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Transapical Aortic Valve Implantation

Incidence and Predictors of Paravalvular Leakage and Transvalvular Regurgitation in a Series of 358 Patients

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Objectives The aim of this study was to evaluate the results when the surgical concept of not accepting intraprocedural paravalvular leakage was applied for transcatheter aortic valve implantation (TAVI).

Background The surgical strategy of conventional aortic valve replacement does not accept paraprosthetic leakage and requires immediate action to eliminate it. However, paravalvular leakage is the major concern after TAVI.

Methods A total of 358 patients underwent transapical TAVI with balloon-expandable prostheses. The modified procedural strategy consisted of precise positioning of the prosthesis using a modified TAVI technique and immediate additional intraprocedural treatment to eliminate relevant paravalvular leakage.

Results Balloon redilation of the transcatheter valve was performed in 18 patients (5%), and additional second valves were implanted in 13 (4%). At the end of the procedure, 186 patients (52%) had no paravalvular or transvalvular regurgitation. In the remaining 172 patients, paravalvular leakage was observed in 113 (32%), transvalvular leakage in 47 (13%), and both in 12 (3%). Leakage was trace in 88 patients (25%), mild in 82 (23%), and moderate in 2 (0.6%). Multivariate analysis identified male sex, New York Heart Association functional class IV, and no previous aortic valve replacement as predictors of post-procedural leakage. Cumulative survival was not dependent on post-procedural regurgitation rate. Overall mortality was 5 ± 1% at 30 days, 14 ± 2% at 6 months, 17 ± 2% at 1 year, and 33 ± 4% at 2 years.

Conclusions The modified procedural strategy of transapical TAVI with a balloon-expandable prosthesis was associated with a low incidence of relevant prosthetic regurgitation. (J Am Coll Cardiol 2012;59:211–21) © 2012 by the American College of Cardiology Foundation

Survival in patients with severe aortic stenosis who cannot undergo surgery has been improved by transcatheter aortic valve implantation (TAVI) (1–3). The early results are encouraging, with reported 30-day mortality rates below 10% and 1-year survival rates above 70% at experienced centers (3–9).

Standard surgical policy accepts only trace paravalvular leakage after conventional aortic valve replacement. Moderate to severe prosthetic dysfunction is a clear indication for immediate revision (10). Even in the era of very sensitive echocardiography, the rate of trace and mild paraprosthetic regurgitation after conventional surgery is clearly below 20% (11). Contrary to these standard surgical policies, paraprosthetic leakage is observed and accepted in the majority of TAVI patients. The reported rates of moderate or severe regurgitation vary between 10% (3,4) and up to 20% or more in larger series (8,12–14), regardless of the type of prostheses. A negative influence of significant paraprosthetic leakage on survival has recently been demonstrated (8). Although only procedural complications are strongly associated with early mortality, post-procedural moderate or severe regurgitation mainly affects late outcomes (8). However, influence of procedural technique, incidence, and predictors of paravalvular regurgitation are not yet clearly defined.

We adopted the "surgical way of thinking" and decided to accept only trivial or mild paraprosthetic regurgitation after TAVI (9). Our institutional procedural policy consisted of a modified TAVI strategy. It included a modified implantation technique (15) that reduces the incidence and severity of leakage and immediate treatment of higher grade paraprosthetic regurgitation by additional balloon redilation and, if

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Abbreviations and Acronyms

HU = Hounsfield units

LVOT = left ventricular outflow tract

MSCT = multislice computed tomography

TAVI = transcatheter aortic valve implantation

TEE = transesophageal echocardiography

necessary, additional implantation of a second prosthesis (9,16).

Here we report our institutional experience with how to manage, avoid, and anticipate regurgitation in transapical TAVI using balloon-expandable transcatheter valves.

Methods

Patients. Between April 2008 and March 2011, 358 consecutive patients (mean age 80 ± 8 years; range: 29 to 99 years) with severe aortic stenosis underwent transapical TAVI. There were 120 men (34%) and 238 women (66%). The mean logistic European System for Cardiac Operative Risk Evaluation score for the whole group was 38 ± 21% (range: 4% to 97%), and the mean Society of Thoracic Surgeons score was 19 ± 16% (range: 1% to 90%). The preoperative patients' characteristics are given in Table 1. The median follow-up period was 331 days (interquartile range: 113 to 585 days), with a total of 358 patient-years of follow-up. The follow-up for this prospective study was 100%. All patients or their representatives gave informed consent. The study was approved by our institutional review board.

Inclusion and exclusion criteria. The risk for conventional aortic valve replacement was evaluated by the heart team. In general, high-risk patients with severe aortic stenosis were considered for TAVI if the logistic European System for Cardiac Operative Risk Evaluation score was at least 20% or

Table 1 Pre-Procedural Parameters of Patient Group as a Whole and Divided Into Subgroups Taking Into Account Post-Procedural Regurgitation

