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ORIGINAL RESEARCH

Determinants of Bioprosthetic Aortic Valve Degeneration

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ABSTRACT

OBJECTIVES The aim of the present long-term study was to assess the incidence and mode of valve hemodynamic deterioration (VHD) of bioprosthetic aortic valves, as well as associated factors.

BACKGROUND Modern definitions of bioprosthetic valve deterioration recommend the use of echocardiography for the assessment of transprosthetic gradients and valvular regurgitation.

METHODS A total of 466 consecutive patients (mean age 73.5 ± 7.5 years, 56.0% women) underwent surgical bioprosthetic aortic valve replacement between 1994 and 2014. Clinical assessment, transthoracic echocardiography, and laboratory testing were performed at baseline and follow-up. VHD was defined as mean transprosthetic gradient ≥30 mm Hg and/or at least moderate valvular regurgitation on echocardiography. Patient-prosthesis mismatch was defined as an effective orifice area indexed to body surface area ≤0.8 cm^2/m^2.

RESULTS Patients were followed for a median of 112.3 months (interquartile range: 57.7 to 147.7 months). Among patients with complete follow-up (n = 383), 70 subjects (18.3%; 4.8% per valve-year) developed VHD after a median of 32.4 months (interquartile range: 12.9 to 87.2 months; stenosis, n = 45; regurgitation, n = 16; both, n = 9). Factors associated with VHD by multivariate regression analysis were serum creatinine >2.1 mg/dl (hazard ratio [HR]: 4.143; 95% confidence interval [CI]: 1.740 to 9.866; p = 0.001), porcine tissue valves (HR: 2.241; 95% CI: 1.356 to 3.706; p = 0.002), arterial hypertension (HR: 3.022; 95% CI: 1.424 to 6.410; p = 0.004), and patient-prosthesis mismatch (HR: 1.931; 95% CI: 1.102 to 3.384; p = 0.022). By Kaplan-Meier analysis, elderly subjects showed faster development of VHD (age <70 years, 133.5 months [95% CI: 116.2 to 150.8 months]; 70 to 80 years, 129.1 months [95% CI: 112.4 to 145.7 months]; >80 years, 100.3 months [95% CI: 63.6 to 136.9 months]; p = 0.023). By multivariate Cox regression, age, diabetes, concomitant coronary artery bypass grafting, creatinine, and VHD (p < 0.05) were significantly associated with mortality.

CONCLUSIONS On the basis of echocardiography, every fifth patient developed VHD after surgical bioprosthetic heart valve replacement. VHD was associated with renal impairment, the use of porcine tissue valves, arterial hypertension, and patient-prosthesis mismatch. Patients younger than 70 years were not affected by faster VHD. (J Am Coll Cardiol Img 2020;13:345–53) © 2020 by the American College of Cardiology Foundation.

Between 300,000 and 400,000 surgical valve replacements are performed annually worldwide. Aortic valve replacement (AVR) accounts for the majority of surgical interventions, followed by mitral and tricuspid valve replacement (1). North American practice guidelines recommend the use of mechanical aortic valves in patients younger than 50 years, biological valves in patients older than 70 years, and either type in patients 50 to 70 years of age (2). According to European

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ABBREVIATIONS AND ACRONYMS

AVR = aortic valve replacement

CI = confidence interval

HR = hazard ratio

IQR = interquartile range

PPM = patient-prosthesis mismatch

VHD = valve hemodynamic deterioration

guidelines, patients eligible for surgical AVR should be treated with mechanical prostheses when <60 years of age and with biological prostheses when >65 years of age, whereas both valve types should be considered at the ages of 60 to 65 years (3). Recently, there has been an ongoing trend toward increased use of biological valves also in younger patients. One justification for this approach is the possibility of transcatheter valve-in-valve replacement in case of valvular degeneration. In addition, recent observational studies showed that in patients 50 to 69 years of age, mortality was not related to the choice of mechanical or biological aortic or mitral valve material (4,5). Structural valve degeneration remains the major determinant of bioprosthetic valve durability (6). Previous studies defined bioprosthetic valve degeneration as the need for reoperation, because careful and regular echocardiographic follow-up was not available. This approach, however, may significantly underestimate the incidence of valve degeneration, as the diagnosis may be missed in patients not eligible for reoperation (7,8). More recently, bioprosthetic valve degeneration has been defined according to echocardiographic criteria (7,9,10). On the basis of changes of transprosthetic gradients and severity of regurgitation, the term "valve hemodynamic deterioration" (VHD) has been introduced.

The aim of the present long-term observational study was to assess the incidence and mode of VHD, as well as associated factors.

