

Predictors of Outcomes in Low-Flow, Low-Gradient Aortic Stenosis

Results of the Multicenter TOPAS Study

Marie-Annick Clavel, DVM; Christina Fuchs, MD; Ian G. Burwash, MD; Gerald Mundigler, MD; Jean G. Dumesnil, MD, FRCPC, FACC; Helmut Baumgartner, MD; Jutta Bergler-Klein, MD; Rob S. Beanlands, MD; Patrick Mathieu, MD; Julien Magne, MSc; Philippe Pibarot, DVM, PhD, FACC, FAHA

Background—Patients with low-flow, low-gradient aortic stenosis have a poor prognosis with conservative therapy but a high operative mortality if treated surgically. Recently, we proposed a new index of aortic stenosis severity derived from dobutamine stress echocardiography, the projected aortic valve area at a normal transvalvular flow rate, as superior to other conventional indices to differentiate true-severe from pseudosevere aortic stenosis. The objective of this study was to identify the determinants of survival, functional status, and change in left ventricular ejection fraction during follow-up of patients with low-flow, low-gradient aortic stenosis.

Methods and Results—One hundred one patients with low-flow, low-gradient aortic stenosis (aortic valve area ≤ 1.2 cm², left ventricular ejection fraction $\leq 40\%$, and mean gradient ≤ 40 mm Hg) underwent dobutamine stress echocardiography and an assessment of functional capacity using the Duke Activity Status Index. A subset of 72 patients also underwent a 6-minute walk test. Overall survival was $70 \pm 5\%$ at 1 year and $57 \pm 6\%$ at 3 years. After adjusting for age, gender, and the type of treatment (aortic valve replacement versus no aortic valve replacement), significant predictors of mortality during follow-up were a Duke Activity Status Index ≤ 20 ($P=0.0005$) or 6-minute walk test distance ≤ 320 m ($P<0.0001$, in the subset of 72 patients), projected aortic valve area at a normal transvalvular flow rate ≤ 1.2 cm² ($P=0.03$), and peak dobutamine stress echocardiography left ventricular ejection fraction $\leq 35\%$ ($P=0.03$). More severe stenosis, defined as projected aortic valve area ≤ 1.2 cm², was a predictor of mortality only in the no aortic valve replacement group. The Duke Activity Status Index, 6-minute walk test, and left ventricular ejection fraction improved significantly during follow-up in the aortic valve replacement group, but remained unchanged or decreased in the no aortic valve replacement group.

Conclusion—In patients with low-flow, low-gradient aortic stenosis, the most significant risk factors for poor outcome were (1) impaired functional capacity as measured by Duke Activity Status Index or 6-minute walk test distance; (2) more severe valve stenosis as measured by projected aortic valve area at a normal transvalvular flow rate; and (3) reduced peak stress left ventricular ejection fraction, a composite measure accounting for both resting left ventricular function and contractile reserve. (*Circulation*. 2008;118[suppl 1]:S234–S242.)

Key Words: aortic stenosis ■ Doppler echocardiography ■ hemodynamics ■ LV dysfunction ■ survival

Although patients with left ventricular (LV) dysfunction and low-flow, low-gradient (LFLG) aortic stenosis (AS) represent only 5% to 10% of patients with AS, they also represent the most challenging and controversial subset of patients with AS to manage. These patients generally have a poor prognosis with conservative therapy but a high operative mortality if treated surgically. Nonetheless, the vast majority of patients with LFLG AS surviving aortic valve replacement (AVR) exhibit a significant improvement in LV ejection

fraction (LVEF) and functional status and have a good long-term survival.^{1,2} Further improvements in the clinical outcome of patients with LFLG AS will likely result, at least in part, from techniques that better evaluate the “actual” underlying severity of the valve stenosis and from a better understanding of the factors important for risk stratification and clinical outcome. To this effect, dobutamine stress echocardiography (DSE) is valuable in determining the “actual” severity of the valve stenosis and for evaluating LV contractile

From the Laval Hospital Research Center/Québec Heart Institute (M.A.C., C.F., J.M., J.G.D., P.M., P.P.), Laval University, Québec, Canada; Vienna General Hospital (C.F., G.M., H.B., J.B.K.), Medical University of Vienna, Vienna, Austria; and the University of Ottawa Heart Institute (I.G.B., R.B.), Ottawa, Ontario, Canada.

Presented at the American Heart Association Scientific Sessions, November 4–7, 2007, Orlando, Fla.

Correspondence to Philippe Pibarot, DVM, PhD, FACC, FAHA, Laval Hospital, 2725 Chemin Sainte-Foy, Québec, Québec, Canada, G1V-4G5. E-mail philippe.pibarot@med.ulaval.ca

© 2008 American Heart Association, Inc.

Circulation is available at <http://circ.ahajournals.org>

DOI: 10.1161/CIRCULATIONAHA.107.757427

reserve.^{1,3} Recently, we proposed a new index: the projected aortic valve area at a normal transvalvular flow rate (AVA_{proj}), to better differentiate true-severe from pseudosevere AS compared with conventional stenotic indices.⁴ The objectives of this study were to identify the major determinants of survival of patients with LFLG AS during follow-up as well as the determinants of the change in functional capacity and change in LVEF.

Methods

The protocol of the True Or Pseudo severe Aortic Stenosis (TOPAS) multicenter prospective observational study has been described in detail in our previous publications.^{4,5} Briefly, between July 2002 and March 2007, we recruited 101 patients with LFLG AS defined as an $AVA \leq 1.2 \text{ cm}^2$, an indexed $AVA \leq 0.6 \text{ cm}^2/\text{m}^2$, a mean transvalvular gradient $\leq 40 \text{ mm Hg}$, and a LVEF $\leq 40\%$.

Clinical data included age, gender, documented diagnosis of hypertension (patients receiving antihypertensive medications or having known, but untreated, hypertension [blood pressure $\geq 140/90 \text{ mm Hg}$]), diabetes (patients with established diagnoses currently receiving oral hypoglycemic medication or insulin), renal failure (creatinine $>150 \text{ mmol/L}$), and coronary artery disease (history of myocardial infarction or $\geq 50\%$ coronary artery stenosis on coronary angiography). Multivessel coronary artery disease was defined as significant stenoses in 2 or more vessels. Myocardial infarction was defined as the presence of at least 2 of the following 3 criteria: ischemic symptoms, electrocardiographic changes, and elevated creatine kinase-MB or troponin levels.

