



Incidence, Timing, and Predictors of Valve Hemodynamic Deterioration After Transcatheter Aortic Valve Replacement

Multicenter Registry

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ABSTRACT

BACKGROUND Scarce data exist on the incidence of and factors associated with valve hemodynamic deterioration (VHD) after transcatheter aortic valve replacement (TAVR).

OBJECTIVES This study sought to determine the incidence, timing, and predictors of VHD in a large cohort of patients undergoing TAVR.

METHODS This multicenter registry included 1,521 patients (48% male; 80 ± 7 years of age) who underwent TAVR. Mean echocardiographic follow-up was 20 ± 13 months (minimum: 6 months). Echocardiographic examinations were performed at discharge, at 6 to 12 months, and yearly thereafter. Annualized changes in mean gradient (mm Hg/year) were calculated by dividing the difference between the mean gradient at last follow-up and the gradient at discharge by the time between examinations. VHD was defined as a ≥ 10 mm Hg increase in transprosthetic mean gradient during follow-up compared with discharge assessment.

RESULTS The overall mean annualized rate of transprosthetic gradient progression during follow-up was 0.30 ± 4.99 mm Hg/year. A total of 68 patients met criteria of VHD (incidence: 4.5% during follow-up). The absence of anticoagulation therapy at hospital discharge ($p = 0.002$), a valve-in-valve (TAVR in a surgical valve) procedure ($p = 0.032$), the use of a 23-mm valve ($p = 0.016$), and a greater body mass index ($p = 0.001$) were independent predictors of VHD.

CONCLUSIONS There was a mild but significant increase in transvalvular gradients over time after TAVR. The lack of anticoagulation therapy, a valve-in-valve procedure, a greater body mass index, and the use of a 23-mm transcatheter valve were associated with higher rates of VHD post-TAVR. Further prospective studies are required to determine whether a specific antithrombotic therapy post-TAVR may reduce the risk of VHD. (J Am Coll Cardiol 2016;67:644-55)
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Structural valve degeneration (SVD) is the main cause of bioprosthetic valve failure after surgical aortic valve replacement (SAVR). The reported incidence of SVD after SAVR at 1, 10, and 15 years has been <1%, 10% to 30%, and 20% to 50%, respectively (1–3). These data traditionally have been determined on the basis of the incidence of reoperation after surgical bioprosthetic valve failure. However, this approach may underestimate the true incidence of SVD (4,5), and several studies have proposed to define SVD occurrence according to the development of valve hemodynamic dysfunction documented by Doppler echocardiography (6–8). With this approach, Mahjoub et al. (8) found a 20% SVD incidence during a mean follow-up of 8 years post-SAVR. Valve hemodynamic deterioration (VHD) as documented by Doppler echocardiography may be related to calcific degeneration of bioprosthetic valve leaflets (i.e., SVD), but it may also result from thrombosis or pannus ingrowth.

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Transcatheter aortic valve replacement (TAVR) is well established for treating patients with symptomatic severe aortic stenosis who are at high or prohibitive surgical risk (9). Although SVD requiring valve replacement is a rare entity within the first years after TAVR (10,11), scarce data exist on subclinical bioprosthetic hemodynamic dysfunction after TAVR. Investigators have suggested that rapid changes in transvalvular gradients may be the hallmark of valve thrombosis despite the absence of clinical symptoms (12–14). Given that antithrombotic or anticoagulation therapies post-TAVR are not currently well established, it is of the utmost importance to determine whether subclinical valve thrombosis could be an underlying pathophysiological mechanism contributing to transcatheter valve failure. We aimed to establish the incidence and risk factors of VHD within a large population of patients who had undergone TAVR.

METHODS

Between May 2007 and October 2014, 2,418 consecutive patients underwent TAVR in 10 participating centers. Patients were considered eligible for this multicenter study if they had undergone at least 2 echocardiograms post-TAVR (at discharge and at a minimum of 6- to 12-month follow-up). A total of 1,521 patients satisfied these criteria and were included in our study. Eligibility for TAVR, valve type, and access route were determined at each center by a local heart team composed of interventional cardiologists and

cardiac surgeons. Clinical, procedural, and echocardiographic data were prospectively gathered within a TAVR database at each participating center. This study was not a pre-specified analysis at the time of the creation of the database; therefore, data were analyzed retrospectively. Clinical follow-up was undertaken during clinical visits or through telephone contact, or both, at 1 month post-TAVR, at 6 to 12 months post-TAVR, and yearly thereafter in all participating centers. Clinical events were prospectively recorded and defined according to VARC-2 (Valve Academic Research Consortium-2) criteria (15).

ECHOCARDIOGRAPHIC ASSESSMENT. Transthoracic echocardiography (TTE) examinations were performed at baseline, at hospital discharge, at 6 to 12 months post-TAVR, and yearly thereafter.

All TTE examinations were conducted according to American Society of Echocardiography guidelines (16,17). Peak transprosthetic flow velocity was determined by continuous-wave Doppler imaging. The mean transprosthetic gradient was calculated using the modified Bernoulli formula. Absolute change in mean gradient was calculated as the gradient at last follow-up minus the gradient at discharge. Annualized change in mean gradient (mm Hg/year) was calculated by dividing the absolute change in gradient by the time between examinations. VHD was defined as an absolute change in gradient of ≥ 10 mm Hg during follow-up (8,18). Early VHD was defined as a ≥ 10 mm Hg increase in mean gradient within the first year after TAVR compared with discharge assessment. Moderate and severe postoperative prosthesis-patient mismatches (PPMs) were defined as an indexed effective orifice area (EOA) of ≥ 0.65 to ≤ 0.85 cm²/m² and < 0.65 cm²/m², respectively (19).

