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Transvalvular Flow, Sex, and Survival After Valve Replacement Surgery in Patients With Severe Aortic Stenosis

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ABSTRACT

BACKGROUND The respective impacts of transvalvular flow, gradient, sex, and their interactions on mortality in patients with severe aortic stenosis undergoing surgical aortic valve replacement (AVR) are unknown.

OBJECTIVES This study sought to compare the impact of pre-operative flow-gradient patterns on mortality after AVR and to examine whether there are sex differences.

METHODS This study analyzed clinical, echocardiographic, and outcome data prospectively collected in 1,490 patients (544 women [37%]), with severe aortic stenosis and preserved left ventricular ejection fraction who underwent AVR.

RESULTS In this cohort, 601 patients (40%) had normal flow (NF) with high gradient (HG), 405 (27%) NF with low gradient (LG), 246 (17%) paradoxical low flow (LF)/HG, and 238 (16%) LF/LG. During a median follow-up of 2.42 years (interquartile range: 1.04 to 4.29 years), 167 patients died. Patients with LF/HG exhibited the highest mortality after AVR (hazard ratio [HR]: 2.01; 95% confidence interval [CI]: 1.33 to 3.03; $p < 0.01$), which remained significant after multivariate adjustment (HR: 1.96; 95% CI: 1.29 to 2.98; $p < 0.01$). Both LF/LG and NF/LG patients had comparable outcome to NF/HG ($p \geq 0.47$). Optimal thresholds of stroke volume index were obtained for men (40 ml/m^2) and women (32 ml/m^2). Using these sex-specific cutpoints, paradoxical LF was independently associated with increased mortality in both women (adjusted HR: 2.05; 95% CI: 1.21 to 3.47; $p < 0.01$) and men (adjusted HR: 1.54; 95% CI: 1.02 to 2.32; $p = 0.042$), whereas guidelines' threshold (35 ml/m^2) does not.

CONCLUSIONS Paradoxical LF/HG was associated with higher mortality following AVR, suggesting that a reduced flow is a marker of disease severity even in patients with HG aortic stenosis. Early surgical AVR (i.e., before gradient attains 40 mm Hg) might be preferable in these patients. Furthermore, the use of sex-specific thresholds (<40 ml/m^2 for men and <32 ml/m^2 for women) to define low-flow outperforms the guidelines' threshold of 35 ml/m^2 in risk stratification after AVR. (J Am Coll Cardiol 2020;75:1897-909) © 2020 by the American College of Cardiology Foundation.

A low-flow (LF) state (i.e., stroke volume index [SVi] ≤35 ml/m^2) in aortic stenosis (AS) can occur not only with reduced (i.e., classical low flow) but also with preserved (i.e., paradoxical low flow [PLF]) left ventricular ejection fraction (LVEF) (1). The prevalence of PLF is between 25% and 35% of patients with AS and preserved LVEF and, due to its increasingly recognized prognostic value, this entity has been incorporated in decision-making algorithms in recent guidelines (2,3). Aortic valve replacement (AVR), either surgical or transcatheter, has been shown to be beneficial in PLF AS patients (4,5). Classical LF has been largely shown to be associated with increased mortality after AVR, but the evidence regarding PLF is discordant (6-8). The impact of a low transvalvular pressure gradient

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ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

AVR = aortic valve replacement

CABG = coronary artery bypass grafting

CI = confidence interval

HG = high gradient

HR = hazard ratio

IQR = interquartile range

LF = low flow

LG = low gradient

LV = left ventricle

LVEF = left ventricular ejection fraction

MG = mean gradient

NF = normal flow

OR = odds ratio

PLF = paradoxical low flow

SV = stroke volume

SVi = stroke volume indexed to body surface area

on mortality after AVR is even less clear (9). Some investigators suggest that low gradient (LG) severe AS is actually a less malignant form of AS that will eventually progress to high-gradient (HG) severe AS and, therefore, should be treated conservatively (10). A flow-gradient pattern classification has been developed (11–13), and its prognostic value has been demonstrated after transcatheter aortic valve replacement (14), but not after surgical AVR.

Sex-specific responses and different thresholds for men and women have been described in both valvular disease (e.g., less calcification and more fibrosis in women) (15–17) and in the myocardial response to AS (e.g., greater degree of LV hypertrophy in men) (18–20). Even though the prevalence of PLF appears to be higher in women than in men (1,21), the influence of female sex on surgical outcomes is controversial (21–24), and little is known about sex differences among PLF AS patients. Furthermore, whether there is an interaction between sex and flow status on mortality after AVR, or if sex-specific thresholds should be used to identify LF status, is unknown.

The objectives of this study were to examine the respective impacts of flow and gradient on mortality after surgical AVR in patients with severe AS and preserved LVEF and to examine whether the SVi cutpoint and the clinical impact of LF differ between men versus women.

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METHODS

STUDY POPULATION. Among 2,170 consecutive patients with severe calcific AS who underwent AVR—with or without coronary artery bypass graft (CABG)—between 2004 and 2015 at the Quebec Heart and Lung Institute, we included 1,490 patients with severe AS and preserved LVEF (**Figure 1**). Data were prospectively collected and stored in an electronic database.

Patients for whom the primary indication for AVR was different from severe AS (e.g., aortic regurgitation, infectious endocarditis, CABG), patients with decreased LVEF (<50%), patients undergoing reoperative surgery, and patients with incomplete echocardiographic evaluation in the 3 months before AVR were excluded. The different type and size of prostheses are listed in Supplemental Table 1.

PRE-PROCEDURAL EVALUATION. All patients were evaluated pre-operatively to assess baseline comorbidities and symptomatic status and all underwent coronary angiography. Clinical data were prospectively collected.

ECHOCARDIOGRAPHY. All patients underwent a comprehensive transthoracic echocardiographic examination before AVR following guideline recommendations (25,26). The echocardiographic indices of AS severity included peak aortic jet velocity, peak and mean gradient (MG) (obtained with the modified Bernoulli equation), and aortic valve area calculated by continuity equation. SV was calculated by multiplying the flow velocity-time integral by the LV outflow tract area and was indexed to body surface area. The LV outflow tract diameter was measured at the aortic annulus (27), and Doppler echocardiographic measurement of stroke volume was corroborated by the 2-dimensional volumetric method. Patient-prosthesis mismatch was defined as the normal reference value of aortic valve area (for the model and size of the implanted prosthesis) indexed to the patient's body surface area with values adjusted for obese patients as per guidelines (28).

FLOW AND GRADIENT PATTERNS. Our population was divided into 2 groups according to flow: normal flow (NF): SVi ≥35 ml/m^2; and PLF: SVi <35 ml/m^2. We further stratified our population according to high (≥40 mm Hg) or low (<40 mm Hg) MG, thus obtaining 4 flow-gradient patterns: normal flow with high gradient (NF/HG), normal flow with low gradient (NF/LG), low flow with high gradient (LF/HG) and low flow with low gradient (LF/LG) (12).

VALVE WEIGHT. Each valve excised at the time of surgery was analyzed by 1 of 3 pathologists and weighted at the same laboratory scale that has an accuracy of +0.01 g. Severe anatomical AS was defined as ≥2.0 g for men and ≥1.2 g for women (29).

