

CLINICAL RESEARCH

Determinants of Significant Paravalvular Regurgitation After Transcatheter Aortic Valve Implantation

Impact of Device and Annulus Discongruence

Delphine Détaint, MD, Laurent Lepage, MD, Dominique Himbert, MD, Eric Brochet, MD, David Messika-Zeitoun, MD, Bernard Iung, MD, Alec Vahanian, MD

Paris, France

Objectives The aim of this study was to assess prosthesis/annulus discongruence and its impact on the occurrence of significant aortic regurgitation (AR) immediately after transcatheter aortic valve implantation (TAVI).

Background Paravalvular AR might occur after TAVI, but its determinants remain unclear.

Methods Comprehensive echocardiographic examinations were performed in 74 patients who underwent TAVI with a balloon expandable device. Congruence between annulus and device was appraised with the cover index: $100 \times (\text{prosthesis diameter} - \text{transesophageal echocardiography annulus diameter}) / \text{prosthesis diameter}$.

Results At baseline aortic valve area was $0.67 \pm 0.2 \text{ cm}^2$, and mean gradient was $50 \pm 15 \text{ mm Hg}$. The TAVI used transfemoral approach in 46 patients (62%) and transapical access in 28 (38%). Prosthesis size was 23 mm in 24 patients (34%) and 26 mm in 50 patients (66%). After TAVI, paravalvular AR was absent in 5 patients (7%), graded 1/4 in 53 (72%), 2/4 in 12 (16%), and 3/4 in 4 (5%). Occurrence of AR $\geq 2/4$ was related to greater patient height, larger annulus, and smaller cover index (all $p < 0.002$) but not to ejection fraction, severity of stenosis, or prosthesis size. AR $\geq 2/4$ was never observed in patients with aortic annulus $< 22 \text{ mm}$ or with a cover index $> 8\%$. Significant improvements were observed from the first 20 cases (AR $\geq 2/4$, 40%) to the last 54 (AR $\geq 2/4$, 15%) ($p = 0.02$). In multivariate analysis, independent predictors of AR $\geq 2/4$ were low cover index (odds ratio: 1.22; per confidence interval: 1.03 to 1.51 per 1% decrease, $p = 0.02$) and first versus last procedures (odds ratio: 2.24; 95% confidence interval: 1.07 to 5.22, $p = 0.03$).

Conclusions Our study shows that the occurrence of AR $\geq 2/4$ is related to prosthesis/annulus discongruence even after adjustment for experience. Hence, to minimize paravalvular AR, appropriate annular measurements and prosthesis sizing are critical. (J Am Coll Cardiol Intv 2009;2:821-7)

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Over the last few years the transcatheter aortic valve implantation (TAVI) technique has been developed (1–4) as an alternative to surgical aortic valve replacement for severe aortic stenosis in patients with high surgical risk or contraindications to surgery (5–9). The evidence that is currently available suggests that this technique is feasible and provides hemodynamic and clinical improvement up to 2 years, but questions remain concerning safety and long-term durability (10). Regarding safety, the occurrence of significant aortic regurgitation (AR) after TAVI was initially described as a limitation of this technique (2,3). Despite improvements, significant AR can still occur, and its determinants have not been specifically studied so far. Thus, we examined in this study the determinants of significant AR occurring immediately after TAVI.

Methods

Patient characteristics. Between October 2006 and December 2008, 74 consecutive patients underwent a TAVI procedure with successful prosthesis implantation.

Abbreviations and Acronyms

AR = aortic regurgitation

AVA = aortic valve area

TAVI = transcatheter aortic valve implantation

TEE = transesophageal echocardiography

TTE = transthoracic echocardiography

TAVI. Procedures were performed by the transfemoral approach (4,5,8) or by the transapical approach when femoroiliac axes were not suitable, as previously described (11–14).

