Outcomes of Patients With Asymptomatic Aortic Stenosis Followed Up in Heart Valve Clinics

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#### **IMPORTANCE** The natural history and the management of patients with asymptomatic aortic stenosis (AS) have not been fully examined in the current era.

**OBJECTIVE** To determine the clinical outcomes of patients with asymptomatic AS using data from the Heart Valve Clinic International Database.

**DESIGN, SETTING, AND PARTICIPANTS** This registry was assembled by merging data from prospectively gathered institutional databases from 10 heart valve clinics in Europe, Canada, and the United States. Asymptomatic patients with an aortic valve area of 1.5 cm2 or less and preserved left ventricular ejection fraction (LVEF) greater than 50% at entry were considered for the present analysis. Data were collected from January 2001 to December 2014, and data were analyzed from January 2017 to July 2018.

#### **MAIN OUTCOMES AND MEASURES** Natural history, need for aortic valve replacement (AVR), and survival of asymptomatic patients with moderate or severe AS at entry followed up in a heart valve clinic. Indications for AVR were based on current guideline recommendations.

**RESULTS** Of the 1375 patients included in this analysis, 834 (60.7%) were male, and the mean (SD) age was 71 (13) years. A total of 861 patients (62.6%) had severe AS (aortic valve area less than 1.0 cm2). The mean (SD) overall survival during medical management (mean [SD] follow up, 27 [24] months) was 93% (1%), 86% (2%), and 75% (4%) at 2, 4, and 8 years, respectively. A total of 104 patients (7.6%) died under observation, including 57 patients (54.8%) from cardiovascular causes. The crude rate of sudden death was 0.65% over the duration of the study. A total of 542 patients (39.4%) underwent AVR, including 388 patients (71.6%) with severe AS at study entry and 154 (28.4%) with moderate AS at entry who progressed to severe AS. Those with severe AS at entry who underwent AVR did so at a mean (SD) of 14.4 (16.6) months and a median of 8.7 months. The mean (SD) 2-year and 4-year AVR-free survival rates for asymptomatic patients with severe AS at baseline were 54% (2%) and 32% (3%), respectively. In those undergoing AVR, the 30-day postprocedural mortality was 0.9%. In patients with severe AS at entry, peak aortic jet velocity (greater than 5 m/s) and LVEF (less than 60%) were associated with all-cause and cardiovascular mortality without AVR; these factors were also associated with postprocedural mortality in those patients with severe AS at baseline who underwent AVR (surgical AVR in 310 patients; transcatheter AVR in 78 patients).

**CONCLUSIONS AND RELEVANCE** In patients with asymptomatic AS followed up in heart valve centers, the risk of sudden death is low, and rates of overall survival are similar to those reported from previous series. Patients with severe AS at baseline and peak aortic jet velocity of 5.0 m/s or greater or LVEF less than 60% have increased risks of all-cause and cardiovascular mortality even after AVR. The potential benefit of early intervention should be considered in these high-risk patients.

In the western world, calcific aortic stenosis (AS), the most common valvular heart disease, represents a major public health burden.1 Currently, there is no pharmacological treat- ment that prevents or slows the progression of AS.2 Surgical aortic valve replacement (SAVR) and transcatheter aortic valve replacement (TAVR) are the only therapies to significantly improve both survival and symptoms3,4 and are recommended in symptomatic patients with severe AS.5,6 The management of patients with asymptomatic severe AS, particularly the choice between early intervention vs watchful waiting, con- tinues to be a matter of debate.7,8 Current guidelines advo- cate delaying AVR until symptoms or left ventricular (LV) sys- tolic dysfunction develop.5,6 However, observational studies in 20109 and 201510 have suggested that early elective AVR might improve outcomes in patients with severe asymptom- atic AS. This approach has been reinforced by continued ad- vances in surgical techniques and aortic valve prostheses, the advent of TAVR, and the low perioperative mortality and mor- bidity rates achieved in valve centers of reference.11,12 How- ever, preemptive surgery before onset of symptoms or LV sys- tolic dysfunction is considered in only a selected group of patients after careful risk stratification. This is at least in part because the evidence for intervention in asymptomatic se- vere AS is derived from small, heterogeneous, retrospective, single-center studies, which have generally included the need for AVR (not always motivated by the development of symp- toms or LV dysfunction) in the composite study end point.13-20 Moreover, decision making for AVR remains particularly dif- ficult in older patients in whom it is sometimes unclear if the

