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Transcatheter Aortic Valve Implantation
Impact on Clinical and Valve-Related Outcomes

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Background—Transcatheter aortic valve implantation is an alternative to open heart surgery in patients with aortic stenosis. However, long-term data on a programmatic approach to aortic valve implantation remain sparse.

Methods and Results—Transcatheter aortic valve implantation was performed in 168 patients (median age, 84 years) in the setting of severe aortic stenosis and high surgical risk. Access was transarterial (n=113) or, in the presence of small iliofemoral artery diameter, transapical (n=55). The overall success rate was 94.1% in this early experience. Intraprocedural mortality was 1.2%. Operative (30-day) mortality was 11.3%, lower in the transarterial group than the transapical group (8.0% versus 18.2%; $P=0.07$). Overall mortality fell from 14.3% in the initial half to 8.3% in the second half of the experience, from 12.3% to 3.6% ($P=0.16$) in transarterial patients and from 25% to 11.1% ($P=0.30$) in transapical patients. Functional class improved over the 1-year postprocedure period ($P<0.001$). Survival at 1 year was 74%. The bulk of late readmission and mortality was not procedure or valve related but rather was due to comorbidities. Paravalvular regurgitation was common but generally mild and remained stable at late follow-up. At a maximum of >3 years and a median of 221 days, structural valve failure was not observed.

Conclusions—Transcatheter aortic valve implantation can result in early and sustained functional improvement in high-risk aortic stenosis patients. Late outcome is determined primarily by comorbidities unrelated to aortic valve disease. (***Circulation*. 2009;119:3009-3016.)**

Key Words: aortic valve ■ aortic valve stenosis ■ catheters ■ prosthesis ■ valves ■ valvuloplasty

Since the initial demonstrations of the feasibility of percutaneous transvenous,[1] transarterial,[2] and transapical[3] aortic valve implantation (AVI), this therapeutic option has rapidly gained credibility as a viable alternative to open heart surgery in high-risk patients with aortic stenosis.[4–8] To date, reports of transcatheter AVI have focused primarily on procedural success, early mortality, and short-term clinical outcomes. However, long-term data on transcatheter AVI outcomes remain limited. In contrast, there is substantial literature demonstrating improved long-term survival in patients with symptomatic severe aortic stenosis undergoing surgical open heart AVI.[9] Although current guidelines suggest surgical valve replacement for all such patients,[10] a substantial number of individuals remain who do not undergo surgery because of comorbidities and the associated increased surgical risk of morbidity or mortality.[11] Here, we report the short- and intermediate-term clinical outcomes in a large single-center experience using a collaborative approach of transarterial and transapical AVI in patients at high surgical risk.

Clinical Perspective on p 3016

Methods

Patients

The present analysis includes all patients (n=168) undergoing transcatheter AVI at our institution between January 2005 and April 2008. This includes the first-in-human transarterial and off-pump transapical case series. Procedures were approved for compassionate use in patients with severe, symptomatic aortic stenosis and no reasonable surgical option because of excessive risk. Acceptance for the procedure required consensus by a group of senior cardiac surgeons and cardiologists that patients were unsuitable for open heart surgery because of excessive risk. Written informed consent was obtained.

Patients were assessed with transthoracic echocardiography, selective coronary angiography, and angiography of the aortic root and the aortoiliofemoral system. With the availability of the transapical procedure in October 2005, this route of access was used selectively in patients with small-diameter femoral arteries (as a result of body size or atherosclerotic disease) and in 3 patients with an unsuccessful previous transarterial procedure. Patients were excluded if they were considered eligible for conventional surgical valve replacement, if

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the aortic annulus diameter was <18 or >26 mm, or if a reasonable quality or duration of life was unlikely. There were no other criteria for exclusion.

Procedures and Devices

Transarterial and transapical procedures were performed as previously described.[2,5,6] Transarterial procedures were performed in a cardiac catheterization laboratory; transapical procedures were performed in an operating room. Transarterial access was gained by percutaneous puncture of the femoral artery, whereas transapical access was obtained by anterior minithoracotomy followed by direct needle puncture of the left ventricular apex. Balloon valvuloplasty was routinely performed before valve implantation. Burst rapid pacing was used to reduce cardiac output during prosthesis deployment.[12] Early in the transarterial experience, the femoral access site was closed surgically, whereas later, percutaneous closure (Prostar XL, Abbott Inc, Chicago, Ill) was routinely used.

The balloon-expandable Cribier-Edwards equine valve[2] was used early in the series, although the majority of procedures used the Edwards SAPIEN bovine valve (Edwards Lifesciences LLC, Irvine, Calif).[6] More recently, a limited number of patients received the next-generation cobalt-chromium bovine valve (SAPIEN XT).[13] Initial transarterial and transapical procedures were performed with the RetroFlex delivery catheter.[6] This was subsequently replaced with the RetroFlex II transarterial catheter incorporating a retractable nose cone[13] and the Ascendra transapical catheter (all Edwards Lifesciences LLC).

Definitions and Data Collection

Patients were followed up as part of an ongoing prospective registry. Transthoracic echocardiograms were obtained at baseline, before discharge, and at 1, 6, and 12 months and yearly thereafter. Clinical follow-up occurred at similar intervals. All patients in whom valve implantation was attempted but in whom the procedure was not successful were followed up to 30 days. No patient was lost to follow-up.