In brief, after crossing of the aortic valve and balloon valvuloplasty, a balloon expandable valve (Edwards-Sapien, Edwards Lifesciences, Inc., Irvine, California) was pushed by a flex-

ible catheter and positioned within the native aortic annulus. The delivery balloon was inflated, and the valved stent was implanted. The device is available in 2 sizes: 23 and 26 mm. A 23-mm device was implanted when the diameter of the aortic annulus was >18 and ≤ 21 mm, and a 26-mm device was implanted when the diameter of the aortic annulus was >21 and ≤ 25 mm.

To account for the potential learning curve, we defined 2 time periods—from October 9, 2006, to January 9, 2008, for the 20 first procedures (early period) and from January 16, 2008, to December 23, 2008, for the last 54 procedures (late period).

Echocardiography. **ECHOCARDIOGRAPHIC EXAMINATIONS BEFORE TAVI.** All the patients underwent a comprehensive transthoracic echocardiography (TTE) at baseline. The severity of aortic stenosis was assessed by the aortic mean gradient and aortic valve area (AVA), which was calculated with the continuity equation (15). Measurements of the aortic annulus were performed in systole in a parasternal long-axis view, zoomed on the left ventricular outflow tract, at the point of insertion of the aortic cusps. Ejection fraction

was calculated with left ventricular volumes, obtained by the 2-dimensional echocardiographic biplane Simpson's rule (16). Aortic regurgitation was evaluated according to published guidelines (17–19).

All the patients underwent a transesophageal echocardiography (TEE) immediately before valve implantation, under general anesthesia, to check aortic annulus diameters obtained by TTE, to qualify the opening of aortic valve (central or eccentric) and to determine aortic valve anatomy: distribution and localization of calcifications (symmetric or asymmetric) and number of cusps (tricuspid or bicuspid).

During the procedure, TEE was used to verify the correct positioning of the catheter, guidewire, and device.

END POINT: EARLY PARAVALVULAR AR AFTER TAVI. The occurrence of paravalvular AR was evaluated immediately after the device deployment and after removal of the catheter and guidewire. Short- and long-axis TEE views were used to assess AR localization and grade. The AR grading was based on color Doppler imaging with the height and the width of the regurgitant jet. When several AR jets were present, AR was expressed as an overall grade. Hence, with color jet extension, AR was classified into 4 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 $AR \geq 2/4$.

This evaluation of AR was performed by an echocardiographer who did not attend to the TAVI procedure and who was blinded to the initial conclusions and to the angiographic evaluation of AR.

To appraise the congruence between the aortic annulus and the device, we defined a “cover index” expressed as a ratio of: $100 \times ([\text{prosthesis diameter} - \text{TEE annulus diameter}] / \text{prosthesis diameter})$.

ECHOCARDIOGRAPHIC EVALUATION BEFORE DISCHARGE. In addition, a complete TTE was performed at discharge or 7 days after device implantation. Aortic valve hemodynamic status (AVA, mean gradient, permeability index) and AR grading were recorded.

Evaluation of the device positioning. To evaluate whether the malpositioning of the prosthesis might be a cause of significant paravalvular AR or not, we have reviewed the positioning of the device by echocardiography and fluoroscopy in the patients with $AR \geq 2$. The re-reading was performed retrospectively by 2 echocardiographers experienced in monitoring the procedure and interventional cardiologists who were blind to each other.

Statistical analysis. Data were expressed as mean \pm SD or percent. Comparisons of clinical, echocardiographic, or procedure-related characteristics of patients according to $AR < 2$ or ≥ 2 used *t* test or chi-square as appropriate. Four significant variables in univariate analysis (age, sex, cover index, early vs. late period) were included in a multivariate logistic regression with a backward selection of independent

Table 1. Clinical, Echocardiographic, and Procedure Characteristics of Patients Undergoing TAVI, According to Occurrence of at Least Moderate AR, Immediately After TAVI

