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Aortic regurgitation after transcatheter aortic valve implantation: incidence and early outcome. Results from the German transcatheter aortic valve interventions registry

Mohamed Abdel-Wahab,[1] Ralf Zahn,[2] Martin Horack,[3] Ulrich Gerckens,[4] Gerhard Schuler,[5] Horst Sievert,[6] Holger Eggebrecht,[7] Jochen Senges,[3] Gert Richardt,[1] for the German transcatheter aortic valve interventions registry investigators

[1]Heart Center, Segeberger Kliniken GmbH, Bad Segeberg, Germany
[2]Department of Cardiology, Clinical Center of Ludwigshafen, Ludwigshafen, Germany
[3]Institute of Myocardial Infarction Research at the University of Heidelberg, Ludwigshafen, Germany
[4]Department of Cardiology, HELIOS Hospital, Siegburg, Germany
[5]Heart Center, University of Leipzig, Leipzig, Germany
[6]Cardiovascular Center Frankfurt, Sankt Katharinen, Frankfurt am Main, Germany
[7]Clinic for Cardiology, West German Heart Center Essen, Essen, Germany

Correspondence to
Dr Mohamed Abdel-Wahab, Heart Center, Segeberger Kliniken GmbH, Academic Teaching Hospital of the University of Kiel, Am Kurpark 1, 23795 Bad Segeberg, Germany; mohamed.abdel-wahab@segebergerkliniken.de

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ABSTRACT

Background Significant aortic regurgitation (AR) is rare following surgical aortic valve replacement and has been associated with worse outcome. Following transcatheter aortic valve implantation (TAVI), AR is common, but little is known about its determinants and its effect on clinical outcome.

Objective To evaluate early outcome and risk factors possibly associated with AR after TAVI.

Methods Data were analysed from 690 patients with severe aortic stenosis treated with TAVI enrolled in the prospective multicentre German transcatheter aortic valve interventions registry. The occurrence of AR was evaluated angiographically after device deployment and removal of the catheter and guidewire. Significant AR was defined as AR≥2/4.

Results The study population's mean age was 81.4±6.3 years and men represented 44%. The mean logistic Euroscore was 20.4±13.1%. Overall, 84% of patients received the Medtronic CoreValve system and 16% received the Edwards Sapien valve. Significant AR occurred in 119 patients (17.2%). Factors independently associated with significant AR were aortic valve area (adjusted OR=0.10), annulus measurement by transoesophageal echocardiography (adjusted OR=1.94), male gender (adjusted OR=1.80), cardiogenic shock (adjusted OR=1.94) and renal failure (adjusted OR=0.53). In-hospital death rates were significantly higher in patients with significant AR than in those with no/mild AR (15.1% vs 6.7%, OR=2.50, 95% CI 1.37 to 4.55), as were rates of low cardiac output (20% vs 4.4%) and respiratory failure (16.5% vs 7.1%). Using multivariate analysis, the presence of post-procedural AR≥2/4 remained a strong independent predictor of in-hospital death (adjusted OR=2.43, 95% CI 1.22 to 4.85).

Conclusion Significant AR after TAVI is common and is associated with increased in-hospital mortality. Long-term follow-up is critical to further define the impact of residual AR on clinical outcome. Until these data become available, every effort should be made to prevent and treat this complication.

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) has rapidly been implemented as an alternative treatment strategy for patients with severe symptomatic aortic stenosis (AS) considered to be at high surgical risk. Registries from multiple centres have shown that TAVI can be accomplished in selected high-risk patients with outcomes that compare favourably with the outcome of surgical valve replacement as predicted by validated risk assessment tools.[1–5] Nevertheless, and despite being less invasive than conventional surgical aortic valve replacement (SAVR), TAVI remains associated with serious complications.

Trivial or mild paraprosthetic aortic regurgitation (AR) is not uncommon after SAVR but does not have significant impact on short-term and long-term clinical outcomes.[6] More severe paraprosthetic regurgitation is rare, but is usually associated with haemodynamic deterioration and often requires re-interventions.[6] Minor paravalvular regurgitation is ubiquitous with current transcatheter valves, with an incidence ranging from 40% to 67%,[3 4 7] probably because of the presence of the calcified native valve between the implanted prosthesis and the aortic annulus preventing complete sealing of the paravalvular space. The incidence of more than mild paravalvular regurgitation after TAVI varies between 7% and 20%[2–4 7] and may have important clinical consequences; nevertheless, the outcome of this complication has not been specifically studied. Therefore, we sought to evaluate both determinants and early outcome of aortic regurgitation after TAVI using data from the German transcatheter aortic valve interventions registry.

METHODS

Study design

The German transcatheter aortic valve interventions registry is a multicentre prospective registry, which has been designed to monitor current use and outcome of transcatheter aortic valve interventions (ie, TAVI and balloon aortic valvuloplasty) in daily clinical practice, and to evaluate safety, effectiveness and health economic data. The registry is completely independent from industry, driven by the scientific interest of the participating hospitals and financed by the Institut für Herzinfarktforschung (Institute of Myocardial Infarction Research) in Ludwigshafen, Germany. Details of the registry have been described elsewhere.[8]

Patient population

Since January 2009, all participating hospitals committed to include all consecutive patients with severe symptomatic AS treated with either balloon valvuloplasty alone or TAVI. Proposed inclusion criteria for treatment were the following: severe symptomatic AS with a valve area ≤1 cm^2, with or without aortic valve regurgitation and (a) age ≥80 years and a logistic Euroscore[9] ≥20% or (b) logistic EuroScore <20% and at least one of the following criteria: liver cirrhosis, chronic pulmonary disease or porcelain aorta. Technical feasibility, such as a feasible arterial access and a fitting aortic annulus diameter according to the available prostheses sizes, was also required for inclusion.