benefits of intervention outweigh the risk.5,6

In recent years, the establishment of multidisciplinary services delivered by experts in valvular heart disease has become the basis for the implementation of heart valve clinics.21 These clinics provide standardized care based on international evidence-based norms and facilitate large clini- cal registries, which may be used to further refine guideline recommendations and quality improvement. The Heart Valve Clinic International Database (HAVEC) is a multicenter registry created for prospective data collection of patients with echocardiographic confirmation of AS and other valve diseases.22 The objective of the present study was to deter- mine the natural history and outcomes of patients with moderate or severe AS who are followed up in a heart valve clinic.

# Methods

The data, analytic methods, and study materials can be made available to other researchers for purposes of repro- ducing the results or replicating the procedure after approval of the HAVEC group. Data are centrally collected at the Department of Cardiology, Centre Hospitalier Universitaire du Sart Tilman, Liège, Belgium. This retrospective analysis of clinically acquired data was approved by the respective institutional review boards of each participating center, and informed consent was waived because collected data were deidentified and retrospective.

**Key Points**

**Question** What is the outcome of patients with asymptomatic aortic stenosis (AS) followed up in a specialized heart valve clinic?

**Findings** In this study using data from the Heart Valve Clinic International Database including 1375 patients from 10 heart valve clinics, left ventricular ejection fraction less than 60% and peak aortic jet velocity greater than 5 m/s were independent factors associated with all-cause and cardiovascular mortality in patients with asymptomatic severe AS. The adverse association of these factors with survival remains significant following aortic valve replacement, suggesting the need for earlier intervention.

**Meaning** Taking into consideration the low procedural risk associated with aortic valve replacement, the potential benefit of earlier intervention should be considered in high-risk patients with asymptomatic severe AS.

Study Population

The HAVEC registry was assembled by merging data from pro- spectively gathered electronic institutional databases of 10 heart valve clinics, as defined by the European Society of Cardiology Working Group in Valvular Heart Diseases,13 collected between 2001 and 2014. The analyses were then performed retrospectively. Patients were eligible for this reg- istry if they had AS diagnosed with the use of 2-dimension echocardiography at 1 of the participating centers and were fol- lowed-up according to available guidelines on a regular basis. Exclusion criteria included aortic valve area (AVA) greater than

1.5 cm2; class I indications for AVR (rest AS–related or exer- cise AS–related symptoms [ie, angina, syncope, and dysp- nea] or LV ejection fraction [EF] less than 50%); concomitant congenital heart valve disease more than mild mitral, tricus- pid, or pulmonic valve disease; or prior valve surgery. The study was conducted in accordance with the respective institutional guidelines, national legal requirements, and the revised Helsinki declaration.23

### Doppler Echocardiography

Transthoracic echocardiography was performed as part of rou- tine clinical practice using commercially available systems. The severity of AS was evaluated according to standard methods. Peak aortic jet velocity was derived from transaortic flow, re- corded with continuous wave Doppler using a multiwindow approach. Peak and mean gradients were calculated using the simplified Bernoulli equation. The continuity equation was used to calculate AVA. Moderate and severe AS were defined as an AVA between 1.0 and 1.5 cm2 and less than 1.0 cm2, respectively. Left ventricular EF was estimated by the Simpson biplane method.

### Follow-up

Follow-up was organized within each participating center ac- cording to available guidelines (every 6-12 months in patients with severe AS) (eTable 1 in Supplement 1). Data collection started after baseline evaluation until last available contact or death. Follow-up data were obtained by direct patient inter- view and clinical examination; telephone calls with physi- cians, patients, or next of kin; or review of autopsy records and death certificates. Information was collected regarding devel- opment of cardiac symptoms, subsequent AVR (performed for development of guideline indications: symptom onset, ab- normal exercise test, peak aortic velocity greater than 5.5 m/s, or rapid progression of AS severity), and death.24 Exercise test- ing was performed in selected patients (572 of 1375 patients [41.6%]), especially when the symptomatic status was un- clear. Cardiac deaths were classified as directly related to AS (ie, sudden death or heart failure) or to other cardiac pathol- ogy (ie, fatal myocardial infarction). All-cause mortality was the primary end point of the study; cardiovascular-related mor- tality was the secondary end point. Follow-up echocardiog- raphy data were obtained in all patients who underwent AVR to confirm the progression of moderate to severe AS (ie, AVA less than 1 cm2).