Procedural success was defined as implantation of a functioning prosthetic valve within the aortic annulus and without intraprocedural mortality. Procedure-related events were defined as occurring during or as a direct result of the index procedure. Events that occurred before extubation were similarly classified as procedural. Outcome measures included procedural success, functional status (New York Heart Association [NYHA] class), major adverse cardiac and cerebrovascular events (MACCEs) at 30 days, major adverse valve-related events (MAVREs), and survival. MACCEs included death, myocardial infarction, stroke, or aortic valve reintervention/operation. MAVREs included valve-related mortality, valve-related morbidity, and need for new permanent pacemaker or defibrillator within 14 days after the procedure. Valve-related morbidity was defined as any structural deterioration or nonstructural prosthesis dysfunction, valve thrombosis, embolism, bleeding events, and prosthetic valve endocarditis.[14]

Frailty was defined according to the criteria of Fried et al.[15] Renal failure was defined according to RIFLE (Risk, Injury, Failure, Loss, and End-stage kidney disease) criteria.[16] Major vascular injury was defined as vascular rupture with fatal bleeding or need for urgent vascular surgery or dissection of the aorta.[14]

To allow comparison with the surgical literature, valve-related morbidity and events were reported in accordance with published reporting guidelines for valve surgery.[14] Major bleeding was defined as any bleeding requiring transfusion, disabling or fatal.[14] Nonstructural valve dysfunction was defined as major valve dysfunction (such as severe paravalvular regurgitation or late embolization) not occurring as a result of a structural problem, thrombosis, or infection.[14]

Statistical Analysis

Continuous variables are presented as mean±SD when normally distributed and as medians and first (Q1) and third quartiles (Q3) when not normally distributed. Categorical variables are given as frequencies and percentages. Normality was tested with the Shapiro-Wilks goodness-of-fit test. Continuous variables were tested for differences between procedure types with the Student t test or the Kruskal-Wallis test. Categorical variables were tested by the χ^2 test or, when necessary, the Fisher exact test. For comparison of continuous variables before and after transcatheter AVI, differences were calculated and the 1-sample Student t test or Wilcoxon signed-rank test was applied. Trends in functional class (NYHA class versus I/II) over time were analyzed with a logistic regression model adjusted for the baseline NYHA class and with general estimating equations methodology assuming compound symmetry to adjust for the correlation between repeated measurements from the same patient; results are presented as odds ratio with 95% confidence intervals (CIs). For comparison of procedural success over time, transarterial and transapical procedures were divided into 2 groups of consecutive patients. Thirty-day MACCE rates are given as percentages. Time-related events up to 2 years included survival, valve-related mortality, MAVREs, and readmission; they are presented as Kaplan-Meier curves and were tested for procedural differences with the log-rank test. Patients with unsuccessful procedures were followed up for 30 days after the procedure. To identify predictors of death after transcatheter AVI, a Cox proportional-hazard model was applied, and results are reported as adjusted hazard ratios with 95% CIs. Testing was carried out as 2-sided tests with a significance level of 0.05. All analyses were conducted with SAS version 9.1 (SAS Institute Inc, 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

Baseline Characteristics

A total of 168 patients underwent attempted transcatheter AVI, 113 transarterial and 55 transarterial. Median age was 84 years (Q1 and Q3, 79 and 87 years). All patients had echocardiographically confirmed severe aortic stenosis with a median calculated aortic valve area of 0.6 cm^2 (Q1 and Q3, 0.5 and 0.7 cm^2). Baseline characteristics are shown in Table 1. Common comorbidities included the presence of coronary artery disease (67.9%), mitral regurgitation grade ≥3+ (39.9%), porcelain aorta (21.4%), frailty (25.9%), and a history of previous thoracotomy (39.9%).

All patients were at high risk for conventional surgery as reflected by a median logistic EuroSCORE of 28.6 (Q1 and Q3, 17.9 and 41.0) and a median Society of Thoracic Surgeons (STS) score of 9.1 (Q1 and Q3, 6.3 and 13.0). Standard estimates of surgical risk predicted a high operative mortality in 73.8% (STS >10% and/or logistic EuroSCORE >20%). In the remaining 26.2% of patients, surgeons identified specific conditions likely to contribute to excessive perioperative risk that were not reflected in EuroSCORE and STS risk scores. Specific conditions were surgical technical concerns (15.9%), age >90 years (13.6%), morbid obesity (body mass index >35; 9.1%), end-stage lung disease (9.1%), moderate to severe mitral regurgitation likely requiring double-valve surgery (9.1%), critical liver disease (6.8%), cancer (2.3%), and multiple debilitating comorbidities associated with frailty, cachexia, and immobility (34.1%). In particular, the presence of a porcelain aorta, a common reason for surgical refusal present in 21.4% of the entire cohort, was not accounted for by STS risk estimates.

Early Outcomes

Intraprocedural mortality was 1.2%. A 23-mm-diameter transcatheter valve was successfully implanted in 59 patients,

Table 1. Baseline Characteristics of 168 Patients Undergoing Transcatheter Aortic Valve Implantation