Parameter	All Patients (n = 358)	No Regurgitation (n = 186)	Regurgitation of Any Kind (n = 172)	Range
Age (yrs)	79.5 ± 8.3	79.2 ± 8.5	79.8 ± 8.0	29–99
Men	120 (34%)	52 (28%)	68 (40%)	—
BMI (kg/m^2)	27.1 ± 5.4	27.4 ± 5.7	26.6 ± 5.1	17–59
EuroSCORE (%)	38.2 ± 20.7	37.2 ± 19.2	39.3 ± 22.1	4–97
STS score (%)	18.7 ± 15.7	17.8 ± 13.4	19.6 ± 17.9	1–90
NT-proBNP (pg/ml)	5,352 ± 8,413	4,748 ± 6,440	5,953 ± 9,984	10,000–77,000
NYHA functional class IV	110 (31%)	48 (26%)	62 (36%)	—
Cardiogenic shock	21 (6%)	9 (5%)	12 (7%)	—
COPD	170 (47%)	84 (45%)	86 (50%)	—
FEV_1 (%)	74.8 ± 23.0	73.8 ± 22.0	75.8 ± 24.0	13–145
SPAP > 50 mm Hg	137 (38%)	64 (34%)	73 (42%)	—
Creatinine (mg/dl)	1.2 ± 0.6	1.3 ± 0.7	1.2 ± 0.6	0.5–6.3
Renal failure	82 (23%)	44 (24%)	38 (22%)	—
Diabetes mellitus	89 (25%)	48 (26%)	41 (24%)	—
Coronary artery disease	211 (59%)	108 (58%)	103 (60%)	—
Atrial fibrillation	110 (31%)	59 (32%)	51 (30%)	—
Cerebral ischemic lesion	87 (24%)	46 (25%)	41 (24%)	—
Peripheral artery disease	252 (70%)	128 (69%)	124 (72%)	—
Severely calcified ascending aorta	54 (15%)	34 (18%)	20 (12%)	—
Previous pacemaker/ICD	36 (10%)	17 (9%)	19 (11%)	—
Previous AVR	19 (5%)	17 (9%)	2 (1%)	—
Previous CABG	59 (16%)	29 (16%)	30 (17%)	—
Previous MVR	9 (3%)	4 (2%)	5 (3%)	—
LVEF (%)	50.0 ± 14.2	49.7 ± 13.8	50.4 ± 14.7	10–70
LVEF ≤ 35%	74 (21%)	42 (23%)	32 (19%)	—
LVEDD (mm)	49.0 ± 7.6	49.3 ± 7.6	48.7 ± 7.6	32–80
dP mean (mm Hg)	48.3 ± 14.7	47.1 ± 14.5	49.6 ± 14.8	8–100
AVA (cm^2)	0.67 ± 0.17	0.67 ± 0.18	0.66 ± 0.17	0.3–1.8
Annulus, TEE (mm)	22.0 ± 1.5	21.8 ± 1.5	22.2 ± 1.5	17–25
Annulus, CT (mm)	23.1 ± 2.3	22.9 ± 1.9	23.3 ± 2.7	17–31
Aortic regurgitation (grade II–IV)	46 (13%)	23 (12%)	23 (13%)	—
Mitral regurgitation (grade III or IV)	22 (6%)	14 (8%)	8 (5%)	—
Tricuspid regurgitation (grade III or IV)	14 (4%)	6 (3%)	8 (5%)	—

Values are mean ± SD or n (%).

AVA = aortic valve area; AVR = aortic valve replacement; BMI = body mass index; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; CT = computed tomography; dP mean = mean transvalvular gradient; EuroSCORE = European System for Cardiac Operative Risk Evaluation; FEV_1 = forced expiratory volume in 1 second; ICD = implantable cardioverter-defibrillator; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; MVR = mitral valve repair or replacement; NT-proBNP = N-terminal pro–brain natriuretic peptide; NYHA = New York Heart Association; SPAP = systolic pulmonary artery pressure; STS = Society of Thoracic Surgeons; TEE = transesophageal echocardiography.

if the Society of Thoracic Surgeons score was 10% or higher. Patients with lower risk scores were accepted for TAVI only if there were specific reasons (e.g., "porcelain aorta"). In accordance with our institutional "no exclusion" policy, no patient was excluded regardless of a very high risk profile, poor left ventricular performance, or even the presence of cardiogenic shock (9). The only exclusion criteria were the presence of endocarditis or too large a native aortic annulus of above 24 mm (7 patients with aortic annuli of 25 mm were also accepted for specific reasons). Concomitant coronary artery disease was not considered a contraindication to TAVI but was treated simultaneously according to our institutional policy (9).

Prerequisites and implantation technique. All procedures were performed under general anesthesia in the special hybrid suite with a monoplane angiographic system (Siemens Artis zee, Siemens AG, Munich, Germany). A consistent heart team of cardiac surgeons, cardiologists, and anesthesiologists performed all valve interventions.

Transapical aortic valve implantation was performed in all patients through a mini left anterior thoracotomy with a balloon-expandable transcatheter stent prosthetic xenograft valve (Edwards Sapien THV, Edwards Lifesciences, Irvine, California). The principal surgical technique, as described in detail by Walther et al. (17), was used with several modifications (15). Simultaneous angiographic monitoring was applied during slow and gradual inflation of the balloon instead of fast and immediate inflation, as originally described (17). This enabled very precise positioning of the valve at a higher position than usual, which reduced the incidence of paravalvular leakage (9,16). Special attention was paid to achieve a higher valve position if there were subvalvular calcified masses in the left ventricular outflow tract (LVOT).

Measurement of annular diameter and valve selection. The annulus was measured pre-operatively using transthoracic echocardiography (parasternal long-axis view) in all patients. Additionally, in 307 patients (86%), we performed annular measurements using multislice computed tomography (MSCT) that influenced valve size selection in borderline cases. In 51 patients (14%), we abandoned MSCT for clinical reasons (urgency, hemodynamic instability, renal failure). The definitive measurements were performed again in the operating room before the intervention using transesophageal echocardiography (TEE) (midesophageal short-axis view and long-axis view at midsystole). Standard TEE also included assessment of the diameters of the LVOT, sinus of Valsalva, sinotubular junction, and ascending aorta. Specific pathologies influencing the procedure and guiding the desired position of the prosthesis, such as localized calcified masses, were identified. A valve size of 23 mm was chosen for aortic valve annuli smaller than 21 mm and a 26-mm prosthesis for annular diameter of 21 mm or larger (16).

Intraprocedural policy with regard to paraprosthetic leakage. In accordance with our institutional procedural policies (9), only trivial or mild paraprosthetic regurgitation was accepted after TAVI. If higher grade regurgitation was present, immediate treatment was performed, applying balloon redilation (with additional 1 to 3 ml) of the implanted transcatheter valve and, if necessary, implantation of a second prosthesis of the same size (9,16).