STUDY ENDPOINTS. The primary endpoint for this study was the cumulative all-cause mortality. Deaths were prospectively obtained from the Quebec National Institute of Statistics. To maximize the interrogation of the central Quebec Institute of Statistics database, a list with multiple demographics (including first and last names, dates of birth, and social security numbers) and a delay of 1 year between the last interrogation and closing follow-up dates were used.

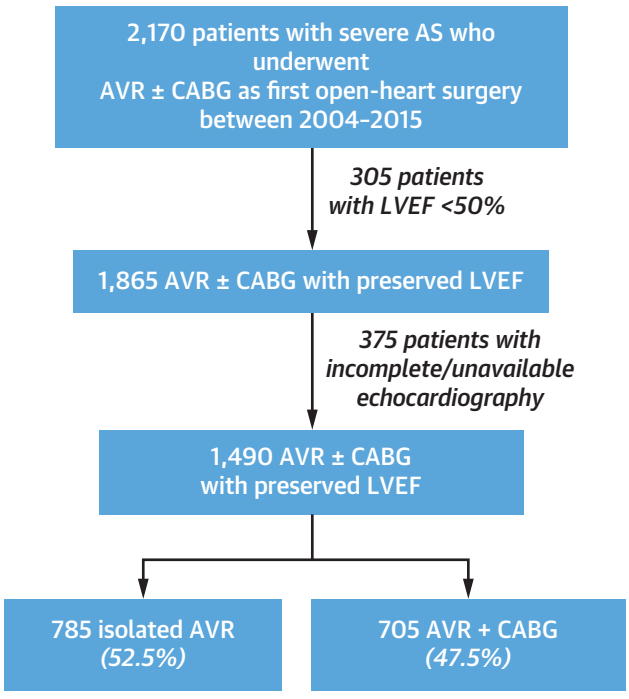
STATISTICAL ANALYSIS. Results are expressed as mean ± SD, median (interquartile range [IQR]), or percentage, as appropriate. For continuous variables, differences were analyzed with the use of

Student's *t*-test or 1-way analysis of variance (followed by the Bonferroni post hoc correction for multiple comparisons), whereas ordinal variables were analyzed using the Kruskal-Wallis test. The chi-square test was used to compare categorical variables. The association between overall mortality and risk factors was assessed using Kaplan-Meier curves (with log-rank test). Multivariate analyses of survival were made using Cox proportional hazard models and are presented as hazard ratio (HR), 95% confidence interval (CI), and p value. A p value of <0.05 was considered statistically significant. All variables with a p value of <0.10 and those of clinical relevance were entered in multivariate models. All variables in the Cox models verified the proportional hazards assumption on the basis of inspection of trends in the Schoenfeld residuals (all $p > 0.15$). Sex, MG, SVi, LVEF, and type of surgery (isolated AVR vs. AVR + CABG) were tested for interaction. The added value of SVi, MG, and LVEF to outcome assessment models was evaluated with likelihood ratio tests and category-free net reclassification index to predict mortality at 5 years post AVR. To analyze the effect of SVi on mortality and to evaluate optimal sex-specific thresholds, we used spline curve graphs where the x-axis represents SVi and the y-axis the relative risk of mortality, first on the whole cohort and then separately in men and women. Thresholds were verified by the use of maximally selected rank statistics (maxstat package in R, R Foundation, Vienna, Austria). Statistical analyses were made using STATA (version 15.1, StataCorp LLC, College Station, Texas) and RStudio (version 1.1.463, Boston, Massachusetts).

RESULTS

BASELINE CHARACTERISTICS. Among the 1,490 patients included in the study, 1,006 (67%) were in the NF group and 484 (33%) in the PLF group (Supplemental Table 2). Regarding flow-gradient patterns, 601 (40%) had NF/HG, 405 (27%) NF/LG, 246 (17%) LF/HG, and 238 (16%) LF/LG (**Figure 2**). **Table 1** shows the baseline characteristics according to the 4 flow-gradient patterns. There were significant differences in the prevalence of diabetes, coronary artery disease, previous myocardial infarction, chronic kidney disease, and atrial fibrillation. Surgical Parsonnet risk score was higher in patients with LG than in those with a HG. Valve weight was higher in patients with HG (both NF and LF) than in those with LG, as was the prevalence of anatomically severe AS (NF/HG: 94% and LF/HG: 92% vs. NF/LG: 78% and LF/LG: 74%; $p < 0.001$).

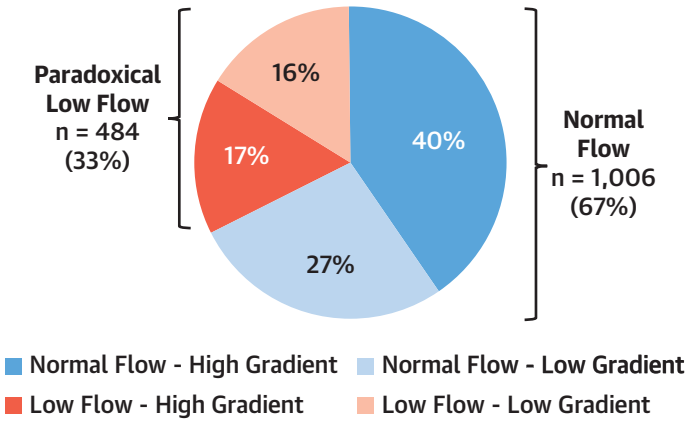
FIGURE 1 Flow Chart of the Study Population



AS = aortic stenosis; AVR = aortic valve replacement; CABG = coronary artery bypass graft; LVEF = left ventricular ejection fraction.

Table 2 shows the baseline characteristics according to the flow status and sex. Overall, women were older (72 ± 10 vs. 69 ± 10 years; $p < 0.001$), had smaller body surface area (1.68 ± 0.18 vs. 1.91 ± 0.18 m^2; $p < 0.001$), were more symptomatic (any symptom: 493 [91%] vs. 812 [86%]; New York Heart Association functional class III/IV: 252 [46%] vs. 319 [34%]; both $p < 0.01$), and had lower prevalence of coronary artery disease (192 [35%] vs. 535 [57%]; $p < 0.001$), lower prevalence of chronic kidney disease (14 [2.6%] vs. 51 [5.4%]; $p = 0.01$) and higher preoperative risk (median Parsonnet risk score: 3 [IQR: 2 to 5] vs. 2 [IQR: 1 to 3]; $p < 0.001$). Regarding echocardiographic parameters, women had smaller LVs (LV end-diastolic diameter: 4.36 ± 0.48 vs. 4.75 ± 0.58 cm, LV end-diastolic volume: 87 ± 23 vs. 107 ± 32 ml, and LV mass index: 104 ± 28 vs. 116 ± 33 g/m^2; all $p < 0.001$), smaller LV outflow tract diameter (20.1 ± 1.4 mm vs. 22.3 ± 1.8 mm, respectively; $p < 0.001$), and slightly smaller AV area index (0.40 ± 0.11 cm^2/m^2 vs. 0.42 ± 0.11 cm^2/m^2; $p < 0.001$). LVEF was marginally higher in women than in men (63 ± 7% vs. 62 ± 7%; $p < 0.01$). There were no significant differences in relative wall thickness ratio (0.49 ± 0.11

FIGURE 2 Prevalence of Flow and Gradient Patterns Before AVR



Prevalence of normal flow and paradoxical low flow and different flow-gradient patterns before aortic valve replacement (AVR).

vs. 0.48 ± 0.11 in women and men, respectively; p = 0.19), peak velocity (4.2 ± 0.8 vs. 4.2 ± 0.8 m/s; p = 0.93), MG (44 ± 17 vs. 44 ± 16 mm Hg; p = 0.33), or SVi (38 ± 8 vs. 39 ± 9 ml/m^2, respectively; p = 0.06).