At entry in the study, all patients underwent a DSE study as previously described^{4,5} and an assessment of functional capacity using the Duke Activity Status Index (DASI).⁶ A subgroup of 72 patients also underwent a 6-minute walk test (6MWT).⁷ To overcome the inherent flow-dependence of conventional stenotic indices (ie, AVA, gradients) and thereby better assess the valve stenosis severity, we recently proposed a new index derived from DSE: the projected AVA at a normal transvalvular flow rate.⁴ For each patient, AVA is plotted against mean transvalvular flow rate (Q) at the different stages of the dobutamine protocol and the projected AVA at a standardized flow rate of 250 mL/s (AVA_{proj}) derived from the equation of the regression line fitted to the AVA versus Q plot. The energy loss index was also calculated using the following formula: $ELCo = [(AVA \times A_A) / (A_A - AVA)] / BSA$, in which A_A is the cross-sectional area measured at the sinotubular junction and BSA is the body surface area.⁸

Statistical Analysis

Results are expressed as mean \pm SD or percentages unless otherwise specified. Differences between patient groups were analyzed with the use of the 2-sample *t* test or the Wilcoxon rank sum test for continuous variables and the χ^2 test or Fisher exact tests for categorical variables as appropriate. A 2-way analysis of variance for repeated measures was used to evaluate the effect of DSE and the effect of treatment (AVR versus no AVR) on Doppler–echocardiographic variables. The significance of the changes in LVEF, DASI, and 6MWT was assessed using a paired *t* test.

The primary end point for this study was overall mortality. The starting time point for survival analysis was the date of the baseline studies performed at study entry. Survival function was obtained by Kaplan-Meier estimates for the levels of various risk factors. Differences among the groups or among the levels of risk factors were compared with the log rank test. The effect of the clinical and Doppler–echocardiographic variables on survival was assessed with the use of Cox proportional hazard models. All the variables presented in Tables 1 and 2 as well as the type of treatment were tested in univariate analysis and those with a probability value <0.05 were incorporated into the multivariate model. Age, gender, and type of treatment were entered into the model regardless of their level of significance. Correlations between variables were determined using Pearson (continuous variables) or Spearman (ordinal variable) methods.

Multivariate linear regression analyses were used to identify the predictors of the changes in LVEF, DASI, and 6MWT distance during follow-up. Variables with a probability value <0.05 on univariate analysis, as well as age and gender, were entered into the multivariate regression analyses.

Statement of Responsibility

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Baseline Data

Baseline characteristics of the patient population are shown in Tables 1 and 2. Among the 101 patients included in the study, 44 patients (44%) underwent AVR and 30 of these patients had concomitant coronary artery bypass grafting surgery (CABG) during follow-up. Complete revascularization, defined as the placement of at least one graft to each of the 3 major vascular regions having a $\geq 50\%$ stenosis, was achieved in 26 of the 30 patients (87%). In the 57 patients who did not undergo AVR, 3 underwent CABG and 11 underwent percutaneous coronary stent implantation during follow-up. Complete revascularization was achieved in 11 (79%) of these patients. The 3 patients undergoing CABG in the no AVR group had an $AVA_{proj} > 1.2 \text{ cm}^2/\text{m}^2$ and the valve stenosis was considered to be only mild to moderate in severity on direct examination of the valve at the time of CABG.

Compared with patients who did not undergo AVR (no AVR group), those treated with AVR (AVR group) were significantly younger, had a lower systolic arterial pressure, and lower prevalence of previous myocardial infarction. There were no differences between the 2 groups in regard to LV size and function or functional capacity as measured by New York Heart Association (NYHA) class, DASI, or 6MWT distance. However, patients treated with AVR had more severe AS as reflected by a smaller AVA_{proj} (Table 2).

Survival According to the Type of Treatment

The mean follow-up time was 20 ± 15 months (median, 15 months; maximum, 53 months). Overall survival in the whole cohort ($n=101$) was $70 \pm 5\%$, $61 \pm 5\%$, and $57 \pm 6\%$ at 1, 2, and 3 years, respectively. In the AVR group ($n=44$), 23 patients (52%) died during follow-up. There were 8 operative deaths (18% operative mortality), ie, death occurring within 30 days of AVR or at any time after AVR if the patient was not discharged. In the no AVR group ($n=57$), 25 patients (44%) died during follow-up. The type of treatment (AVR versus no AVR) did not significantly influence overall survival in the whole cohort (hazard ratio [HR], 0.85; 95% CI, 0.61 to 1.16; P =nonsignificant; Figure 1A). However, AVR was associated with significantly better survival when the analysis was restricted to the subset of patients with a resting $AVA \leq 1.0 \text{ cm}^2$ at study entry (HR, 0.57; 95% CI, 0.40 to 0.82; $P=0.02$). When excluding operative mortality, patients treated with AVR had significantly better late survival compared with patients not undergoing AVR (HR, 0.58; 95% CI, 0.37 to 0.86; $P=0.006$; age-adjusted HR, 0.62; 95% CI, 0.39 to 0.93; $P=0.02$; Figure 1B). A revascularization

Table 1. Demographic and Clinical Data

Variables	All Patients (n=101)	No AVR Group (n=57, 56%)	AVR Group (n=44, 44%)	P
Demographics				
Age, years	71±10	73±9	67±10	0.003
Male gender, n (%)	78 (77)	44 (77)	34 (77)	0.82
Body surface area, m ²	1.87±0.23	1.86±0.24	1.88±0.21	0.62
NYHA functional class ≥III, n (%)	49 (49)	26 (47)	23 (52)	0.64
DASI	26±14	27±15	26±13	1.0
6MWT distance, m	310±120	309±123	311±118	0.96
Systolic blood pressure, mm Hg	119±20	123±19	115±20	0.04
Diastolic blood pressure, mm Hg	72±11	72±10	72±12	0.78
Heart rate, beats/min	71±13	70±13	72±13	0.48
BNP, pg/mL (range)	534 (215–964)	410 (166–859)	695 (395–1310)	0.029
Risk factors and concomitant diseases				
Coronary artery disease, n (%)	76 (75)	44 (77)	32 (73)	0.78
Multivessel coronary disease, n (%)	46 (46)	25 (44)	21 (48)	0.85
Previous myocardial infarction, n (%)	61 (60)	42 (74)	19 (43)	0.004
Previous CABG, n (%)	28 (28)	16 (28)	12 (27)	0.9
Diabetes, n (%)	40 (40)	19 (33)	21 (48)	0.21
Hypertension, n (%)	60 (59)	37 (65)	23 (52)	0.28
Renal failure, n (%)	24 (24)	16 (28)	8 (18)	0.43
COPD, n (%)	27 (27)	13 (23)	14 (32)	0.36
Current medications				
β-blocker, n (%)	63 (62)	37 (65)	26 (59)	0.70
ACEI/ARB, n (%)	71 (70)	43 (75)	28 (64)	0.29
Statin, n (%)	81 (80)	46 (80)	35 (80)	0.98
Coronary revascularization during follow-up, n (%)				
CABG, n (%)	33 (33)	3 (5)	30 (68)	<0.001
PCI, n (%)	11 (11)	11 (19)	0 (0)	<0.001