STATISTICAL ANALYSIS. Categorical variables are reported as number (percent) and continuous variables as mean $\pm$ SD or median (25th to 75th interquartile range [IQR]), depending on variable distribution. Group comparisons were analyzed with the Student *t* test or Wilcoxon rank sum test for continuous variables and the chi-square test or Fisher exact test for categorical variables. Changes in mean transaortic gradient measurements over time (discharge, 6 months to 1, 2, 3, and 4 years) were evaluated with repeated-measures analyses of variance. The normality assumption was verified with the Shapiro-Wilk tests on the error distribution from the Cholesky factorization of the statistical model. Mean

ABBREVIATIONS AND ACRONYMS

AR = aortic regurgitation
BMI = body mass index
CT = computed tomography
EOA = effective orifice area
PPM = prosthesis-patient mismatch
SAVR = surgical aortic valve replacement
SVD = structural valve degeneration
TAVR = transcatheter aortic valve replacement
TE = transthoracic echocardiography
TEE = transesophageal echocardiography
THV = transcatheter heart valve
VHD = valve hemodynamic deterioration

gradient elevation values were log-transformed to stabilize variances. The predictors of mean gradient progression were determined using linear regression analyses. Univariable and multivariable Cox proportional hazards models were used to identify potential determinants of VHD over time. Univariable and multivariable logistic regression analyses were used to identify independent factors associated with VHD within the first year post-TAVR. The variables with a probability value <0.10 were candidates for the multivariable regression model building. The final statistical model was built using a forward approach and Akaike's and Schwarz's bayesian criteria. For the Cox models, Martingale residuals were used to examine the functional form of the continuous variables. After model building, the adequacy of the proportional hazards assumption was checked. All analyses were performed using a hierarchical method to account for intercenter variability. All results were considered significant with p values <0.05 . Data were analyzed with the statistical packages SAS version 9.4 (SAS Institute Inc., Cary, North Carolina) and SPSS version 21 (IBM Corporation, Armonk, New York).

RESULTS

The main baseline and procedural characteristics of the study population are shown in [Table 1](#). A detailed comparison between patients included in the study and patients at risk with lost echocardiographic follow-up ([Online Appendix](#)) includes a comparison of study patients with patients at risk who did not have available echocardiographic follow-up at 2 years ([Online Table 1](#)).

TAVR was performed through the transfemoral approach in the majority of patients, with valves used distributed equally between balloon-expandable and self-expanding types. More than one-half of these patients were discharged with dual antiplatelet therapy; 28% received vitamin K antagonists.

All patients ($n = 1,521$) had an echocardiogram performed at 6 to 12 months; 625 patients had an echocardiogram at 2 years (65% of patients at risk), 258 patients at 3 years (56% of patients at risk), and 129 patients at 4 years (45% of patients at risk). The mean echocardiographic follow-up was 20 ± 13 months, and the mean clinical follow-up was 28 ± 16 months.

TRANSPROSTHETIC GRADIENT PROGRESSION OVER TIME.

The average mean transaortic gradient decreased from 45.9 ± 16.1 mm Hg at baseline to 9.96 ± 5.37 mm Hg at discharge. The overall absolute change in transprosthetic gradient from discharge to follow-up was 0.59 ± 5.50 mm Hg ($p < 0.001$), and the annualized

TABLE 1 Baseline and Procedural Characteristics (N = 1,521)

Age, yrs	81 $\pm$ 7
Female	791/1,520 (52.0)
BMI, kg/m ²	27.4 $\pm$ 5.2
Hypertension	1,271/1,517 (83.8)
Diabetes mellitus	469/1,455 (32.2)
Coronary artery disease	793/1,516 (52.3)
Cerebrovascular disease	127/831 (15.3)
COPD	415/1,508 (27.5)
CKD, eGFR <60 ml/min	758/1,507 (50.3)
Log. EuroSCORE, %	17.82 $\pm$ 12.5
Porcelain aorta	134/1,230 (10.9)
Baseline echocardiogram	
LVEF, %	55.6 $\pm$ 14.4
Peak gradient, mm Hg	74.6 $\pm$ 24.6
Mean gradient, mm Hg	45.8 $\pm$ 16.1
Aortic regurgitation	
None or trace	487/1,433 (34.0)
Mild	552/1,433 (38.5)
Moderate	277/1,433 (19.3)
Severe	117/1,433 (8.2)
Procedural approach	
Transfemoral	1221/1,518 (80.4)
Transapical or transaortic	261/1,518 (17.2)
Prosthesis type	
Edwards*	738/1,521 (48.5)
CoreValve	756/1,521 (49.7)
Others	27/1,521 (1.8)
Valve size	
≤ 23 mm	335/1,514 (22.1)
>23 mm	1179/1,514 (77.9)
Valve-in-valve	86/1,513 (5.7)
Discharge echocardiogram	
LVEF, %	57.3 $\pm$ 13.2
Peak gradient, mm Hg	17.2 $\pm$ 9.5
Mean gradient, mm Hg	9.9 $\pm$ 5.4
Aortic regurgitation	
None or trace	708/1,521 (46.5)
Mild	519/1,521 (34.1)
Moderate	270/1,521 (17.8)
Severe	24/1,521 (1.6)
PPM	476/1,194 (39.9)
Severe PPM	117/1,194 (9.8)
Discharge medication	
Aspirin	1234/1,506 (81.9)
Clopidogrel	1061/1,508 (70.4)
VKA	423/1,501 (28.2)