Preinterventional patient screening included transthoracic as well as transoesophageal echocardiography (TOE) to confirm diagnosis, multislice CT to assess aortic and aortic valve dimensions and morphology, grade and distribution of calcifications, annulus dimension in a multiplanar reconstruction as well as access site anatomy, and invasive cardiac evaluation with coronary and supra-aortic angiography and left ventriculography. The baseline operative risk of the patients was estimated by the logistic Euroscore. The patient was considered at high risk if the inclusion criteria were met as confirmed by an independent senior cardiologist and senior cardiac surgeon. The decision to treat a patient and the decision to perform a balloon valvuloplasty alone or to do a TAVI was left to the treating doctor. However, we strongly suggested that such a decision should be made by a multidisciplinary team, typically consisting of an interventional cardiologist, a cardiac surgeon and an anaesthesiologist, as suggested by current recommendations.[10 11]

For this analysis, we only report on patients treated with TAVI, while patients treated with balloon aortic valvuloplasty alone were excluded.

Device description

Our registry is open to all available prostheses. Currently, only two prostheses are available in Germany: the Medtronic CoreValve and the Edwards Sapien prosthesis.

The Medtronic CoreValve (Medtronic CoreValve, Irvine, California, USA) consists of a tri-leaflet bioprosthetic porcine pericardial tissue valve, which is mounted and sutured in a self-expanding nitinol stent frame. The size of the delivery system is currently 18 French, which facilitates vascular access and deployment of the device. Two different device sizes are available for different annulus dimensions: the 26 mm prosthesis for aortic valve annulus sizes from 20 to 23 mm, and the 29 mm prosthesis for aortic valve annulus sizes from 23 to 27 mm. Details of the implantation technique have been previously reported.[2 12 13]

The Edwards Sapien valve (Edwards Lifesciences, Irvine, California, USA) is a balloon-expandable prosthesis consisting of a tri-leaflet bovine pericardial valve. Initially, transarterial and transapical procedures were performed with the RetroFlex delivery catheter. Later on, the RetroFlex II transarterial catheter incorporating a retractable nose cone and the Ascendra transapical catheter were used. Arterial access was performed via a 21 or 24 French delivery system. Two prosthesis sizes were available, with a 23 mm and 26 mm expanded diameter for aortic valve annulus sizes between 18 and 24 mm. Details of the implantation technique have been previously reported.[3 14 15]

Evaluation of post-procedural AR

The degree of post-procedural AR was angiographically evaluated at the end of the TAVI procedure after final device deployment and removal of the catheter and guidewire. Qualitative angiographic assessment of the severity of AR was performed by visual estimation of the concentration of contrast medium in the left ventricle, using the method of Sellers *et al*.[16] AR was classified into four grades: absent (0), trace or mild (1/4), mild-to-moderate (2/4), moderate-to-severe (3/4) and severe (4/4). Significant AR was defined as AR≥2/4. The evaluation was performed by the treating doctor.

Adjunctive medication

Medical treatment included aspirin (100 mg/day, indefinitely) and clopidogrel (600 mg loading dose followed by 75 mg/day for 6–12 months). Heparin was administered according to the patient's weight to achieve an activated clotting time ≥250 s. All patients provided written informed consent before the procedure and also gave written informed consent for the processing of their anonymous data.

Statistics

Data collection

Data were collected via the internet by the Institut für Herzinfarktforschung at the Heart Centre Ludwigshafen.

Data analysis

Statistical analysis was performed using the SAS statistical package, version 9.1 (Cary, North Carolina, USA). Absolute numbers and percentages as well as means (with SD) are computed to describe the patient population. Categorical values were compared by χ^2 test and continuous variables were compared by two-tailed Wilcoxon rank sum test. p Values <0.05 were considered significant. All p values are results of two-tailed tests. Two multivariable logistic regression models were used to analyse factors associated with in-hospital mortality and significant final post-procedural AR. The first model (for in-hospital mortality) included age, male gender, cardiogenic shock/decompensation, renal failure, coronary artery disease, previous myocardial infarction, Euroscore, American Society of Anesthesiologists class, New York Heart Association (NYHA) class, peripheral arterial disease, left ventricular ejection fraction (LVEF) ≤30%, operative TAVI (transapical and transaortic), significant post-procedural AR and vascular complications. The second model (for post-procedural AR) included male gender, cardiogenic shock, pulmonary hypertension, renal failure, Euroscore, previous cardiac surgery, aortic aneurysm, aortic valve area (AVA), LVEF ≤30%, severe valve calcification (extensive thickening and calcification of all cusps), bicuspid aortic valve, pre-procedural AR, aortic annulus size, annulus estimation by TOE and CoreValve prosthesis. The variables entered into both models had a p value <0.2 in the univariate analysis and/or were clinically relevant to the outcome. The authors had full access to, and take full responsibility for, the integrity of the data. All authors have read and agreed to the manuscript as written.