Variables	Overall (n = 74)	Paravalvular AR <2/4 (n = 58)	Paravalvular AR ≥2/4 (n = 16)	p Value
Clinical characteristics				
Age, yrs	82 ± 8	81 ± 8	86 ± 5	0.03
Sex (men)	38 (51%)	25 (43%)	13 (81%)	0.005
Weight, kg	69 ± 5	68 ± 14	74 ± 18	0.20
Height, cm	163 ± 8	161 ± 9	170 ± 6	0.007
BSA, m ²	1.7 ± 0.2	1.7 ± 0.2	1.8 ± 0.2	0.19
Echocardiographic characteristics				
TTE systolic aortic annulus, mm	22.9 ± 1.6	22.5 ± 1.7	24 ± 1	0.001
TEE systolic aortic annulus, mm	23.3 ± 1.7	23 ± 1.9	24.7 ± 1.2	0.002
Ejection fraction, %	51 ± 17	49 ± 17	56 ± 18	0.13
Aortic valve area, cm ²	0.67 ± 0.2	0.65 ± 0.2	0.71 ± 0.2	0.25
Aortic valve mean gradient, mm Hg	50 ± 15	51 ± 15	47 ± 13	0.18
Asymmetric AV calcifications	16 (35%)	14 (38%)	2 (22%)	0.36
Eccentric AV opening	10 (16%)	8 (17%)	2 (14%)	0.36
Procedure				
Implantation access (femoral)	46 (62%)	34 (59%)	12 (75%)	0.23
Prosthesis size (26 mm)	50 (66%)	37 (64%)	13 (81%)	0.19
Cover index*, %	6.7 ± 4	7.6 ± 5	3.2 ± 3	0.002
Values are mean ± SD or n (%). *Cover index defined as 100 × ((prosthesis diameter – TEE annulus diameter)/prosthesis diameter). AR = aortic regurgitation; AV = aortic valve; BSA = body surface area; TAVI = transcatheter aortic valve implantation; TEE = transesophageal echocardiography; TTE = transthoracic echocardiography.				

variables, with a significant level of $p = 0.05$. Adjusted odds ratio is presented with 95% confidence interval.

Comparisons of patients' characteristics between the 2 time-frame periods of the study used t test or chi-square as appropriate.

A p value <0.05 was considered statistically significant.

Results

Baseline characteristics. All 74 patients (median age: 82 ± 8 years, men: 38 [51%]) had severe aortic stenosis: median value for AVA was 0.67 ± 0.2 cm² and for mean gradient was 50 ± 15 mm Hg (Table 1). Large range of ejection fraction was observed from 14% to 81% (mean ejection fraction $51 \pm 17\%$). The TAVI used transfemoral access in 46 patients and transapical access in 28 patients. Overall, 50 patients (66%) received a 26-mm prosthesis, and 24 patients (34%) received a 23-mm prosthesis.

Early AR after TAVI: frequency. Assessment of paravalvular AR showed the absence of AR in 5 patients (7%), trivial or mild AR (1/4) in 53 patients (72%), mild-to-moderate (2/4) in 12 patients (16%), and moderate-to-severe (3/4) in 4 patients (5%). No severe AR (4/4) was observed. Thus significant AR ($\geq 2/4$) occurred in 16 patients (22%) immediately after TAVI. The outcome of these 16 patients is detailed in Figure 1. At the end of the procedure, balloon re-dilation was performed in the 4 patients with AR 3/4 and in 1 patient with AR 2/4 (Fig. 1). After re-dilation AR decreased in 1 patient, remained unchanged in 3 patients,

and increased in 1 patient. For the latter, the balloon inflation caused severe transvalvular AR, which required emergent implantation of a second prosthesis. A second prosthesis was also implanted in a patient with initial AR 3/4 but did not result in a decrease in the degree of AR (Fig. 1). Of note, in patients with AR 3/4, there was no particular undersizing of the prosthesis.