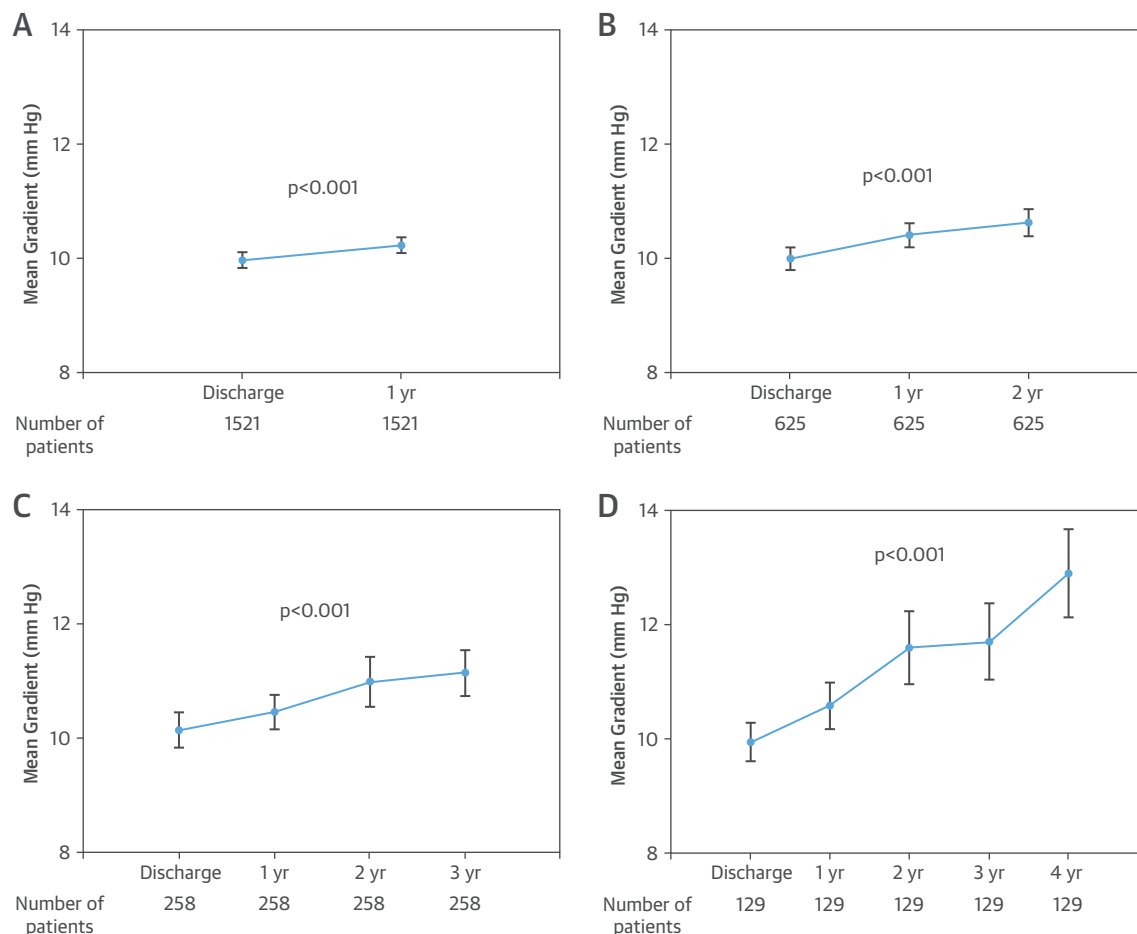
Values are mean $\pm$ SD or n/N (%). *SAPIEN and SAPIEN XT.

BMI = body mass index; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; PPM = prosthesis-patient mismatch; VKA = Vitamin K antagonist.

change in gradient was 0.30 ± 4.99 mm Hg/year (median: 0.00 [IQR: -1.38 to 2.00]) ([Figure 1](#), [Central Illustration](#)).

According to univariable and multivariable analyses, the variables independently associated with increased rates of transprosthetic gradient

FIGURE 1 Progression of Mean Gradient Post-TAVR



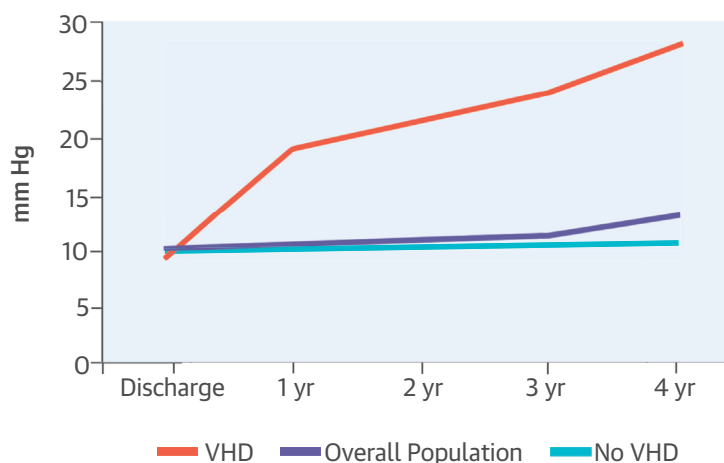
Transvalvular gradients significantly increase after transcatheter aortic valve replacement (TAVR), at 1-year (A), 2-year (B), 3-year (C), and 4-year (D) follow-up.

progression over time were as follows: lack of anti-coagulation therapy (β coefficient = 0.395; $p = 0.009$); a valve-in-valve (TAVR in a surgical bioprosthesis) procedure (β coefficient = 0.34; $p = 0.036$); and use of a ≤ 23 -mm transcatheter valve (β coefficient = 0.22; $p = 0.012$) (Table 2).

INCIDENCE AND PREDICTORS OF VALVE HEMODYNAMIC DETERIORATION. The incidence of VHD, defined as an absolute increase in mean transprosthetic gradient ≥ 10 mm Hg between discharge and last follow-up, was 4.5% (overall VHD) and 2.8% within the first year (early VHD). The mean transprosthetic gradient in patients with VHD increased from 9.5 ± 5.0 mm Hg at hospital discharge to 26.1 ± 11.0 mm Hg at follow-up ($p < 0.0001$). Among patients meeting criteria for VHD, 47 patients (70%) had mean gradients ≥ 20 mm Hg at follow-up, 15 patients (22%) had gradients ≥ 30

mm Hg, and 8 patients (12%) had gradients ≥ 40 mm Hg. The main clinical and procedural characteristics of patients according to the occurrence of VHD are shown in Table 3. Patients with VHD ($n = 68$) were younger ($p = 0.022$), had a higher body mass index (BMI) ($p < 0.001$), were more likely to have received smaller valves ($p = 0.038$) and to have had valve-in-valve procedures ($p = 0.008$), exhibited a higher rate of PPM post-procedure ($p = 0.034$), and were less likely to have received anticoagulation therapy as antithrombotic treatment post-TAVR ($p < 0.001$).