RESULTS

Between January and December 2009 a total of 833 transcatheter aortic valve interventions were performed at 22 hospitals: 136 plain balloon valvuloplasties and 697 transcatheter aortic valve implantations. Of the latter, 666 (95.6%) procedures were performed percutaneously (644 (92.4%) transfemoral and 22 (3.2%) trans-subclavian), and 31 (4.4%) procedures were performed surgically (26 (3.7%) transapical and 5 (0.7%) transaortic). For this analysis on post-procedural AR, only patients treated with TAVI have been considered. The degree of post-procedural AR was not reported in seven patients, and therefore, a total of 690 patients constitute the population of this study.

Baseline characteristics

Baseline clinical, echocardiographic and angiographic characteristics for patients treated with TAVI are shown in tables 1 and 2. Mean patient age was 81.4±6.3 years, 44% were male and the mean logistic Euroscore was 20.4±13.1%. Mean LVEF was 52.1±15.1%, with 13% of patients having a severely reduced LVEF of <30%. Mean AVA was 0.65±0.18 cm^2. The mean aortic annulus diameter was 23.5±2.6 mm and was most commonly (64%) estimated by TOE. At baseline, 77% of patients had any degree of AR, mostly (55%) mild.

Procedural details

Procedural characteristics are shown in table 3. Most interventions (84.5%) were performed as elective procedures and only 0.4% as emergency procedures. The Medtronic CoreValve prosthesis was used in 84% while the Edwards Sapien prosthesis was used in 16% of cases. Mean intervention time, from arterial puncture until vascular closure, was 86.1±47.0 min, with a fluoroscopy time of 15.1±6.9 min. Technical success, defined as completion of the procedure and lowering of the mean pressure gradient, was achieved in 98.6% of cases. The mean post-procedural transaortic pressure gradient dropped from 48.3±17.5 to 5.5±6.1 mm Hg (p<0.0001).

Early AR after TAVI

Assessment of post-procedural AR showed absence of AR in 191 patients (27.7%), trivial or mild AR (1/4) in 380 patients (55.1%), moderate (2/4) in 103 patients (14.9%), moderate-to-severe (3/4) in 14 patients (2%) and severe AR (4/4) in 2 patients (0.3%). Thus, significant AR according to our definition (≥2/4) occurred in 119 patients (17.2%) immediately after TAVI (table 3, figure 1).

Patients who developed significant post-procedural AR were more commonly male (57%) and were generally sicker than patients with no/mild AR (significantly more patients with cardiogenic shock or decompensated heart failure (p=0.01), more patients with pulmonary hypertension (p=0.02) and three-vessel coronary artery disease (p=0.01)), and had a higher mean logistic Euroscore at baseline (24±15.6 vs 19.6±12.5, respectively, p=0.01), but patient frailty as assessed by the American Society of Anesthesiologists physical status class was similar in both groups (table 1).

With regard to echocardiographic characteristics, post-procedural AR≥2/4 was significantly associated with a smaller AVA (p=0.001) and a lower LVEF (p=0.005), and tended to be more common in patients with bicuspid aortic valves but this did not reach the accepted significance level (3.4% vs 1.4%, p=0.13).

Table 1 Clinical characteristics of patients undergoing TAVI according to the occurrence of at least moderate post-procedural AR

Characteristics	AR≥2/4 (n=119)	AR<2/4 (n=571)	p Value	OR (95% CI)
Age (years)	81.1±6.3	81.4±6.4	0.72	–
Male gender	68 (57)	239 (42)	0.002	1.85 (1.24 to 2.76)
Weight (kg)	74.8±16.2	73.6±16.2	0.48	–
Height (cm)	166±11.4	166±8.8	0.37	–
BMI (kg/m^2)	28.4±20.2	26.8±6.8	0.86	–
Cardiogenic shock/decompensation	42 (35)	135 (24)	0.01	1.74 (1.14 to 2.65)
Pulmonary hypertension	85 (72)	340 (61)	0.02	1.67 (1.08 to 2.59)
Atrial fibrillation	33 (28)	124 (22)	0.17	1.37 (0.88 to 2.15)
Diabetes mellitus	38 (32)	201 (35)	0.46	0.85 (0.56 to 1.30)
Previous MI	23 (20)	90 (16)	0.32	1.30 (0.78 to 2.16)
Coronary artery disease	75 (64)	336 (59)	0.40	–
Three-vessel disease	42 (36)	138 (24)	0.01	1.71 (1.12 to 2.62)
Left main disease	6 (5.1)	33 (5.9)	0.74	0.86 (0.35 to 2.11)
Previous cardiac surgery	38 (32)	125 (22)	0.02	1.66 (1.08 to 2.56)
Peripheral arterial disease	24 (20)	94 (17)	0.34	1.27 (0.77 to 2.09)
Aortic aneurysm	6 (5)	10 (1.8)	0.03	2.96 (1.05 to 8.30)
Previous stroke	12 (10)	43 (7.6)	0.35	1.37 (0.70 to 2.68)
Renal failure*	62 (56)	360 (63)	0.02	0.64 (0.43 to 0.95)
COPD	35 (29)	137 (24)	0.23	1.31 (0.85 to 2.03)
Logistic Euroscore (%)	24±15.6	19.6±12.5	0.01	–
ASA physical status class				
1=normal healthy patient	0 (0)	13 (2.3)	0.09	–
2=patient with mild systemic disease	38 (32)	180 (32)	0.96	1.01 (0.66 to 1.55)
3=patient with severe systemic disease (limits function but is not incapacitating)	65 (55)	294 (52)	0.57	1.12 (0.75 to 1.67)
4=patient with severe systemic disease that is a constant threat to life	12 (10)	71 (13)	0.46	0.78 (0.41 to 1.50)
5=moribund patient	3 (2.5)	5 (0.9)	0.12	2.91 (0.69 to 12.35)
NYHA functional class				
0/I	1 (0.9)	10 (1.8)	0.47	0.48 (0.06 to 3.78)
II	7 (6)	61 (11)	0.11	0.53 (0.23 to 1.18)
III	82 (70)	400 (71)	0.89	0.97 (0.63 to 1.50)
IV	27 (23)	95 (17)	0.11	1.49 (0.92 to 2.41)