Two patients died during the first week. The causes of death were pulmonary infection in 1 case (immediate AR: 1/4) and heart failure in the second case (immediate AR: 2/4). Evaluation of AR after 7 days was available for all 72 surviving patients and showed a slight decrease in AR grading from 2/4 to 1/4 in 3 patients and from 1/4 to 0/4 in 9 patients (Fig. 2). At day 7, significant paravalvular AR was present in 10 patients (14%). In 1 patient, significant paravalvular AR caused refractory heart failure, and because this patient was considered inoperable after multidisciplinary evaluation, re-direction toward surgery was not made.

Clinical and echocardiographic determinants of paravalvular AR. The occurrence of paravalvular AR $\geq 2/4$ immediately after valve implantation was related to older age, male sex, and greater height but not to larger body surface area or weight (Table 1).

The AR $\geq 2/4$ was—with regard to echocardiographic characteristics—significantly associated with larger aortic annulus dimensions, as measured by TTE or TEE ($p < 0.002$) (Table 1, Figs. 3 and 4). No relation to ejection

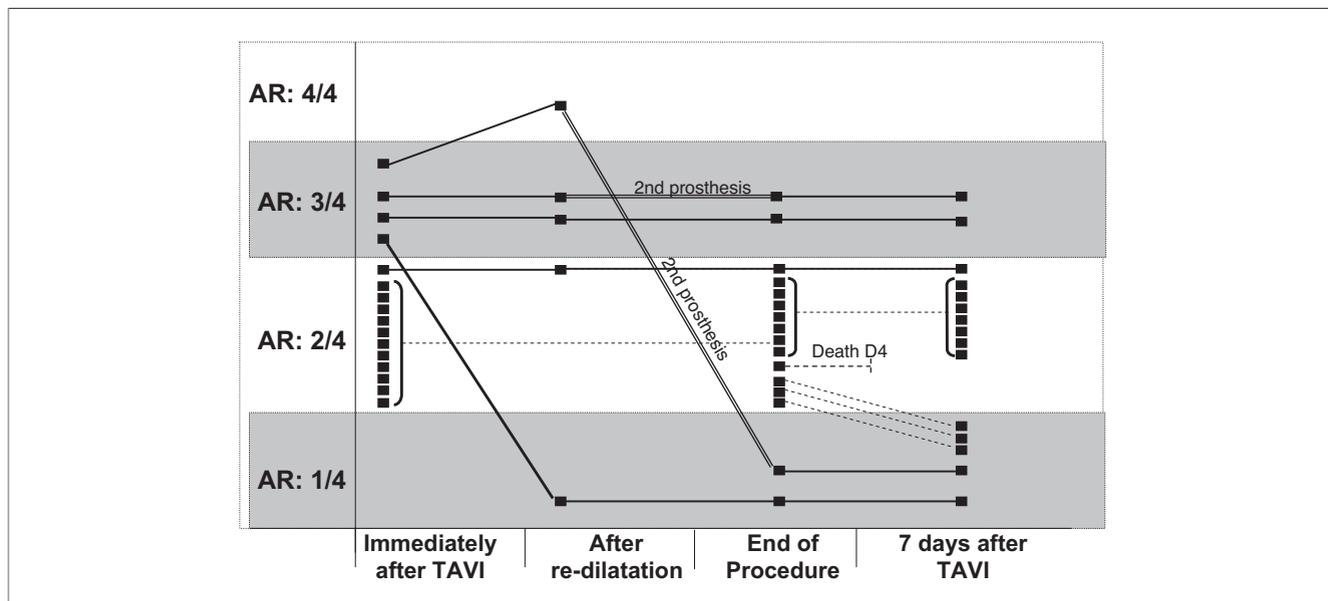


Figure 1. AR Evaluation in the 16 Patients With AR $\geq 2/4$

Assessment of aortic regurgitation (AR) grade in the 16 patients with paravalvular AR $\geq 2/4$, immediately after valve implantation (**on the left**), after balloon re-dilatation (if performed), at the end of the procedure after potential second prosthesis implantation and at 7 days (**on the right**). Grade of AR are indicated on the **left**. **Solid lines** indicate evolution of AR in patients undergoing balloon re-dilatation. **Double solid lines** indicate evolution of AR after implantation of a second prosthesis. **Dotted lines** represent evolution of AR in patients who did not undergo balloon re-dilatation or implantation of a second prosthesis. D4 = day 4 (this patient died 4 days after TAVI); TAVI = transcatheter aortic valve implantation.

fraction, severity of baseline aortic stenosis, eccentric aortic valve opening, or asymmetry of aortic valve calcification was observed. As shown in Figures 3 and 4, AR $\geq 2/4$ was never observed in patients with TTE or TEE aortic annulus < 22 mm.