The results of the multivariable analysis for determining VHD predictors are summarized in Table 3 and Figure 2. The independent predictors of the multivariable analysis were the absence of anti-coagulation therapy at hospital discharge ($p = 0.002$), a valve-in-valve procedure ($p = 0.032$), use of a

CENTRAL ILLUSTRATION VHD After TAVR: Progression and Predictors**Progression of Transvalvular Mean Gradients Following TAVR****Predictors of Transcatheter Valve Hemodynamic Deterioration Post-TAVR**

- Absence of Anticoagulation Therapy at Discharge
- Valve-in-Valve Procedure (TAVR in a Surgical Valve)
- ≤ 23 mm Transcatheter Heart Valve
- Greater Body Mass Index

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(Top) Progression of mean gradient post-transcatheter aortic valve replacement (TAVR) according to the occurrence of valve hemodynamic deterioration (VHD). **(Bottom)** Independent predictors of valve hemodynamic deterioration.

TABLE 2 Factors Associated with Increased Transvalvular Gradient Progression

	Univariable Analyses		Multivariable Analyses	
	β Coefficient	p Value	β Coefficient	p Value
Peak gradient at discharge, mm Hg	0.010	0.047	—	—
Valve-in-valve	0.36	0.026	0.34	0.036
23-mm THV	0.258	0.009	0.266	0.026
Severe PPM	0.388	0.014	—	—
Absence of VKA at discharge	0.199	0.031	0.370	0.026

THV = transcatheter heart valve; other abbreviations as in Table 1.

23-mm valve ($p = 0.016$), and a greater BMI ($p = 0.001$). The rates of VHD, according to these factors, are presented in Figure 3.

Among the 60 patients meeting criteria for VHD and not receiving anticoagulation therapy at the time of diagnosis, 6 patients were treated with warfarin. Of these 6 patients, 4 patients demonstrated a normalization of the mean transprosthetic gradient, and 1 failed to respond to oral anticoagulation therapy and finally underwent another TAVR procedure; the sixth patient was lost to follow-up. Another 4 patients underwent another TAVR after observation of a rising transprosthetic gradient.

Compared with the whole cohort of at-risk patients, patients with echocardiographic follow-up at

TABLE 3 Baseline and Procedural Characteristics According to VHD Occurrence

	Valve Hemodynamic Deterioration		Univariate Model		Multivariate Model	
	No VHD (n = 1,453)	VHD (n = 68)	HR (95% CI)	p Value	HR (95% CI)	p Value
Age, yrs	81 ± 7	78 ± 9	0.97 (0.94-0.99)	0.022	—	—
Female	51.9	55.9	1.12 (0.66-1.91)	0.669	—	—
BMI, kg/m ²	27.3 ± 5.1	29.4 ± 5.9	1.08 (1.03-1.12)	<0.001	1.08 (1.03-1.13)	0.001
Hypertension	83.3	85.3	0.98 (0.49-1.94)	0.951	—	—
Dyslipidemia	65.9	80.0	1.64 (0.76-3.52)	0.208	—	—
Diabetes mellitus	31.7	42.4	1.51 (0.91-2.51)	0.110	—	—
Coronary artery disease	52.0	58.8	1.23 (0.74-2.03)	0.421	—	—
Cerebrovascular disease	14.6	10.0	0.75 (0.32-1.81)	0.527	—	—
COPD	27.6	25.0	0.87 (0.49-1.55)	0.640	—	—
CKD, eGFR <60 ml/min	50.1	54.4	0.93 (0.56-1.52)	0.757	—	—
Log. EuroSCORE, %	17.9 ± 12.6	16.5 ± 9.9	0.98 (0.96-1.00)	0.098	—	—
Porcelain aorta	10.9	10.2	0.60 (0.25-1.45)	0.254	—	—
Baseline echocardiogram						
LVEF, %	55.6 ± 14.6	54.6 ± 11.2	0.99 (0.98-1.01)	0.483	—	—
Peak gradient, mm Hg	74.6 ± 24.6	73.1 ± 24.3	1.00 (0.99-1.01)	0.757	—	—
Mean gradient, mm Hg	45.8 ± 16.1	45.9 ± 16.5	1.01 (0.99-1.02)	0.517	—	—
Moderate to severe aortic regurgitation	27.0	23.1	1.76 (0.77-4.02)	0.183	—	—
Procedural characteristics						
Balloon-expandable THV	47.7	66.2	1.94 (0.89-2.65)	0.190	—	—
≤23-mm THV	21.5	35.3	1.57 (1.03-2.42)	0.038	2.07 (1.14-3.76)	0.016
Valve-in-valve	5.3	13.2	2.74 (1.31-5.77)	0.008	2.32 (1.07-5.04)	0.032
Discharge echocardiogram variables						
LVEF, %	57.2 ± 13.2	57.4 ± 11.2	1.01 (0.99-1.03)	0.400	—	—
Peak gradient, mm Hg	19.1 ± 9.6	19.6 ± 8.4	0.99 (0.96-1.03)	0.733	—	—
Mean gradient, mm Hg	10.0 ± 5.3	9.5 ± 4.9	0.96 (0.90-1.01)	0.133	—	—
Moderate to severe aortic regurgitation	19.1	23.5	1.23 (0.29-5.27)	0.779	—	—
PPM						
Moderate to severe	39.7	55.2	1.97 (1.05-3.70)	0.034	—	—
Severe	9.4	20.0	2.63 (1.25-5.51)	0.010	—	—
Discharge medication						
Aspirin	81.6	88.2	1.28 (0.59-2.78)	0.527	—	—
Clopidogrel	70.2	73.5	1.45 (0.81-2.61)	0.210	—	—
VKA	29.0	11.8	3.16 (1.49-6.69)*	<0.001	3.17 (1.49-6.73)*	0.003
Echocardiographic follow-up, months	20 ± 13	20 ± 15	—	—	—	—

Values are mean ± SD or %, unless otherwise noted. *Absence of anticoagulation at discharge.