Values are n (%) or mean±SD.
*Defined as glomerular filtration rate <60 ml/min/1.73 m^2.
AR, aortic regurgitation; ASA, American Society of Anesthesiologists; BMI, body mass index; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; NYHA, New York Heart Association; TAVI, transcatheter aortic valve implantation.

Table 2 Echocardiographic and angiographic characteristics of the study population according to the occurrence of at least moderate post-procedural AR

Characteristics	AR≥2/4 (n=119)	AR<2/4 (n=571)	p Value	OR (95% CI)
Aortic valve area (cm^2)	0.6±0.16	0.66±0.18	0.001	—
Mean aortic gradient (mm Hg)	46.8±18.1	48.6±17.3	0.22	—
LVEF (%)	48.6±15.9	52.8±14.8	0.005	—
LVEF≤30%	24 (20)	68 (12)	0.01	1.87 (1.12 to 3.13)
Bicuspid aortic valve	4 (3.4)	8 (1.4)	0.13	2.47 (0.73 to 8.34)
Degree of leaflet calcification				
Mild	9 (7.8)	28 (5)	0.22	1.62 (0.74 to 3.53)
Moderate	44 (38)	188 (33)	0.32	1.23 (0.81 to 1.87)
Severe	62 (54)	346 (62)	0.13	0.73 (0.49 to 1.09)
Aortic annulus diameter (mm)	23.4±2.3	23.5±2.6	0.72	—
Measured with CT	28 (24)	215 (39)	0.002	0.50 (0.32 to 0.79)
Measured with TOE	88 (76)	338 (61)	0.002	2.00 (1.26 to 3.16)
Pre-procedural AR				
None	19 (16)	141 (25)	0.04	0.59 (0.35 to 0.99)
Grade I	74 (63)	300 (53)	0.04	1.54 (1.02 to 2.32)
Grade II	16 (14)	105 (18)	0.21	0.70 (0.40 to 1.23)
Grade III	4 (3)	15 (3)	0.64	1.31 (0.43 to 4.01)
Grade IV	4 (3)	7 (1)	0.09	2.84 (0.82 to 9.85)
Any mitral regurgitation	108 (92)	494 (87)	0.11	1.80 (0.87 to 3.70)
Porcelain aorta	11 (9.5)	56 (10)	0.88	0.95 (0.48 to 1.87)

Values are n (%) or mean±SD.
AR, aortic regurgitation; LVEF, left ventricular ejection fraction; TOE, transoesophageal echocardiography.

Aortic annulus diameter was not different between the groups, but patients with significant AR had their annulus more commonly measured by TOE than those with no/mild AR (76% vs 61%, p=0.002), while the latter group had the annulus diameter more commonly determined by CT (39% vs 24%, p=0.002). Of note, mean annular diameter was significantly smaller in the TOE-measured group than in the CT-measured group (23.0±2.4 vs 24.4±2.6, p<0.0001). No relation between post-procedural significant AR and mean transvalvular gradient, degree of leaflet calcification or pre-procedural aortic or mitral regurgitation was seen (table 2). In addition, the occurrence of significant AR was not related to the type of valve (CoreValve or Edwards) or valve size (table 3), and did not differ between patients treated transfemorally (17.4%) and those treated transapically (20.8%, p=0.66).

In-hospital outcome

In-hospital events stratified by the presence or absence of significant post-procedural AR are shown in table 4. In-hospital death rates were significantly higher in patients with significant AR than in those with no/mild AR (15.1% vs 6.7%, OR=2.50, 95% CI=1.37 to 4.55, p=0.002). There was no significant difference in hospital mortality between patients with no and mild AR (7.9% vs 6.1%), and the step-up in hospital death was seen in patients with at least moderate AR (figure 2). Rates of low cardiac output (20% vs 4.4%), respiratory failure (16.5% vs

Table 3 Procedural details of 690 patients undergoing TAVI stratified according to the occurrence of at least moderate post-procedural AR