	Combined (n=168)	Transarterial (n=113)	Transapical (n=55)	*P*
Age, y	84 (79–87)	85 (79–88)	83 (76–87)	0.13
Body mass index, kg/m^2	24.9 (21.7–27.45)	25.7 (22.3–28.3)	23.4 (21.6–26.8)	0.02*
Creatinine, μmol/L	98 (81–130)	101 (80–128)	91 (81–132)	0.65
Predicted risk by logistic EuroSCORE	28.6 (17.9–41.0)	25.0 (16.0–37.0)	35.0 (20.0–50.3)	0.01*
Predicted risk by STS	9.1 (6.3–13.0)	8.7 (6.0–12.1)	10.3 (6.8–17.7)	0.02*
Male gender, n (%)	87 (51.8)	65 (57.5)	22 (40.0)	0.03*
Diabetes mellitus, n (%)	39 (23.2)	30 (26.5)	9 (16.4)	0.14
Hyperlipidemia, n (%)	114 (70.4)	71 (66.4)	43 (78.2)	0.12
Hypertension, n (%)	109 (64.9)	68 (60.2)	41 (74.5)	0.07
Smoking, n (%)	89 (53.0)	55 (48.7)	34 (61.8)	0.11
Previous myocardial infarction, n (%)	123 (73.2)	77 (68.1)	46 (83.6)	0.03*
Previous coronary artery bypass, n (%)	62 (36.9)	41 (36.3)	21 (38.2)	0.81
Previous cerebrovascular event, n (%)	30 (17.9)	16 (14.2)	14 (25.5)	0.07
Coronary artery disease, n (%)	114 (67.9)	73 (64.6)	41 (74.5)	0.20
Congestive heart failure, n (%)	90 (53.6)	61 (54.0)	29 (52.7)	0.88
NYHA class ≥III, n (%)	145 (86.3)	103 (91.2)	42 (76.4)	0.01*
Porcelain aorta, n (%)	36 (21.4)	20 (17.7)	16 (29.1)	0.09
Atrial fibrillation, n (%)	69 (41.1)	47 (41.6)	22 (40)	0.84
Pacemaker, n (%)	25 (14.9)	15 (13.3)	10 (18.2)	0.40
Severe chronic pulmonary disease, n (%)	35 (20.8)	25 (22.1)	10 (18.2)	0.55
Chronic renal failure, n (%)	20 (11.9)	14 (12.4)	6 (10.9)	0.78
Peripheral vascular disease, n (%)	60 (35.7)	18 (15.9)	42 (76.4)	<0.0001*
Frailty,[14] n (%)	43 (25.9)	28 (24.8)	15 (28.3)	0.63
LVEF ≤35%, n (%)	27 (16.1)	18 (15.9)	9 (16.4)	0.94
Mitral regurgitation ≥3+	67 (39.9)	44 (38.9)	23 (41.8)	0.72
Mean systolic transaortic gradient, mm Hg	46 (34–55)	48 (35–57)	41 (29–51)	0.06
Aortic valve area, cm^2	0.6 (0.5–0.7)	0.6 (0.5–0.7)	0.6 (0.5–0.7)	0.97
Systolic pulmonary artery pressure, mm Hg	44 (35–60)	44 (35.0–60.0)	45 (35–54)	0.97
Aortic annulus, mm	22.74+2.01	23.0+2.0	22.3+1.9	0.05
Pulmonary hypertension >60 mm Hg, n (%)	45 (26.8)	28 (24.8)	17 (30.9)	0.40

LVEF indicates left ventricular ejection fraction. Continuous variables are presented as mean±SD or median (Q1 to Q3). Categorical variables are defined on the basis of STS definitions unless noted otherwise.

*Significant difference between procedural types.

and a 26-mm valve was implanted in 100 patients. With transcatheter AVI, the echocardiographic median aortic valve area increased from 0.6 cm^2 (Q1 and Q3, 0.5 and 0.7 cm^2) to 1.6 cm^2 (Q1 and Q3, 1.3 and 1.9 cm^2) ($P<0.001$). Median hospital stay was 6 days (Q1 and Q3, 4 and 10 days).

Procedural success was 94.1%, increasing from 89.3% to 98.8% from the initial half to the second half of the experience ($P<0.01$). Mortality at 30 days was 11.3% overall, decreasing from 14.3% in the initial half to 8.3% in the second half ($P=0.22$) (Figure 1). Logistic EuroSCORE and STS estimates of surgical risk were not significantly different between the first and second halves of the experience.

In the first half of the experience, 4 patients had unsuccessful transfemoral procedures. Three went on to have successful transapical procedures, and 1 had a successful repeat transfemoral procedure. Results are based on the initial 168 procedures, with unsuccessful procedures followed up for 30 days after the procedure.

In-hospital and 30-day adverse outcomes are detailed in Table 2. The most common complications observed were the need for transfusion (11.5%), major vascular surgery (6.6%), or a pacemaker (5.4%); renal failure (6.0%); and pneumonia (4.8%). The rate of combined MACCEs at 30 days was 14.9% (Figure 2). MACCEs were accounted for primarily by mortality in that no patient underwent repeat valve intervention, myocardial infarction was infrequent, and stroke was generally a fatal event. Only 1 patient surviving to 30 days

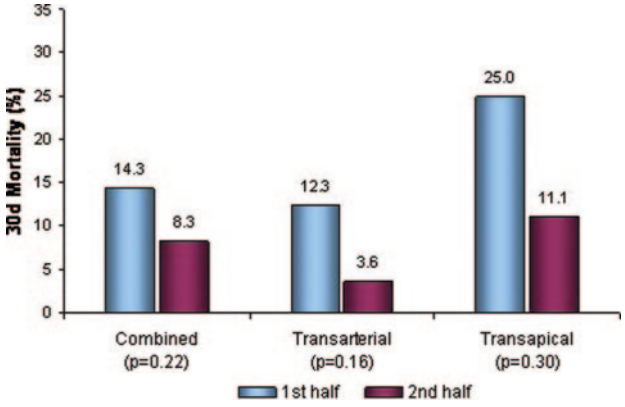

Figure 1. Procedural success and 30-day mortality combined and separated by procedure type and experience. Combined and transarterial procedures are displayed by temporal halves. *Significant differences between the first and second halves.

Table 2. Adverse Outcomes at Hospital Discharge and 30 Days for All Patients Combined and Separated by Procedure Type

Adverse Outcome	Combined (n=168), n (%)	Transarterial (n=113), n (%)	Transapical (n=55), n (%)	*P*
Transfusion ≥5 packed cells	19 (11.5)	13 (11.6)	6 (11.1)	0.93
Cardiac tamponade	4 (2.4)	2 (1.8)	2 (3.6)	0.60
Major vascular injury	11 (6.6)	9 (8.0)	2 (3.6)	0.51
Cardiopulmonary bypass, emergent	4 (2.4)	1 (0.9)	3 (5.5)	0.19
Conversion to open heart surgery	1(0.6)	0 (0)	1 (1.8)	0.72
Acute renal failure[15]	10 (6.0)	5 (4.4)	5 (9.1)	0.30
Temporary hemodialysis	3 (1.8)	0 (0)	3 (5.5)	0.03*
Atrial fibrillation, new	7 (4.2)	0 (0)	7 (12.7)	<0.001*
Need for permanent pacemaker	9 (5.4)	5 (4.4)	4 (7.3)	0.48
Ventilation >48 h	4 (2.4)	2 (1.8)	2 (3.6)	0.60
Pulmonary embolism	2 (1.2)	0 (0)	2 (3.6)	0.11
Pneumonia	8 (4.8)	4 (3.5)	4 (7.3)	0.44
Local infection	4 (2.4)	3 (2.7)	1 (1.8)	1.00
Septicemia	5 (3.0)	3 (2.7)	2 (3.6)	0.66
Multiorgan failure	6 (3.6)	3 (2.7)	3 (5.5)	0.39
Hospital stay, median (Q1–Q3), d	6 (4–10)	5 (3–9)	7 (5–12)	<0.0001*
Stroke	7 (4.2)	6 (5.3)	1 (1.8)	0.43
Mortality at 30 d	19 (11.3)	9 (8)	10 (18.2)	0.07
MACCEs at 30 d	25 (14.9)	14 (12.4)	11 (20.0)	0.19