The AR $\geq 2/4$ after prosthesis implantation was significantly associated with a lower cover index ($p = 0.002$). As shown in Figure 5, AR of at least moderate degree was never observed in patients with a cover index $> 8\%$.

Role of procedure in occurrence of AR. The AR $\geq 2/4$ was not associated with the type of access, femoral or apical ($p = 0.23$), (Table 1). The AR $\geq 2/4$ occurred more frequently in the first 20 procedures than in the second time-frame period (after January 9, 2008) ($p = 0.02$), (Table 2). As shown in Table 2, this difference was not related to differences in age, sex, height, or annulus size between the 2 periods.

Determinants of paravalvular AR in multivariate analysis. In multivariate analysis, the 2 independent predictors of occurrence of AR $\geq 2/4$ were low cover index (adjusted odds ratio: 1.22; 95% confidence interval: 1.03 to 1.51 per 1% decrease, $p = 0.02$) and early versus late period of the study (adjusted odds ratio: 2.24; 95% confidence interval: 1.07 to 5.22, $p = 0.03$).

Evaluation of the device positioning. Evaluation of the device positioning showed an overall good agreement of the subjective positioning of the prosthesis between echocardiographers and interventional cardiologists. The device was in a too-low position in 2 patients who received a second prosthesis (Fig. 1). This malpositioning probably contrib-

uted to the occurrence of paravalvular AR. In the other patients, the prosthesis was found in a good position.

Discussion

This study shows that significant paravalvular AR might occur after TAVI. The results suggest that the occurrence of significant AR is related to the lack of congruence between the annulus and the device and to the experience of the operators.

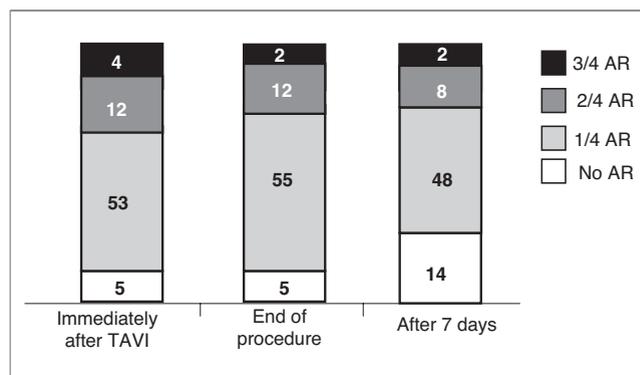


Figure 2. Assessment of AR in the Study Population

Evaluation of paravalvular AR in 4 grades, immediately after valve implantation (**left**), at the end of the procedure after potential re-dilatation or second prosthesis implantation (**middle**), and at 7 days (**right**). Number of patients in each grade is indicated on **each bar**. Abbreviations as in Figure 1.