	AR≥2/4 (n=119)	AR<2/4 (n=571)	p Value	OR (95% CI)
Operative TAVI	5 (4.2)	25 (4.4)	0.93	0.96 (0.36 to 2.56)
Transapical	5 (4.2)	19 (3.3)	0.64	1.27 (0.47 to 3.48)
Transaortic	0	6 (1.1)	0.26	—
Percutaneous TAVI	114 (95.8)	546 (95.6)	0.93	1.04 (0.39 to 2.78)
Transfemoral	111 (93.3)	527 (92.3)	0.71	1.16 (0.53 to 2.53)
Transaxillary	3 (2.5)	19 (3.3)	0.65	0.75 (0.22 to 2.58)
Valve type				
CoreValve	104 (87)	478 (84)	0.31	1.35 (0.75 to 2.42)
Edwards	15 (13)	93 (16)	0.33	0.75 (0.42 to 1.35)
Procedural duration (min)	92.9±49.6	84.7±46.3	0.08	—
Fluoroscopy time (min)	15.5±7.1	14.9±6.8	0.39	—
Contrast amount (ml)	174.7±70.4	168.4±68.6	0.44	—
Post-procedural mean transvalvular PG (mm Hg)	3.6±5.2	5.9±6.2	<0.0001	—
Post-procedural AR	119 (100)	380 (66.5)	<0.0001	—
None	0	191 (33.5)	—	—
Grade I	0	380 (66.5)	—	—
Grade II	103 (86.6)	0	—	—
Grade III	14 (11.8)	0	—	—
Grade IV	2 (1.7)	0	—	—

Values are n (%) or mean±SD.
AR, aortic regurgitation; PG, pressure gradient; TAVI, transcatheter aortic valve implantation.

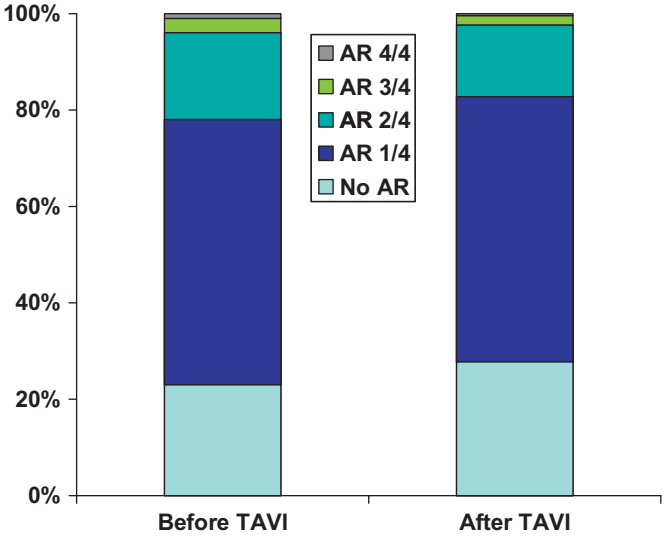

Figure 1 Assessment of AR in the study population. Evaluation of AR in four grades, before (left) and at the end of the TAVI procedure (right). AR, aortic regurgitation; TAVI, transcatheter aortic valve implantation.

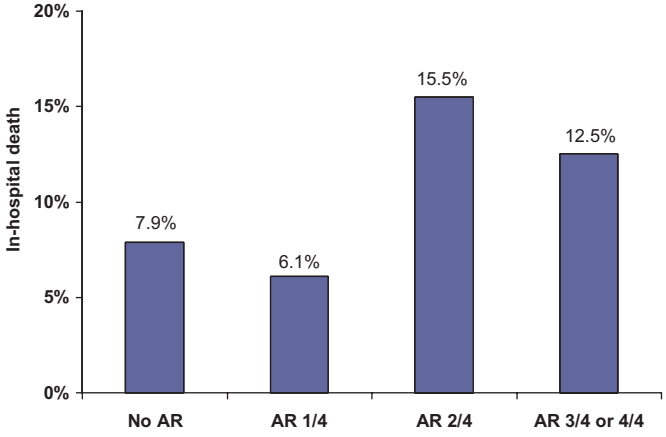

Figure 2 In-hospital mortality and post-procedural AR. In-hospital mortality rates stratified according to the degree of post-procedural AR. AR, aortic regurgitation, p for trend=0.005.

7.1%) and post-procedural delirium (18% vs 7.4%) were also significantly higher in the group with significant AR, while rates of myocardial infarction, stroke, advanced atrioventricular block, major vascular events and renal failure requiring dialysis were similar.

Owing to the obvious differences in baseline characteristics between patients with and without significant AR, we performed a multivariable logistic regression analysis to determine the factors independently associated with in-hospital death. After adjustment for various confounders, the presence of post-procedural AR≥2/4 remained a strong independent predictor of in-hospital death (adjusted OR=2.43, 95% CI=1.22 to 4.85). Other factors independently associated with in-hospital death are presented in table 5.

For patients who survived the in-hospital period and for whom a complete 30-day follow-up status has been obtained (n=464), the NYHA functional class was not significantly different between patients with and without significant AR, but there was a strong trend towards a worse functional class in patients with significant AR (40.6% vs 50% with NYHA I and 23.4% vs 14.4% with NYHA III for patients with and without significant AR, p=0.17 and p=0.007, respectively).