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METHODS

STUDY POPULATION. Between 1994 and 2009, 504 consecutive adult patients undergoing AVR, mitral valve replacement, or tricuspid valve replacement with bioprosthetic heart valves agreed to participate in the present observational study at the Vienna General Hospital, a university-affiliated tertiary center. Given the small number of mitral (n = 36) and tricuspid (n = 2) valve replacements, those patients were excluded from the study. From study entry, all data were collected prospectively. Clinically relevant VHD was defined as an elevated mean transprosthetic gradient (≥30 mm Hg) and/or at least moderate intraprosthetic regurgitation. Criteria for the diagnosis of subclinical VHD were an elevated mean transprosthetic gradient (≥20 mm Hg) and/or at least mild to moderate intraprosthetic regurgitation (6,9). VHD was defined as the presence of clinically relevant VHD. Reference values for the effective orifice area for each size and model of prosthesis used in our study population have previously been published (11,12). Patient-prosthesis mismatch (PPM) was defined as an effective orifice area indexed to body surface area ≤0.8 cm^2/m^2 (12). According to the study design (noninterventional, purely observational), written informed consent was not required. The study was approved by the ethics committee of the Medical University of Vienna.

CLINICAL MEASURES AND FOLLOW-UP. Clinical evaluation, medical history, blood samples, and a transthoracic echocardiogram were collected at baseline. Traditional cardiovascular risk factors were recorded according to the respective guidelines, and the European System for Cardiac Operative Risk Evaluation score was calculated. Patients were followed up before discharge from the hospital, after 6 months, and every 1 to 2 years thereafter. Follow-up comprised clinical evaluation, electrocardiography, transthoracic echocardiography, and laboratory assessment. All-cause mortality was selected as primary study endpoint.

ECHOCARDIOGRAPHIC ASSESSMENT. Standard echocardiography was performed by board-certified cardiologists using commercially available equipment (Vivid 5 and Vivid 7 [GE Healthcare, Little Chalfont, United Kingdom] and Acuson Sequoia [Siemens Medical Solutions USA, Mountain View, California]). Cardiac morphology was assessed using diameters in standard 4- and 2-chamber views. Left ventricular ejection fraction was calculated using the biplane Simpson method. Valvular stenosis and regurgitation were quantified using an integrated approach and graded as none, mild, mild to moderate, moderate, moderate to severe, or severe according to the respective guidelines (13,14). Systolic pulmonary artery pressure was calculated by adding the peak tricuspid regurgitation systolic gradient to the estimated central venous pressure. Data on follow-up were retrieved from the latest echocardiogram available. To determine delay to VHD development, the date of first detection of VHD was included in the final analysis. Annualized change in mean gradient (mm Hg/year) was calculated by dividing the difference between latest and first follow-up echocardiogram by the time interval between the 2 assessments. For calculation of VHD incidence per valve-year, the number of VHD patients was divided by the total number of years with echocardiographic follow-up.

STATISTICAL METHODS. Discrete data are presented as count and percentage and were analyzed by using a

chi-square test. Continuous data are presented as median (interquartile range [IQR]) and were compared using the Mann-Whitney *U* test. Univariate and multivariate Cox proportional hazard regression analysis was used to identify parameters associated with VHD. To determine a cutoff value for serum creatinine levels with regard to VHD development, receiver-operating characteristic curve analysis was performed. Furthermore, univariate and multivariate Cox proportional hazard regression analysis was applied to assess the impact of demographic, echocardiographic, and laboratory variables on postoperative long-term survival. Here, VHD was entered as a time-dependent covariate. For multivariate Cox regression analysis, variables with a significant univariate influence ($p < 0.05$) were included in the respective multiple regression analysis with forward selection. Kaplan-Meier analysis was applied to evaluate the impact of age on VHD and compared using the log-rank test. All statistical analyses were computed using SPSS version 24 (IBM, Armonk, New York).

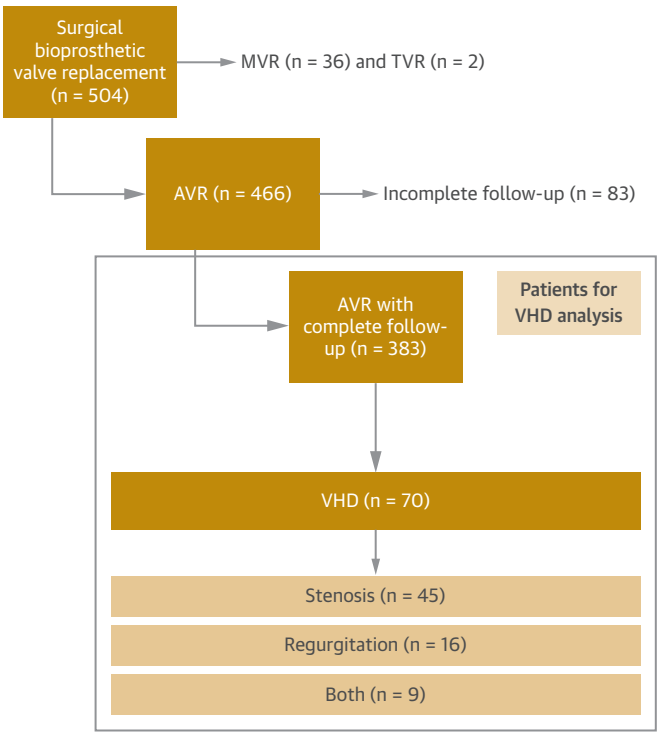
RESULTS

CLINICAL AND BASELINE DATA. In total, 466 patients underwent surgical bioprosthetic AVR and were prospectively enrolled. The median follow-up period was 113.2 months (IQR: 57.4 to 148.2 months), for a total of 4,023 valve-years. Echocardiographic and laboratory follow-up was complete in 82.2% of patients (n = 383) (Figure 1).