Determination of regurgitation. The occurrence of paraprosthetic and transvalvular regurgitation was always evaluated using TEE and angiography in all patients. For assessment with TEE, long-axis and short-axis views were used. A first assessment with TEE was performed immediately after the valve was deployed. While the stiff guidewire was still in place, a rough grading of regurgitation was performed by means of color Doppler flow echocardiography. In the presence of relevant regurgitation, additional acts were performed (as described earlier). If there was no relevant paravalvular or valvular regurgitation, the stiff guidewire was removed and the procedure was finished. Regurgitation was further evaluated using contrast echocardiography with agitated succinylated gelatin (Gelafundin 4%, B. Braun Melsungen AG, Melsungen, Germany) after the sheath and guidewire were removed from the heart. Aortic root angiography with 20 ml iopromide (Ultravist-370, Bayer AG, Leverkusen, Germany) was performed in all patients. The severity of regurgitation was qualitatively assessed (10,18) and precisely graded using TEE according to the guidelines (10,19). The width and height of regurgitation jets as well as "jet anatomy" (20) were assessed in color Doppler flow. Aortic regurgitation was categorized according to the localization as paravalvular, transvalvular, or combined paravalvular and transvalvular regurgitation. Overall aortic regurgitation was classified as absent (0), trace (<I), mild (I), moderate (II), and severe (III or IV) (10,19). Post-procedural assessment using TEE and angiography was made uniformly under stable hemodynamic conditions in all patients, with a mean arterial blood pressure of 70 mm Hg and a mean heart rate of 90 beats/min.

Assessment of aortic valve morphology by MSCT. Retrospective analysis of MSCT was performed in all patients who needed another valve intervention to minimize intraprocedural regurgitation as well as in all patients with post-procedural regurgitation of more than grade I. A control group of matched patients without any post-procedural regurgitation and without any further intraprocedural valve intervention was generated. Matching was done according to congruence in general patient parameters that were found to be predictive for regurgitation in univariate analysis (sex, absence or presence of previous aortic valve replacement, TEE-measured annular diameter, and New York Heart Association functional class). The amount of calcification in the device landing zone (consisting of the aortic annulus, valvular cusps, and LVOT) was assessed semiquantitatively by visual estimation (grade 0 to IV) (21). The shape of the aortic annulus was classified as oval when 2 orthogonal diameters differed by more than 25%; otherwise, it was classified as round. The number of open or fused commissures was

counted (0 to 3). Furthermore, the Agatston calcium score (22) was calculated and applied to quantify the degree of calcification of the device landing zone (21). The cutoff level to detect calcium was set between 450 and 600 Hounsfield units (HU). Standard calcium scoring software was used (syngo, Siemens AG).

Statistical analysis. Continuous variables are expressed as mean ± SD and as maximal and minimal absolute numbers. Statistical analyses of post-operative changes in echocardiographic parameters were carried out using paired *t* tests. The Kaplan-Meier survival functions for subgroups with and without post-procedural regurgitation were calculated. A Gehan test was used to analyze differences between survival functions. Logistic regression was used to identify possible risk factors for post-procedural regurgitation. First, a univariate approach for all possible risk factors was evaluated. In the second step, several risk factors were combined in multivariate logistic regression models. The best model was chosen according to the Akaike information criterion. Accordingly, multislice computed tomographic parameters from the regurgitation group and the matched control group were analyzed using univariate and multivariate logistic regression statistics. Data were evaluated using IBM SPSS version 19 (IBM, Armonk, New York). A p value <0.05 was considered significant.

Results

Intraprocedural TAVI course. Technical success of valve implantation was 99%, with conversion to conventional surgery because of annulus rupture in 2 patients (0.6%). There was no conversion to conventional surgery because of regurgitation, prosthesis migration, or aortic dissection. A 23-mm prosthesis was used in 124 patients (35%) and a 26-mm prosthesis in 234 (65%).

Moderate or severe regurgitation requiring additional intraprocedural intervention. The rate of moderate or severe regurgitation (paraprosthetic and/or central) after primary implantation was 6% (23 of 358 patients). Additional redilation (with additional 1 to 3 ml) of the primarily implanted valve was performed in 18 patients (5%) (Fig. 1). Additional valves of the same size were implanted in 13