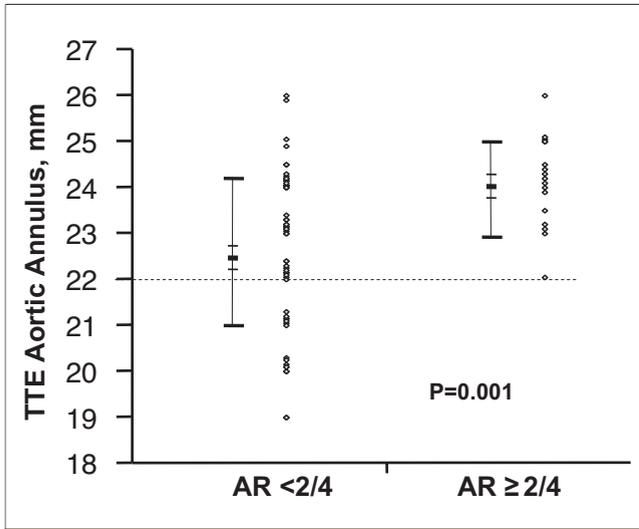


Figure 3. TTE Aortic Annulus Dimensions in Patients With AR <2/4 and ≥2/4

Scatter plots aortic annulus dimension measured with transthoracic echocardiography (TTE) stratified according to paravalvular aortic regurgitation (AR) classified as mild or less (AR <2/4) and at least of moderate degree (AR ≥2/4). The mean and SD are represented by the bars in each groups. The dotted line indicates the value of aortic annulus (22 mm) under which significant AR is never observed.

AR with TAVI. On the basis of TEE performed immediately after the device implantation, the occurrence of paravalvular AR was frequent, as previously described (2,20), and reached 93% of cases. In the majority of cases (77%), AR

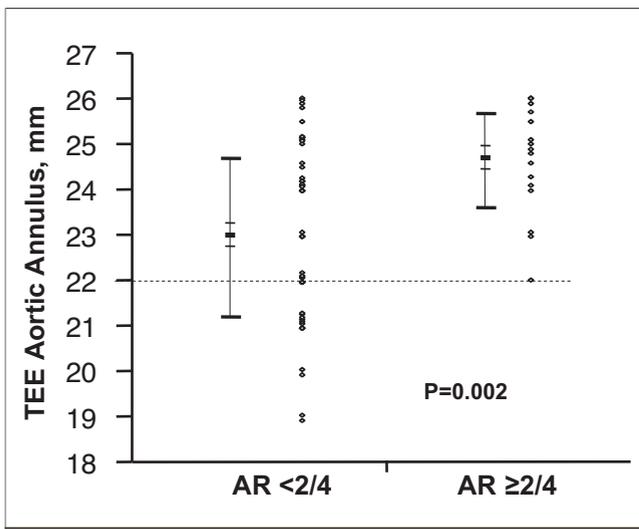


Figure 4. TEE Aortic Annulus Dimensions in Patients With AR <2/4 and ≥2/4

Scatter plots aortic annulus dimension measured with transesophageal echocardiography (TEE) stratified according to paravalvular aortic regurgitation (AR) classified as mild or less (AR <2/4) and at least of moderate degree (AR ≥2/4). The mean and SD are represented by the bars in each groups. The dotted line indicates the value of aortic annulus (22 mm) under which significant AR is never observed.