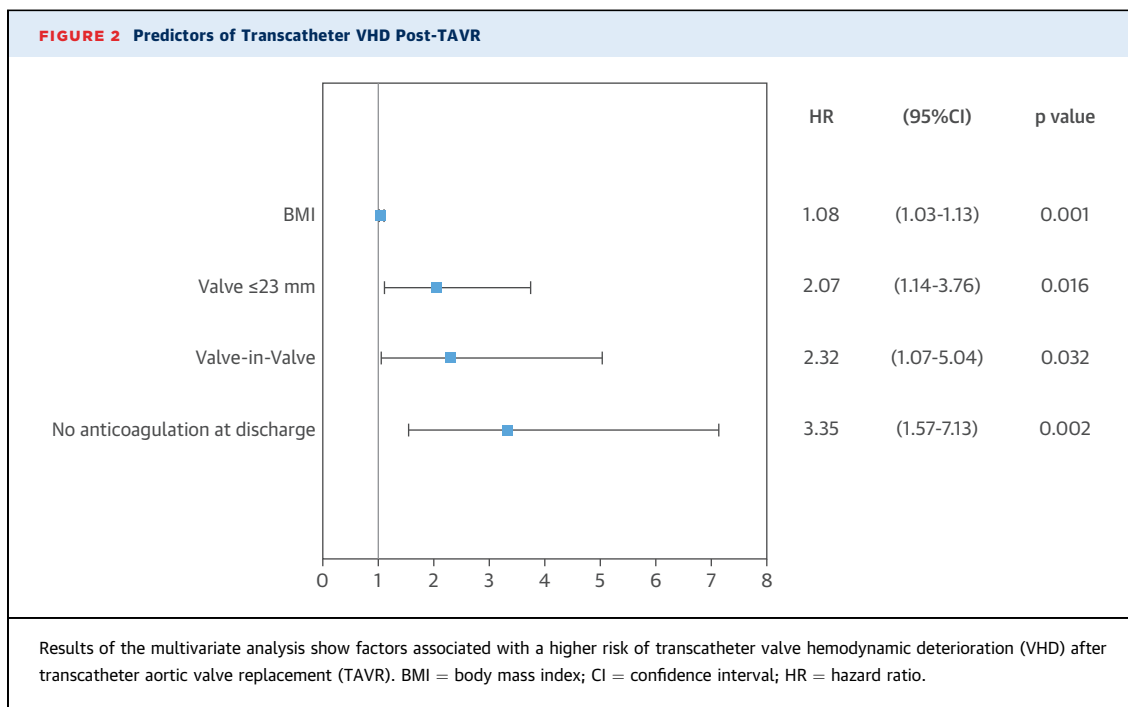
CI = confidence interval; HR = hazard ratio; VHD = valve hemodynamic deterioration; other abbreviations as in [Tables 1 and 2](#).

2 years were more likely to have a previous history of SAVR and chronic kidney disease and to have a greater BMI, and they were more frequently treated with small valves ([Online Table 2](#)). Given that aortic regurgitation (AR) at discharge may influence mean gradients during follow-up, a subanalysis excluding patients with prosthesis size ≤23 mm, valve-in-valve, and AR that was moderate to severe, was conducted. In this subanalysis, the absence of anticoagulation therapy at discharge was the only independent predictor of VHD (hazard ratio [HR]: 4.58; 95% confidence interval [CI]: 1.07 to 19.57; $p = 0.04$) ([Online Table 3](#)).

An additional analysis was performed to evaluate the factors associated with VHD within the year after TAVR (early VHD), defined as a ≥10 mm Hg increase

in mean transprosthetic gradient within the first year post-TAVR compared with discharge assessment. A total of 42 patients met criteria for early VHD. The main clinical and procedural characteristics of patients according to the occurrence of early VHD are shown in [Online Table 3](#). In multivariate analysis, the independent predictors of early VHD were the absence of anticoagulation therapy (HR: 6.17; 95% CI: 1.87 to 20.3; $p = 0.003$), a valve-in-valve procedure (odds ratio [OR]: 3.61; 95% CI: 1.48 to 8.84; $p = 0.005$); and greater BMI (OR for each increase in 1 kg/m²: 1.10; 95% CI: 1.04 to 1.16; $p < 0.001$).

Of the 42 patients presenting with early VHD, 2 underwent another TAVR procedure, and a further 4 patients were treated with warfarin. After the diagnosis of early VHD, additional echocardiography data



were available in 9 of the 36 patients who did not receive specific treatment for their VHD. No significant progression of mean transprosthetic gradients between 1 and 2 years post-TAVR were noted in these patients ($p = 0.26$) (Figure 4). A landmark analysis was conducted at 1-year follow-up to determine whether early VHD was associated with poorer clinical outcomes. There were no significant differences between the groups in death, cardiovascular death, or stroke at follow-up (Figure 5).

DISCUSSION

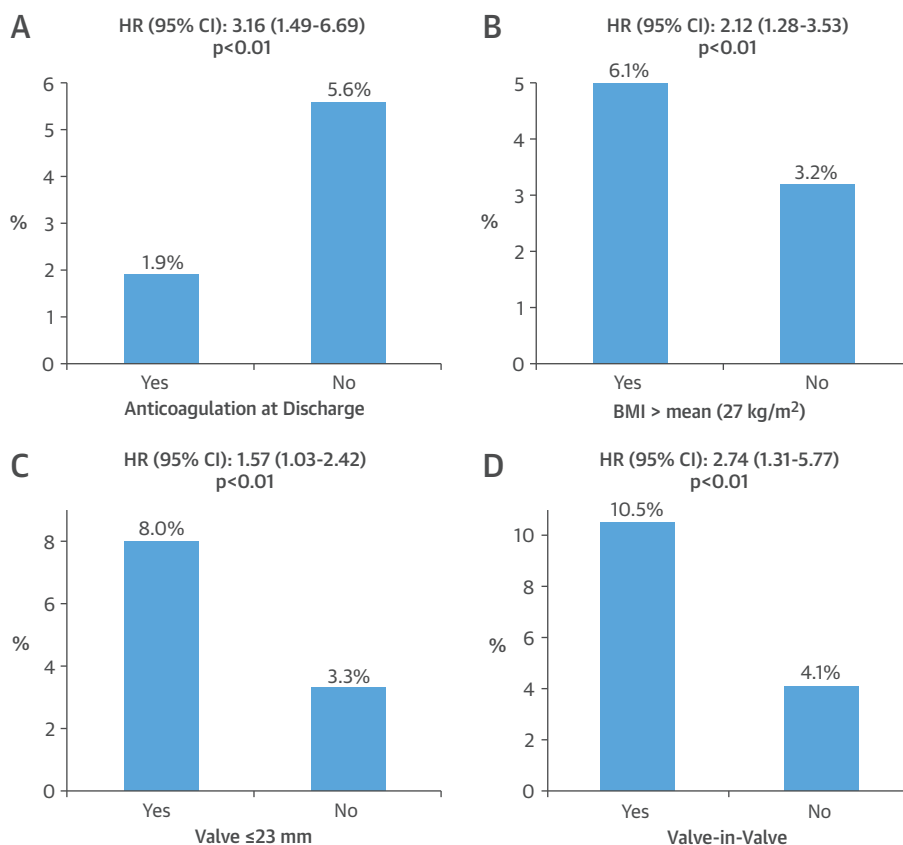
To the best of our knowledge, this is the first study systematically assessing the incidence, timing, and risk factors associated with VHD within a large TAVR cohort. The lack of anticoagulation therapy, a valve-in-valve procedure, a greater BMI, and the use of a 23-mm transcatheter heart valve (THV) were factors associated with higher rates of VHD post-TAVR. Identifying factors posing the greatest risk for incident THV deterioration is of utmost clinical relevance considering the recent rapid expansion of THV technologies, the inevitable push to treat lower-risk and younger patients with THV technologies, and the current lack of evidence-based post-TAVR antithrombotic therapeutic strategies.