IMPACT OF FLOW, GRADIENT, AND LVEF ON MORTALITY. There were 167 deaths during a median follow-up of 2.42 (IQR: 1.04 to 4.29) years. Eighteen patients (1.3 ± 0.3%) were dead within 30 days, 82 (6.6 ± 0.7%) at 2 years, and 134 (15.3 ± 1.4%) at 5 years. Advanced age (odds ratio [OR]: 1.07; 95% CI: 1.01 to 1.13 per 1-year increment; p = 0.02), female sex (OR: 2.83; 95% CI: 1.09 to 7.35; p = 0.03), and SVi (OR: 1.39; 95% CI: 1.06 to 1.83; p = 0.019) were associated with increased 30-day mortality, whereas MG (p = 0.82), LVEF (p = 0.18), or surgery type (p = 0.81) were not. PLF as a binary classification was also associated with increased 30-day mortality (OR: 2.69; 95% CI: 1.06 to 6.87; p = 0.038).

Overall, patients with PLF had increased cumulative all-cause mortality (HR: 1.60; 95% CI: 1.17 to 2.18; p < 0.01) compared with patients with NF (**Figure 3A**). Regarding transvalvular gradient, there was no difference in overall mortality in patients with HG (≥40 mm Hg) versus LG (<40 mm Hg) in univariate analysis (p = 0.64) (**Figure 3B**). Patients with an LVEF at the lower end of the normal spectrum (i.e., 50% to 59%) had increased overall mortality versus those with LVEF >60% (HR: 1.57; 95% CI: 1.12 to 2.20; p < 0.01) (**Figure 3C**). Finally, regarding flow-gradient patterns, LF/HG was the only pattern associated with increased mortality (HR: 2.0; 95% CI: 1.33 to 3.03; p < 0.01), considering NF/HG as the referent (**Figure 3D**).

Variables associated with overall mortality in univariate analyses are detailed in **Table 3**.

After multivariate analyses, age, New York Heart Association functional class III/IV, diabetes, chronic kidney disease, and chronic obstructive pulmonary disease remained independent predictors of overall mortality (all p ≤ 0.02) (**Table 4**). PLF remained an independent predictor of overall cumulative mortality after comprehensive multivariate adjustment (HR: 1.53; 95% CI: 1.11 to 2.10; p < 0.01) (**Table 4**, background model in Supplemental Table 3 and Cox-adjusted survival curves in Supplemental Figure 1). A higher transvalvular MG was independently associated with increased mortality. When dichotomized, patients with LG (i.e., <40 mm Hg) showed a trend to lower mortality (HR: 0.74; 95% CI: 0.54 to 1.01; p = 0.056). Finally, LF/HG (but not the other flow-gradient patterns) remained independently associated with increased mortality (Supplemental Figure 2). SVi remained independently associated with increased mortality and provided additional prognostic value to the nested predictive models adjusted for clinical variables, LVEF, and MG (likelihood ratio test p = 0.01; net reclassification improvement 0.23 ± 0.10; p = 0.026) (Supplemental Table 4). The additive prognostic value of SVi remained significant even when analyzing only the subgroup of patients with HG (likelihood ratio test p < 0.001; net reclassification improvement 0.37 ± 0.14; p = 0.008).

Higher post-operative (discharge) MG was independently associated with increased mortality when added to the multivariate model described in **Table 4** (HR: 1.05 for 1 mm Hg increase; 95% CI: 1.02 to 1.08; p < 0.001). However, both pre-operative LF (HR: 1.53; 95% CI: 1.11 to 2.11; p < 0.001) and LF/HG pattern (HR: 1.81; 95% CI: 1.18 to 2.77; p = 0.007) remained significant after adjustment for post-operative MG.

There was no interaction among MG or SVi and LVEF, atrial fibrillation, or previous myocardial infarction (all p > 0.51). (Supplemental Figure 3). Even though patients undergoing combined surgery (AVR + CABG) had longer cardiopulmonary bypass and clamp time than did patients undergoing isolated AVR (120 vs. 86 min and 95 vs. 65 min, respectively; both p < 0.001), there was no interaction between type of surgery and LF regarding mortality (p = 0.31) (Supplemental Figure 3).

INFLUENCE OF SEX AND FLOW STATUS IN OVERALL MORTALITY AND SEX-SPECIFIC THRESHOLDS. Overall mortality was not different in women and men (66 [44 ± 13%] vs. 101 [55 ± 1 2%], respectively, log rank p = 0.28), although early mortality was

TABLE 1 Baseline Characteristics According to Transvalvular Flow and Gradient Patterns