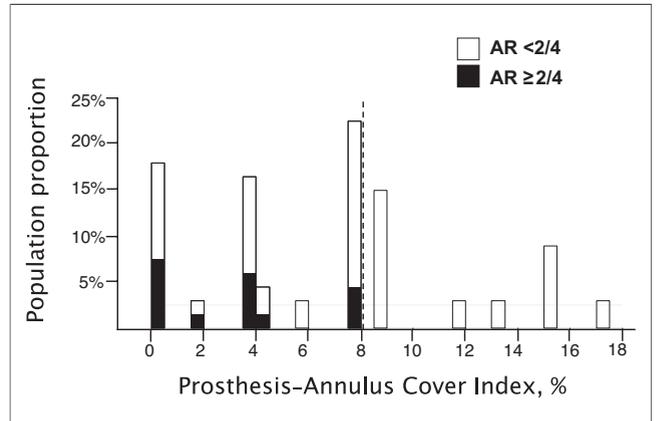


Figure 5. Distribution of Prosthesis-Annulus Cover Index

Distribution of prosthesis-annulus cover index defined as $100 \times ((\text{prosthesis diameter} - \text{TEE annulus diameter}) / \text{prosthesis diameter})$. Bar height represents the number of patients. Solid bars indicate patients with AR ≥2/4, and open bars indicate patients with AR <2/4. As shown with the dotted line, AR ≥2/4 was never observed in patients with cover index >8%. Abbreviations as in Figure 4.

was mild (<2/4), which is likely to have limited consequences, especially in the elderly population. The occurrence of minor leaks with no hemodynamic consequences has been also described after surgical implantation of mechanical and biological prostheses (21–23). Trivial paraprosthetic regurgitations are generally associated with a favorable outcome (22,23). However, more severe paraprosthetic regurgitations might cause hemodynamic deterioration, left ventricular remodeling, or hemolytic anemia or require

Table 2. Comparison of the Clinical, Echocardiographic, and Procedure Characteristics of Patients Undergoing TAVI Between the 2 Time-Frame Periods of the Study

Variables	Period 1* (n = 20)	Period 2* (n = 54)	p Value
Age, yrs	85 ± 6	82 ± 9	0.12
Sex (men)	13 (65%)	25 (46%)	0.15
Weight, kg	66 ± 16	71 ± 14	0.23
Height, cm	164 ± 11	162 ± 8	0.52
BSA, m ²	1.7 ± 0.2	1.8 ± 0.2	0.46
TTE systolic aortic annulus, mm	22.8 ± 2.1	22.9 ± 1.5	0.61
TEE systolic aortic annulus, mm	23.6 ± 2.3	23.3 ± 1.7	0.84
Ejection fraction, %	46 ± 16	53 ± 18	0.17
Aortic valve area, cm ²	0.58 ± 0.1	0.70 ± 0.2	0.003
Aortic valve mean gradient, mm Hg	44 ± 14	52 ± 14	0.03
Implantation access (femoral)	14 (70%)	32 (59%)	0.40
Prosthesis size (26 mm)	14 (70%)	36 (67%)	0.79
Cover index†, %	6.6 ± 6	6.7 ± 5	0.92
AR ≥2/4 immediately after TAVI	8 (40%)	8 (15%)	0.02

Values are mean ± SD or n (%). *Period 1: October 9, 2006 to January 9, 2008; and Period 2: January 16, 2008 to December 23, 2008. †Cover index defined as $100 \times ((\text{prosthesis diameter} - \text{TEE annulus diameter}) / \text{prosthesis diameter})$. Abbreviations as in Table 1.

reintervention (22). Similarly, after TAVI, significant paravalvular AR can occur (4,5,8,11,24,25) and might be related to undersized prosthesis, malpositioning of the device, the presence of heavily calcified aortic cusps of the native valve, or a bicuspid valve (26). In this study significant AR represented 22% of the patients, close to what has been previously published (20).

In this study, the assessment of AR was performed immediately after prosthesis implantation to avoid bias due to balloon re-dilation or implantation of a second valve prosthesis. In a previous study using the same device, less frequent AR was observed at early follow-up with TTE assessment than after immediate post-implantation with TEE evaluation (20). This raises the hypothesis that AR grading is susceptible to change with the timing, as previously shown after valve replacement (21,23). Differences in techniques (TTE and TEE) of AR evaluation might also contribute to explain the variations observed in AR grading. Slight fluctuations were similarly observed in the current study when AR grading was re-evaluated after 7 days by TTE.