### Statistical Analysis

Data are reported as means with standard deviations for con- tinuous variables or numbers and percentages of individuals for categorical variables. Group comparisons for categorical variables were obtained with χ2 test and for continuous vari- ables with Mann-Whitney *U* test if the normality of data was violated based on a Shapiro-Wilk test. Analyses of overall and cardiovascular mortality were performed by censoring data at the time of AVR. Multivariable analysis was then performed by including covariates selected on the basis of their known link to outcome in patients with AS (ie, age, sex, comorbidi- ties, AS severity, and LVEF) into a Cox proportional hazard model. Peak aortic jet velocity (greater than or equal to 5 m/s) and LVEF (less than 60%) were also expressed as categorical variables.6,25 Survival curves were computed based on the Kaplan-Meier method. Regarding the prediction of all-cause and cardiovascular death, receiver operating characteristic curve analyses were performed, and areas under the curve (AUCs) were reported. The most accurate cutoff values (ie, best com- promise between sensitivity and specificity) were obtained using Youden index. A *P* value less than .05 was considered sta- tistically significant, and all *P* values were 2-tailed. Statistical analyses were performed using SPSS version 23 (IBM).

# Results

A total of 1763 patients were included in the present registry, of whom 388 (22.0%) were excluded because of missing data regarding LVEF or AS severity. The characteristics of the re- maining 1375 patients who fulfilled inclusion criteria are de- scribed in Table 1. The mean (SD; range) AVA was 0.94 (0.3; 0.30-1.50) cm2 and was less than 1 cm2 in 861 patients (62.6%) (Table 1).

### Outcome During Medical Management

Clinical follow-up information for patients in the 10 centers is shown in eTable1 in Supplement 1. Echocardiographic data re- garding the rate of progression of initially moderate to severe AS were not routinely available, although severe AS was docu- mented in all patients with moderate AS at baseline who underwent AVR during follow-up. The mean (SD; range) follow-up time was 27 (24; 2-224) months. A total of 542 patients (39.4%) required AVR (SAVR, 429 [79.2%]; TAVR, 113 [20.8%]). The 2-year, 4-year, and 8-year overall survival rates for the entire cohort during medical management were 93% (1%), 86% (2%), and 75% (4%), respectively. The cardiovascular death–free survival rates were 96% (1%) at 2 years, 90% (1%) at 4 years, and 83% (3%) at 8 years. Of the 104 deaths during medical management, 57 (54.8%) were from a cardiovascular cause, including 38 from heart failure and 7 from sudden cardiac death. The incidence rate of sudden death was 2.5 cases per 1000 patient-years.

Patients With Severe AS at Entry

Among the 861 patients with severe AS at entry, the 2-year, 4-year, and 8-year overall survival rates were 92% (1%), 80% (3%), and 65% (8%), respectively (Figure 1A); the cardiovas- cular death–free survival rates at 2 years, 4 years, and 8 years were 96% (1%), 87% (3%), and 71% (9%), respectively (Figure 1B); and the 2-year, 4-year, and 8-year AVR-free sur- vival rates were 54% (2%), 32% (3%), and 12% (3%), respec- tively (Figure 1C). Of the 64 deaths during medical manage- ment in patients with severe AS, 32 (50%) were from a cardiovascular cause, including 23 from heart failure, 4 from sudden cardiac death, 2 from myocardial infarction, 2 from stroke, and 1 from pulmonary embolism.

Aortic valve replacement was performed in 388 of 861 pa tients with severe AS (45.1%), with SAVR performed in 310 (79.9%) (Table 2). Indications for AVR were development of a class I indication in 366 patients (94.3%), a class IIa indica- tion in 18 (4.6%), and a class IIb indication in 4 (1.0%). In these patients, the mean (SD) time between inclusion and AVR was 14.4 (16.6) months, and the median (range) time was 8.7 (0-133) months. Combined coronary artery revascularization was performed in 82 patients (26.5%) at the time of SAVR.