Factors associated with significant post-procedural AR

Determinants of occurrence of post-procedural AR≥2/4 are shown in table 6. Using multivariate analysis, factors independently associated with significant AR were AVA (adjusted OR=0.10), annulus measurement by TOE (adjusted OR=1.94), male gender (adjusted OR=1.80), cardiogenic shock (adjusted OR=1.94) and renal failure (adjusted OR=0.53). There was a trend towards a higher odds of significant AR with bicuspid aortic valves and after the CoreValve prosthesis, though this did not reach statistical significance.

Institutional volume and post-procedural AR

We performed a subgroup analysis examining the incidence of significant post-procedural AR according to the volume of the participating centres. Centres that recruited >100 TAVI patients in the study time period were considered high-volume centres (n=2; 279 patients), those with 30–100 patients were deemed intermediate-volume centres (n=7; 254 patients), and those with <30 patients were considered low-volume centres (n=12; 164 patients). The incidence of significant AR was highest in patients treated at intermediate-volume centres (23.3%) compared with high-volume (14.6%) and low-volume centres (12.3%, p for trend=0.004) (figure 3). In-hospital mortality was not significantly different at centres with different institutional volume (8.2%, 7.5% and 9.1% for high, intermediate and low-volume centres, respectively, p=0.83).

DISCUSSION

Since the first description by Cribier *et al* in 2002,[14] over 20 000 TAVI procedures have been performed globally,[17] and initial results for procedural success, improvement in quality of life and short- and medium-term outcomes have been promising,[2 3 18]

Table 4 In-hospital outcome

	Overall (n=690)	AR≥2/4 (n=119)	AR<2/4 (n=571)	p Value	OR (95% CI)
Death	56 (8.1)	18 (15.1)	38 (6.7)	0.002	2.50 (1.37 to 4.55)
Myocardial infarction	2 (0.3)	0	2 (0.4)	0.52	–
Cerebrovascular stroke	18 (2.7)	3 (2.6)	15 (2.7)	0.95	0.96 (0.27 to 3.37)
Major vascular complication	27 (4.1)	3 (2.6)	24 (4.3)	0.39	0.59 (0.18 to 2.01)
New 2nd or 3rd degree AV block	156 (23)	28 (24)	128 (23)	0.89	1.03 (0.65 to 1.65)
Low cardiac output	46 (7)	22 (20)	24 (4.4)	<0.0001	5.35 (2.87 to 9.94)
Respiratory failure	58 (8.7)	19 (16.5)	39 (7.1)	0.001	2.61 (1.45 to 4.71)
Delirium	62 (9.3)	21 (18)	41 (7.4)	<0.001	2.81 (1.59 to 4.97)
ARF requiring dialysis	27 (4)	5 (4.2)	22 (3.9)	0.63	1.42 (0.34 to 5.96)

Values are n (%).
AR, aortic regurgitation; ARF, acute renal failure; AV, atrioventricular.

Table 5 Determinants of in-hospital mortality in multivariate analysis (c=0.78)

Determinants	OR (95% CI)	p Value
Cardiogenic shock	2.65 (1.34 to 5.23)	0.005
Post-procedural AR≥2/4	2.43 (1.22 to 4.85)	0.01
Operative TAVI	3.79 (1.34 to 10.70)	0.01
LVEF≤30%	2.47 (1.07 to 5.69)	0.03
Peripheral arterial disease	2.09 (1.05 to 4.19)	0.03

AR, aortic regurgitation; LVEF, left ventricular ejection fraction; TAVI, transcatheter aortic valve implantation; operative TAVI, transapical and transaortic access.

with impressive benefits compared with conservative medical treatment in the only available randomised controlled trial.[19] Presently, most experience has been achieved with the Edwards Sapien and the Medtronic CoreValve systems. However, although both these valves have been shown to have similar haemodynamics compared with conventionally implanted surgical bioprostheses, this is commonly at the expense of an increased incidence of paravalvular AR,[20] which occurs in any form in up to 65–90% of patients,[3 4 21] and is at least moderate in 7–20%.[2–4 7] So far, aortic regurgitation after TAVI has been usually considered an acceptable and probably transient trade-off, though the effect of post-procedural AR on outcome was generally unknown. Our results, which arise from one of the largest reported series of TAVI procedures, strongly suggest a worse short-term outcome, with increased in-hospital mortality, in patients developing at least moderate post-procedural AR following TAVI.

The problem of AR after TAVI

Paravalvular AR after surgical aortic valve replacement is not uncommon, but moderate or severe forms are rare. During SAVR, the aortic valve is inspected, the diseased native tissue and calcific regions of the annulus can be excised and surgeons can finally make the annulus conform to the appropriate sewing ring with their stitches.[22] Obviously, the interventional approach for valve implantation is different, and the rates of paravalvualr AR following TAVI are therefore naturally higher. In our series, at least moderate AR occurred in 17.2% of patients, which is in line with previous studies.[2–4 7] With percutaneous valvular therapies, the aortic valve is initially compressed against the aortic annulus, followed by positioning and expansion of the collapsible stent-mounted prosthesis. This process probably results in a non-uniform compression of the native aortic valve against the aortic wall, with ridges of calcium hindering adequate stent expansion and resulting in paravalvular AR.[23] The variable aortic valve anatomy and calcification in different patients has been suggested to account for the unpredictability of the localisation and degree of regurgitation.[21] This may explain why unusual valve morphologies and smaller valve orifices are strongly associated with significant AR in our