Impact of annulus/prosthesis incongruence. Lack of congruence between prosthesis and annulus size has been previously described with surgical aortic valve replacement (27-29). With a valved stent, inadequate apposition of the device on the aortic annulus might result in different complications, such as severe AR or device migration (20). The present study shows a relationship between large annulus size and the occurrence of significant paravalvular AR. In patients with a large annulus, the prostheses that are currently available might be undersized, resulting in incongruence between the annulus and the device. To appraise the congruence between annulus and device we used a cover index that integrates aortic annulus diameter as well as prosthesis diameter. The significant relationship between low cover index and significant AR suggests that a certain degree of prosthesis oversizing is needed to ensure a good adequation of the prosthesis to the aortic annulus. This further stresses the importance of avoiding any undersizing of the prosthesis. Conversely, the systematic implantation of oversized prostheses might lead to aortic annulus rupture.

Other factors might be involved in the occurrence of paravalvular AR. In this study, the comparison of 2 time-periods showed that AR was larger at the beginning of the study than in the second time-frame period. Hence, the frequency of significant AR can be lessened with careful echocardiographic examination of the annulus size, which should lead to exclude patients with borderline annulus size and with improvement in TAVI technique, in particular accurate prosthesis positioning, which plays an essential role in success of TAVI (5).

Accurate annulus size evaluation is difficult, because no reference method has been described. With echocardiography, the potential oval shape of the annulus might be not

taken into account. Other techniques, including electron-beam computed tomography or 3-dimensional echocardiography, should be evaluated to provide accurate assessment of the aortic annulus, even if the quality of the reconstructions faces technical difficulties. A recent study suggests that balloon sizing with intra balloon pressures might help in annulus size evaluation (30). In our experience, regarding annulus measurement, successive steps are followed for each patient: we initially evaluate the annulus size with TTE at baseline; then we confirmed the measurements immediately before the procedure with TEE, which was our reference method. Comprehensive echocardiographic examinations by trained teams are required to accurately evaluate the annulus dimensions and to identify optimal prosthesis sizes. Thus experience in echocardiographic evaluation and technical achievement of TAVI might influence the occurrence of significant AR. The fact that the cover index remains an independent determinant of AR even after adjustment for experience suggests that it is a valuable tool to appraise annulus and prosthesis incongruence. Its calculation in clinical practice associated with the availability of larger prosthesis sizes in the future might contribute to improve the outcome of patients undergoing TAVI.

Study limitations. Conclusions of the present study were obtained with a balloon expandable prosthesis and might not be valid with other devices.

Accurate assessment of paravalvular AR is difficult in the absence of standardized methods and only relies on color flow imaging with direct measures of the number of jets and jet size (31).

Accurate annulus size evaluation is difficult and might require different techniques. However, this study was not performed to examine the best tools for aortic annulus evaluation but to demonstrate the link between annulus size measured by methods currently available and paravalvular AR.

Outcomes of grade I paravalvular AR after TAVI are still unknown. However, in this study we choose to focus on AR $\geq 2/4$, which are more prone than AR < 2 to have significant clinical consequences.

We focused on a limited number of potential predictive factors, given the relatively few cases of significant AR. Nevertheless, given the limited experience in this topic, the identification of the cover index and learning curve as predictors of AR is a relevant contribution to the evaluation of the results of TAVI.

Conclusions

This study points out that the lack of congruence between prosthesis and annulus size, as assessed by the cover index, is a strong determinant of paravalvular AR. Thus, to minimize significant paravalvular AR, correct prosthesis sizing is critical. This requires an accurate evaluation of aortic annulus dimension. The identification of a rela-

tionship between the device-annulus discongruence and occurrence of significant AR can lead to significant improvements. In the future, the consequences of AR occurring after TAVI should be carefully evaluated, and prosthesis design should be further improved to limit this complication.

Reprint requests and correspondence: Dr. Delphine Détaint, Cardiology Department, Bichat Hospital, 46 rue Henri Huchard, 75018 Paris, France. E-mail: delphine.detaint@bch.aphp.fr.

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