THV dysfunction has yet to be systematically examined on a large-scale prospective basis. According to VARC-2 recommendations (15), assessing THV

stenosis requires an integrative process using multiple measures of valve function (15). Limitations of both flow-dependent (peak aortic jet velocity and mean gradient) and flow-independent (EOA and Doppler velocity index) parameters are, however, well recognized within this consensus document. Mean transprosthetic gradients ranging from 20 to 40 mm Hg have been proposed in VARC-2 to indicate mild valve stenosis, whereas a mean gradient >40 mm Hg is considered to represent moderate to severe THV stenosis post-TAVR. In fact, most patients (70%) with VHD in our study exhibited mean gradients ≥ 20 mm Hg at follow-up, 22% had gradients ≥ 30 mm Hg, and 12% had gradients ≥ 40 mm Hg. However, the use of a fixed cutoff point could lead to an overdiagnosis of acquired THV stenosis in patients with elevated mean transprosthetic gradients at discharge caused by suboptimal valve sizing, positioning, or deployment or as a result of PPM. Similarly, relevant changes in valve hemodynamics over time could be underestimated in patients with low mean transprosthetic gradients at discharge (e.g., mean gradient increasing from 5 to 18 mm Hg).

Previous studies in surgical patients used an annualized change in mean gradient of >3 mm Hg/year to define SVD post-SAVR (7). Although this definition seemed appropriate in surgical cohorts with longer-term follow-up, its direct extrapolation to TAVR-treated patients with a mean follow-up of 20 months could be misleading. As proposed in a recent study (8),

FIGURE 3 Incidence of VHD According to Different Risk Factors

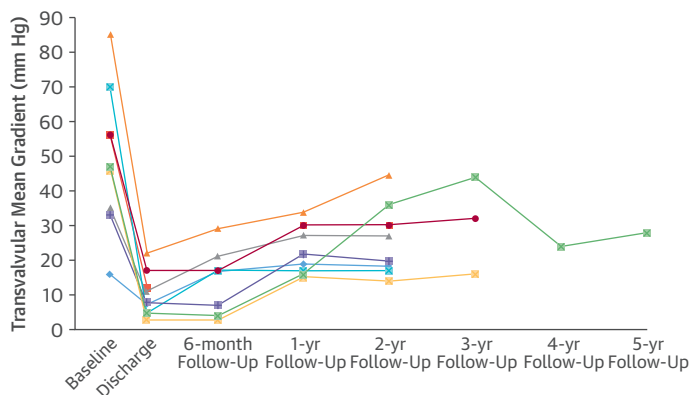


Incidence of valve hemodynamic deterioration (VHD) after transcatheter aortic valve replacement varied according to antithrombotic treatment (A), body mass index (BMI) (B), valve size (C), and valve-in-valve procedure (D). Abbreviations as in Figure 2.

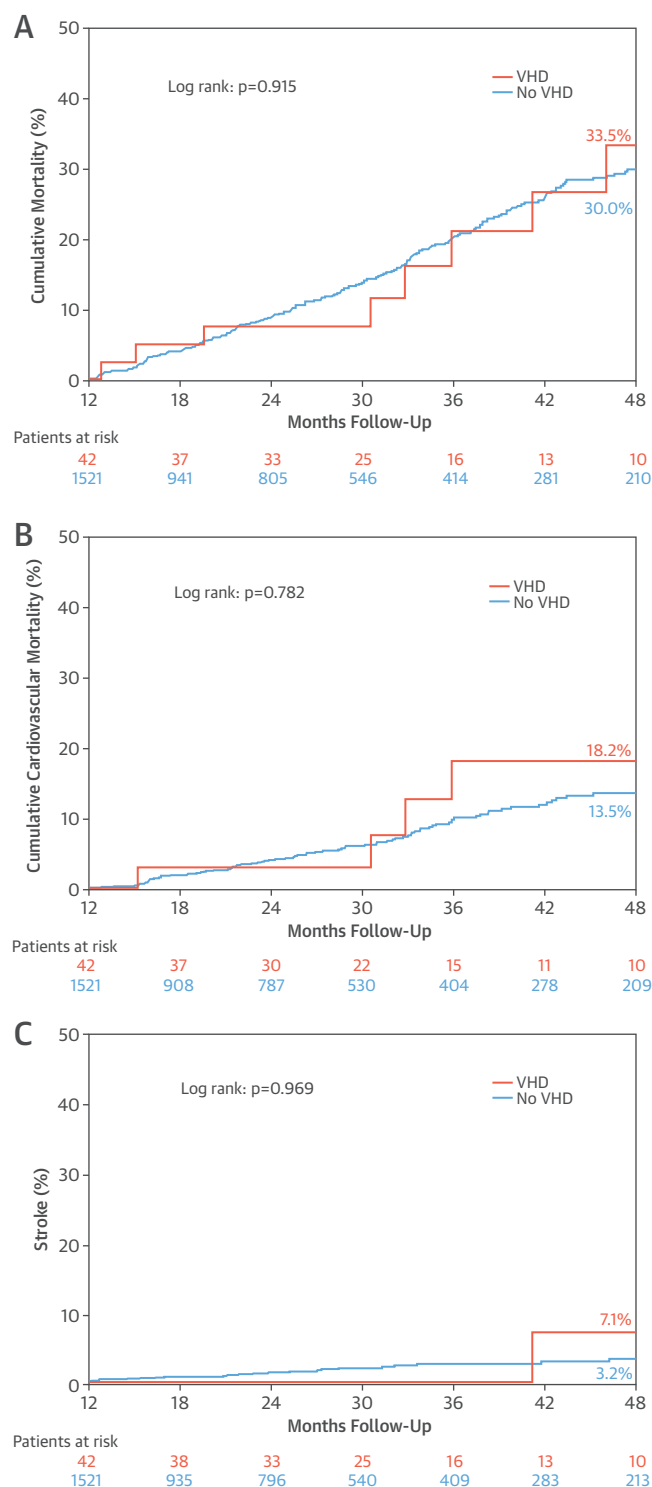
we defined VHD as an absolute increase in mean transprosthetic gradient of ≥ 10 mm Hg over time. In an attempt to describe the process of VHD more accurately, we further calculated the annualized change in mean transprosthetic gradient. Importantly, the main determinants of VHD were also associated with greater annualized change in transprosthetic gradient, thus highlighting the consistency of these phenomena and their etiological implications.