Data are mean±SD, no. of patients (%), or median (25–75% range) where appropriate. Coronary artery disease was defined as the presence of ≥50% coronary artery stenosis. P value refers to the comparison of AVR versus no AVR treatment groups.

BNP indicates brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; PCI, percutaneous coronary stent implantation.

procedure (CABG or percutaneous coronary stent implantation) during follow-up, and whether these interventions achieved complete revascularization, had no significant effect on survival in this series. However, a history of previous CABG (ie, done before entry in the study) was associated with a lower mortality during follow-up (HR, 0.68; 95% CI, 0.50 to 0.94; $P=0.02$).

Predictors of Overall Mortality

Univariate Analysis

Among the factors measured at baseline, significant predictors of mortality in the whole cohort were age ≥70 years (HR, 1.39; 95% CI, 1.01 to 1.94; $P=0.04$), DASI ≤20 (HR, 1.90; 95% CI, 1.38 to 2.65; $P<0.0001$; Figure 2A), 6MWT distance ≤320 m (HR, 2.51; 95% CI, 1.63 to 4.18; $P<0.0001$; Figure 2B), peak stress transvalvular flow rate ≤250 mL/s (HR, 1.46; 95% CI, 1.07 to 1.99; $P=0.02$), peak DSE LVEF (LVEF_{peak}) ≤35% (HR, 1.38; 95% CI, 1.01 to 1.91; $P=0.04$; Figure 2C), rest AVA ≤1.0 cm² (HR, 1.63;

95% CI, 1.21 to 2.44; $P=0.006$), rest energy loss index ≤0.55 cm²/m² (HR, 1.54; 95% CI, 1.06 to 2.38; $P=0.02$), and AVA_{proj} ≤1.2 cm² (HR, 1.56; 95% CI, 1.02 to 2.69; $P=0.04$; Figure 2D). Cutoff values for these predictive variables were selected based on previous studies^{4,5,8} and/or because they corresponded to the median value in the study cohort. Plasma level of brain natriuretic peptide was measured in 76 (75%) patients and in this subset, a brain natriuretic peptide level ≥550 pg/mL (HR, 2.14; 95% CI, 1.42 to 3.42; $P=0.0002$) was a strong predictor of overall mortality, consistent with our previous results.⁵

Patients with a 6MWT ≤320 m had a poor outcome independent of the type of treatment (Figure 3A). Patients with a 6MWT >320 had better outcome ($P=0.045$) when treated with AVR. Similar results were observed with the DASI, although the difference in outcome between the AVR and no AVR patients did not reach statistical significance among patients with a DASI >20 (Figure 3B). NYHA class correlated with the DASI ($r=-0.65$; $P<0.0001$) and 6MWT

Table 2. Resting and Dobutamine Stress Echocardiographic Data

Variables	All Patients (n=101)	No AVR Group (n=57, 56%)	AVR Group (n=44, 44%)
LV geometry and function			
LVED diameter, mm	62±10	62±12	61±8
LVES diameter, mm	51±12	52±13	49±10
LV stroke volume, mL			
Rest	60±19	62±21	59±16
Peak DSE	73±23*	74±25*	73±20*
LVEF, %			
Rest	29±9	29±8	29±11
Peak DSE	37±12*	36±10*	39±13*
Mean flow rate, mL/s ⁻¹			
Rest	199±55	201±63	196±43
Peak DSE	280±84*	283±92*	277±72*
Aortic valve hemodynamics			
Mean gradient, mm Hg			
Rest	21±8	18±7	26±8†
Peak DSE	32±13*	27±10*	39±13*†
AVA, cm ²			
Rest	0.92±0.24	0.99±0.20	0.82±0.18†
Peak DSE	1.11±0.29*	1.21±0.30*	0.98±0.23*†
Projected AVA, cm ²	1.03±0.22	1.12±0.22	0.91±0.16†
Indexed projected AVA, cm ² /m ²	0.56±0.14	0.61±0.15	0.49±0.10†

Data are mean±SD.

*Significant difference ($P<0.05$) between DSE and rest.†Significant difference between no AVR versus AVR group (all significant P values were <0.001).

ED indicates end diastolic; ES, end systolic.

distance ($r=-0.66$; $P<0.0001$), but was not a significant predictor of mortality.

Multivariate Analysis

After adjusting for patient age, gender, and type of treatment, predictors of overall mortality were a history of previous CABG (HR, 0.68; 95% CI, 0.49 to 0.94; $P=0.02$), DASI ≤ 20 (HR, 1.83; 95% CI, 1.30 to 2.61; $P=0.0005$), and AVA_{proj} ≤ 1.2 cm² (HR, 1.67; 95% CI, 1.04 to 2.93; $P=0.03$; Table 3). There was also a strong trend toward significance for LVEF_{peak} $\leq 35\%$

(HR, 1.37; 95% CI, 0.98 to 1.92; $P=0.06$). Further adjustment for previous myocardial infarction did not change the significance of the variables in the multivariate model.

After adjusting for the same variables in the subset of patients ($n=72$) who underwent 6MWT, predictors of overall mortality were previous CABG (HR, 0.64; 95% CI, 0.43 to 0.97; $P=0.03$), 6MWT distance ≤ 320 m (HR, 2.55; 95% CI, 1.60 to 4.35; $P<0.0001$), AVA_{proj} ≤ 1.2 cm² (HR, 1.92; 95% CI, 1.10 to 3.75; $P=0.02$), and LVEF_{peak} $\leq 35\%$ (HR, 1.55; 95% CI, 1.03 to 2.38; $P=0.03$; Table 3).