Detailed baseline characteristics of the study population with complete follow-up are displayed in Table 1. Apart from a higher percentage of porcine tissue valves in the VHD group (52.9% vs. 30.6%; $p < 0.001$), there were no significant differences between patients with and without VHD. Eighteen patients (4.7%) underwent reoperation for VHD (n = 15) or infective endocarditis (n = 3). Among patients with VHD, exertional dyspnea was significantly more common in those undergoing redo surgery (76.9% vs. 46.3%; $p = 0.047$). Baseline echocardiographic data are presented in Table 2. Regarding echocardiographic data prior to surgery, no significant differences between patients with and without VHD were found.

ECHOCARDIOGRAPHIC AND LABORATORY FOLLOW-UP DATA. Detailed patient characteristics at follow-up are displayed in Tables 1 and 2. A total of 262 patients (68.4%) had multiple echocardiograms, allowing the calculation of annualized change in mean gradient. In patients with VHD, left and right heart chambers were enlarged in comparison with those without VHD (left atrial diameter: 62.0 mm [IQR: 58.0 to 67.0 mm] vs. 58.0 mm [IQR: 54.0 to 64.0 mm], $p < 0.001$; LVEDD: 47.0 mm [IQR: 41.0 to 52.0 mm] vs. 45.0 mm [IQR: 41.0 to 48.0 mm], $p = 0.022$; right atrial diameter: 60.5 mm [IQR: 55.0 to 67.0 mm] vs. 56.0 mm [IQR: 52.0 to 62.0 mm], $p = 0.001$; right ventricular end-diastolic diameter: 35.0 mm [IQR: 32.0 to 38.3 mm] vs. 33.5 mm [IQR: 30.0 to 37.0 mm], $p = 0.044$). Furthermore, tricuspid regurgitation velocity and estimated systolic pulmonary artery pressure were higher in patients with VHD (3.3 m/s [IQR: 2.9 to 3.8 m/s] vs. 2.9 m/s [IQR: 2.6 to 3.2 m/s], $p < 0.001$; 51.0 mm Hg [IQR: 39.0 to 65.0 mm Hg] vs. 39.0 mm Hg [IQR: 32.0 to 49.0 mm Hg], $p < 0.001$). PPM was significantly more common among patients with VHD (72.3% vs. 49.8%; $p = 0.001$). In addition, they developed higher serum creatinine levels, and there was a strong trend toward higher N-terminal pro-brain natriuretic peptide level at follow-up (1.15 mg/dl [IQR: 0.96 to 1.34 mg/dl] vs. 1.04 mg/dl [IQR: 0.87 to

FIGURE 1 Patient Population



A total of 504 patients undergoing surgical bioprosthetic valve replacement were screened for the study. Reasons for exclusion are displayed. AVR = aortic valve replacement; MVR = mitral valve replacement; TVR = tricuspid valve replacement; VHD = valve hemodynamic deterioration.

TABLE 1 Clinical Characteristics of Study Population at Baseline and Follow-Up

	All Patients (N = 383)	No VHD (n = 313, 81.7%)	VHD (n = 70, 18.3%)	p Value
Baseline clinical parameters				
Age, yrs	73.6 (68.5–77.7)	73.5 (68.5–77.9)	73.8 (68.4–77.4)	0.851
Male	44.4	43.5	48.5	0.448
BMI, kg/m^2	26.8 (24.3–30.1)	26.7 (24.3–30.2)	27.4 (25.2–29.4)	0.583
Hypertension	79.3	78.1	84.8	0.219
Atrial fibrillation	17.6	17.8	16.7	0.829
Diabetes	20.5	19.0	27.3	0.132
Hyperlipidemia	47.8	47.6	48.5	0.898
CAD	35.4	36.5	30.3	0.338
COPD	10.0	8.9	15.2	0.123
Concomitant CABG	22.5	24.1	14.7	0.091
Additive EuroSCORE	6.0 (5.0–7.0)	6.0 (5.0–7.0)	6.0 (5.0–7.0)	0.976
NYHA functional class ≥III	33.2	31.7	42.2	0.165
CCS class ≥II	32.9	33.6	28.9	0.535
NT-proBNP, pg/ml	952 (363–2,573)	955 (354–2,042)	885 (349–3,883)	0.583
Creatinine, mg/dl	1.0 (0.85–1.17)	0.98 (0.84–1.16)	1.04 (0.88–1.21)	0.155
Bioprosthesis features				
Stented valve	89.2	82.1	78.0	0.531
Porcine tissue valve	34.6	30.6	52.9	<0.001
Clinical parameters at follow-up				
Age, yrs	77.6 (72.5–82.0)	77.3 (72.1–82.0)	79.3 (74.7–82.6)	0.090
NYHA functional class ≥III	11.0	8.6	22.4	0.001
CCS class ≥II	4.5	3.9	7.5	0.316
Creatinine, mg/dl	1.05 (0.88–1.27)	1.04 (0.87–1.25)	1.15 (0.96–1.34)	0.009
NT-proBNP, pg/ml	1,212 (482–3,328)	1,115 (457–2,625)	1,865 (621–5,182)	0.061

Values are median (interquartile range) or %.