	Baseline Normal Flow (n = 1,006, 67%)		Baseline Paradoxical Low Flow (n = 484, 33%)		
	Normal Flow/High Gradient (n = 601, 40%)	Normal Flow/Low Gradient (n = 405, 27%)	Low Flow/High Gradient (n = 246, 17%)	Low Flow/Low Gradient (n = 238, 16%)	p Value
Clinical data					
Age, yrs	70 ± 10*‡§	71 ± 9†‡§	69 ± 11*‡§	71 ± 9†‡§	0.003
Female	206 (34)	152 (37)	107 (44)	79 (33)	0.05
Body surface area, m^2	1.82 ± 0.20‡§	1.80 ± 0.20‡§	1.84 ± 0.22*†‡§	1.88 ± 0.22†‡§	<0.001
Systolic blood pressure, mm Hg	128 ± 18	131 ± 20	128 ± 18	130 ± 19	0.12
Diastolic blood pressure, mm Hg	71 ± 10‡§	71 ± 11‡§	74 ± 11*†‡§	74 ± 10*†‡§	<0.001
Heart rate, beats/min	65 ± 10‡§	64 ± 11‡§	73 ± 12*†‡§	70 ± 11*†‡§	<0.001
Symptomatic	520 (87)	357 (88)	222 (90)	206 (87)	0.46
NYHA functional class III/IV	213 (35)	158 (39)	103 (42)	97 (41)	0.25
Hypertension	411 (68)	302 (75)	173 (70)	182 (76)	0.05
Diabetes	148 (25)‡§	116 (29)	84 (34)†	81 (34)†	0.008
COPD	67 (11)	50 (12)	25 (10)	38 (16)	0.19
CAD	246 (41)*§	244 (60)†‡	89 (36)*§	148 (62)†‡	<0.001
Previous myocardial infarction	69 (11)*§	74 (18)†‡	27 (11)*§	51 (21)†‡	<0.001
Concomitant CABG	236 (40)*§	239 (59)†‡	93 (38)*§	137 (58)†‡	<0.001
Chronic kidney disease	18 (3)§	24 (6)	6 (2)	17 (7)†	0.009
Atrial fibrillation	45 (7)§	25 (6)§	25 (10)	36 (15)*†	0.001
Obesity	173 (29)‡§	110 (27)‡§	98 (40)*†	95 (40)*†	<0.001
Parsonnet risk score	2 (1–3)*§	3 (2–5)†‡	2 (1–4)*	3 (2–5)†	<0.001
Valve weight, g	3.18 ± 1.33*§	2.27 ± 1.11†‡	2.95 ± 1.31*§	2.32 ± 1.08†‡	<0.001
Anatomically severe AS	445 (94)*§	231 (78)†‡	187 (92)*§	137 (74)†‡	<0.001
Echocardiographic data					
Before AVR					
LV end-diastolic diameter, cm	4.65 ± 0.59‡	4.65 ± 0.62‡	4.48 ± 0.53*†	4.56 ± 0.53	<0.001
LV end-diastolic volume, ml	102 ± 30‡	102 ± 34‡	93 ± 26*†	97 ± 27	<0.001
Relative wall thickness ratio	0.49 ± 0.11*	0.45 ± 0.10‡§	0.51 ± 0.11*§	0.47 ± 0.11*†	<0.001
LV mass index, g/m^2	119 ± 32*§	105 ± 32†	112 ± 32§	102 ± 26†‡	<0.001
Peak aortic jet velocity, m/s	4.7 ± 0.5*§	3.6 ± 0.4†‡	4.7 ± 0.6*§	3.5 ± 0.5†‡	<0.001
Mean gradient, mm Hg	55 ± 13*§	30 ± 7†‡	55 ± 14*§	29 ± 8†‡	<0.001
LVOT diameter, cm	2.19 ± 0.21‡§	2.16 ± 0.20‡§	2.07 ± 0.18*†	2.11 ± 0.17*†	<0.001
Aortic valve area, cm^2	0.71 ± 0.17*‡§	0.91 ± 0.19†‡§	0.54 ± 0.14*†§	0.77 ± 0.18*†‡	<0.001
Indexed aortic valve area, cm^2/m^2	0.39 ± 0.08*‡	0.51 ± 0.10†‡§	0.29 ± 0.07*†§	0.41 ± 0.09*‡	<0.001
Z_{va}, mm Hg/ml/m^2	4.3 ± 0.8*‡§	3.9 ± 0.7†‡§	6.0 ± 1.1*†§	5.3 ± 1.0*†‡	<0.001
LV ejection fraction, %	63 ± 7‡§	63 ± 7‡	61 ± 6*†	62 ± 7†	<0.001
LVEF 50%–59%	87 (14)‡§	75 (19)	61 (25)†	49 (21)†	0.003
Mean transvalvular flow, ml/s	257 ± 57‡§	247 ± 43‡§	187 ± 35*†	200 ± 38*†	<0.001
Stroke volume, ml	79 ± 17*‡§	76 ± 13†‡§	56 ± 9*†	57 ± 9*†	<0.001
SVi, ml/m^2	44 ± 8*‡§	42 ± 6†‡§	31 ± 3*†	31 ± 3*†	<0.001
After AVR					
SVi - discharge, ml/m^2	34 ± 8‡§	34 ± 8‡§	31 ± 8*†	30 ± 7*†	<0.001
Patient-prosthesis mismatch					0.69
Moderate	110 (19.8)	66 (17.7)	46 (19.6)	42 (18.8)	
Severe	4 (0.7)	0 (0)	2 (0.9)	2 (0.9)	

Values are mean ± SD, n (%), or median (interquartile range). *Different to NF/LG. †Different to NF/HG. ‡Different to LF/HG. §Different to LF/LG.

AS = aortic stenosis; AVR = aortic valve replacement; CABG = coronary artery bypass graft; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; HG = high gradient; LF = low flow; LG = low gradient; LV = left ventricle; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; NF = normal flow; NYHA = New York Heart Association; SVi = stroke volume index; Z_{va} = valvulo-arterial impedance.

higher in women than in men: 30 days: 11 (2.1 ± 0.6%) versus 7 (0.8 ± 0.3%), respectively (p = 0.026); 1 year: 33 (6.7 ± 1.1%) versus 29 (3.4 ± 0.6%), respectively (p = 0.037); and 2 years: 40 (8.6 ± 1.3%) versus 42 (5.4 ± 0.8%), respectively (p = 0.012) (**Figure 4**).

Using the standard definition of 35 ml/m^2, PLF was associated with increased mortality in women (HR: 1.95; 95% CI: 1.18 to 3.22; p < 0.01), but not in men (HR: 1.25; 95% CI: 0.79 to 1.85; p = 0.39) (Supplemental Figure 4). There was a significant

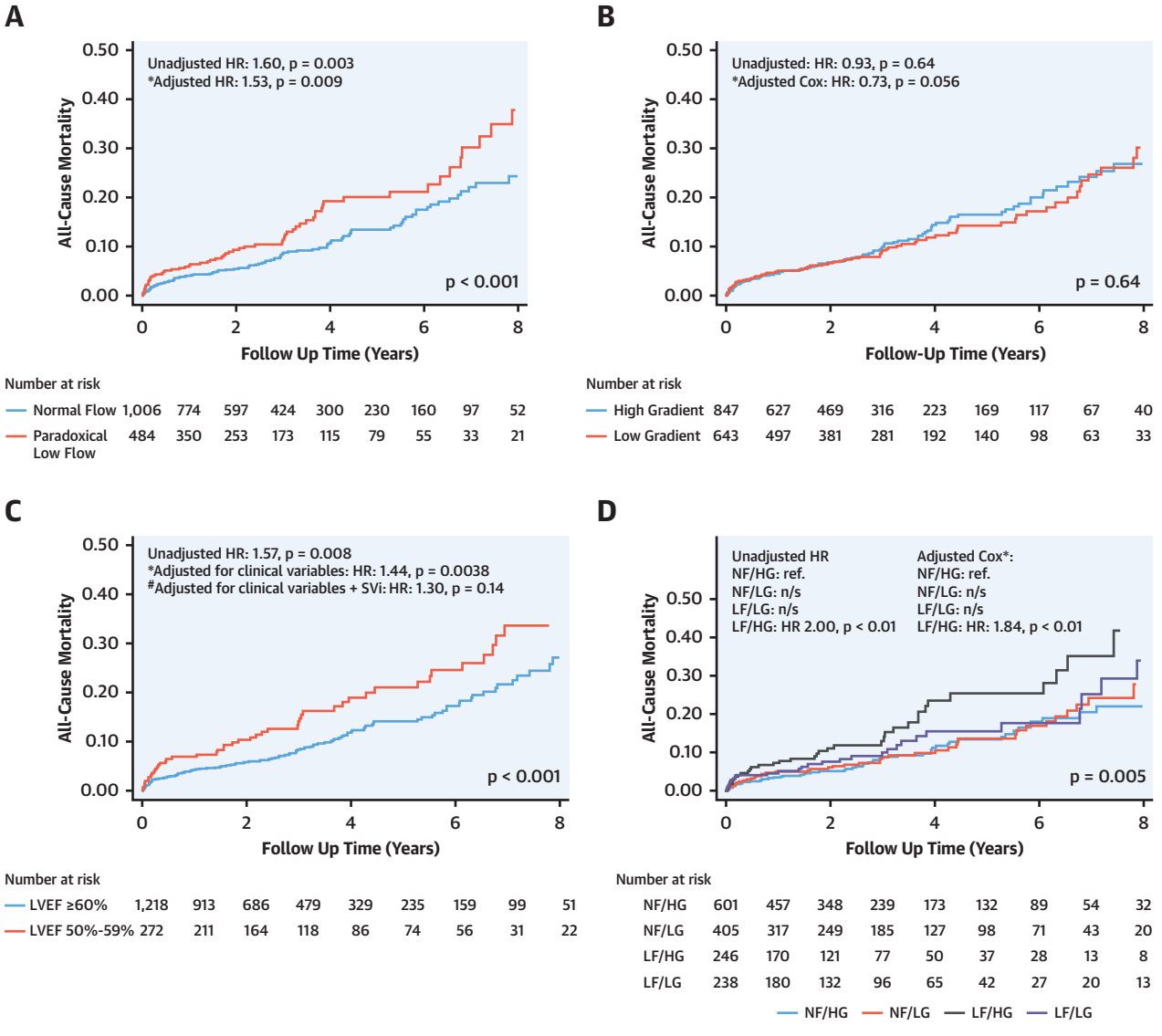
TABLE 2 Baseline Characteristics According to Sex and Flow Status