Predictors of Mortality in the Aortic Valve Replacement and No Aortic Valve Replacement Groups

When data for the AVR and no AVR groups were analyzed separately, DASI and 6MWT distance remained a significant predictor of overall mortality in both groups. However, AVA_{proj} ≤ 1.2 cm² (HR, 2.28; 95% CI, 1.26 to 4.61; $P=0.006$) and LVEF_{peak} $\leq 35\%$ (HR, 2.61; 95% CI, 1.37 to 5.48; $P=0.003$) were predictors of overall mortality only in the no AVR group.

Change in Left Ventricular Function and Functional Capacity During Follow-Up

Among the 101 patients included in this study, 42 underwent DSE, 6MWT, and assessment of DASI at 1-year follow-up. In this subset, AVA_{proj} increased markedly with AVR (Δ AVA_{proj} [1 year-baseline]: $+1.0\pm 0.4$ cm²; $P<0.001$) but decreased significantly during follow-up in the no AVR group (Δ AVA_{proj}: -0.14 ± 0.16 ; $P<0.001$; Figure 4A). The DASI, 6MWT, and LVEF improved significantly in the AVR group but remained unchanged or decreased in the no AVR group during follow-up (Δ DASI: $+5.9\pm 3.3$ versus -5.5 ± 2.6 , $P=0.01$; Δ 6MWT: $+66\pm 27$ versus -9 ± 22 m, $P=0.04$; Δ LVEF: $+10\pm 14$ versus $+1\pm 6\%$, $P=0.015$; Figure 4B–D). On univariate analysis, the predictors of an improvement in DASI and LVEF were AVR treatment (Δ DASI: $r=0.39$, $P=0.01$ and Δ LVEF: $r=0.40$, $P=0.02$, respectively), baseline DASI (Δ DASI: $r=-0.58$, $P<0.0001$), and Δ AVA_{proj} (Δ DASI: $r=0.36$, $P=0.03$ and Δ LVEF: $r=0.42$, $P=0.02$, respectively). The presence of coronary artery disease and the realization of revascularization procedures had no significant effect on these outcome variables. On multivariate analysis, the predictors of an improvement in

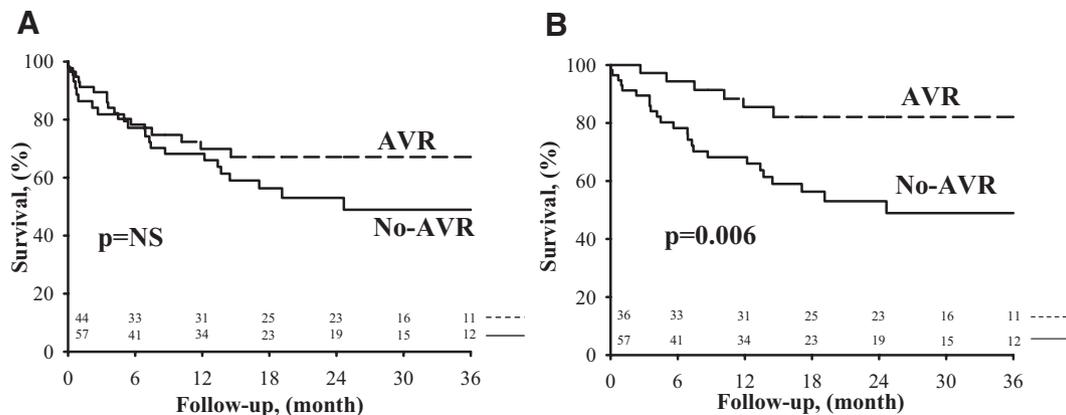


Figure 1. Survival as a function of the type of treatment in the whole cohort (A) and after excluding operative mortality in the AVR group (B). The numbers at the bottom of the survival curves represent the number of patients at risk at various time points.

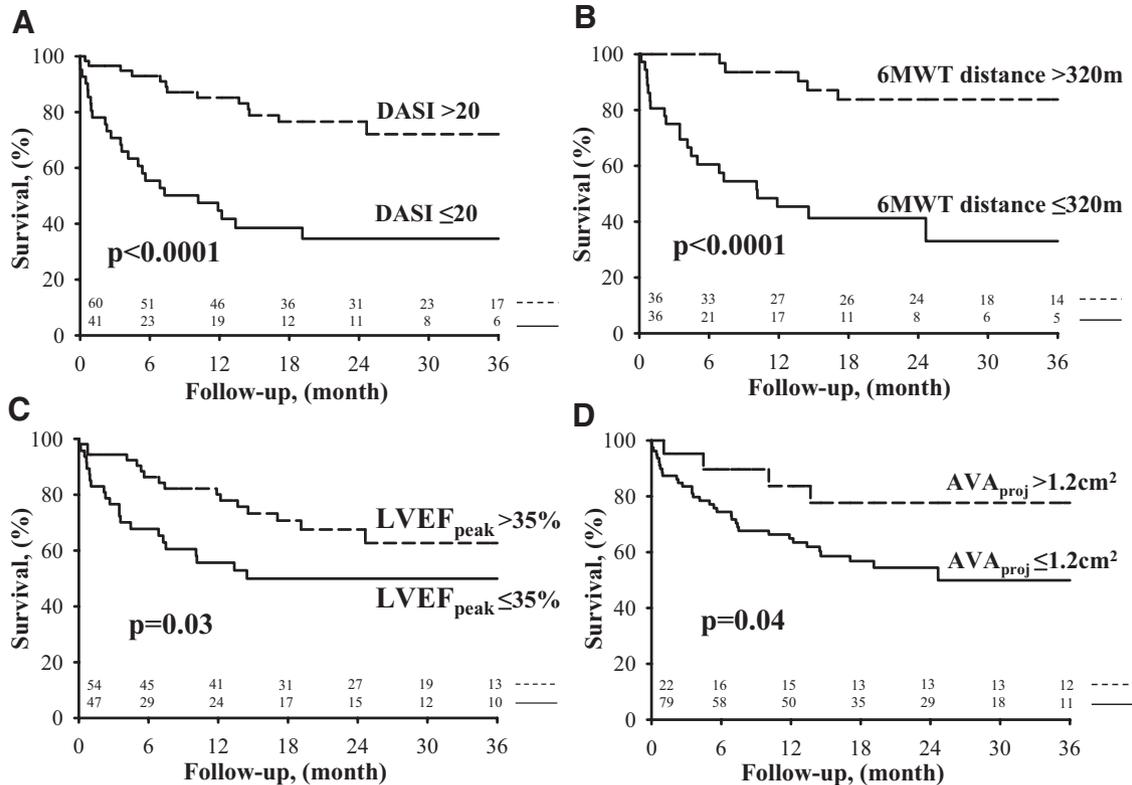


Figure 2. Impact of DASI (A), 6MWT (B), LVEF at peak dobutamine stress echocardiography (LVEF_{peak}, C), and AVA_{proj} (D) on overall survival in the whole cohort (A, C, D) and in the subset (n=72) of patients who performed a 6MWT (B). The numbers at the bottom of the survival curves represent the number of patients at risk at various time points.