Table 6 Multivariate predictors of the occurrence of at least moderate post-procedural AR (c=0.74)

	OR (95% CI)	p Value
Aortic valve area (per cm^2)	0.10 (0.02 to 0.41)	0.001
Cardiogenic shock	1.94 (1.18 to 3.21)	0.009
Annulus estimation by TOE	1.94 (1.14 to 3.29)	0.01
Renal failure	0.53 (0.33 to 0.85)	0.01
Male gender	1.80 (1.07 to 3.06)	0.02
Bicuspid aortic valve	2.95 (0.73 to 11.89)	0.12
Corevalve prosthesis	1.58 (0.73 to 3.40)	0.25

AR, aortic regurgitation; TOE, transoesophageal echocardiography.

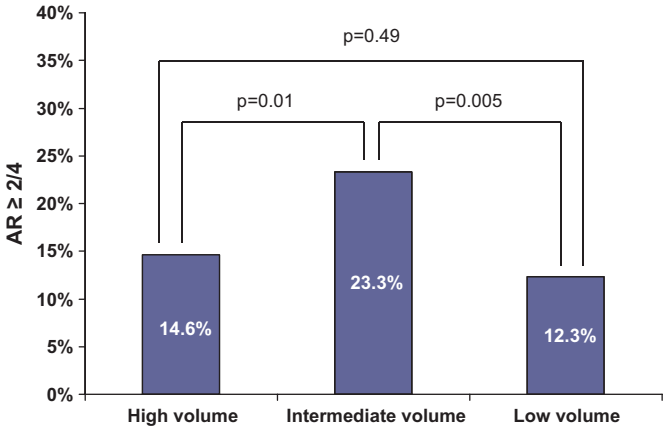

Figure 3 Institutional volume and post-procedural AR, Post-procedural AR rates stratified according to the institutional volume of the participating centres (see text for definitions). AR, aortic regurgitation.

analysis. In a recent pathological study in patients with calcific AS, valvular ossifications were more commonly seen in men,[24] and this might explain why male gender further predicts the occurrence of post-procedural AR.

Another problem with the interventional approach is that of valve sizing. With surgical valve replacement, the annulus can be measured intraoperatively with sizers, and surgeons can choose from multiple sizes of valves. With the interventional approach, only indirect annulus sizing with echocardiography (transthoracic or transoesophageal), multislice CT or invasive angiography is possible, and the interventionalist has currently a limited number of TAVI sizes to choose from (two for each of the available valve types). The problem with indirect annular sizing using imaging is that the aortic annulus varies from patient to patient. In addition, the annulus is rather oval and not round,[25] and therefore sizing with two-dimensional imaging such as echocardiography can 'cut' the oval plane at many angles, each producing a different answer for the annular diameter.[22] A number of comparative studies have shown that annulus measurements performed by echocardiography probably underestimate annulus size as compared with multislice CT,[26 27] which may lead to the implantation of undersized valves. This might explain the strong association between annulus estimation by TOE and post-procedural AR in this analysis, especially the finding that the mean annular diameter was 1.4 mm smaller in the TOE-measured group than in the CT-measured group, but this remains speculative. Nevertheless, lack of congruence between prosthesis and annulus size has been previously described with SAVR[28] and has recently been linked to the occurrence of significant paravalvular AR after TAVI.[29]

An interesting observation is the low frequency of significant AR in centres with a low institutional volume, particularly in comparison with intermediate-volume centres. The adoption of TAVI in interventional practice has been accompanied by an unprecedented, firmly supervised, proctoring programme, which optimises technical success rates in the initial implantation phase. As centres and operators become independent, technical problems probably increase until a certain level of experience in patient selection and in the procedure itself has been achieved.

Outcome of AR after TAVI

Historically, the presence of paravalvular AR after SAVR was judged by cardiac surgeons to be a complication of surgery.[30]

More than mild paraprosthetic regurgitation following SAVR might cause haemodynamic deterioration, promote haemolysis, trigger endocarditis, and therefore might often require re-intervention.[6] Following TAVI, moderate degrees of AR are usually considered benign, but this lacks solid scientific evidence, and seems to be in contradiction with the surgical experience. We therefore evaluated patients with moderate post-procedural AR (14.9%) together with the minority with more severe forms (2.3%), as opposed to patients with mild or no AR. And indeed, these patients had higher in-hospital mortality. Importantly, and particularly in this group of patients, moderate AR may lead to the development of heart failure, as these patients often have non-compliant ventricles. In an experimental model, Azadani *et al* found that, owing to paravalvular leaks, TAVI imposes a significantly higher workload on the left ventricle than an equivalently sized surgically implanted bioprosthesis.[31] This may be more problematic in patients with reduced LV systolic function at baseline, where the additional workload of even moderate forms of AR cannot be tolerated by a failing non-compliant ventricle. Both factors were independently associated with in-hospital mortality in our series, and patients with an LVEF≤30% who developed significant post-procedural AR had more than a fivefold increase in in-hospital mortality in our series (OR=5.18, 95% CI 2.05 to 13.10). Therefore, it is not surprising that low cardiac output syndromes (usually signifying advanced heart failure), respiratory failure and delirium were more common in patients with significant AR; all are probably secondary to a worse haemodynamic state in this group of patients. Nevertheless, longer-term follow-up is required to determine these outcome parameters and to further analyse the clinical impact of this complication.