Categorical variables are defined on the basis of the STS definitions unless noted otherwise.
*Significant difference between procedural types.

was left with a disabling stroke (0.6%). The causes and times of death occurring within 30 days of the procedure are detailed in Table 3.

Procedure Type

Patients selected for a transapical procedure as opposed to a transarterial procedure were more likely to have peripheral vascular disease (76.4% versus 15.9; $P<0.0001$), have prior myocardial infarction (83.6% versus 68.1%; $P=0.03$), be female (60.0% versus 42.5%; $P=0.03$), have a lower body mass index (23.4 kg/m^2 [Q1 and Q3, 21.6 and 26.8 kg/m^2] versus 25.7 kg/m^2 [Q1 and Q3, 22.3 and 28.3 kg/m^2], $P=0.02$), and be in NYHA class I or II (23.6% versus 8.8%; $P=0.01$). Transapical patients were at higher risk for conventional surgery as predicted by both a higher STS score (10.3% [Q1 and Q3, 6.8% and 17.7%] versus 8.7% [Q1 and Q3, 6.0 and 12.1%]; $P<0.03$) and logistic EuroSCORE (35.0% [Q1 and Q3, 20.0 and 50.3%] versus 25.0% [Q1 and Q3, 16.0 and 37.0%]; $P=0.01$).

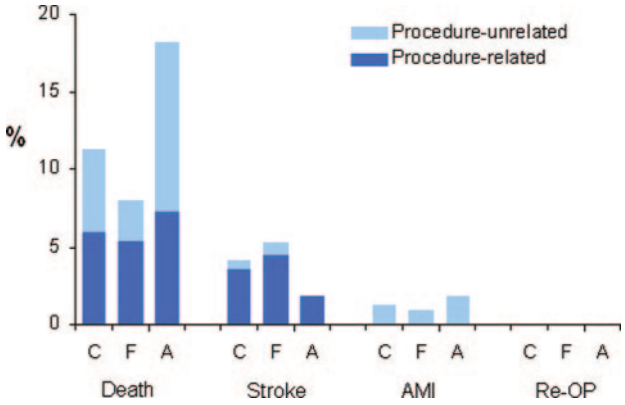

Figure 2. MACCEs at 30 days as defined by current surgical standards.[14] C indicates combined transapical and transarterial; F, femoral access; A, apical access; AMI, acute myocardial infarction; and Re-OP, subsequent cardiac surgery.

Table 3. Time and Cause of Death Occurring Within 30 Days

Time From Procedure to Death, d	Mortality Cause	Procedure
0	Major bleeding	Femoral
0	Cardiogenic shock	Apical
0	Major bleeding	Femoral
2	Respiratory	Apical
3	Arrhythmia	Apical
4	Unexplained sudden	Femoral
5	Multiorgan failure	Femoral
5	Major bleeding	Apical
5	Multiorgan failure	Apical
5	Multiorgan failure	Apical
6	Cerebral embolism	Apical
9	Septicemia	Apical
10	Noncerebral embolism	Apical
12	Respiratory	Apical
13	Multiorgan failure	Femoral
21	Congestive failure	Femoral
25	Arrhythmia	Femoral
29	Cerebral embolism	Femoral
30	Cerebral embolism	Femoral

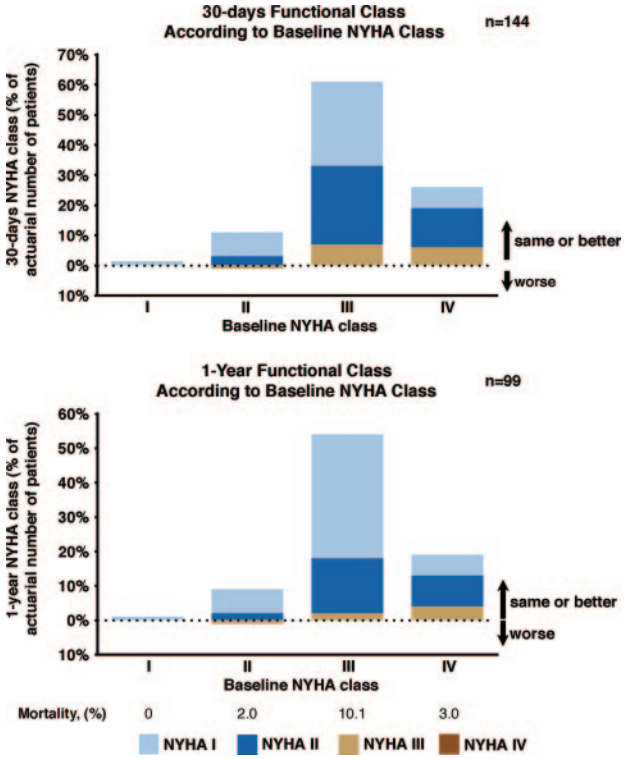

Figure 3. Functional NYHA class in patients with successful transcatheter AVI and alive at 30 days. Data are given for patients with actuarial 30-day and 1-year follow-up. N is the number of patients with actuarial follow-up, which includes all patients alive and with actual follow-up for a given time point, as well as patients theoretically at follow-up but who died in the meantime. To compare changes among patients with different baseline functional classes, data are presented according to the baseline NYHA class, and whether the functional class improved or deteriorated is indicated. Mortality is the percentage of deaths in relation to the actuarial number of patients and is given for the 1-year follow-up. For all follow-up time points, most patients were in NYHA class I or II regardless of baseline functional class.