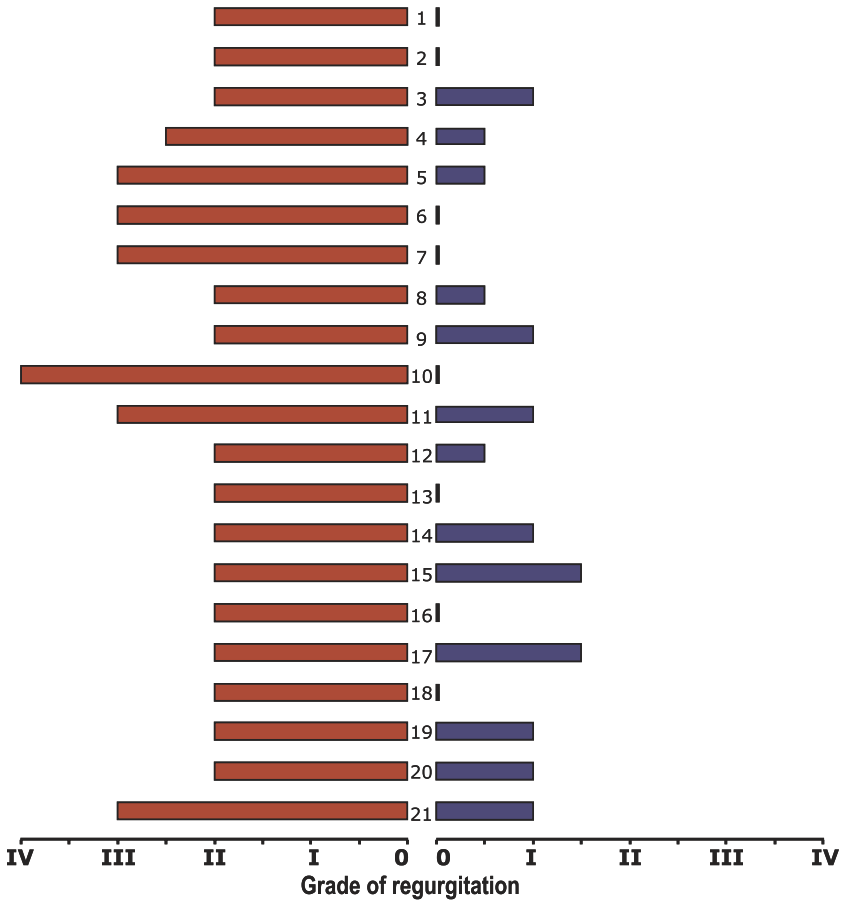

Figure 1 Effect of Intraprocedural Reintervention to Minimize Regurgitation

Intraprocedural grade of regurgitation **(left)** in all 21 patients (from top to bottom in chronological order) who underwent additional redilation and/or implantation of a second prosthesis before reintervention and final grade of regurgitation at the end of the procedure **(right)** are given.

Table 2 Intraprocedural Parameters of Patient Group as a Whole and Divided Into Subgroups Taking Into Account Post-Procedural Regurgitation

Parameter	All Patients (N = 358)	No Regurgitation (n = 186)	Regurgitation of Any Kind (n = 172)	p Value
Contrast medium (ml)	111 ± 63	105 ± 53	118 ± 72	0.061
Radiation time (min)	9.4 ± 6.4	9.0 ± 5.4	9.8 ± 7.3	0.235
Dose-area product (μGy · m^2)	7,764 ± 5,899	7,077 ± 3,934	8,476 ± 7,351	0.031*
26-mm prosthesis	234 (65%)	125 (67%)	109 (63%)	0.505
dP mean (mm Hg)	4.8 ± 2.5	4.5 ± 2.3	5.1 ± 2.6	0.072
Simultaneous PCI	39 (11%)	21 (11%)	18 (11%)	0.866
Use of CPB	27 (8%)	11 (6%)	16 (9%)	0.237
Redilation	18 (5%)	6 (3%)	12 (7%)	0.146
Second prosthesis	13 (4%)	6 (3%)	7 (4%)	0.780

Values are mean ± SD or n (%). *Statistically significant ($p < 0.05$).
CPB = cardiopulmonary bypass; dP mean = mean transvalvular gradient; PCI = percutaneous coronary intervention.

patients (regardless of previous redilation). Second 23-mm prostheses were implanted in 5 patients and second 26-mm prostheses in 8 patients. Two patients (0.6%) with moderate regurgitation (grade II) had intraprocedural bleeding near the apically placed introducer (because of very fragile myocardium) during primary valve implantation, and the apex was safely closed without intention to treat moderate regurgitation (which would have jeopardized the TAVI procedure). The reintervention rate dropped from 8% in first 100 patients to 3% in the last 58 patients. All procedural parameters are given in Table 2.

Transvalvular regurgitation. The occurrence of severe transvalvular regurgitation related to lacking or restricted leaflet movements was observed in 6 patients (2%). Tentative manipulations with the pigtail catheter successfully eliminated aortic regurgitation in 3 patients (0.8%). Additional prostheses of the same size were implanted in 3 patients (0.8%), reducing aortic regurgitation from grade III (severe) to grade I (mild) in 1 patient and eliminating regurgitation completely in the other 2 patients.

Paraprosthetic regurgitation. Significant paraprosthetic regurgitation with or without transvalvular regurgitation occurred more frequently than transvalvular. Redilation without implanting a second valve (Fig. 2) was performed in 8 patients (2%), reducing aortic regurgitation from grade I to II (mild) in 1 patient, grade I (mild) in 4 patients, and grade <I (trace) in 1 patient and eliminating regurgitation (grade 0) in 2 patients. Redilation followed by the implantation of a second prosthesis was performed in 10 patients (3%). At the end of the procedure, regurgitation was reduced to grade I to II (mild) in 1 patient, grade I (mild) in 2 patients, and grade <I (trace) in 3 patients, and regurgitation was eliminated in 4 patients.

Complications after additional intraprocedural intervention. The rate of complications, problems, and the way we managed them in the first 194 patients have recently been reported (16). In all 21 patients who underwent redilation and/or the implantation of a second prosthesis, there was no annular rupture, aortic dissection, or coronary ostia occlusion. One patient developed acute pulmonary edema related to severe transvalvular aortic regurgitation after initial valve deployment. Immediate implantation of a second prosthesis was performed under emergency femoro-femoral cardiopulmonary bypass. To achieve pulmonary recovery, the patient received extracorporeal membrane oxygenation support for 24 h. After initial recovery, the patient developed sepsis and multiple-organ failure. Within this subgroup of 21 patients, there were 3 in-hospital deaths related to septic multiple-organ failure in 2 patients and lack of myocardial recovery in 1 patient. Surgical revision for bleeding was necessary in 1 patient. The implantation of a permanent pacemaker was required in 2 of 21 patients. Weaning from the respirator was prolonged in 3 of 21 patients who underwent tracheostomy during further follow-up. There were no neurological deficits in the postoperative courses of these 21 patients.

Grade of regurgitation at the end of the TAVI procedure. At the end of the TAVI procedure, no regurgitation was observed in 186 patients (52%), and 172 patients (48%) had some regurgitation. The grades of regurgitation were trace in 88 patients (24% of all 358 patients), mild in 82 (23%), and moderate in 2 (0.6%). There was no severe (>II) regurgitation (Fig. 3).

With regard to the group of 172 patients with any regurgitation, it was trace in 51% of these patients, mild in 48%, and moderate in 1%. Regurgitation was paravalvular in 32% (113 of 358 patients), transvalvular in 13% (47 of 358), and combined paravalvular and transvalvular in 3% (12 of 358). In the 172 patients with regurgitation, it was paravalvular, transvalvular, and combined in 66%, 27%, and 7%, respectively.