DASI were a lower baseline DASI ($\Delta r^2=0.25$; $P=0.003$) and higher ΔAVA_{proj} ($\Delta r^2=0.10$; $P=0.004$). Only higher ΔAVA_{proj} was a predictor of the improvement in LVEF after adjustment for other factors ($\Delta r^2=0.01$; $P=0.048$).

Discussion

The results of this multicenter prospective study confirm that patients with LFLG AS represent a high-risk population with an operative mortality of 18% and a 3-year survival of only 57%, consistent with the results of previous studies.^{1,9-11} In addition, we have demonstrated in LFLG AS that: (1) poor functional capacity is associated with a markedly reduced survival regardless of the type of treatment. Moreover, our data suggest that the assessment of functional capacity should go beyond the determination of NYHA class, but rather include more objective and comprehensive measures of functional capacity such as the DASI and 6MWT; (2) more severe impairment of LV function as measured by the LVEF at peak DSE is associated with lower overall survival, especially in those patients who do not undergo AVR; (3) greater severity of valve stenosis is associated with reduced survival in those patients who are not treated by AVR; and (4) most patients who survive AVR have an improvement in functional capacity as measured by DASI and 6MWT distance and an improvement in LVEF.

Prognostic Importance of the Functional Capacity Assessment on Clinical Outcome

NYHA functional class was not a significant predictor of patient survival in the present study. This may be due to the

fact that the assessment of NYHA class is highly subjective, semiquantitative with 4 classes, and difficult to standardize when evaluating patients of various ages and physical expectations, especially in the context of a multicenter study. In contrast to NYHA class, more objective and standardized measures of functional capacity such as the DASI and 6MWT distance were strong predictors of clinical outcome in this population. Consistent with the results reported in our previous study,⁵ plasma brain natriuretic peptide was also a powerful risk marker for mortality. Hence, the consideration of these factors, which are easy to measure in the clinical setting and do not require pharmacological stress, may provide important information for risk stratification and clinical decision-making in these challenging patients with LFLG AS.

Prognostic Importance of Left Ventricular Myocardial Impairment on Clinical Outcome

In our series, peak LVEF achieved during DSE was superior to the relative increase in stroke volume to predict clinical outcome. In a European multicenter study, Monin et al reported that the absence of LV contractile reserve, defined by a relative increase in stroke volume <20% during DSE, was a powerful independent predictor of overall mortality in patients with LFLG AS treated medically and of operative mortality in those treated surgically.^{1,2} However, in the TOPAS study, this parameter was not found to be an independent predictor of outcome.^{4,5} The discrepancy between the 2 studies may be due to differences in the DSE

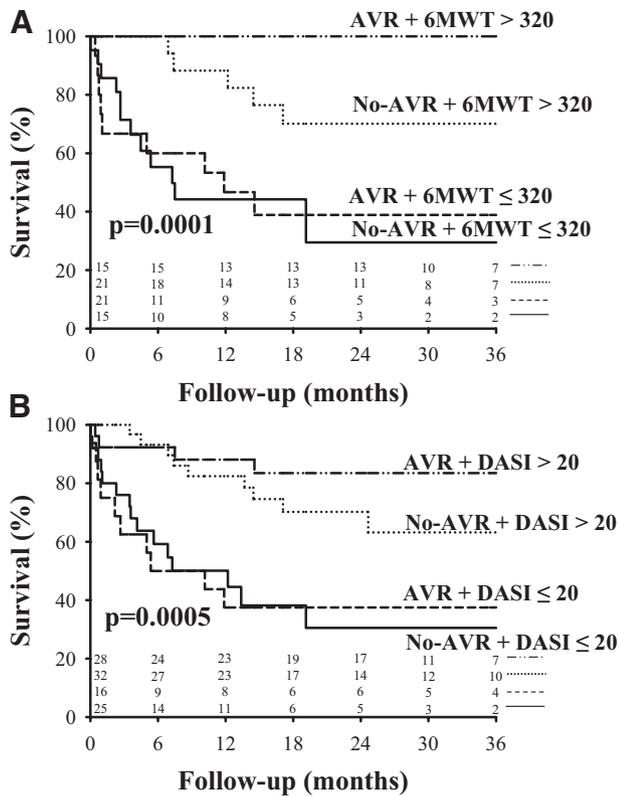


Figure 3. Impact of 6MWT (A) and DASI (B) on overall survival as a function of the type of treatment. The numbers at the bottom of the survival curves represent the number of patients at risk at various time points.

protocol and/or baseline characteristics of the study populations. In the European multicenter study, the dobutamine infusion was discontinued when the heart rate increased by ≥ 10 beats/min from baseline. However, in the TOPAS study, DSE was only terminated based on heart rate criteria if the heart rate was \geq the target value of 220 minus age (in beats/min). In addition, the prevalence of diabetes, hypertension, coronary artery disease, and previous myocardial infarc-

tion were higher in the TOPAS population. Our observed superiority of peak stress LVEF over the relative increase in stroke volume may be explained by the fact that the former measure provides a better estimate of the maximum ejection capacity under β -adrenergic stimulation. Intuitively, a patient with a peak stress LVEF of 40% and no contractile reserve on DSE (defined by a relative increase in stroke volume $< 20\%$) would be expected to have a better prognosis than another patient with a peak stress LVEF of 20% and no contractile reserve. In essence, the peak stress LVEF is a composite index that accounts for both baseline resting LV function and contractile reserve.