On the other hand, we must emphasise here that the precise characterisation of the magnitude of AR remains challenging, especially with eccentric jets such as those developing after TAVI. Owing to the three-dimensional nature of the aortic regurgitant jet, a qualitative assessment in two dimensions (with angiography and even with echocardiography) can be difficult. Eccentric jets like those we see after TAVI may become entrained along the LV wall, which tends to alter their appearance and hence the perception of AR severity and might lead to underestimation of the degree of AR, particularly with echocardiography.[32] In addition, operator bias in judging the degree of AR after TAVI is not uncommon, and operators may tend to underestimate the degree of post-procedural jets. Therefore, it remains possible that some of our patients classified as having moderate AR had actually more severe forms, which may—in part—explain the higher mortality seen in this group of patients.

Impact of type of prosthesis

In addition to the inherent limitations of the interventional approach for valve therapy that lead to the higher incidence of AR, specific device-related factors may also have an impact. Though not statistically significant, the Medtronic CoreValve bioprosthesis (compared with the Edwards Sapien valve) was associated with higher odds for significant AR in the multivariate analysis in our study (OR=1.58, 95% CI 0.73 to 3.40, p=0.25). Sherif *et al* have recently described a predictive model for the occurrence of significant AR after implantation of the CoreValve prosthesis, where the occurrence of AR was strongly related to the angle between ascending aorta and left ventricular outflow tract and to the final depth of the prosthesis.[33] Proper device positioning is an important factor related to the occurrence of AR in both available devices, and deep implantation would result in severe AR, since the covered skirt would be situated below the native annulus, allowing blood to regurgitate through the holes of the uncovered portion of the stent frame. Nevertheless, the Medtronic CoreValve prosthesis is a long device (53 mm for the 26 mm inflow device and 55 mm for the 29 mm inflow device) and allows for a wide range of implant depths. Moreover, the haemodynamic performance of the prosthesis within the aortic annulus may depend on a number of factors including the ascending aorta and the left ventricular outflow tract, which may affect the ability of the nitinol stent to provide adequate radial force. Whether these differences represent a real benefit for one device over the other is still not known and will only be answered through randomised controlled studies. Importantly, the next generation transcatheter aortic valve prostheses should match standard criteria for accepted quality, including a low incidence and degree of AR.

Study limitations

The study has all the shortcomings of a registry, yet its value lies in the large number of patients recruited, and in the fact that despite broad effectiveness in real-world use, safety must be considered with TAVI. We cannot ultimately explain the cause of the association between significant post-procedural AR and mortality, as the registry was not designed to classify adverse events according to their underlying cause. Moreover, the degree of post-procedural AR and all adverse events were not centrally adjudicated, which may have contributed to the differences based on differences in self-reports, and the angiographic technique for AR assessment was not standardised (eg, rate and amount of contrast material). Correcting manoeuvres after prosthesis implantation such as post-dilatation, snare adjustment or valve-in-valve have not been recorded. Until now, no formal audit of the participating hospitals has been performed. Long-term follow-up would have added to the robustness of the outcome data.

CONCLUSION

Significant AR after TAVI is common and is associated with increased in-hospital mortality. Long-term follow-up is critical to further define the impact of AR on clinical outcome. Until these data become available, every effort should be made to prevent and treat this complication.

Competing interests None.

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APPENDIX 1

List of participating centers (in order of numbers of included patients)

Klinikum Siegburg: U Gerckens, Universität Leipzig Herzzentrum: G Schuler, Herzzentrum Ludwigshafen: R Zahn, Universitätsklinikum Essen: H Eggebrecht, Cardio Vasculäres Centrum (CVC) Frankfurt Sankt Katharinen: H Sievert, Krankenhaus der barmherzigen Brüder Trier: KE Hauptmann, Asklepios Klinik St Georg Hamburg: KH Kuck, Klinikum Links der Weser Bremen, R Hambrecht, Segeberger Kliniken GmbH: G Richardt, Universitätsklinikum Bonn, Med Klinik und Poliklinik II: G Nickenig, Elisabeth - Krankenhaus Essen: CH Naber, Klinikum Schwabing, München: S Sack, Universitätsklinikum Jena: HR Figulla, Augustinum Klinik München: M Block, Städt Klinikum München Klinik Bogenhausen: E Hoffmann, Robert-Bosch-Krankenhaus, Stuttgart: U Sechtem, HELIOS Klinikum Wuppertal: H Gülker, Universitäts Klinikum Regensburg: G Riegger, Krankenhaus München—Neuperlach: H Mudra, Herzzentrum Bad Krozingen: FJ Neumann, Universitätsklinikum Freiburg: C Bode, Klinikum Coburg: J Brachmann.

Heart

Aortic regurgitation after transcatheter aortic valve implantation: incidence and early outcome. Results from the German transcatheter aortic valve interventions registry

Mohamed Abdel-Wahab, Ralf Zahn, Martin Horack, Ulrich Gerckens, Gerhard Schuler, Horst Sievert, Holger Eggebrecht, Jochen Senges, Gert Richardt and for the German transcatheter aortic valve interventions registry investigators

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