Patients undergoing a transarterial procedure had (nonsignificantly) higher rates of major vascular surgery (8.0% versus 3.6%; $P=0.5$) and stroke (5.3% versus 1.8%; $P=0.43$). A transapical procedure was more likely to be associated with the need for temporary hemodialysis (5.5% versus 0%; $P=0.03$), new atrial fibrillation (12.7% versus 0%; $P<0.001$), and longer median hospital stay (7 days [Q1 and Q3, 5 and 12 days] versus 5 days [Q1 and Q3, 3 and 9 days]; $P<0.0001$; Table 2).

Outcomes are shown in Figure 1 for sequential halves of the entire group and the transarterial and transapical experiences. In the combined group, there was a significant increase in the rate of procedural success from 89.3% in the first half to 98.8% in the later half ($P<0.01$). In the transarterial experience, mortality at 30 days fell from 12.3% to 3.6% ($P=0.16$). Similarly, mortality at 30 days fell from 25.0% to 11.1% in the first and second halves of the transapical experience ($P=0.30$).

NYHA Functional Class

For patients surviving to 1 year, there was an improving trend in the functional class over the year ($P<0.001$); patients were less likely to be in class NYHA III/IV compared with NYHA I/II (odds ratio, 0.66; 95% CI, 0.55 to 0.78). After transcatheter AVI, substantial improvement was observed within the first month (Figure 3). At baseline, 2 (1%), 17 (12%), 88 (61%), and 37 (26%) of the 144 patients with successful transcatheter AVI and alive at 30 days were in NYHA class I, II, III, and IV, respectively; at the 30-day follow-up, 124 (86%) were in class I or II. The most improvement occurred in patients who were in class III and IV at baseline, of whom 78 (88.6%) and 37 (100%) had improved by at least 1 functional class. This increase in functional class was sustained over time, with 77 (78%) of the 99 patients with actuarial follow-up at 1 year being in class I or II.

Echocardiographic Valve Function

Transaortic mean gradient decreased from 46.1±6.7 mm Hg at baseline to 10.0±0.4 mm Hg before discharge ($P<0.01$). Subsequently, the gradient increased slightly to 11.2±4.9 mm Hg at 1 year ($P=0.07$). Aortic valve area increased from 0.6±0.2 cm^2 at baseline to 1.6±0.4 cm^2 before discharge ($P<0.01$); it subsequently decreased slightly to 1.5±0.3 cm^2 at 1 year ($P=0.04$). Paravalvular aortic regurgitation was a frequent finding at all time points but was trace to mild in the majority of cases; eg, immediately after the procedure, 84 (58%), 53 (37%), and 7 (5%) of the patients alive at 30 days showed grade 0/1+, 2+, and 3+ paravalvular aortic regurgitation, respectively (Figure 4). The degree of valvular regurgitation was even less, with 97 (77%) and 66 (67%) of the patients with actuarial follow-up at 6 and 12 months, respectively, showing only none/trace or mild valvular regurgitation. No severe aortic regurgitation was observed. A minority of patients showed moderate regurgitation, which remained unchanged over time. At a median follow-up of 221 days (Q1 and Q3, 49 and 401 days) and a maximum of 1111 days, structural valve deterioration was not observed.

Late Outcomes

Survival at 1, 12, and 24 months was 88.7%, 73.8%, and 60.9%, respectively. The following variables were examined as possible predictors of death: age, gender, history of prior coronary artery bypass, poor left ventricular systolic function, chronic renal failure, moderate to severe mitral regurgitation at baseline, moderate to severe functional class impairment at baseline, logistic EuroSCORE >20%, STS score >10%, presence of frailty, body mass index, and baseline creatinine. By multivariate analysis, only transapical access and chronic renal failure were significantly associated with increased mortality (hazard ratios, 1.85 [95% CI, 0.99 to 3.43] and 3.48 [95% CI, 1.78 to 6.83], respectively).

Two patients underwent late reoperation: one 4 months after an unsuccessful but uncomplicated transarterial attempt and a second who developed prosthetic endocarditis 1 year after successful AVI. Major bleeding (n=9) was the predominant event, observed in the 29 patients experiencing MAVREs at the last follow-up (Table 4). The incidence of late valve-related events was low (Figure 5).

Discussion

Early Outcomes

The high rate of procedural success is encouraging in this early experience. It appears that with careful screening,