	Men (n = 946, 63%)			Women (n = 544, 37%)		
	Normal Flow (n = 648, 69%)	Low Flow (n = 298, 31%)	p Value	Normal Flow (n = 358, 66%)	Low Flow (n = 186, 34%)	p Value
Clinical data						
Age, yrs	69 ± 10	69 ± 10	0.77	72 ± 9	71 ± 10	0.31
Body surface area, m^2	1.90 ± 0.17	1.94 ± 0.19	<0.01	1.65 ± 0.16	1.73 ± 0.20	<0.01
Systolic blood pressure, mm Hg	128 ± 18	128 ± 18	0.61	130 ± 20	130 ± 20	0.79
Diastolic blood pressure, mm Hg	72 ± 10	75 ± 10	<0.01	70 ± 10	73 ± 10	0.01
Heart rate, beats/min	64 ± 11	71 ± 12	<0.01	67 ± 10	72 ± 12	<0.01
Symptomatic	553 (85)	259 (87)	0.41	324 (91)	169 (91)	0.89
NYHA functional class III/IV	206 (32)	113 (38)	0.06	165 (46)	87 (47)	0.88
Hypertension	455 (70)	211 (71)	0.85	258 (72)	144 (77)	0.18
Diabetes	181 (28)	99 (33)	0.10	83 (23)	66 (35)	<0.01
COPD	77 (12)	39 (13)	0.60	40 (11)	24 (13)	0.55
CAD	363 (56)	172 (58)	0.62	127 (35)	65 (35)	0.90
Previous myocardial infarction	107 (17)	55 (19)	0.46	36 (10)	23 (12)	0.41
Concomitant CABG	349 (54)	163 (55)	0.81	126 (35)	67 (36)	0.85
Chronic kidney disease	35 (5.4)	16 (5.4)	0.98	7 (2)	7 (4)	0.21
Atrial fibrillation	37 (6)	41 (14)	<0.01	33 (9)	20 (11)	0.57
Obesity	183 (28)	108 (36)	0.01	100 (28)	85 (46)	<0.01
Parsonnet risk score	2 (1–4)	2 (1–4)	0.26	3 (2–5)	4 (2–5)	0.37
Valve weight, g	3.25 ± 1.36	2.97 ± 1.32	0.008	2.06 ± 0.82	2.10 ± 0.86	0.65
Anatomically severe AS	425 (86)	188 (77)	0.004	251 (92)	136 (94)	0.35
Echocardiographic data						
Before AVR						
LV end-diastolic diameter, cm	4.8 ± 0.6	4.6 ± 0.5	<0.01	4.4 ± 0.5	4.3 ± 0.5	0.32
LV end-diastolic volume, ml	110 ± 33	101 ± 27	<0.01	88 ± 23	86 ± 22	0.31
Relative wall thickness ratio	0.47 ± 0.11	0.49 ± 0.11	<0.01	0.48 ± 0.11	0.50 ± 0.10	0.14
LV mass index, g/m^2	118 ± 34	110 ± 30	<0.01	105 ± 28	102 ± 29	0.30
Peak aortic jet velocity, m/s^1	4.3 ± 0.7	4 ± 0.8	<0.01	4.2 ± 0.7	4.1 ± 0.9	0.26
Mean gradient, mm Hg	45 ± 16	41 ± 16	<0.01	44 ± 17	44 ± 18	>0.99
Mean gradient <40 mm Hg	253 (39)	159 (53)	<0.01	152 (42)	79 (42)	>0.99
LVOT diameter, cm	2.26 ± 0.19	2.16 ± 0.16	<0.01	2.03 ± 0.14	1.96 ± 0.13	<0.01
Aortic valve area, cm^2	0.84 ± 0.21	0.69 ± 0.19	<0.01	0.71 ± 0.17	0.57 ± 0.18	<0.01
Indexed aortic valve area, cm^2/m^2	0.44 ± 0.11	0.36 ± 0.10	<0.01	0.43 ± 0.11	0.33 ± 0.10	<0.01
Z_{va}, mm Hg/ml/m^2	4.1 ± 0.8	5.5 ± 1.1	<0.01	4.2 ± 0.8	5.8 ± 1.1	<0.01
LVEF, %	63 ± 7	61 ± 7	<0.01	64 ± 8	62 ± 6	<0.01
LVEF 50%–59%	116 (18)	73 (25)	0.018	46 (13)	37 (20)	0.03
Mean transvalvular flow, ml/s	269 ± 51	208 ± 34	<0.01	225 ± 39	171 ± 28	<0.01
Stroke volume, ml	82 ± 15	60 ± 9	<0.01	70 ± 12	52 ± 8	<0.01
SVi, ml/m^2	43 ± 7	31 ± 3	<0.01	43 ± 7	30 ± 3	<0.01
After AVR						
SVi – discharge, ml/m^2	34 ± 8	32 ± 7	<0.01	33 ± 8	30 ± 8	<0.01
Patient-prosthesis mismatch			0.16			0.62
Moderate	135 (23)	76 (27)		117 (34)	77 (43)	
Severe	2 (0.3)	3 (1)		6 (2)	6 (3)	

Values are mean ± SD, n (%), or median (interquartile range).
Abbreviations as in Table 1.

interaction between sex and flow status (p for interaction = 0.04), as well as between sex and flow-gradient patterns (p = 0.009). The effect of flow-gradient patterns was also significant in women (log-rank test p < 0.001; Cox-adjusted HR for LF/HG: 3.33; 95% CI: 1.68 to 6.6; p < 0.01), but not in men (log-rank test p = 0.65; Cox-adjusted HR for LF/HG: 1.29; 95% CI: 0.73 to 2.29; p = 0.38) (Supplemental Figure 5). An interaction was also found between sex and LVEF (p = 0.03). LVEF 50% to 59% was associated with increased mortality in women (HR: 2.08; 95% CI: 1.22 to 3.56; p = 0.007), but not in men (HR: 1.36; 95% CI: 0.88 to 2.10; p = 0.16) (Supplemental Figure 6).