Prognostic Importance of the Valve Stenosis Severity on Clinical Outcome

Previous studies in LFLG AS^{1,2,9-12} have failed to demonstrate an association between the severity of the valve stenosis and mortality in contrast to studies in patients with AS with preserved LV systolic function.¹³ This discrepancy may relate to the fact that resting transvalvular gradient and AVA may not reflect the “true” severity of the valve stenosis in the context of a low flow state.⁴ Furthermore, the change or peak transvalvular gradient and AVA obtained during DSE largely depends on the magnitude of flow augmentation achieved, which may vary considerably from one patient to another. This may, in turn, limit the ability of the stress values of gradient and AVA to adequately assess the stenosis severity. In contrast, AVA_{proj} corrects for the interindividual variability in the flow response to DSE and thereby provides a more accurate assessment of stenosis severity in patients with LFLG AS.⁴ In the present study, a smaller AVA_{proj} was associated with worse survival. Interestingly, a significant impact on survival was observed for a projected AVA ≤ 1.2 cm², which is higher than the cutoff value recommended in the American College of Cardiology/American Heart Association guidelines to define a severe stenosis (< 1.0 cm²) and potentially warrant surgical intervention. This finding is consistent with the concept that a moderate stenosis may be

Table 3. Predictors of Overall Mortality on Multivariate Analysis

Variables	Multivariate Analysis					
	Whole Cohort (n=101)			Subset Who Underwent 6MWT (n=72)		
	Patients with Variable, n (%)	P	HR (95% CI)	Patients With Variable, n (%)	P	HR (95% CI)
Demographics and history						
Age ≥ 70 years	54 (54)	0.04	1.43 (1.01–2.08)	40 (56)	NS	1.10 (0.68–1.83)
Female gender	23 (23)	NS	1.05 (0.69–1.52)	11 (15)	NS	1.18 (0.62–1.99)
Previous CABG	28 (28)	0.02	0.68 (0.49–0.94)	22 (31)	0.03	0.64 (0.43–0.97)
Treatment (AVR)	44 (44)	NS	1.09 (0.76–1.56)	22 (31)	NS	1.3 (0.80–2.17)
Functional capacity						
DASI ≤ 20	41 (41)	0.0005	1.83 (1.30–2.61)
6MWT distance ≤ 320 m	36 (50)	< 0.0001	2.55 (1.60–4.35)
LV function						
Ejection fraction at peak $\leq 35\%$	47 (47)	0.06	1.37 (0.98–1.92)	34 (47)	0.03	1.55 (1.03–2.38)
Stenosis severity						
Projected AVA ≤ 1.2 cm ²	79 (78)	0.03	1.67 (1.04–2.93)	56 (78)	0.02	1.92 (1.10–3.75)

Downloaded from <http://circ.ahajournals.org/> by guest on October 4, 2017

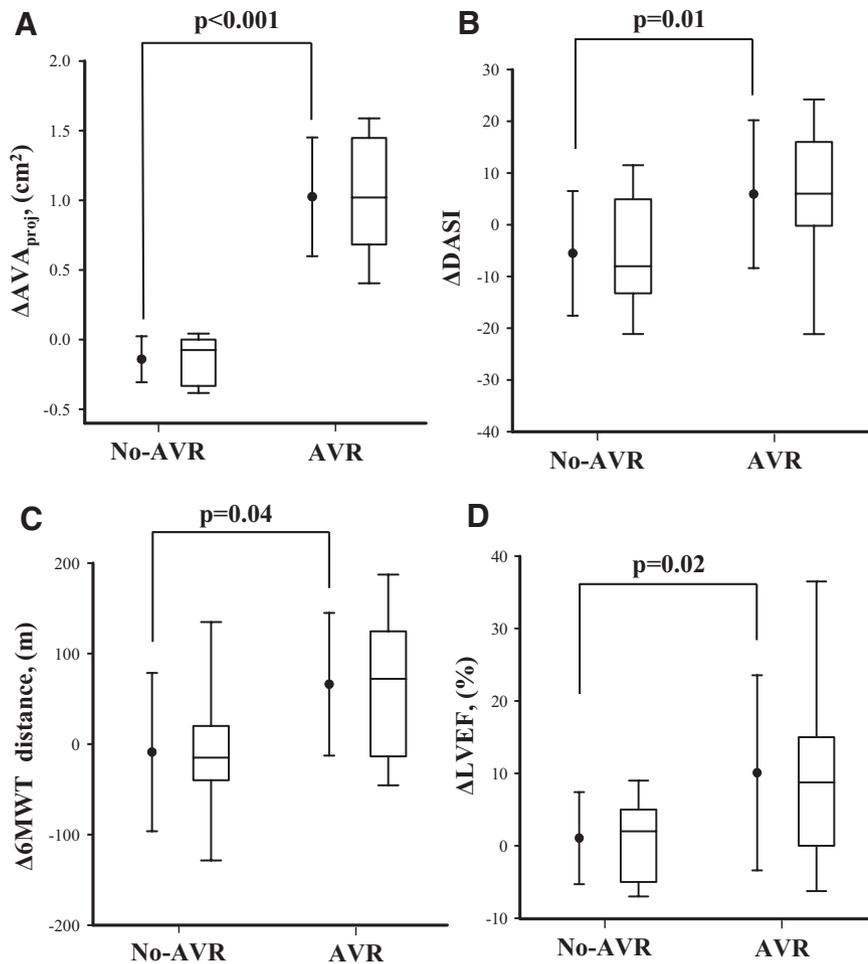


Figure 4. DASI (A), 6MWT (B), LVEF (C), and AVA_{proj} (D) at baseline and 1-year follow-up in the AVR group and the no AVR group. Solid horizontal line indicates median values; hatched box, quartiles; and vertical line attached to the box, highest and lowest values. The dot and attached vertical lines represent the mean and SD.

less well tolerated by a poorly functioning ventricle than by a normal ventricle. In light of this finding, different criteria may be warranted for surgical decision-making in patients with LFLG AS.