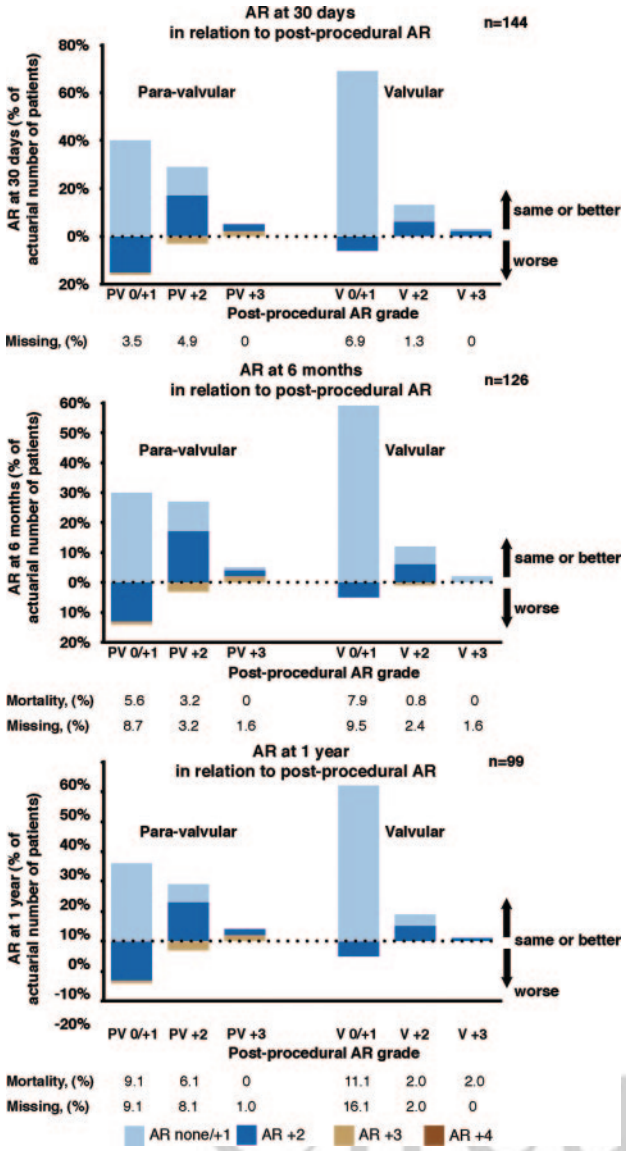

Figure 4. Aortic regurgitation (AR) in patients with successful transcatheter AVI and alive at 30 days. Data are given for patients with actuarial 30-day, 6-month, and 1-year follow-up. N is the number of patients with actuarial follow-up, which includes all patients alive and with actual follow-up for a given time point, as well as patients theoretically at follow-up but with missing/incomplete echocardiography data or death in the meantime. For each time point, paravalvular (PV) AR is presented to the left and valvular (V) AR to the right. To compare changes among patients with different postprocedural AR grades, data are presented according to the degree of AR after successful transcatheter AVI, and whether the grade improved or deteriorated is indicated. For completeness, patients with incomplete echocardiographic follow-up or mortality are indicated. Severe AR was not observed, and only a minority of patients showed moderate AR, which improved or remained unchanged over time.

current techniques, and experience, short-term procedural success can be achieved in most patients in whom the procedure is attempted. Similarly, a 30-day mortality of 11.3% with a transcatheter approach in very-high-risk patients compares favorably with standard estimates of surgical mortality. In particular, the low mortality (3.6%) in the final half of the transarterial experience suggests that outcomes may further improve. An early learning curve is evident in the overall experience. The transapical experience probably benefited from lessons learned in the earlier transarterial experience. This learning curve has implications for dissemination of this technology.

Table 4. MAVREs at the Last Follow-Up

MAVRE	Patients, n	Femoral, n	Apical, n
Bleeding			
Gastrointestinal	16	10	6
Chest	1	0	1
Cerebral embolic			
Stroke	4	4	0
Transient ischemic attack	2	1	1
Other			
Endocarditis	2	1	1
Bleeding (fatal)			
Cerebral	3	3	0
Embolic (fatal)			
Cerebral	1	1	0
Noncerebral	4	2	2
Other (fatal)			
Late valve migration	1	0	1

Late Outcomes

At a follow-up with a median time of 7.4 months and a maximum of >3 years, the incidence of late adverse valve-related events[14] was low. In particular, structural valve failure was not observed, and reoperation and endocarditis were rare. The most common late valve-related event was bleeding related to gastrointestinal disease, often seen in warfarin-treated patients receiving postprocedural dual antiplatelet therapy. Currently, we avoid combined antiplatelet and antithrombotic therapy in our elderly patients with comorbidities. Paravalvular regurgitation was common but generally mild and remained stable at late follow-up.

Functional class improved at 1 month and was sustained, with the majority of patients alive at 1 year being class I or II. Admittedly, NYHA functional class is a relatively insensitive and subjective measure. Future evaluation will require more detailed measures of functional status. Survival at 1, 12, and 24 months was 89%, 74%, and 61%, respectively. A 1-year survival of 74% in patients declined surgery compares favorably with other reports. By way of comparison, Kojodjojo et al[17] reported a 1-year survival of 51% in elderly aortic stenosis patients who were not considered to be surgical candidates and 66% in elderly surgical candidates who declined surgery. Bach et al[18] reported a 1-year survival of 62% in unoperated patients.

Stroke

Stroke occurred in 4.2% overall. Prior smaller studies report an incidence varying from 0% to 9%.[6–8,19–22] Transcatheter AVI may carry an inherent risk of aortic atheroemboli and valvular calcific emboli. This concern may be greater with the retrograde approach to the aortic valve, a concept that is

