 25 patients to 96% in the second 25, and 30-day mortality fell from 16% to 8%. After valve insertion, there was a significant improvement in left ventricular ejection fraction, mitral regurgitation, and functional class. Clinical improvement and valve function were maintained at 1 year. Percutaneous valve replacement may be an alternative to conventional open heart surgery in selected high-risk patients with severe aortic stenosis.
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