FIGURE 3 **Impact of Flow, Gradient, and LVEF on Mortality After AVR**



Kaplan-Meier curves of cumulative mortality for **(A)** normal flow (NF) versus paradoxical low flow (LF), **(B)** high gradient (HG) versus low gradient (LG), **(C)** LVEF 50% to 59% versus LVEF >60%, and **(D)** according to flow-gradient patterns. *Cox analyses were adjusted for age, sex, coronary artery disease, New York Heart Association functional class III/IV, systemic hypertension, atrial fibrillation, diabetes, chronic obstructive pulmonary disease, and chronic kidney disease. Adjustment for LVEF, mean transvalvular gradient, and stroke volume index (SVi) were made as appropriate. HR = hazard ratio; n/s = not significant; ref = referent; other abbreviations as in **Figure 1**.

Optimal cutpoints were obtained for men (40 ml/m^2) and women (32 ml/m^2) by the use of spline curves and maximally selected rank statistics (**Central Illustration**, panels A and B). Using these sex-specific cutpoints, PLF was independently associated with increased mortality in both women (adjusted HR: 2.05; 95% CI: 1.21 to 3.47; p < 0.01) and men (adjusted HR: 1.54; 95% CI: 1.02 to 2.32; p = 0.042) (**Central Illustration**, panel C, Supplemental Figure 4). Using the newly proposed optimal cutpoints, PLF remained independently associated with higher mortality (adjusted HR: 1.75; 95% CI: 1.25 to 2.46; p = 0.001) (Supplemental Figure 7). When analyzing survival according to flow-gradient patterns using sex-specific cutpoints, LF/HG was still the only pattern associated with increased mortality (HR: 1.91; 95% CI: 1.24 to 2.94; p = 0.003) (Supplemental Figure 8). Using sex-specific thresholds, there was also no interaction

TABLE 3 Univariate Predictors of Overall Mortality

		Univariate		
	Increment	HR	95% CI	p Value
Age	1 yr	1.06	1.04–1.08	<0.0001
Sex	Female	1.18	0.87–1.62	0.29
Type of surgery	Concomitant CABG	1.20	0.88–1.62	0.24
NYHA functional class III/IV	Yes	1.86	1.37–2.52	<0.0001
CAD	Yes	1.50	1.11–2.05	0.009
Diabetes	Yes	1.77	1.29–2.42	<0.0001
COPD	Yes	1.88	1.30–2.72	0.001
AF	Yes	2.20	1.44–3.37	<0.0001
CKD	Yes	3.21	2.07–4.96	<0.0001
Hypertension	Yes	1.95	1.33–2.87	0.001
Obesity	Yes	1.11	0.80–1.53	0.54
Parsonnet risk score	1 point	1.12	1.09–1.14	<0.0001
LVEF 50%–59%	Yes	1.57	1.12–2.20	0.008
Mean gradient	5 mm Hg increase	1.03	0.98–1.07	0.28
Mean gradient <40 mm Hg	Yes	0.93	0.68–1.27	0.64
Peak aortic velocity	1 m/s increase	1.17	0.96–1.43	0.12
AVA_i	0.1 cm^2/m^2 decrease	1.28	1.10–1.48	0.001
Z_{va}	1 mm Hg/ml/m^2 increase	1.29	1.14–1.47	<0.0001
SVi	5 ml/m^2 decrease	1.20	1.08–1.32	<0.0001
PLF, guidelines threshold	SVi <35 ml/m^2	1.60	1.17–2.18	0.003
PLF, sex-specific threshold	Men: SVi <40 ml/m^2 Women: SVi <32 ml/m^2	1.65	1.21–2.23	0.001
Flow-gradient patterns, guidelines threshold				
NF/HG	Referent	–	–	–
NF/LG		1.08	0.72–1.60	0.71
LF/HG		2.0	1.33–3.03	0.001
LF/LG		1.33	0.84–2.09	0.22
Flow-gradient patterns, sex-specific threshold				
NF/HG		–	–	–
NF/LG		1.04	0.66–1.63	0.87
LF/HG		1.88	1.23–2.81	0.002
LF/LG		1.46	0.95–2.25	0.08

Guidelines threshold: SVi <35 ml/m^2. Sex-specific threshold: men: SVi <40 ml/m^2 and women: SVi <32 ml/m^2.
AF = atrial fibrillation; AVA_i = indexed aortic valve area; CI = confidence interval; HR = hazard ratio; CKD = chronic kidney disease; PLF = paradoxical low flow; other abbreviations as in Table 1.

among MG or SVi and LVEF, type of surgery, atrial fibrillation, or previous myocardial infarction (Supplemental Figure 3).

DISCUSSION

The main findings of this study among patients with severe AS and LVEF >50% who underwent AVR are as follows: 1) PLF is associated with increased overall mortality using the guidelines-established SVi cut-point of <35 ml/m^2 among women, but not in men; 2) PLF as defined by using sex-specific thresholds of 40 ml/m^2 for men and 32 ml/m^2 for women for predicted mortality in both sex categories; and 3) patients with PLF/HG had the highest mortality risk after AVR.

IMPACT OF PLF. The occurrence of adverse outcomes (heart failure and death) in patients with AS is ultimately more related to the repercussions of AS in cardiac function (i.e., staging of cardiac damage) than on the severity of the valve stenosis severity per se (30). SVi represents a robust surrogate marker of the state of LV pump function and a strong predictor of adverse outcomes in AS both before and after AVR (5,6,14,31). Up to 35% of patients with AS and preserved LVEF (i.e., >50%) have an LF state, defined as an SVi ≤35 ml/m^2 (1). This threshold, originally proposed in 2007 by Hachicha et al. (32) and derived from pathophysiological reasoning (it is the lower tertile of normal values of SVi), was later validated in an independent cohort and proved to be the optimal cut-point that predicted mortality in a population of severe LG AS with preserved LVEF (33). This study, however, also showed that an SVi <43 ml/m^2 was already associated with worse survival than that expected for an age- and sex-matched cohort. PLF has since then been incorporated into clinical guidelines (2,3), and it has been extensively proven to be a marker of adverse prognosis (1). As opposed to classical (i.e., with depressed LVEF) LF AS, evidence of the impact of PLF on post-operative mortality after surgical AVR has been inconclusive. Some studies have shown similar post-operative survival in PLF and NF patients (6), whereas PLF was a predictor of increased mortality in others (7,8). Inclusion criteria were, however, heterogeneous, and several caveats exist regarding the measurement of SVi and indexed aortic valve area, mainly related to the measurement of the LV outflow tract diameter (27,34). Therefore, the marked difference in the prevalence of PLF among studies (e.g., 5% in the study by Eleid et al. (8) vs. 28% in the studies by Mohty et al. (7) and Clavel et al. (6) and 33% in our study) might be related to technical differences in the measurement of LV outflow tract diameter and/or the velocity-time integral and not to real population differences.