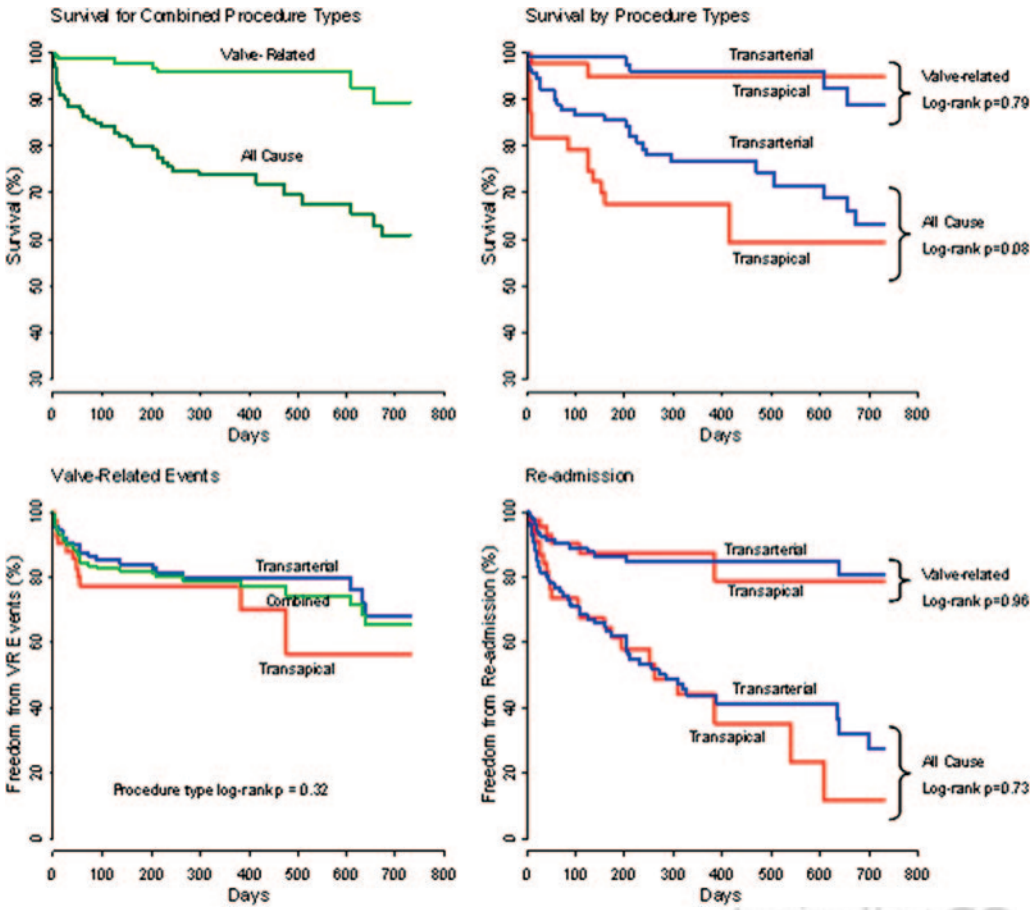

Figure 5. Kaplan-Meier curves of survival, valve-related mortality, and freedom from valve-related (VR) events and readmission. Late survival was determined primarily by non–valve-related comorbidities.

consistent with the trend to a lower stroke rate with transapical access. Approaches to reducing this risk include preprocedural screening for friable aortic atheroma, more attention to a gentle passage of catheters through the aortic arch, and the use of embolic protection devices. The current trend to lower-profile and less traumatic transarterial catheters will likely reduce embolic risk.[8,23,24] Importantly, major stroke was generally a fatal event and was largely accounted for in the overall mortality. Only 1 patient surviving to 30 days was left with a disabling stroke (0.6%).

Vascular Injury

Major vascular injury, primarily iliofemoral dissection or perforation, was the most common transarterial complication, occurring in 8% of patients. With improved screening, case selection, and experience, it appears that the incidence of vascular injury is falling. Still, given the large diameter of current transarterial catheters, the potential for arterial injury argues for transapical access in borderline cases. As with stroke, it is hoped that the development of lower-profile and less traumatic catheters will reduce the risk of vascular injury.[8,23,24]

Renal Failure

Even mild worsening of renal function after conventional cardiac surgery is associated with significant morbidity and short- and long-term mortality.[25] Preexisting renal impairment was a common reason for referral for transcatheter AVI, and in this experience, renal impairment, even dialysis dependency, was not an exclusion criterion. Postprocedural acute renal failure was seen in 6%. Temporary hemodialysis was required in 1.8% of the entire group (0% transarterial, 5.5% transapical; $P=0.03$). By multivariate analysis, chronic renal failure was the strongest single predictor of mortality at late follow-up.

Estimates of Risk

Available predictors of surgical risk are often helpful. Nevertheless, many determinants of operative risk (such as porcelain aorta, frailty, planned multivalve surgery) are not incorporated into commonly used predictive models. Approximately one quarter of the patients in this experience would not be considered high risk by logistic EuroSCORE or STS risk estimates and yet were declined surgery because of such factors. Of note, neither model predicted transcatheter AVI mortality. Presumably, factors that determine risk with open heart surgery, sternotomy and cardiopulmonary bypass, cardioplegia, and aortic cross-clamping are different from those that predict risk with a transcatheter procedure.

Conclusions

Transcatheter AVI can result in early and sustained functional improvement in high-risk aortic stenosis patients. Early out-

comes compare favorably with high-risk surgery, and late outcome is determined primarily by comorbidities other than aortic valve disease. An early learning curve has implications for training and maintenance of competence.

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Disclosures

Drs Cheung, Munt, and Webb are consultants to Edwards Lifesciences. The other authors report no conflicts.