Further findings on TEE. The mean transvalvular gradient was significantly ($p = 0.001$) reduced from 48.3 ± 14.7 mm Hg (range: 8 to 100 mm Hg) to 4.8 ± 2.4 mm Hg (range: 1 to 20 mm Hg). The aortic valve area increased significantly ($p = 0.001$) from 0.7 ± 0.2 cm^2 (range: 0.3 to 1.8 cm^2) to 2.1 ± 0.5 cm^2 (range: 0.9 to 3.5 cm^2).

General predictors of regurgitation. Predictors of post-procedural regurgitation of any kind with statistical significance in univariate analysis (Table 3) were male

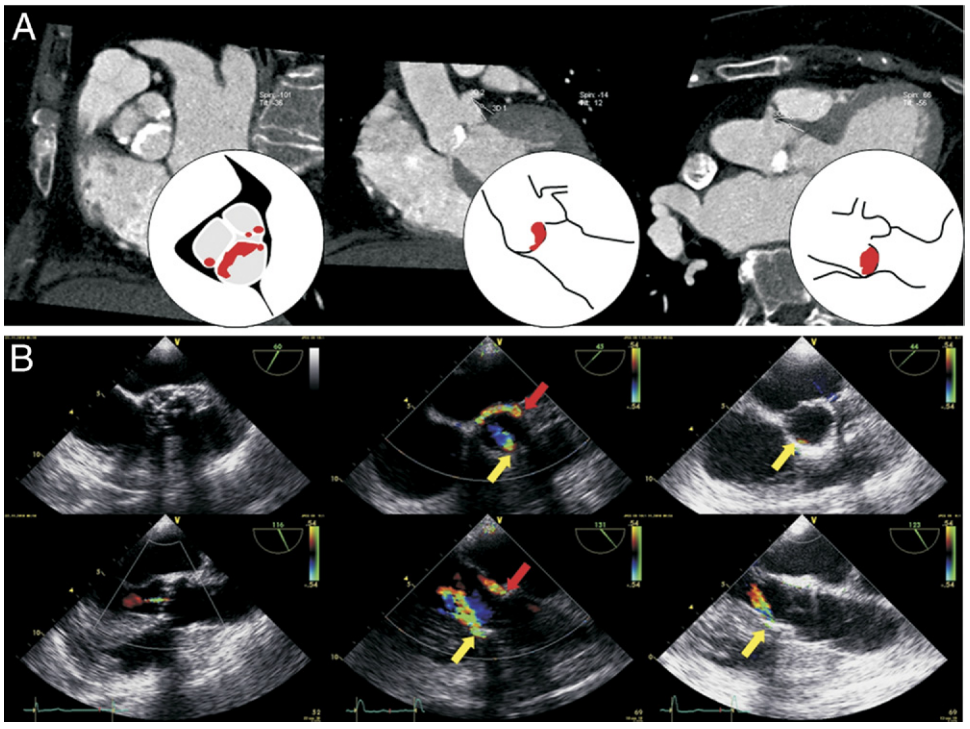

Figure 2 **Asymmetric Distribution of Calcification Within Aortic Valve Cusps Indicating Risk for Post-Procedural Leakage**

Paravalvular regurgitation was reduced by redilation. **(A)** Different multislice computed tomographic views and schematic drawings indicating severe calcification (red) of the noncoronary cusp. **(B)** Short-axis and long-axis transesophageal echocardiographic views before transcatheter aortic valve implantation **(left)**, after prosthesis deployment **(middle)**, and after redilation **(right)**. The jet at the left noncoronary commissure disappeared **(red arrow)**, and the jet at the left-right coronary commissure was reduced **(yellow arrow)**.

sex, New York Heart Association functional class, no previous aortic valve replacement, and annular size (on TEE). There was a weak correlation (r = 0.260) between annular size measurements on TEE and MSCT. By multivariate analysis, the absence of previous aortic valve replacement, male sex, and New York Heart Association functional class IV were the strongest predictors of post-procedural regurgitation (Table 4).

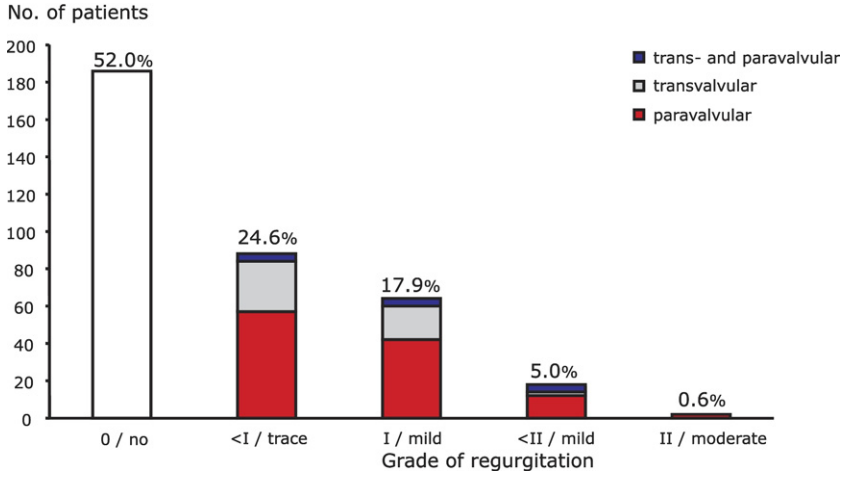

Figure 3 **Final Grade of Regurgitation**

Distribution of regurgitation at the end of the transcatheter aortic valve implantation procedure is given, taking into account grade and location of leakage.