Previous research from our group (6), which also included patients with classical LF/LG AS, showed that PLF was independently associated with increased 30-day mortality, but failed to show a significant increase in mortality after multivariate analysis. Our study, powered by a larger number of patients and excluding patients with LVEF <50%, provides strong evidence that PLF is independently associated with worse prognosis after AVR. We further confirm previous findings (6–8) that SVi does indeed yield incremental prognostic value besides traditional surgical risk scores (e.g., Parsonnet risk score), transvalvular gradient, and LVEF and should therefore be routinely

TABLE 4 Multivariate Predictors of Overall Mortality

		Model With Guidelines Thresholds			Model With New Sex-Specific Thresholds		
	Increment	HR	95% CI	p Value	HR	95% CI	p Value
Mean gradient	5 mm Hg increase	1.08	1.03–1.13	<0.01	1.01	1.01–1.02	<0.01
PLF	Yes	1.53	1.11–2.10	<0.01	1.75	1.25–2.46	<0.01
Flow-gradient patterns							
NF/HG	Referent	–	–	–	–	–	–
NF/LG		0.86	0.58–1.29	0.47	0.83	0.53–1.31	0.43
LF/HG		1.84	1.20–2.80	<0.01	1.89	1.23–2.91	<0.01
LF/LG		1.06	0.67–1.68	0.81	1.26	0.80–2.00	0.32

Guidelines threshold: SVi <35 ml/m^2. Sex-specific threshold: men: SVi <40 ml/m^2 and women: SVi <32 ml/m^2. Models adjusted for age, sex, NYHA functional class III/IV, CAD, diabetes, COPD, AF, CKD, hypertension, and LVEF (results for background model in Supplemental Table 3).

Abbreviations as in Tables 1 and 3.

incorporated into pre-operative risk evaluation and decision making, even in HG patients.

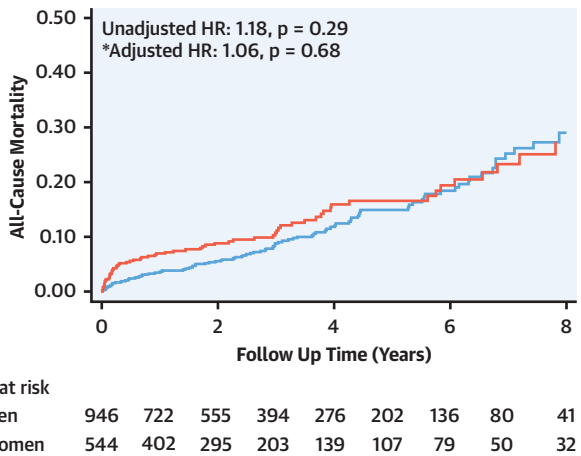
Interestingly, as has been recently suggested (35,36), our findings confirm that the threshold of 50% to define a "normal" LVEF might already be too low and that a "borderline" LVEF (50% to 59%) might be an early marker of intrinsic irreversible myocardial impairment. Indeed, in our cohort, an LVEF of 50% to 59% was independently associated with increased mortality even after adjustment for clinical variables. Its predictive value was, however, overpowered by SVi, confirming that this parameter is a more integral marker of pump function than LVEF is. This further reinforces the need to include SVi in surgical risk assessment scores.

IMPACT OF SEX AND FLOW STATUS. Sex differences exist in the etiology, pathophysiology, diagnosis, prognosis, and treatment of several cardiovascular diseases and specifically in AS (15,17–21,36). Women with AS have been reported to be underdiagnosed and undertreated, and AS is diagnosed at an older age in women than in men (20). Consequently, women are frequently more symptomatic, and their overall prognosis is worse. Previous studies have shown that female sex is associated with worse early outcomes after surgical or transcatheter AVR (23,24), but evidence regarding long-term outcome is controversial (21,22).

Our results further confirm previous findings that female sex is associated with increased early post-operative mortality (23,24) after AVR. We further demonstrated that increased mortality is maintained up to 2 years after AVR, whereas long-term outcomes (i.e., after 3 years) are comparable.

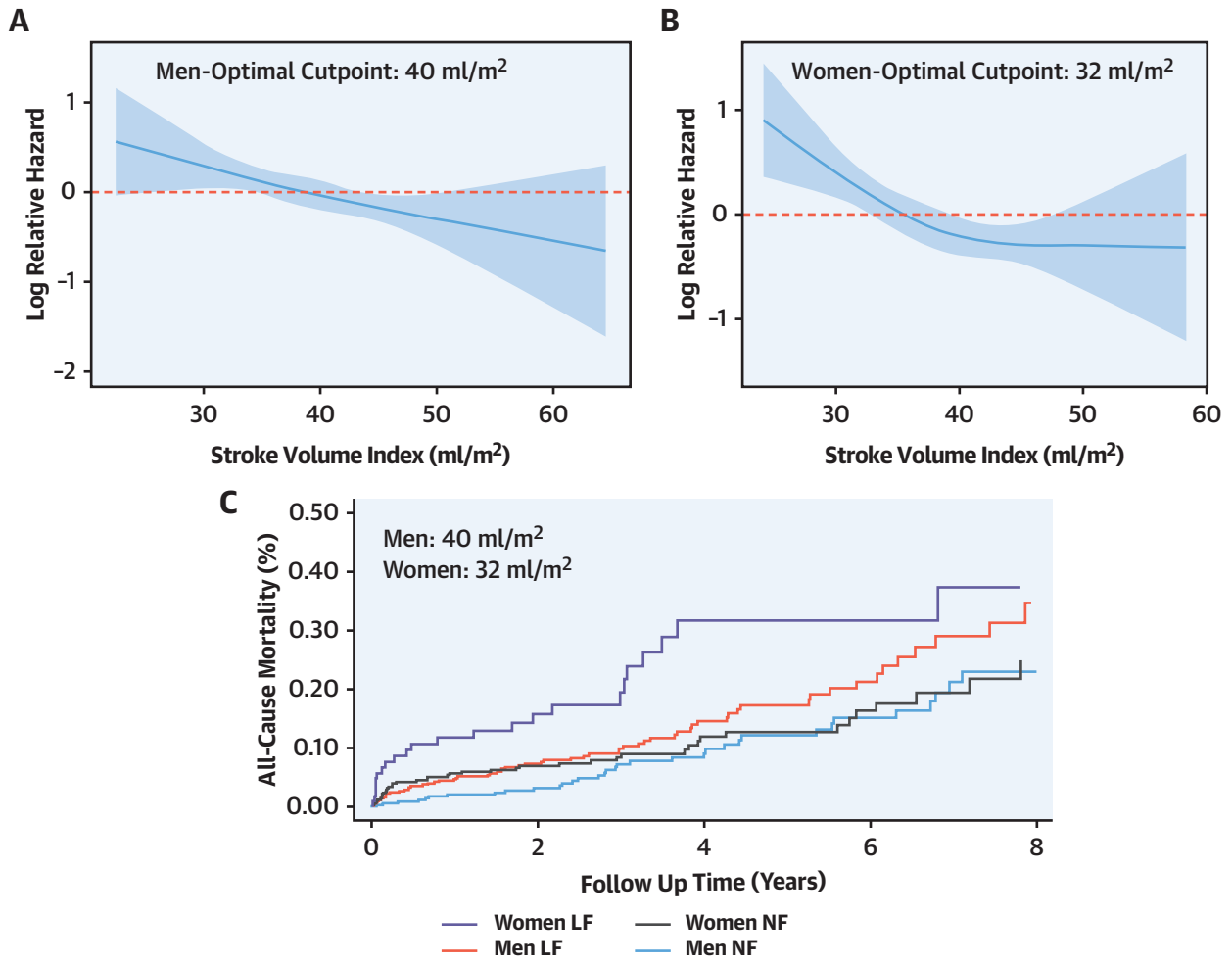
Women with AS have greater diffuse or focal fibrosis (37), and higher prevalence of concentric remodeling (19) than men. Sex-specific thresholds exist for several parameters such as LV mass or AS anatomical severity (assessed either by valve weight [29] or computed tomography [16]). Furthermore, normal values for LV internal dimensions and volumes (even normalized by body-surface area) are smaller in women than in men (25). All these factors may lead to a lower SVi in women and/or a differential impact of an LF state on outcomes. However, the accuracy of the 35 ml/m^2 threshold for defining LF in prognostic assessment in men and women has, to the best of our knowledge, never been tested until now. Our results show that the standard threshold adopted by guidelines adequately predicted post-operative mortality in women but not in men. Spline curve and maximally selected rank statistics analyses showed that the optimal cutpoint is higher for men (40 ml/m^2) than for women (32 ml/m^2). This may be partially explained by the fact that women (with or