Influence of Coronary Artery Disease

The vast majority (75%) of patients included in this series had concomitant coronary artery disease (CAD). This finding is not surprising given that AS is frequently associated with CAD and that patients with low-flow AS generally have several cardiovascular risk factors, including older age, hypertension, diabetes, and so on (Table 1). The presence and severity of CAD, anti-ischemic medications, coronary revascularization interventions, and whether these interventions achieve complete revascularization could potentially have an impact on the functional and clinical outcomes of patients with low-flow AS. In a previous study,¹⁴ prior myocardial infarction was identified as a powerful independent predictor of mortality in patients with low-flow AS undergoing AVR. In the present study, only a previous history of CABG was associated with reduced mortality. The presence of CAD, multivessel disease, previous myocardial infarction, and undergoing a revascularization procedure (CABG or percutaneous coronary intervention) after study entry did not significantly influence survival, change in functional status, or LVEF during follow-up. This is consistent with the results of

the European multicenter study in which CAD, previous myocardial infarction, and CABG were not significantly associated with outcomes.^{1,2,12} In the European multicenter study, only multivessel disease was found to be a weak predictor of mortality and postoperative change in LVEF in the subset of patients undergoing AVR.^{2,12} The limited number of patients included in the present study as well as the relatively small proportion of patients with no CAD may have limited our ability to detect significant associations between some of the CAD-related factors and outcomes. Further studies in even larger series of patients are needed to precisely define the contribution of CAD severity and therapeutic interventions targeting CAD on the outcome of patients with low-flow AS. In this context, it would be important to evaluate the potential role of myocardial viability, measured by single photon emission CT or positron emission tomography, in predicting the outcome of these patients. It is well known that the extent of myocardial viability predicts survival and improvement in LVEF after CABG in patients with CAD. However, this factor has not yet been explored in the context of low-flow AS.

Implications of the Type of Treatment on Patient Outcome

The type of treatment did not influence survival in our series of patients with LFLG AS, although surgery may impart a

survival advantage in the subset of patients with LFLG AS with the most severe valve stenosis. The lack of superiority of AVR versus no AVR treatment in this series is at least in part due to the high operative mortality associated with AVR (Figure 1). In this regard, patients who survived AVR had an excellent outcome, whereas those treated medically (ie, not undergoing AVR) had markedly reduced survival, which is consistent with the results of the European multicenter study.² These findings emphasize the importance of developing strategies to reduce operative mortality in these patients with LFLG AS. In this context, previous studies have reported that prosthesis–patient mismatch has a major impact on mortality in patients with pre-existing LV dysfunction.^{15–17} As opposed to other risk factors, prosthesis–patient mismatch can largely be avoided or its severity reduced by the use of a prospective strategy at the time of operation.^{18,19} The prevention of prosthesis–patient mismatch may eventually contribute to a reduction in operative mortality in the subset of patients with LFLG AS undergoing AVR. Further studies are needed to determine whether transcatheter prosthetic valve implantation using the transfemoral or transapical approach will also reduce operative risk in these patients.

One important finding of this study is that the majority of patients who survived surgery had a significant improvement in LVEF and functional capacity, whereas those patients not undergoing AVR had no improvement. Interestingly, the magnitude of the functional improvement was dependent on the augmentation of AVA_{proj} achieved with AVR. Our results are consistent with the observations of Rajappan et al in patients with severe AS and preserved LV systolic function, in whom the improvement in coronary flow reserve after AVR was strongly related to the increase in AVA obtained with AVR.²⁰ These findings highlight the importance of implanting prostheses with superior hemodynamic performance to optimize the postoperative augmentation of AVA and thereby avoid any residual valve stenosis or afterload that may be highly detrimental in the context of a severely impaired LV function.

Most importantly, the results of this study suggest that patients with LFLG AS can have both a good early and late prognosis if operated on before significant functional deterioration has occurred (Figures 1B and 3A). Nonetheless, the fact that approximately 50% of these patients received medical treatment and did not undergo AVR suggests that the severity of the valve stenosis may often be underestimated due to some apparent ambiguity in the markers of AS severity (eg, low-pressure gradient despite a small valve area). In fact, pressure gradients were significantly lower in patients on medical treatment (see Table 2). Waiting for the appearance of functional deterioration (eg, 6MWT \leq 320) before proceeding to surgery does not appear to be an acceptable solution because patients having reached this stage of their disease have a very high operative risk and a poor prognosis regardless of treatment (Figure 3A). Hence, the most important practical implication of these observations would be that patients presenting with a combination of ambiguous findings potentially compatible with severe AS in the setting of poor LV function should systematically undergo DSE. If identified as having true severe stenosis on the basis of the AVA_{proj}, they

should be promptly referred to surgery. Ideally, this should be done as soon as possible in the evolution of the disease and in particular before further deterioration of the patient's functional status and/or LV function have occurred.

Limitations

The population size may have limited our ability to detect significant interactions among the identified risk factors and significant associations with other factors. However, a larger study in this high-risk population would be difficult to achieve due to the low prevalence of LFLG AS (5% of AS population) and the poor prognosis of these patients.

Therapeutic decisions in the present study were left to the discretion of the patient's treating physician and the baseline characteristics of patients in the AVR and no AVR groups were, as expected, different. However, randomized treatment would not have been appropriate for ethical reasons.

Conclusion

In LFLG AS, the most significant risk factors for poor outcome are (1) impaired functional capacity as measured by DASI or 6MWT; (2) more severe valvular stenosis as measured by AVA_{proj}; and (3) reduced peak stress LVEF, a composite measure accounting for both resting LV function and contractile reserve. Although AVR was not associated with better survival in this series, it was associated with a significant improvement in LV function and functional status. Moreover, the magnitude of the functional improvement was dependent on the augmentation of AVA achieved with AVR. This new knowledge will assist clinicians in predicting the prognosis of patients with LFLG AS and improve operative risk stratification and therapeutic management.

Acknowledgments

We thank Jocelyn Beauchemin, Dominique Labrèche, and Isabelle Laforest for the data collection and their technical assistance.

Sources of Funding

This work was supported by a grant (# 57445) from the Canadian Institutes of Health Research Ottawa, Canada. P.P. holds the Canada Research Chair in Valvular Heart Diseases, Canadian Institutes of Health Research. P.M. is a research scholar from the Fonds de Recherches en Santé du Québec, Montreal, Canada.

Disclosures

None.

References

1. Monin JL, Quere JP, Monchi M, Petit H, Baleynaud S, Chauvel C, Pop C, Ohlmann P, Lelguen C, Dehant P, Tribouilloy C, Gueret P. Low-gradient aortic stenosis: operative risk stratification and predictors for long-term outcome: a multicenter study using dobutamine stress hemodynamics. *Circulation*. 2003;108:319–324.
2. Quere JP, Monin JL, Levy F, Petit H, Baleynaud S, Chauvel C, Pop C, Ohlmann P, Lelguen C, Dehant P, Gueret P, Tribouilloy C. Influence of preoperative left ventricular contractile reserve on postoperative ejection fraction in low-gradient aortic stenosis. *Circulation*. 2006;113:1738–1744.
3. deFilippi CR, Willett DL, Brickner E, Appleton CP, Yancy CW, Eichhorn EJ, Grayburn PA. Usefulness of dobutamine echocardiography in distinguishing severe from nonsevere valvular aortic stenosis in patients with depressed left ventricular function and low transvalvular gradients. *Am J Cardiol*. 1995;75:191–194.