BMI = body mass index; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CCS = Canadian Cardiovascular Society; COPD = chronic obstructive pulmonary disease; EuroSCORE = European System for Cardiac Operative Risk Evaluation; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; NYHA = New York Heart Association; VHD = valve hemodynamic deterioration.

1.25 mg/dl], p = 0.009; 1,865 pg/ml [IQR: 621 to 5,182 pg/ml] vs. 1,115 pg/ml [IQR: 457 to 2,625 pg/ml], p = 0.061).

FACTORS RELATED TO THE OCCURRENCE OF VHD. Seventy patients (18.3%; 4.8% per valve-year) developed VHD during a median follow-up period of 33.0 months (IQR: 9.0 to 77.0 months). The modes of VHD were stenosis (n = 45), regurgitation (n = 16), and both (n = 9). Median delay from surgery to VHD was 32.4 months (IQR: 12.9 to 87.2 months). By receiver-operating characteristic curve analysis, a cutoff value of 2.1 mg/dl serum creatinine was found as most closely associated with VHD development (p = 0.015). Further parameters associated with VHD in the univariate Cox regression analysis were the use of porcine tissue prostheses (p = 0.003), arterial hypertension (p = 0.014), and PPM (p = 0.017). These variables were then included in a multivariate Cox regression model. Elevated serum creatinine (hazard ratio [HR]: 4.143; 95% confidence interval [CI]: 1.740 to 9.866; p = 0.001), the use of porcine tissue valves (HR: 2.241; 95% CI: 1.356 to 3.706; p = 0.002), arterial hypertension (HR: 3.022; 95% CI: 1.424 to 6.410; p = 0.004), and PPM (HR: 1.931; 95% CI: 1.102 to 3.384; p = 0.022) remained independently associated with VHD. Results of the Cox regression analyses are presented in Table 3.

IMPACT OF AGE ON THE TIME COURSE OF VHD. By Kaplan-Meier analysis, elderly subjects showed shorter event-free survival with regard to the development of VHD (<70 years, 133.5 months [95% CI: 116.2 to 150.8 months]; 70 to 80 years, 129.1 months [95% CI: 112.4 to 145.7 months]; >80 years, 100.3 months [95% CI: 63.6 to 136.9 months]; p = 0.023) (Figure 2). VHD rates according to age were 2.0% (<70 years), 4.7% (70 to 80 years), and 5.4% (>80 years) per valve-year, respectively. Median delay from subclinical to clinically relevant VHD was 24.2 months (IQR: 13.7 to 61.9 months).

FACTORS ASSOCIATED WITH OUTCOMES. Uni- and multivariate Cox regression analyses are displayed in Table 4. After a median follow-up period of 113.2 months (IQR: 57.4 to 148.1 months), 69.3% of patients (n = 323) had died. Cardiovascular death accounted for 59.4% (n = 192) of mortality. Univariate predictors of all-cause mortality were age (p < 0.001), serum creatinine at the time of surgery (p < 0.001), coronary artery disease (p < 0.001), concomitant coronary artery bypass grafting (p < 0.001), additive European System for Cardiac Operative Risk Evaluation score (p < 0.001), diabetes (p = 0.009), the use of stented bioprostheses (p = 0.005), PPM (p = 0.017), atrial fibrillation (p = 0.030), and VHD as a time-dependent covariate (p = 0.029).

By multivariate analysis, age (HR: 1.057; 95% CI: 1.040 to 1.074; p < 0.001), serum creatinine (HR: 1.423; 95% CI: 1.254 to 1.615; p < 0.001), concomitant coronary artery bypass grafting (HR: 1.480; 95% CI: 1.148 to 1.907; p = 0.002), diabetes (HR: 1.377; 95% CI: 1.045 to 1.813; p = 0.023), and VHD (HR: 1.433; 95% CI: 1.014 to 2.023; p = 0.041) remained significantly associated with outcomes.