FIGURE 4 Kaplan-Meier Mortality Curves of Men Versus Women



All-cause mortality in men **(blue line)** and women **(red line)**. *Adjusted for age, sex, coronary artery disease, New York Heart Association functional class III/IV, systemic hypertension, atrial fibrillation, diabetes, chronic obstructive pulmonary disease, chronic kidney disease, LVEF, and mean transvalvular gradient. Abbreviations as in Figures 1 and 3.

CENTRAL ILLUSTRATION **Sex-Specific Thresholds for Post-Transvalvular Valve Replacement Surgery for LF**



Guzzetti, E. et al. J Am Coll Cardiol. 2020;75(16):1897–909.

The spline curves show the impact of stroke volume index (x-axis) on mortality (y axis, on logarithmic scale) after aortic valve replacement in men **(A)** and women **(B)**. **Dashed red line** shows the mean mortality of our cohort (hazard ratio [HR] of 1). **Blue-shadowed areas** show 95% confidence intervals. **(C)** Kaplan-Meier mortality curves for men and women according to their flow status using the sex-specific cutpoints. *Adjusted for age, Parsonnet risk score, and left ventricular ejection fraction (LVEF). LF = low flow; NF = normal flow.

without AS) have smaller LV volumes than do men (even after indexation for body surface area) (25), which may lead to a decreased SV (38). The use of sex-specific thresholds significantly improved risk stratification in women and provided a radical improvement in men. Interestingly, spline curves show a more linear response to decrease in flow in men, whereas risk of mortality grows exponentially below 35 ml/m^2 in women (i.e., an LF status is more detrimental in women than in men). These findings could be explained by a sex-specific myocardial response to AS (e.g., a higher level of myocardial fibrosis linked to AS in women). These concepts, however, are hypothesis generating and warrant further study.

Remarkably, women also exhibited a greater susceptibility to an LVEF in the lower limit of normal (i.e., 50% to 59%) than men do, which might be explained by their smaller LV volumes that require a higher LVEF to maintain adequate forward SV and cardiac output.

Our findings confirm the need for a sex-specific approach to AS diagnosis and, specifically, these sex-specific cutpoints for defining LF status should be further validated in different cohorts (i.e.,

asymptomatic severe AS) to improve risk assessment and allow for a timely intervention.

IMPACT OF FLOW-GRADIENT PATTERNS. Evidence regarding the association of transvalvular gradient and post-operative mortality is less compelling, with one study showing worse outcomes in LG AS, but without taking flow status into consideration (39). The impact of flow-gradient patterns has been formally evaluated after transcatheter (14) but not surgical AVR. This study by Le Ven et al. (14) (which, as opposed to our study, included patients with both reduced and preserved LVEF) showed that patients in NF/HG, LF/HG, and NF/LG had similar outcomes, whereas the LF/LG group (including both classical and paradoxical LF/LG AS patients) had increased cumulative mortality. Indeed, both American (3) and European (2) guidelines categorize AS as HG (irrespective of flow) or LG. The latter is further classified into classical LF, PLF (i.e., LVEF >50%) LG, and NF/LG, assumed to be mostly due to truly moderate AS, whereas the former is assumed to be a homogeneous group with comparable outcomes.

Our study provides important findings that shed light on this flow-gradient conundrum. As opposed to what is suggested by current guidelines, in our cohort, 78% of patients with NF/LG AS proved to have anatomically severe AS (as assessed by explanted valve weight, a flow-independent parameter), a proportion comparable to those with LF/LG. HG groups (both NF and LF) showed to have higher valve weight and a larger proportion of anatomically severe AS (92% to 94%) than those with an LG. Our results show that the pattern with the worse post-operative survival is LF/HG as opposed to LF/LG, which showed comparable outcomes with NF/HG and NF/LG patients. These findings suggest that earlier AVR (i.e., before the transvalvular MG reaches 40 mm Hg) might be justified. On the other hand, they further reinforce the concept that SVi is a more powerful predictive parameter than transvalvular gradient and the hypothesis that LF/LG AS might be a variant of a myocardial response to severe AS in some patients (and not a consequence of HG or severely increased valvular afterload) (40).

STUDY LIMITATIONS. First, and most importantly, despite the fact that data were prospectively collected, they were retrospectively analyzed. However, our design, routine clinical practice, and interrogation of the central Quebec Institute of Statistics database limited enrollment and follow-up bias. Furthermore, the large number of patients and relatively large number of overall deaths allowed us to perform exhaustive multivariate and sensitivity analyses that add robustness to our results.

Second, roughly one-half of our cohort underwent combined surgery (AVR + CABG). Even though we performed thorough multivariate adjustments and sensitivity analyses to account for these and found no interaction between type of surgery and LF or flow-gradient patterns, subgroup analyses should be considered exploratory and results extrapolated with caution.

Finally, despite its potentially great interest as a marker of early clinical dysfunction, data for myocardial strain analyses were not available in this cohort.

CONCLUSIONS

In this series of patients with severe AS and LVEF >50%, patients with PLF had increased all-cause mortality. Patients with LF/HG pattern showed worse post-operative outcomes, whereas mortality in those with LF/LG, NF/LG, and NF/HG was comparable. An LVEF in the lower normal range (50% to 59%) was associated with increased mortality, but this difference was no longer significant after adjusting for SVi, suggesting that SVi is a more sensitive marker of LV pump dysfunction than LVEF is. Women had increased early mortality, but comparable midterm outcomes compared with men. The established 35 ml/m^2 cutpoint for LF might be appropriate for women, but not for men. Our results indeed reveal that sex-specific thresholds of <32 ml/m^2 in women and <40 ml/m^2 in men improve risk assessment and merit further validation in independent cohorts.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Low transvalvular blood flow in patients with severe AS and preserved LVEF (SV: 40 ml/m^2 in men and 32 ml/m^2 in women) is associated with increased mortality after AVR surgery. Furthermore, among patients with LF volumes according to these sex-specific criteria, HGs of transvalvular pressure are associated with worse outcomes than LGs.

TRANSLATIONAL OUTLOOK: Further studies are needed to validate these sex-specific criteria for LF AS and clarify their implications for the timing and type of intervention to relieve valve obstruction.

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APPENDIX For supplemental figures and tables, please see the online version of this paper.