4. Blais C, Burwash IG, Mundigler G, Dumesnil JG, Loho N, Rader F, Baumgartner H, Beanlands RS, Kadem L, Garcia D, Chayer B, Durand LG, Pibarot P. The projected valve area at normal flow rate improves the assessment of stenosis severity in patients with low flow aortic stenosis: the multicenter TOPAS (Truly or Pseudo Severe Aortic Stenosis) study. *Circulation*. 2006;113:711–721.
5. Bergler-Klein J, Mundigler G, Pibarot P, Burwash IG, Dumesnil JG, Blais C, Beanlands R, Hachicha Z, Mohty D, Fuchs C, Loho N, Florian R, Baumgartner H. B-type natriuretic peptide in low-flow, low-gradient aortic stenosis: relationship to hemodynamics and clinical outcome. *Circulation*. 2007;115:2848–2855.
6. Hlatky MA, Boineau RE, Higginbotham MB, Lee KL, Mark DB, Califf RM, Cobb FR, Pryor DB. A brief self-administered questionnaire to determine functional capacity (The Duke Activity Status Index). *Am J Cardiol*. 1989;64:651–654.
7. Cahalin LP, Mathier MA, Semigran MJ, Dec GW, DiSalvo TG. The six-minute walk test predicts peak oxygen uptake and survival in patients with advanced heart failure. *Chest*. 1996;110:325–332.
8. Garcia D, Pibarot P, Dumesnil JG, Sakr F, Durand LG. Assessment of aortic valve stenosis severity: a new index based on the energy loss concept. *Circulation*. 2000;101:765–771.
9. Connolly HM, Oh JK, Schaff HV, Roger VL, Osborn SL, Hodge DO, Tajik AJ. Severe aortic stenosis with low transvalvular gradient and severe left ventricular dysfunction. Result of aortic valve replacement in 52 patients. *Circulation*. 2000;101:1940–1946.
10. Nishimura RA, Grantham JA, Connolly HM, Schaff HV, Higano ST, Holmes DR Jr. Low-output, low-gradient aortic stenosis in patients with depressed left ventricular systolic function: the clinical utility of the dobutamine challenge in the catheterization laboratory. *Circulation*. 2002;106:809–813.
11. Schwammenthal E, Vered Z, Moshkowitz Y, Rabinowitz B, Ziskind Z, Smolinski AK, Feinberg MS. Dobutamine echocardiography in patients with aortic stenosis and left ventricular dysfunction: predicting outcome as a function of management strategy. *Chest*. 2001;119:1766–1777.
12. Levy F, Laurent M, Monin JL, Maillet JM, Pasquet A, Le Tourneau T, Petit-Eisenmann H, Gori M, Jobic Y, Bauer F, Chauvel C, Leguerrier A, Tribouilloy C. Aortic valve replacement for low-flow/low-gradient aortic stenosis: operative risk stratification and long-term outcome: a European multicenter study. *J Am Coll Cardiol*. 2008;51:1466–1472.
13. Otto CM, Burwash IG, Legget ME, Munt BI, Fujioka M, Healy NL, Kraft C, Miyake-Hull CY, Schwaegler RG. Prospective study of asymptomatic valvular aortic stenosis. Clinical, echocardiographic, and exercise predictors of outcome. *Circulation*. 1997;95:2262–2270.
14. Powell DE, Tunick PA, Rosenzweig BP, Freedberg RS, Katz ES, Applebaum RM, Perez JL, Kronzon I. Aortic valve replacement in patients with aortic stenosis and severe left ventricular dysfunction. *Arch Intern Med*. 2000;160:1337–1341.
15. Blais C, Dumesnil JG, Baillet R, Simard S, Doyle D, Pibarot P. Impact of prosthesis–patient mismatch on short-term mortality after aortic valve replacement. *Circulation*. 2003;108:983–988.
16. Kulik A, Burwash IG, Kapila V, Mesana TG, Ruel M. Long-term outcomes after valve replacement for low-gradient aortic stenosis: impact of prosthesis–patient mismatch. *Circulation*. 2006;114:15553–15558.
17. Ruel M, Al-Faleh H, Kulik A, Chan K, Mesana TG, Burwash IG. Prosthesis–patient mismatch after aortic valve replacement primarily affects patients with pre-existing left ventricular dysfunction: impact on survival, freedom from heart failure, and left ventricular mass regression. *J Thorac Cardiovasc Surg*. 2006;131:1036–1044.
18. Pibarot P, Dumesnil JG. Prosthesis–patient mismatch: definition, clinical impact, and prevention. *Heart*. 2006;92:1022–1029.
19. Bleiziffer S, Eichinger WB, Hettich I, Guenzinger R, Ruzicka D, Bauernschmitt R, Lange R. Prediction of valve prosthesis–patient mismatch prior to aortic valve replacement: which is the best method? *Heart*. 2007;93:615–620.
20. Rajappan K, Rimoldi OE, Camici PG, Bellenger NG, Pennell DJ, Sheridan DJ. Functional changes in coronary microcirculation after valve replacement in patients with aortic stenosis. *Circulation*. 2003;107:3170–3175.

Predictors of Outcomes in Low-Flow, Low-Gradient Aortic Stenosis: Results of the Multicenter TOPAS Study

Marie-Annick Clavel, Christina Fuchs, Ian G. Burwash, Gerald Mundigler, Jean G. Dumesnil, Helmut Baumgartner, Jutta Bergler-Klein, Rob S. Beanlands, Patrick Mathieu, Julien Magne and Philippe Pibarot

Circulation. 2008;118:S234-S242

doi: 10.1161/CIRCULATIONAHA.107.757427

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 2008 American Heart Association, Inc. All rights reserved.

Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://circ.ahajournals.org/content/118/14_suppl_1/S234

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

Reprints: Information about reprints can be found online at:
<http://www.lww.com/reprints>

Subscriptions: Information about subscribing to *Circulation* is online at:
<http://circ.ahajournals.org/subscriptions/>