INCIDENCE OF VALVE HEMODYNAMIC DETERIORATION POST-TRANSCATHETER AORTIC VALVE REPLACEMENT. In this study, the annualized increment in mean transprosthetic gradient post-TAVR was 0.3 mm Hg/year. Some, but not all, previous studies assessing longer-term hemodynamic results post-TAVR have reported similar progression rates. In the Canadian multicenter experience (10), 339 patients were followed for a mean follow-up of 45-months, and a similar tendency of increasing gradients over

FIGURE 4 Evolution of VHD in the Absence of Specific Treatment



Changes in transvalvular gradient over time are seen in a selected group of patients ($n = 9$) diagnosed with valve hemodynamic deterioration (VHD) who did not receive any specific treatment for this condition.

FIGURE 5 1-Year Event Curves

At 1-year follow-up, there were no significant differences in death (A), cardiovascular death (B), or stroke (C), between patients with or without valve hemodynamic deterioration (VHD).

time was found (from 11.4 mm Hg at discharge to 12.4 mm Hg at 3-year follow-up). Similarly, Toggweiler et al. (20) reported 5-year outcomes of 88 patients undergoing TAVR. Mean transprosthetic gradients increased, on average, by 0.27 mm Hg/year ($p = 0.06$). In this previous study, the incidence of THV failure was 3.4%, with 1 patient presenting with moderate THV stenosis. In a cohort of 70 patients who underwent balloon-expandable TAVR, Gurvitch et al. (21) reported a significant elevation in mean gradients over 3 years (from 10 mm Hg at discharge to 12.1 mm Hg after 3 years; $p = 0.03$). Ussia et al. (22) conducted a multicenter prospective study of 126 patients treated with self-expanding THVs and described similar progression rates of transprosthetic gradients (from 8.5 mm Hg at discharge to 9 mm Hg at 2-year follow-up). In contrast, no significant increases in mean THV gradient or cases of prosthetic valve failure were reported during the 5-year follow-up of the PARTNER (Placement of Aortic Transcatheter Valves) randomized trial (11) (mean gradient at discharge 10.7 mm Hg vs. 10.6 mm Hg at 5-year follow-up; $p = 0.92$). Furthermore, the 3-year follow-up of the CoreValve Italian Registry (22) reported stable THV gradients over time (mean gradient: 10.3 mm Hg at discharge and at 3-year follow-up).

We showed that increment in mean gradient is not a uniform process occurring in all patients undergoing TAVR. In our study, no significant progression of mean transprosthetic gradients was found after exclusion of the 68 patients who demonstrated overt VHD (annualized overall change in mean transprosthetic gradient was -0.2 mm Hg/year for patients without VHD). This finding implies that VHD occurs within a specific subset of patients undergoing TAVR. Among the patients who satisfied criteria for VHD, only a small proportion received specific treatment. Additionally, most patients diagnosed with VHD failed to display a continued increase in gradient beyond 1 year (Figure 4).

DETERMINANTS OF VALVE HEMODYNAMIC DETERIORATION POST-TRANSCATHETER AORTIC VALVE REPLACEMENT. Bioprosthetic valve thrombosis is a life-threatening but unusual complication post-SAVR, with an incidence ranging between 0.36% and 1.26%, depending on valve type (23). Both U.S. and European guidelines highlight an increased risk of valve thrombosis within 3 months post-SAVR and suggest oral anticoagulation for most patients during this period. However, the incidence and possible prevention of valve thrombosis in patients treated with TAVR have not been well established. Recently, several concerns have arisen regarding valve

thrombosis post-TAVR. In a multicenter retrospective analysis focused on THV thrombosis that included 4,266 patients, the incidence of valve thrombosis was 0.61% ($n = 26$) (14). Exertional dyspnea was the most common clinical presentation (65%), but up to 31% of patients had no worsening symptoms. The mean transprosthetic gradient of patients with valve thrombosis was 41 ± 14 mm Hg. Anticoagulation therapy was effective in 88% of patients, even in those without visible thrombus on echocardiography, and this therapy resulted in a significant decrease in mean gradient within 2 months. In our study, no systematic transesophageal echocardiography (TEE), computed tomography (CT), or investigation for valve thrombosis was performed; however, the higher VHD incidence in patients without anticoagulation therapy suggested thrombotic mechanism as one of the likely causes of an increasing mean gradient over time. In a current ongoing study using 4-dimensional CT (NCT02426307), the relationship between valve thrombosis and medical therapy after TAVR will be assessed. Importantly, in our study, the incidence of VHD was as low as $<2\%$ among those patients receiving anticoagulation therapy, and it increased to close to 6% in those patients treated with antiplatelet but not anticoagulant therapy. In addition, the absence of anticoagulant therapy remained an independent predictor of VHD in a subanalysis excluding patients with small valves (≤ 23 mm), previous SAVR (valve-in-valve procedure), and moderate to severe AR at discharge. This subanalysis supported valve thrombosis as one of the main mechanisms underlying VHD and suggested that the incidence of subclinical valve thrombosis post-TAVR may be higher than previously reported. In addition, no significant differences in clinical outcomes were observed in patients with VHD at 1-year follow-up. This finding concurred with previous studies assessing valve thrombosis post-TAVR. In a study using multidetector CT, Leetmaa et al. (24) reported that the incidence of THV thrombosis after TAVR was higher than expected; however, most patients diagnosed with THV thrombosis were asymptomatic. Despite this lack of major clinical consequences, close follow-up of such patients may be recommended because a potentially higher rate of major valve degeneration, leading to structural valve failure and clinical events, cannot be excluded. Notably, this finding may also have important implications in TAVR clinical trials. There are ongoing randomized trials evaluating the potential benefits of anticoagulation (vs. antiplatelet) therapy after TAVR. It would be important to use these trial opportunities for embedding pre-specified subanalyses of the