DISCUSSION

Whether to implant a mechanical or a biological aortic valve, particularly in patients 50 to 70 years of age, is a matter of discussion. The risks associated with the need for anticoagulation after mechanical valve implantation have recently led to an increasing use of bioprosthetic valves in patients older than 50 years. This trend has been supported by clinical data, suggesting extended durability of new-generation bioprostheses (2,15,16). Moreover, percutaneous

TABLE 2 Echocardiographic Assessment at Baseline and Follow-Up

	All Patients (N = 383)	No VHD (n = 313, 81.7%)	VHD (n = 70, 18.3%)	p Value
Baseline echocardiographic parameters				
LA diameter, mm	57.0 (53.0 to 62.0)	57.0 (53.0 to 62.0)	59.0 (52.5 to 62.0)	0.490
RA diameter, mm	54.0 (50.0 to 60.0)	54.0 (50.0 to 60.0)	54.0 (50.0 to 60.0)	0.700
LV EDD, mm	45.0 (42.0 to 50.0)	45.0 (42.0 to 49.3)	46.0 (42.5 to 51.0)	0.251
RV EDD, mm	32.0 (29.0 to 36.0)	32.0 (29.0 to 36.0)	32.0 (29.0 to 36.0)	0.827
Asc Ao diameter, mm	32.0 (30.0 to 36.5)	32.0 (30.0 to 37.0)	32.0 (30.0 to 35.0)	0.941
Aortectasis	10.0	9.7	11.1	0.757
IVS, mm	16.0 (14.0 to 17.0)	16.0 (14.0 to 17.0)	15.0 (14.0 to 17.0)	0.522
LVEF, %	50.0 (40.0 to 61.0)	50.0 (40.0 to 60.0)	44.3 (34.3 to 60.8)	0.977
AV PPG	96.0 (77.4 to 116.7)	92.2 (77.4 to 112.4)	100.0 (81.0 to 121.0)	0.145
AV MPG	62.0 (51.0 to 76.8)	61.0 (51.0 to 75.0)	68.0 (51.0 to 81.0)	0.276
AV Vmax	4.9 (4.4 to 5.4)	4.8 (4.4 to 5.3)	5.0 (4.5 to 5.5)	0.145
Peak TR velocity, m/s	3.0 (2.7 to 3.4)	3.1 (2.7 to 3.4)	3.0 (2.7 to 3.2)	0.357
sPAP, mmHg	45.0 (35.0 to 53.0)	43.0 (35.0 to 53.8)	41.0 (36.0 to 51.0)	0.767
Echocardiographic parameters at follow-up				
LA diameter, mm	59.0 (55.0 to 64.8)	58.0 (54.0 to 64.0)	62.0 (58.0 to 67.0)	<0.001
RA diameter, mm	57.0 (53.0 to 62.0)	56.0 (52.0 to 62.0)	60.5 (55.0 to 67.0)	<0.001
LV EDD, mm	45.0 (41.0 to 49.0)	45.0 (41.0 to 48.0)	47.0 (41.0 to 52.0)	0.022
RV EDD, mm	34.0 (30.0 to 37.0)	33.0 (30.0 to 37.0)	35.0 (32.0 to 38.3)	0.044
Asc Ao diameter, mm	35.0 (31.0 to 39.0)	35.0 (31.0 to 39.0)	35.0 (31.0 to 41.0)	0.464
IVS, mm	14.0 (13.0 to 16.0)	14.0 (13.0 to 16.0)	14.0 (13.0 to 15.0)	0.461
LVEF, %	45.5 (39.5 to 54.5)	49.0 (41.0-57.0)	41.0 (38.5 to 53.0)	0.531
AV PPG	31.0 (23.0 to 40.0)	29.0 (21.0 to 36.0)	57.0 (49.0 to 70.0)	<0.001
AV MPG	18.0 (13.0 to 24.0)	16.0 (12.0 to 21.0)	34.0 (30.0 to 41.0)	<0.001
AV Vmax	2.8 (2.4 to 3.2)	2.7 (2.3 to 3.0)	3.8 (3.4 to 4.2)	<0.001
Annualized change in AV MPG from pre-discharge to latest follow-up, mm Hg/yr	0.5 (−0.4 to 2.4)	0.1 (−0.7 to 1.6)	2.5 (1.5 to 5.9)	<0.001
Peak TR velocity, m/s	3.0 (2.6 to 3.3)	2.9 (2.6 to 3.2)	3.3 (2.9 to 3.8)	<0.001
sPAP, mm Hg	41.0 (34.0 to 51.0)	39.0 (32.0 to 49.0)	51.0 (39.0 to 65.0)	<0.001
PPM	53.8	49.8	72.3	0.001

Values are median (interquartile range) or %.

Asc Ao = ascending aorta; AV = aortic valve; EDD = end-diastolic diameter; IVS = interventricular septum; LA = left atrial; LV = left ventricular; LVEF = left ventricular ejection fraction; MPG = mean pressure gradient; PPG = peak pressure gradient; PPM = patient-prosthesis mismatch; RA = right atrial; RV = right ventricular; sPAP = systolic pulmonary artery pressure; TR = tricuspid regurgitation; other abbreviations as in Table 1.

valve-in-valve technology provides a new, less invasive option to treat potential degeneration of bioprosthetic valves (16,17).