Table 3 Predictive Factors of Post-Procedural Regurgitation (Results of Univariate Logistic Regression)

Parameter	Odds Ratio	95% Confidence Interval	p Value
Age	1.01	0.98–1.03	0.444
Male	1.66	1.06–2.58	0.025*
BMI	0.97	0.94–1.01	0.164
EuroSCORE	1.01	1.00–1.02	0.336
STS score	1.01	0.99–1.02	0.299
NT-proBNP	1.00	1.00–1.00	0.251
NYHA functional class IV	1.58	1.04–2.42	0.033*
Cardiogenic shock	1.46	0.60–3.55	0.501
COPD	1.19	0.79–1.80	0.459
FEV_1	1.00	0.99–1.01	0.449
SPAP > 50 mm Hg	1.45	0.94–2.22	0.103
Creatinine	0.90	0.64–1.25	0.520
Renal failure	0.96	0.59–1.57	0.900
Diabetes mellitus	0.94	0.58–1.52	0.808
Coronary artery disease	1.10	0.72–1.68	0.669
Atrial fibrillation	0.94	0.60–1.48	0.819
Cerebral ischemic lesion	0.92	0.55–1.53	0.797
Peripheral artery disease	1.19	0.75–1.88	0.488
Severely calcified ascending aorta	0.85	0.68–1.07	0.167
Previous pacemaker/ICD	1.12	0.61–2.43	0.602
Previous AVR	0.12	0.03–0.51	0.001*
Previous CABG	1.13	0.65–1.97	0.776
Previous MVR	1.35	0.36–5.10	0.744
LVEF	1.00	0.99–1.02	0.634
LVEDD	0.99	0.96–1.02	0.444
dP mean	1.01	1.00–1.03	0.115
Annulus, TEE	1.18	1.03–1.37	0.020*
Annulus, CT	1.07	0.97–1.18	0.186
Aortic regurgitation (grade II–IV)	1.08	0.58–2.01	0.875
Mitral regurgitation (grade III or IV)	0.35	0.07–1.75	0.286
Tricuspid regurgitation (grade III or IV)	0.64	0.15–2.70	0.725

*Statistically significant ($P < 0.05$).
Abbreviations as in Table 1.

Morphological substrates of intraprocedural regurgitation. Retrospective detailed analysis of preoperatively performed MSCT was performed in 78 patients (22%). Within the regurgitation subgroup of 39 patients (11%), there were 15 (38% of 39) with oval-shaped annuli, 13 (33%) with severe calcification of the LVOT (grade III or IV) (Fig. 4), 26 (67%) with severe calcification of the cusps (grade III or IV), 29 (74%) with asymmetric distribution of calcium within the cusps, and 29 (74%) with 2 or 3 nonfused commissures. There were 22 patients (56%) with severely calcified device landing zones. The mean Agatston calcium scores were 1,363 ± 766 HU (range: 66 to 3,181 HU) in the regurgitation subgroup and 986 ± 586 HU (range: 48 to 2,993 HU) in the matched control group. In univariate analysis, Agatston calcium score was found to be a significant predictor of intraprocedural regurgitation (odds ratio per 100 units: 1.09; 95% confidence interval: 1.01 to 1.17; p = 0.029). Results from the multivariate analysis are given in Table 5. A schematic overview of morphological risk factors for post-procedural regurgitation is given in Figure 5.

Survival. There was no statistically significant difference (p = 0.771) in survival between patients without intraprocedural regurgitation and patients with trace or mild regurgitation. The observed 1-year survival rates were 83 ± 3% in patients without regurgitation, 85 ± 4% in patients with trace regurgitation, and 83 ± 5% in patients with mild regurgitation. The 2-year survival rates in patients without regurgitation and in those with trace and mild regurgitation were 66 ± 6%, 72 ± 8%, and 67 ± 7%, respectively. All Kaplan-Meier survival functions are given in Figure 6.

Later aortic valve interventions. During the follow-up of all 358 patients, 3 patients underwent conventional aortic valve replacement (endocarditis in 2 patients, progression from mild to severe paravalvular regurgitation in 1 patient). Another patient underwent a second TAVI procedure (new-onset severe transvalvular regurgitation). The overall rate of later aortic valve interventions was 1%.

Discussion

Occurrence of leakage after TAVI versus conventional aortic valve replacement. Our reported strategy consists of a modified TAVI technique in combination with immediate intraprocedural treatment of relevant paravalvular (or transvalvular) regurgitation resulting in a very low regurgitation rate. Although TAVI procedures are imperfect compared with precise surgical valve replacement with regard to the occurrence of paraprosthetic regurgitation, the modified TAVI strategy reaches the results of conventional aortic valve replacement. At the end of the procedure, moderate regurgitation was observed in only 2 patients and was accepted as an exception. The majority of our patients (52%) had no regurgitation at the end of the TAVI procedures. Trace paravalvular regurgitation is associated with benign prognoses in the majority of surgically treated patients (11). Transferring this finding to our TAVI group, trace or mild regurgitation seems to be acceptable in these high-risk patients. During the follow-up, 1% of our patients needed additional aortic valve replacements because of endocarditis (0.6%) or progression of regurgitation (0.6%). The midterm follow-up results are comparable with those of surgically implanted bioprosthetic valves (11).

Table 4 Predictive Factors of Post-Procedural Regurgitation (Results of Multivariate Logistic Regression)

Parameter	Odds Ratio	95% Confidence Interval	p Value
Sex	1.96	1.23–3.12	0.005*
NYHA functional class IV	1.71	1.08–2.73	0.023*
Previous AVR	0.08	0.02–0.38	0.001*

*Statistically significant ($p < 0.05$).
Abbreviations as in Table 1.