Patients With Moderate AS at Entry Among the 514 patients with moderate AS at baseline, 154 (30.0%) underwent AVR (SAVR, 110 [71.4%]; TAVR, 44 [28.6%]); 128 patients (83.1%) developed class I indications, 22 (14.3%) developed class IIa indications, and 4 (2.6%) developed class IIb indications. Echocardiography preceding AVR confirmed that the stenosis had progressed to the severe stage (AVA less than 1.0 cm2) in all patients. Combined coro- nary artery revascularization was performed in 34 patients at the time of AVR. The mean (SD) time between inclusion and AVR was 29.9 (24.4) months, and the median (range) time was 22.6 (0-98) months. The mean (SD) overall survival rate was 94% (1%) at 2 years, 89% (2%) at 4 years, and 78% (4%) at 8 years follow-up (eFigure 1 in Supplement 1). In these patients with moderate AS at baseline, AVR-free survival rates are provided in eFigure 2 in Supplement 1. Of the 40 deaths during medical management, 25 were cardiovascular in nature, including heart failure in 14 and sudden death in 3. Of note, 2 of 3 patients who died suddenly had confirmed severe AS on echocardiography.

Predictors of Outcome

For the entire cohort, age, dyslipidemia, chronic obstructive pulmonary disease, higher systolic blood pressure, peak aor- tic jet velocity, and LVEF were associated with all-cause mor tality. Age, peak aortic jet velocity, and LVEF were also asso- ciated with cardiovascular death (eTable 2 in Supplement 1). In patients with severe AS (Table 3), echocardiographic de- terminants of all-cause mortality identified in the multivari- able analysis were peak aortic jet velocity greater than 5 m/s

and LVEF. Independent determinants of cardiovascular mor- tality were age, diabetes, peak aortic jet velocity greater than 5 m/s, and LVEF. When peak aortic jet velocity and LVEF were taken as continuous variables, both were independently as- sociated with cardiovascular mortality (Table 3). Using re ceiver operating characteristic curve analysis, the best cutoff values regarding the prediction of overall death were 59.6% for LVEF (AUC, 0.73; sensitivity, 81%; specificity, 56%) and 4.7 m/s for peak aortic jet velocity (AUC, 0.50; sensitivity, 30%; specificity, 80%). The AUCs for LVEF and peak aortic jet ve- locity were 0.68 and 0.59, respectively, for the prediction of cardiovascular death. Of note, there was a graded association of reduced survival with increased peak aortic jet velocity and with decreased LVEF (Figure 2). No EF threshold higher than 65% further affected survival. For peak aortic jet velocity, no additional prognostic information was obtained for veloci- ties between 4 and 5 m/s. Similar data were obtained for AVA (eTable 3 and eFigure 3 in Supplement 1) for both total and car- diovascular mortality. In patients with initially moderate AS, the best cutoffs associated with the outcomes were 64% for LVEF and 3.0 m/s for peak aortic jet velocity (eTable 4 in Supplement 1).

### Post-AVR Outcomes

Thirty-day mortality following AVR was very low (n = 13 [0.9%]; SAVR, 7; TAVR, 6). During follow-up, a total of 69 patients who underwent AVR died (SAVR, 49; TAVR, 20), including 22 from a cardiovascular cause, of which 17 were from heart failure and 2 were from sudden death. The mean (SD) 2-year, 4-year, and 6-year postprocedural overall survival rates were 83% (2%), 75% (4%), and 68% (6%), respectively. Patients with severe AS at baseline and peak aortic velocity greater than 5 m/s had sig- nificantly lower mean (SD) postoperative survival rates than those with peak aortic velocity less than 5 m/s (2 years: 73% [8%] vs 84% [2%]; 4 years: 65% [10%] vs 78% [4%]; 6 years:

54% [13%] vs 70% [6%]; *P* = .03). Similarly, patients with se- vere AS at entry with reduced baseline LVEF less than 60% also had lower mean (SD) postoperative survival rates than those with baseline LVEF of 60% or greater (2 years: 67% [7%] vs 87% [5%]; 4 years: 63% [8%] vs 78% [4%]; 6 years: 63% [8%] vs 69% [7%]; *P* = .02). In multivariable analysis, age (hazard ratio [HR], 1.03; 95% CI, 1.01-1.06; *P* = .003), diabetes (HR, 2.62; 95% CI, 1.90-4.95; *P* = .003), dyslipidemia (HR, 0.2; 95% CI, 0.10-0.37; *P* < .001), and peak aortic velocity greater than 5 m/s (HR, 2.20; 95% CI, 1.16-4.18; *P* = .02) were independently associated with postoperative survival. Of note, LVEF less than 60% was not associated with reduced postoperative survival in multivariable analysis.