Considering the ongoing discussion about age limits for valve selection, the present study is the first to use thorough echocardiographic follow-up at a single echocardiography laboratory to provide long-term data on VHD-associated factors, including age. Echocardiographic, laboratory, and clinical data were collected at baseline and follow-up, and patients were followed for a median of 9.4 years. An incidence of clinically relevant VHD of 18.3% (n = 70; 4.8% per valve-year) was found. Median delay to VHD was 32.4 months (IQR: 12.9 to 87.2 months), and event-free survival with regard to the development of VHD was significantly shorter in elderly subjects (<70 years, 133.5 months [95% CI: 116.2 to 150.8 months]; 70 to 80 years, 129.1 months [95% CI: 112.4 to 145.7 months]; >80 years, 100.3 months [95% CI: 63.6 to 136.9 months]; p = 0.023). Risk factors determining the onset of VHD were elevated serum creatinine, porcine tissue valves, arterial hypertension, and PPM.

INCIDENCE OF VHD. Studies that applied thorough echocardiographic follow-up for the detection of VHD are scarce. Moreover, a lack of standardized definitions for the diagnosis of bioprosthetic valve degeneration complicates robust comparison among clinical trials (18). In their echocardiography-based study, Sénage et al. (9) reported an incidence of 6.3% (1.7% per patient-year) for degeneration of Mitroflow aortic bioprostheses. The mean delay was 3.8 ± 1.4 years. Valve degeneration was defined as progression of aortic transprosthetic gradient ≥30 mm Hg, associated with decreased effective orifice area (≤1 cm^2) or at least moderate intraprosthetic aortic regurgitation. Very long-term results for the

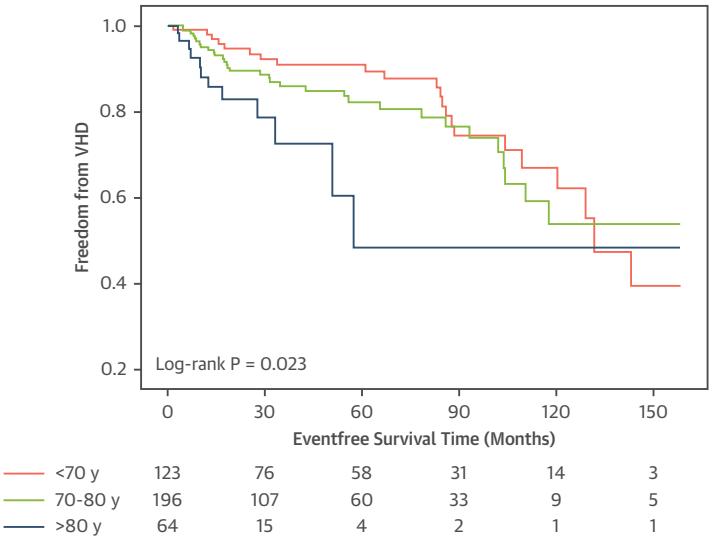
TABLE 3 Univariate and Multivariate Cox Regression Analyses Assessing the Association of Factors With the Development of Valve Hemodynamic Deterioration

	Univariate		Multivariate	
	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value
Age at surgery	1.036 (0.998–1.076)	0.601		
Male	1.063 (0.661–1.709)	0.801		
BMI	1.013 (0.959–1.070)	0.653		
Hypertension	2.308 (1.183–4.503)	0.014	3.022 (1.424–6.410)	0.004
Atrial fibrillation	0.858 (0.447–1.645)	0.644		
Diabetes	1.616 (0.939–2.782)	0.083		
Hyperlipidemia	0.872 (0.538–1.413)	0.577		
CAD	0.854 (0.506–1.441)	0.554		
COPD	1.515 (0.770–2.981)	0.229		
Concomitant CABG	0.571 (0.292–1.117)	0.102		
CCS class ≥II at surgery	0.845 (0.451–1.584)	0.599		
Creatinine >2.1 mg/dl at surgery	2.022 (0.491–1.584)	0.599		
PPM	1.916 (1.123–3.270)	0.017	1.931 (1.102–3.384)	0.022
Stented AV	1.135 (0.562–2.293)	0.724		
Porcine tissue valve	2.067 (1.286–3.322)	0.003	2.241 (1.356–3.706)	0.002
CCS class ≥II at follow-up	0.966 (0.340–2.746)	0.949		
Creatinine >2.1 mg/dl at follow-up	2.850 (1.227–6.619)	0.015	4.143 (1.740–9.866)	0.001

CI = confidence interval; other abbreviations as in Tables 1 and 2.