References

1. Cribier A, Eltchaninoff H, Bash A, Borenstein N, Tron C, Bauer F, Derumeaux G, Anselme F, Laborde F, Leon MB. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. *Circulation*. 2002;106:3006–3008.
2. Webb JG, Chandavimol M, Thompson C, Ricci DR, Carere R, Munt B, Buller CE, Pasupati S, Lichtenstein S. Percutaneous aortic valve implantation retrograde from the femoral artery. *Circulation*. 2006;113:842–850.
3. Ye J, Cheung A, Lichtenstein SV, Carere RG, Thompson CR, Pasupati S, Webb JG. Transapical aortic valve implantation in humans. *J Thorac Cardiovasc Surg*. 2006;131:1194–1196.
4. Cribier A, Eltchaninoff H, Tron C, Bauer F, Gerber L. Percutaneous implantation of aortic valve prosthesis in patients with calcific aortic stenosis: technical advances, clinical results and future strategies. *J Invasive Cardiol*. 2006;19:S88–S96.
5. Lichtenstein SV, Cheung A, Ye J, Thompson CR, Carere RG, Pasupati S, Webb JG. Transapical transcatheter aortic valve implantation in man. *Circulation*. 2006;114:591–596.
6. Webb JG, Pasupati SJ, Humphries K, Thompson C, Altwegg L, Moss R, Sinhal A, Carere RG, Munt B, Ricci D, Ye J, Cheung A, Lichtenstein SV. Percutaneous transarterial aortic valve replacement in selected high risk patients with aortic stenosis. *Circulation*. 2007;116:755–763.
7. Walther TFV, Kempfert J, Borger MA, Fassl J, Chu MWA, Schuler G, Mohr FW. Transapical minimally invasive aortic valve implantation; the initial 50 patients. *Eur J Cardiothorac Surg*. 2008;33:983–988.
8. Grube E, Schuler G, Buellesfeld L, Gerckens U, Linke A, Wenaweser P, Sauren B, Mohr FW, Zickmann B, Ivesen S, Felderhoff T, Cartier R, Bonan R. Percutaneous aortic valve replacement for severe aortic stenosis in high-risk patients using the second and current third generation self-expanding CoreValve prosthesis: device success and 30 day outcome. *J Am Coll Cardiol*. 2007;50:69–76.
9. Varadarajan P, Kapoor N, Bansal RC, Pai RG. Survival in elderly patients with severe aortic stenosis is dramatically improved by aortic valve replacement: Results from a cohort of 277 patients aged > or =80 years. *Eur J Cardiothorac Surg*. 2006;30:722–727.
10. Bonow RO, Carabello BA, Kanu C, de Leon AC Jr, Faxon DP, Freed MD, Gaasch WH, Lytle BW, Nishimura RA, O'Gara PT, O'Rourke RA, Otto CM, Shah PM, Shanewise JS, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Lytle BW, Nishimura R, Page RL, Riegel B. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2006;114:e84–e231.
11. Iung B, Baron G, Butchart EG, Delahaye F, Gohlke-Barwolf C, Levang OW, Tornos P, Vanoverschelde JL, Vermeer F, Boersma E, Ravaud P, Vahanian A. A prospective survey of patients with valvular heart disease in Europe: the Euro Heart Valve Survey on Valvular Disease. *Eur Heart J*. 2003;24:1231–1243.
12. Webb JG, Pasupati S, Achtem L, Thompson CR. Rapid pacing to facilitate transcatheter prosthetic heart valve implantation. *Catheter Cardiovasc Interv*. 2006;68:199–204.
13. Webb JG, Altwegg L, Masson JB, Al Bugami S, Al Ali A, Boone RA. A new transcatheter aortic valve and percutaneous valve delivery system. *J Am Coll Cardiol*. 2009;53:1855–1858.
14. Akins CW MD, Turina MI, Kouchoukos NT, Blackstone EH, Grunkemeier GL, Takkenberg JJM, David TE, Butchart EG, Adams DH, Shahian DM, Hagle S, Mayer JE, Lytle BW. Guidelines for reporting mortality and morbidity after cardiac valve interventions. *Eur J Cardiothorac Surg*. 2008;33:523–528.
15. Fried LP TC, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA. Frailty in older adults: evidence for a phenotype. *J Gerontology*. 2001;56A:M146–M156.
16. Uchino SBR, Goldsmith D, Bates S, Ronco C. An assessment of the RIFLE criteria for acute renal failure in hospitalized patients. *Crit Care Med*. 2006;34:1913–1917.
17. Kojodjojo PGN, Barker D, Youssefi P, Salukhe TV, Choong A, Koa-Wing M, Bayliss J, Hackett DR, Khan MA. Outcomes of elderly patients aged 80 and over with symptomatic, severe aortic stenosis: impact of patient's choice of refusing aortic valve replacement on survival. *Q J Med*. 2008;101:567–573.
18. Bach DS, Cimino N, Deeb M. Unoperated patients with severe aortic stenosis. *J Am Coll Cardiol*. 2007;50:2018–2019.
19. Berry C, Asgar A, Lamarche Y, Marcheix B, Couture P, Basmadjian A, Ducharme A, Laborde JC, Cartier R, Bonan R. Novel therapeutic aspects of percutaneous aortic valve replacement with the 21F CoreValve Revalving System. *Cathet Cardiovasc Interv*. 2007;70:610–616.
20. Grube E, Laborde JC, Gerckens U, Felderhoff T, Sauren B, Buellesfeld L, Mueller R, Menichelli M, Schmidt T, Zickmann B, Iversen S, Stone GW. Percutaneous implantation of the CoreValve self-expanding valve prosthesis in high-risk patients with aortic valve disease: the Siegburg first-in-man study. *Circulation*. 2006;114:1616–1624.
21. Walther T, Simon P, Dewey T, Wimmer-Greinecker G, Falk V, Kasimir MT, Doss M, Borger MA, Schuler G, Glogar D, Fehske W, Wolner E, Mohr FW, Mack M. Transapical minimally invasive aortic valve implantation. Multicenter experience. *Circulation.* 2007;116(suppl):I-240–I-245.
22. Svensson LG, Dewey T, Kapadia S, Roselli EE, Stewart A, Williams M, Anderson WN, Brown D, Leon M, Lytle B, Moses J, Mack M, Tuzcu M, Smith C. United States feasibility study of transcatheter insertion of a stented aortic valve by the left ventricular apex. *Ann Thorac Surg*. 2008;86:46–55.
23. Webb JG. Percutaneous aortic valve replacement will be a common treatment for aortic valve disease. *J Am Coll Cardiol Interv*. 2008;1:122–126.
24. Chiam PTL RC. Percutaneous transcatheter aortic valve implantation: assessing results, judging outcomes, and planning trials: the interventionalist perspective. *J Am Coll Cardiol Interv*. 2008;1:341–350.
25. Ihle BU. Acute renal dysfunction after cardiac surgery: still a big problem! *Heart Lung Circ*. 2007;16:S39–S44.

CLINICAL PERSPECTIVE

Transcatheter aortic valve implantation was performed in 168 patients with severe aortic stenosis and high surgical risk in this transarterial (n=113) and off-pump transapical (n=55) single-center experience. Intraprocedural mortality was 1.2%. Operative (30-day) mortality was 11.3%, lower in the transarterial group than the transapical group (8.0% versus 18.2%). Mortality fell from the initial half to the second half of this experience, from 12.3% to 3.6% in transarterial patients and from 25% to 11.1% in transapical patients. There was early and sustained functional improvement. At a maximum of >3 years and a median of 221 days, structural valve failure was not observed. Paravalvular regurgitation was common but generally mild and remained stable at late follow-up. The bulk of late readmission and mortality was not procedure or valve related but rather due to comorbidities. Late outcome after transcatheter aortic valve implantation for aortic stenosis is determined primarily by comorbidities unrelated to aortic valve disease.