# Discussion

The management of patients with asymptomatic AS has con- tinued to challenge clinicians.6,21 A randomized clinical trial (Evaluation of Transcatheter Aortic Valve Replacement Com- pared to Surveillance for Patients With Asymptomatic Severe Aortic Stenosis; [NCT03042104](https://clinicaltrials.gov/ct2/show/NCT03042104)) has been initiated to com- pare outcomes of asymptomatic patients with severe AS who are randomized to transfemoral TAVR vs clinical and echocar- diographic follow-up (ie, active surveillance). To our knowl- edge, a randomized surgical trial has not been performed, and current practice patterns vary widely. In the present registry, for patients with asymptomatic moderate or severe AS and pre- served LVEF greater than 50% at baseline followed up in heart valve clinics over the intermediate term, the mean 2-year and 4-year overall survival rates under medical management were 93% and 86%, respectively. The crude rate of sudden death over the follow-up interval was low (0.65%) and represented ap- proximately one-tenth of all cardiovascular deaths.

In patients with severe AS at entry, age, systolic blood pres- sure level, comorbidities (eg, chronic obstructive pulmonary disease), peak aortic jet velocity greater than 5 m/s, and LVEF less than 60% were associated with all-cause mortality. Age, peak aortic jet velocity of 5 m/s or greater, and LVEF less than 60% were also independently associated with cardiovascular death.

During follow-up, 34% of patients required AVR, and this rate rose to 59% at 4 years. Most AVRs were dictated by a class I indication (ie, symptom development), and most cardiovas- cular deaths were related to heart failure. The 30-day mortal- ity following AVR in this series was very low (0.9%). After AVR, the negative effect of peak aortic jet velocity remained signifi- cant, while LVEF less than 60% was no longer associated with cardiovascular death. Interestingly, in patients with moderate AS at entry who progressed to severe AS and were referred for AVR, the baseline variables predicting worse outcomes were di- rectionally similar (peak aortic jet velocity of 3.0 m/s or greater and LVEF less than 60%). Two of 3 patients with moderate AS at entry who had sudden cardiac death during follow-up had confirmed severe AS on surveillance echocardiography.

Approximately one-half of patients diagnosed with mod- erate or severe AS do not report symptoms.8,15 The clinically silent phase of severe AS is associated with a risk of sudden death ranging from 0.25% to 1.7% per year.18,19,25 Given the cur- rent low periprocedural mortality rates for SAVR and trans- femoral TAVR, earlier intervention has been advocated, and to our knowledge, the current strategy of watchful waiting has not been examined in a large cohort of patients with asymp- tomatic moderate or severe AS monitored in specialized heart valve clinics. Delay in reporting symptoms is common in pa- tients with AS.12 Considering an annual mortality rate of ap- proximately 30% for patients with severe AS, once symp-

toms develop, early recognition of symptoms and timely referral to intervention are critical.3,4 It has been shown that when patients are regularly followed up within a heart valve clinic program, symptoms are recognized at an earlier and less severe stage, thus optimizing timing of AVR.12,26 Compared with previous studies, the low rate of sudden death, the good overall midterm survival rates, and the very low rate of 30- day mortality following AVR observed in the HAVEC registry likely reflect appropriate monitoring, planning, and high ad- herence to guidelines.13-18 However, our data highlight the need for additional efforts with probably closer follow-up in these patients, since the occurrence of overt heart failure remains a

significant problem even in heart valve centers of excellence. Comorbidities are frequent in elderly individuals with AS, and AS increases the mortality from myocardial infarction, stroke, trauma, or emergency noncardiac surgery.27-31 The HAVEC registry data highlighted that age and chronic obstruc- tive pulmonary disease significantly worsen patients’ prog- nosis. Age has not been consistently reported as an outcome predictor in the literature. However, many older adults with severe AS are not candidates for surgical AVR because of high surgical risk, advanced age, frailty, or comorbid conditions.32 Some complications after transcatheter AVR (eg, vascular in-

juries) are more common in very elderly patients.3,4

Although supportive data are limited, an LVEF less than 50% is considered the appropriate threshold for defining LV systolic dysfunction in AS.5,6,33 In the HAVEC registry, pa- tients with EF between 50% and 59% had less favorable out- comes and experienced more heart failure–related deaths than those with EF greater than 60%. These data reinforce obser- vations from previous retrospective studies33,34 and provide support for adjusting the cutoff for LVEF (less than 60% in- stead of less than 50%) to define dysfunction and consider AVR in asymptomatic severe AS.