Carpentier-Edwards Perimount aortic valve were studied by Bourguignon et al. (7). Diagnosis of valve degeneration was made whenever severe aortic stenosis (mean transvalvular gradient >40 mm Hg) or severe aortic regurgitation (effective regurgitant orifice area >0.3 cm², vena contracta >0.6 cm) occurred. After a mean follow-up period of 6.7 ± 4.8 years, the incidence reached 5.7% (0.85% per valve-year). However, both were retrospective observational studies (7,9). Echocardiographic data were obtained from resident physicians and cardiologists, precluding standardized core laboratory echocardiographic workup as performed in our study. Salaun et al. (10) very recently published data of aortic bioprosthesis carriers, who underwent systematic prospective echocardiographic follow-up to determine VHD. Echocardiography was performed fairly late after surgery, on average 6.7 years after implantation and 3 years thereafter. In that work, VHD was defined as an annualized change in mean transprosthetic gradient ≥3 mm Hg/year and/or worsening of intraprosthetic regurgitation by ≥1/3 class. The incidence of VHD reached 4.4% per valve-year. However, because of the study design, hemodynamic changes early and very late after surgery were not assessed. Large randomized controlled trials such as SURTAVI (Surgical Replacement and Transcatheter Aortic Valve Implantation) and PARTNER 1 (Placement of Aortic Transcatheter Valve) compared transcatheter with surgical AVR and provided data on 2- and 5-year outcomes, respectively, including transprosthetic gradients (19,20). However, in SURTAVI, echocardiographic follow-up was available only for transcatheter AVR patients (19), and in PARTNER 1, numbers at 2-year follow-up were very small (fewer than one-third of patients within the surgical AVR group) (20).

FIGURE 2 Kaplan-Meier Event-Free Survival Curve



Freedom from valve hemodynamic deterioration (VHD) according to age.

RISK FACTORS FOR BIOPROSTHETIC VALVE DEGENERATION. Risk factors previously reported to be associated with bioprosthetic degeneration include young age, mitral valve position, end-stage renal disease, hypertension, metabolic syndrome, lipid-mediated inflammation, diabetes, and PPM, whereas data on porcine tissue valves are conflicting (8,10,21–26). In the present study, VHD was associated with the use of porcine tissue valves, renal impairment, hypertension, and PPM. In contrast to previous studies, here young age was not associated with more rapid VHD, but there was a strong trend toward shorter time to VHD in patients older than 80 years. However, this age group comprised only 64 patients, and these results should therefore be considered with caution. Valvular calcification has previously been proposed as a major mechanism of bioprosthesis degeneration (27,28). To avoid immune system reaction against xenograft antigens, bioprosthetic leaflet tissue is fixed in glutaraldehyde, thereby crosslinking and masking antigens, rendering the bioprosthesis "immunologically inert." However,

residual xenoantigens on valves pre-treated with glutaraldehyde may induce immune response and cause valvular calcification (29). Porcine and bovine tissue exhibit different sets of antigens, presumably making tissue less or more prone to immunoreactivity. This phenomenon might provide an explanation for the increased incidence of VHD of porcine tissue valves in our study. In previous studies, bovine pericardial valves were shown to have superior hemodynamic status during exercise and at rest in comparison with porcine tissue valves (26,30). Free aldehyde groups in pre-treated prostheses bind calcium ions and phospholipids, resulting in accelerated mineralization in states of hypercalcemia und hyperphosphatemia (31). Renal impairment frequently causes dysregulation of phosphocalcic metabolism, thereby leading to a more rapid progression of valvular degeneration. These mechanisms are commonly held accountable for its development in renal insufficiency, which was also found in our patients. Patients with renal impairment have a high coprevalence of arterial hypertension, which may additionally accelerate VHD by increasing diastolic closure stress on the prosthesis (21). Another factor independently related to VHD in the present study was PPM. Elevated transprosthetic gradients such as those due to PPM cause mechanical leaflet stress. Over time, leaflet thickening and calcification may ensue, making PPM a substantial factor for valvular degeneration (32–34).

Age as a determinant of VHD has been investigated in a limited number of studies that defined bioprosthesis degeneration on the basis of echocardiography or time to explantation for valve degeneration (7,10,35,36). Bourguignon et al. (7) investigated the effect of age on Carpentier-Edwards Perimount aortic valve degeneration. Freedom from degeneration at 15 and 20 years was 66.8 ± 4.2% and 37.2 ± 5.4%, respectively, for patients 60 years of age or younger, 77.7 ± 3.4% and 53.0 ± 8.0% for those 60 to 70 years of age, and 91.6 ± 2.3% at 15 years and greater for the oldest group. However, as stated previously, this study was retrospective in design, and echocardiographic assessment was not standardized. Moreover, that study began in 1984, when the quality of echocardiographic equipment was not comparable with that of more modern ultrasound machines (7). Younger age at the time of valve surgery has been reported to be a risk factor for reoperation by further studies, which, however, lack systematic, prospective echocardiographic follow-up or did not provide data on echocardiography at all. Time to the development of valvular degeneration was defined as freedom from reoperation, while strict echocardiographic criteria, as used in our study, were not applied (35,36). Reluctance to perform reoperation in elderly patients and incomplete echocardiographic assessment might thus have caused substantial bias in these earlier trials. The recently published data by Salaun et al. (10), which were based on echocardiography several years after AVR, did not show an association of young age with more rapid hemodynamic valve deterioration. However, data on subgroup analysis comparing valve degeneration rates in various age groups were not available.