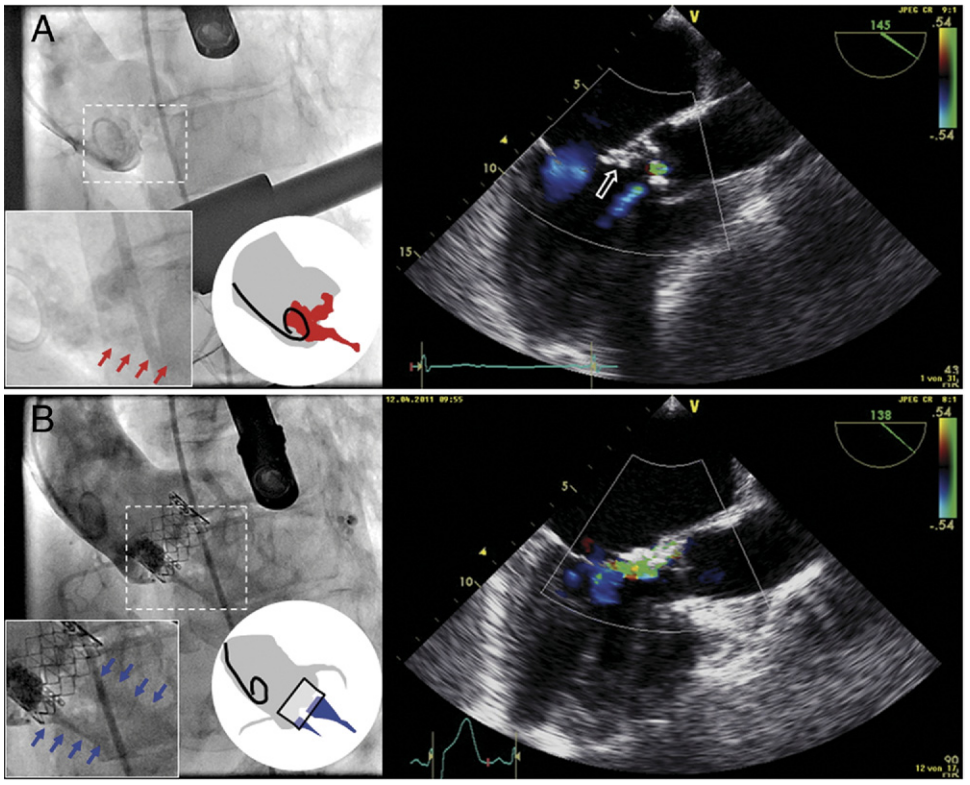

Figure 4 Calcification of the LVOT Indicating Risk for Post-Procedural Leakage

Post-procedural regurgitation was preoperatively anticipated and minimized by a higher position of the prosthesis. **(A)** Angiography, schematic drawing **(left)**, and transesophageal echocardiography **(right)** indicating a severely calcified rim **(red arrows)** in the left ventricular outflow tract (LVOT). **(B)** The prosthesis was implanted specifically in a high position (3/4 above the annulus). There was mild regurgitation on angiography **(blue arrows)** and on transesophageal echocardiography.

Overall outcome. Our overall clinical results, with a 1-year survival rate up to 85% and a 2-year survival rate up to 72%, are a continuation of our previous encouraging reports (9,16,23). Contrary to the report by Tamburino et al. (8), our reported modified TAVI strategy achieved a lower rate of leakage and had no impact on midterm survival. This is the most important benefit of the modified strategy to avoid regurgitation during TAVI (9).

Regurgitation after TAVI with balloon-expandable versus self-expandable valves. Only a few previous studies analyzed local predictive factors for regurgitation in a limited number of inhomogenous TAVI cohorts. Détaint et al. (24) focused on annular size in 28 and 46 patients treated with transapical and transfemoral implantation, respectively, of the Edwards Sapien valve, with a rate of 17% for moderate or severe regurgitation. They introduced a cover index and found prosthesis-annulus incongruence to be a predictor of regurgitation. Our clinical observations support the findings that the degree of oversizing of the balloon-expandable valve prosthesis is inversely related to the risk for paravalvular regurgitation. This might explain why regurgitation occurs more often in tall men than in smaller women. More precise methods of the assessment of the diameter of the native annulus are necessary. Further improvements to the prosthesis itself without increasing the risk for annular rupture need to be made.

It also seems that paravalvular leakage might be less frequent after implantation of balloon-expandable valves in comparison with self-expandable valves. Sherif et al. (25) analyzed regurgitation in 50 patients treated with transfemoral implantation of the self-expanding Medtronic CoreValve prosthesis (Medtronic, Inc., Minneapolis, Minnesota), with a rate of 40% for regurgitation of grades II and III. An increasing LVOT-aorta angle as well as increasing

Table 5 Predictive Morphological Factors (Parameters From Multislice Computed Tomography) of Significant Intraprocedural and/or Post-Procedural Regurgitation (Results of Multivariate Logistic Regression)

Parameter	Odds Ratio	95% Confidence Interval	p Value
Asymmetric cusp calcification	5.65	0.44–3.03	0.009*
Device landing zone calcification	4.90	0.79–2.39	0.001*
Oval-shaped annulus	9.16	0.68–3.75	0.005*

*Statistically significant ($p < 0.05$).

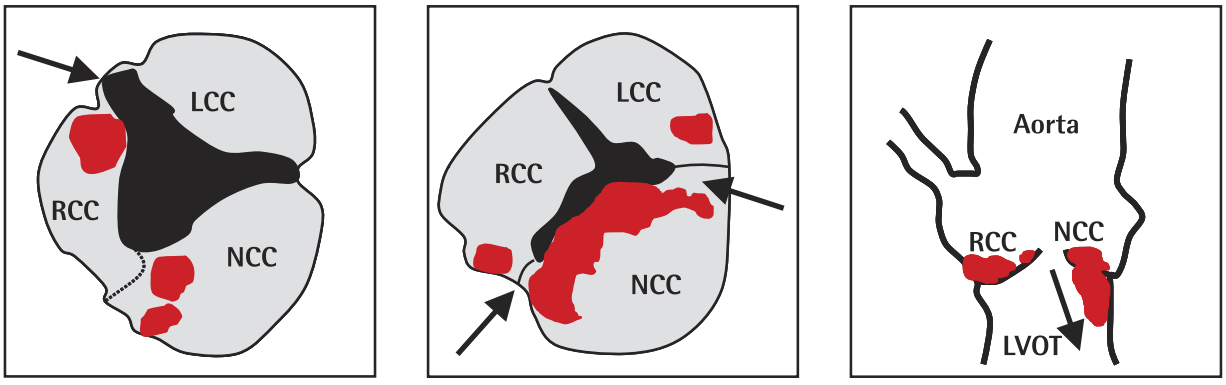

Figure 5 Schematic Drawings Indicating Morphological Risk Factors for Post-Procedural Regurgitation