Despite limited evidence with a class IIa indication, asymp- tomatic patients with very severe AS (peak aortic jet velocity greater than 5 to 5.5 m/s) are often referred for AVR.5,6,14 Peak aortic jet velocity is recorded directly with the use of continu- ous Doppler interrogation and, unlike AVA, does not require calculations and has high reproducibility. Peak aortic jet ve- locity is a robust prognostic parameter in AS, with increas- ingly worse outcome from patients with mild to very severe (greater than 5 m/s) stenosis.14,15,19 This gradual effect of ste- nosis severity was challenged in a 2015 large multicenter ret- rospective Japanese study.10 However, the main limitations of this study were the inclusion of patients with LVEF less than

50% and the absence of standardized follow-up and treat- ment strategy. By contrast, the HAVEC registry confirmed pre- vious observations regarding stenosis severity in a very large population of patients with asymptomatic AS evaluated and monitored in heart valve clinics. In fact, very severe obstruc- tion (peak aortic jet velocity of 5 m/s or greater) was predic- tive of all-cause mortality and cardiovascular death regard- less of treatment strategy in asymptomatic patients with AS.14 Although AVA encompassed a broad range of values from 0.3 to 1.50 cm2, it was also associated with outcomes in these pa- tients (eFigure 3 in Supplement 1). An AVA less than 0.8 cm2 was associated with markedly increased risk of all-cause and cardiovascular mortality.

### Limitations

Our study had limitations. Data from a centralized database (clinical and echocardiographic data at baseline and clinical data at follow-up) were obtained from each center. However, because of incomplete echocardiographic data at baseline and/or during follow-up, a total of 22% of the initially in- cluded patients were not included in the final study analysis. Follow-up echocardiographic data were also collected from all patients who underwent AVR to confirm the progression from moderate to severe AS (ie, AVA greater than 1 cm2). However, in the context of this study, we did not collect the echocardio- graphic parameters of AS severity and LV function at follow-up visits. This precluded the analysis of the rate of pro- gression from moderate to severe AS. Although exercise test- ing was commonly performed (572 patients), some patients were considered asymptomatic based solely on question- naire on symptom status (not available in all centers). The as- sessment of myocardial strain, which could identify patients with subclinical LV dysfunction,20 was not systematically per- formed. The reasons for which symptomatic patients died un- der medical management could not be ascertained.

# Conclusions

This study shows that asymptomatic patients with severe AS followed up in heart valve clinics have a low risk of sudden death and good midterm survival. Asymptomatic patients with very severe AS (peak aortic jet velocity of 5 m/s or greater) or with LVEF less than 60% have higher all-cause and cardiovascular mortality even after successful AVR. These findings provide support for consideration of early elective AVR in these patients. Closer and more frequent (every 6 to 12 months) clinical and echocardiographic follow-up might be implemented in patients with moderate AS and a peak aortic jet velocity of 3.0 m/s or greater or LVEF less than 60%.

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**Author Contributions:** Drs Lancellotti and Magne had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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**Conflict of Interest Disclosures:** All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

Dr Vannan has received grants from Abbott, Medtronic, and Siemens. Dr Lloyd has received personal fees from Edwards Lifesciences, grants from Medtronic, and nonfinancial support from Sorin Group. Drs Delgado and Bax have received grants from Biotronik, Boston Scientific, Edwards Lifesciences, and Medtronic paid to the Department of Cardiology of Leiden University Medical Center. Dr Delgado has received personal fees from Abbott Vascular. Dr Pibarot has received grants from Edwards Lifesciences an Medtronic. Dr Oury is a senior research associate at the National Fund for Scientific Research (FRS-FNRS). No other disclosures were reported.

**Data Sharing Statement:** See Supplement 2.

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