TABLE 4 Univariate and Multivariate Cox Regression Analyses Regarding Long-Term Mortality

	Univariate		Multivariate	
	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value
Age at surgery	1.057 (1.040–1.074)	<0.001	1.060 (1.041–1.080)	<0.001
Male	1.092 (0.884–1.349)	0.414		
BMI	0.979 (0.955–1.003)	0.086		
Hypertension	1.066 (0.831–1.367)	0.617		
Atrial fibrillation	1.329 (1.027–1.720)	0.030		
Diabetes	1.396 (1.027–1.794)	0.009	1.377 (1.045–1.813)	0.023
Hyperlipidemia	0.816 (0.660–1.008)	0.060		
CAD	1.567 (1.265–1.940)	<0.001		
COPD	1.199 (0.859–1.674)	0.285		
Concomitant CABG	1.659 (1.317–2.089)	<0.001	1.480 (1.148–1.907)	0.002
Additive EuroSCORE	1.205 (1.139–1.276)	<0.001		
NYHA functional class ≥III at surgery	1.127 (0.869–1.463)	0.368		
CCS class ≥II at surgery	0.875 (0.665–1.150)	0.337		
Creatinine at surgery	1.292 (1.160–1.441)	<0.001	1.423 (1.254–1.615)	<0.001
PPM	1.313 (1.050–1.641)	0.017		
Stented AV	1.758 (1.187–2.603)	0.005		
Porcine tissue valves	0.820 (0.657–1.023)	0.079		
Time-dependent VHD	1.412 (1.036–1.922)	0.029	1.433 (1.014–2.023)	0.041

Abbreviations as in Tables 1 to 3.

OUTCOMES AFTER SURGICAL BIOPROSTHETIC VALVE REPLACEMENT. There are few data on determinants of survival after surgical implantation of bioprostheses. Across most studies, mechanical and biological valves were not analyzed separately, thus hindering proper comparison with our data. Renal impairment was reported to inversely affect both in-hospital and long-term outcomes after valve replacement therapy (37). Likewise, in the present cohort, elevated serum creatinine levels were associated with long-term outcomes. Patients with diabetes are not only known to be more likely to develop cardiovascular disease, but they are further disadvantaged with worse outcomes after cardiac surgery (22). Furthermore, concomitant coronary artery bypass grafting proved to have a significant impact on all-cause mortality (38,39). Also, hemodynamic deterioration of aortic bioprostheses has recently

been established as an important predictor of outcomes (10). With regard to reoperation, among 70 patients with VHD, only 15 (21.4%) underwent reintervention. Thirteen patients were reoperated, and 2 received valve-in-valve transcatheter prostheses. This low rate of reintervention is attributable to the fact that during the bigger part of the study period, transcatheter valve-in-valve intervention was not a therapeutic option. Patients who eventually underwent reoperation were highly symptomatic and had to be deemed operable by our heart team.

FUTURE IMPLICATIONS. Present data and similar results from other trials suggest good durability of bioprosthetic aortic valves in younger patients (4,5). These results will potentially further enhance the rapid growth in the number of TAVR procedures. The option of treating a failing aortic bioprosthesis with a valve-in-valve intervention further supports this development (40,41). However, more data from large randomized controlled trials addressing transcatheter AVR durability in young patients are warranted to justify lower age limits for such interventions (42).

STUDY LIMITATIONS. The present data were collected in a single-center setting. Therefore, a center-specific bias cannot be excluded, and all results and conclusions should be interpreted with caution. However, the major advantages of limiting data collection to a single center are 1) inclusion of a homogenous patient population; 2) adherence to a constant clinical routine; and 3) constant quality of echocardiographic workup. Furthermore, the use of various valve types with different hemodynamic profiles limits the interpretation of data. The group of patients older than 80 years was small, and follow-up was shorter compared with the other age groups. This limits the interpretation of long-term follow-up in elderly patients. Furthermore, echocardiographic follow-up was incomplete in 17.8% of patients (n = 83 of 466), potentially creating a selection bias in the population eligible for final analysis. Additionally, PPM and VHD are not totally independent from each other, which should be considered when interpreting the VHD-associated factors. However, only clinically relevant VHD was included in the multivariate Cox regression model.

CONCLUSIONS

On the basis of echocardiographic criteria, we observed a significant incidence of VHD in bioprosthetic aortic valves. VHD was associated with renal impairment, the use of porcine tissue valves, arterial hypertension, and PPM. Patients younger than 70 years were not affected by faster VHD.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The present echocardiography-based study demonstrates that after surgical bioprosthetic valve replacement for aortic stenosis, younger patients (<70 years of age) were not affected by faster hemodynamic deterioration of the bioprostheses (VHD). Determinants of VHD were renal impairment, porcine tissue valves, arterial hypertension, and PPM.

TRANSLATIONAL OUTLOOK: The present data challenge previous reports on faster VHD in younger patients. As transcatheter AVR is increasingly performed, also in intermediate-risk, low-risk, and young patients, future studies need to confirm the present results to justify such procedures in young and low-risk patients.

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APPENDIX For a supplemental table, please see the online version of this paper.