The anticipated occurrence of leakage is marked **(arrow)**. Nonfused commissures in the neighborhood of bulky masses **(left)**, an asymmetric distribution of calcified masses **(red)** within the cusps **(middle)**, and calcified structures in the left ventricular outflow tract (LVOT) **(right)** are anatomical regurgitation substrates. LCC = left coronary cusp; NCC = noncoronary cusp; RCC = right coronary cusp.

depth of the prosthesis in relation to the noncoronary cusp was associated with a higher likelihood of paravalvular regurgitation. In agreement with a report on the self-expanding Medtronic CoreValve prosthesis (21), we observed severe calcification in the device landing zone as a morphological cause of paraprosthetic regurgitation in our group.

Predictive factors for regurgitation. The presence of a degenerated bioprosthesis was clearly associated with a very low risk for regurgitation. It indicates that the "valve-in-valve" concept is a safe procedure avoiding repeat sternotomy and providing good performance of the prosthesis (23). Male gender, signs of advanced heart failure, and larger annuli were found to be predictive of regurgitation. Most likely, the annular size was sex related. It indicates that larger annuli in male patients are related to an increased risk for regurgitation or even that the annular diameter was underestimated. Our results are in contrast to those from

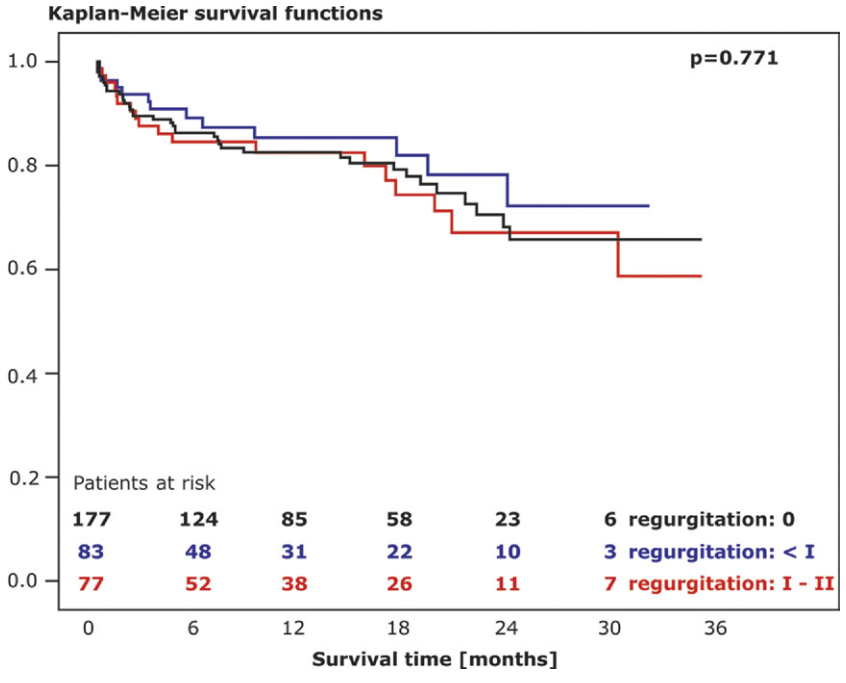

Figure 6 Midterm Survival After Transcatheter Aortic Valve Implantation

Kaplan-Meier survival functions of all patients without cardiogenic shock divided into 3 groups are given: no regurgitation **(black)**, trace regurgitation **(blue)**, and mild regurgitation **(red)**.

conventional aortic valve replacement, for which a smaller body surface area was among the strongest predictors of paravalvular regurgitation (11). In conclusion, morphological factors of the aortic valve and its environment seem to be much more important for paravalvular regurgitation than general parameters.

How to minimize or avoid paravalvular regurgitation. The risk for postprocedural paravalvular regurgitation can be anticipated from pre-operative MSCT and TEE. We agree with others that MSCT provides helpful additional information (21,26). The following morphological constellations are associated with a higher risk for regurgitation: asymmetrically calcified cusps, especially in combination with a large annular size or an oval annular shape; nonfused commissures in the neighborhood of calcified masses; and the presence of LVOT calcification.

The main reason for our low post-procedural regurgitation rate is our modified implantation technique, which has been described elsewhere (15). Any uncertainty regarding the desired valve position must be avoided. Furthermore, we were able to implant the valve at a higher position, which we found to be very effective to prevent regurgitation. Angiographic monitoring preserves from obstructions of the coronary ostia, which were rare in our cohort (16).

Redilation with or without the implantation of a second valve is a suitable option if paravalvular regurgitation is observed after TAVI. Both options were rarely necessary in our group of patients but were found to be very effective. If severe transvalvular regurgitation occurs, it is worth trying manipulation with the pigtail catheter to mobilize a nonmoving leaflet first. Then, if necessary, the implantation of a second valve will eliminate it definitively.

Study limitations. We exclusively used 23-mm and 26-mm devices, because the 29-mm prosthesis only recently became commercially available. Another limitation of the study is the relatively short follow-up period of up to 35 months. The risk for early valve degeneration, the probability of progressive regurgitation, and the rate of endocarditis need to be assessed over a longer period, and therefore, long-term follow-up is needed.

Conclusions

TAVI procedures need to achieve the results obtained with surgical valve replacement. Until this has been accomplished, an anticipated high risk for regurgitation should influence the decision-making process of whether a patient with aortic stenosis should undergo TAVI or conventional surgery. Our initial experience with modified transapical approach in 358 patients demonstrates that a low rate of paravalvular regurgitation after TAVI can be achieved.

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