changes in transvalvular gradients in these studies. In addition, VHD could be included as a secondary endpoint in TAVR trials.

Smaller prosthesis size was also an independent risk factor for VHD. As expected, post-implantation EOA is smaller in patients undergoing TAVR with 23-mm THVs than in those treated with >23 -mm valves. Given the EOA-gradient relationship is curvilinear, a small decrease in EOA during follow-up may result in a large increase in mean gradient in the patients with a small EOA at discharge. This may explain why patients with a small valve (and thus a smaller EOA) display a larger increase in a gradient compared to patients with larger valves. Consistently, previous studies (25,26) reported that PPM was an independent predictor of surgical bioprosthesis degeneration. This finding may explain the “smaller EOA reserve” of patients with PPM. In our study, severe PPM was associated with a higher incidence of VHD on univariate analysis ($p = 0.010$), but it failed to reach statistical significance after adjusting for prosthesis size and other factors. Future studies are needed to evaluate the impact of PPM on post-TAVR VHD further.

Higher post-procedural mean transprosthetic gradients have been described in several valve-in-valve-TAVR series (27). Eggebrecht et al. (28) suggested that this finding could raise concerns with respect to longer-term durability of the valve-in-valve TAVR procedures and proposed close echocardiographic follow-up for detecting early signs of VHD in these patients. In the present analysis, a greater increase in mean transprosthetic gradient over time as well as a higher incidence of VHD over time were found in patients who underwent TAVR after a previous SAVR. Calcification of surgical bioprostheses is not a uniform process and occurs predominantly in the areas of the valve leaflets where mechanical stress is higher (29). Accordingly, valve-in-valve implantation could result in increased mechanical stress on the THV leaflets, as well as abnormal flow turbulences, which could promote leaflet calcification, SVD, and associated VHD. The alteration of transvalvular flow pattern by the valve-in-valve procedure could also predispose to thrombosis and thus VHD.

The present analysis also highlights the association between larger BMIs and a higher risk of incident VHD. Several studies have suggested that lipid-mediated inflammatory mechanisms may contribute to aortic bioprosthetic degeneration (6,8). Metabolic syndrome and diabetes, which are directly linked to obesity, have been associated with SVD in SAVR (7,30). These conditions may also predispose to a

higher risk of thrombosis, thereby supporting the concept that this pathological process may contribute to VHD. Unfortunately, data on lipid or inflammatory factors were not available in our study, and the role of the lipid-mediated inflammatory path in post-TAVR VHD will need to be determined in future studies.

STUDY LIMITATIONS. This study is a retrospective analysis of prospectively collected data. Only patients who survived 6 months post-TAVR were included in the present analysis; thus, our data may have underestimated actual VHD incidence. Gradient assessment was made on the basis of the results of transthoracic echocardiograms analyzed and reported by each center. There was no independent echocardiographic core laboratory analysis in this study. Only echocardiographic examinations from patients with complete serial echocardiographic follow-up examinations were analyzed. This strict criterion for echocardiographic evaluation led to a decrease in the number of echocardiographic examinations available for analysis (at 2-year follow-up, 36% of patients had missing echocardiography data), and this may have influenced the results. The measures of EOA were missing in a significant number of patients; therefore, this parameter was not used to assess VHD. Data on stroke volume, heart rate, and hemoglobin at the time of different echocardiograms were not available for most patients, and these factors may have influenced mean gradient. Furthermore, systematic TEE or CT studies were not systematically performed in patients meeting criteria for VHD, to seek the underlying process (i.e., SVD, thrombosis, pannus) of the apparent VHD further. However, recent reports have outlined the limited sensitivity of both TEE and CT to detect valve thrombosis (13,24). Marked increases in gradients on TTE post-TAVR invariably imply the possibility of valve thrombosis necessitating empirical oral anticoagulation, which is often effective at reducing transprosthetic gradients (14,31). Additionally, the need for and the nature of treatment for VHD were empirically determined at each participating center, and no systematic follow-up after diagnosis of VHD was undertaken.

CONCLUSIONS

There was a mild but significant increase in transvalvular gradients over time after TAVR. In this large series, 4.5% of patients had a significant VHD during a mean follow-up of approximately 2 years, and 2.8% of patients had experienced VHD within the first year post-TAVR. Lack of anticoagulation therapy, use of a smaller valve, a valve-in-valve procedure, and greater BMI were associated with increased risk of VHD. These findings suggest the need for closer clinical and echocardiographic follow-up in patients with such characteristics. In addition, future large-scale, prospective studies involving centralized, standardized echocardiographic core laboratory and events adjudication are required to identify whether a specific antithrombotic regimen post-TAVR could reduce the risk of incident VHD.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Patients who have undergone TAVR are prone to progressively increasing transvalvular pressure gradients over time. Factors associated with hemodynamic deterioration include greater BMI, smaller valve diameter, a valve-in-valve procedure, and lack of anticoagulation.

TRANSLATIONAL OUTLOOK: Future studies should quantify the impact of early hemodynamic deterioration and compare the effects of different antithrombotic regimens on long-term clinical outcomes after TAVR.

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APPENDIX For supplemental tables, please see the online version of this article.