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ORIGINAL ARTICLE

Clinical Value of Stress Transaortic Flow Rate During Dobutamine Echocardiography in Reduced Left Ventricular Ejection Fraction, Low-Gradient Aortic Stenosis: A Multicenter Study

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BACKGROUND: Low rest transaortic flow rate (FR) has been shown previously to predict mortality in low-gradient aortic stenosis. However limited prognostic data exists on stress FR during low-dose dobutamine stress echocardiography. We aimed to assess the value of stress FR for the detection of aortic valve stenosis (AS) severity and the prediction of mortality.

METHODS: This is a multicenter cohort study of patients with reduced left ventricular ejection fraction and low-gradient aortic stenosis (aortic valve area <1 cm^2 and mean gradient <40 mm Hg) who underwent low-dose dobutamine stress echocardiography to identify the AS severity and presence of flow reserve. The outcome assessed was all-cause mortality.

RESULTS: Of the 287 patients (mean age, 75±10 years; males, 71%; left ventricular ejection fraction, 31±10%) over a mean follow-up of 24±30 months there were 127 (44.3%) deaths and 147 (51.2%) patients underwent aortic valve intervention. Higher stress FR was independently associated with reduced risk of mortality (hazard ratio, 0.97 [95% CI, 0.94–0.99]; *P*=0.01) after adjusting for age, chronic kidney disease, heart failure symptoms, aortic valve intervention, and rest left ventricular ejection fraction. The minimum cutoff for prediction of mortality was stress FR 210 mL/s. Following adjustment to the same important clinical and echocardiographic parameters, among the three criteria of AS severity during stress, ie, the guideline definition of aortic valve area <1cm² and aortic valve mean gradient ≥40 mm Hg, or aortic valve mean gradient ≥40 mm Hg, or the novel definition of aortic valve area <1 cm² at stress FR ≥210 mL/s, only the latter was independently associated with mortality (hazard ratio, 1.72 [95% CI, 1.05–2.82]; *P*=0.03). Furthermore aortic valve area <1cm² at stress FR ≥210 mL/s was the only severe aortic stenosis criterion that was associated with improved outcome following aortic valve intervention (*P*<0.001). Guideline-defined stroke volume flow reserve did not predict mortality.

CONCLUSIONS: Stress FR during low-dose dobutamine stress echocardiography was useful for the detection of both AS severity and flow reserve and was associated with improved prediction of outcome following aortic valve intervention.

Key Words: cohort studies ■ echocardiography, stress ■ heart failure ■ prognosis ■ stroke volume

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CLINICAL PERSPECTIVE

In patients with low-gradient aortic stenosis and low left ventricular ejection fraction who underwent low-dose dobutamine stress echocardiography for the determination of the aortic valve stenosis severity and the presence of flow reserve, lower stress flow rate, but not the absence of stroke volume flow reserve, was an independent predictor of mortality. Aortic valve area at normalized stress flow rate of ≥210 mL/s was superior to guideline-defined criteria of severe aortic valve stenosis for the prediction of mortality. Patients with severe aortic valve stenosis based on this criterion showed improved outcome with aortic valve intervention compared with medical therapy. Decision to proceed to aortic valve intervention or medical therapy may be taken on the basis of this novel criterion. This criterion provides insight into both the presence of flow reserve and the underlying aortic valve stenosis severity. The study may influence the present guidelines for the management of patients with low-gradient aortic stenosis following low-dose dobutamine stress echocardiography. However, these data may require further validation in randomized controlled studies.

Nonstandard Abbreviations and Acronyms

AS	aortic valve stenosis
AVA	aortic valve area
AVMG	aortic valve mean gradient
FR	flow rate
HR	hazard ratio
LDDSE	low-dose dobutamine stress echocardiography
LGAS	low-gradient aortic stenosis
LVEF	left ventricular ejection fraction
LVET	left ventricular ejection time
LVOT	left ventricular outflow tract
SV	stroke volume
SVi	stroke volume index
TOPAS	truly or pseudo-severe aortic stenosis

Severe aortic valve stenosis (AS) is defined as an aortic valve area (AVA) <1 cm^2 and a transvalvular aortic valve mean gradient (AVMG) ≥40 mm Hg.[1] However, discordant hemodynamics may occur whereby AVA is in the severe range of AS but AVMG is low. This may occur because transvalvular gradient and to a lesser degree AVA are dependent on the transaortic flow. Thus, low transaortic flow conditions will result in reductions of both AVMG and AVA, classically in patients with reduced left ventricular ejection fraction (LVEF) an entity called classical low-flow, low-gradient aortic stenosis (LGAS). The recommendation by international societies is to perform low-dose dobutamine stress echocardiography (LDDSE) to increase transaortic flow, which in patients with severe aortic stenosis (AS) will result in increase in AVMG ≥40 mm Hg with AVA remaining <1 cm^2, while the test will also give an indication of flow (contractile) reserve for risk stratification, defined as >20% increase in stroke volume (SV).[2,3] If stress AVA exceeds 1 cm^2, the AS is considered moderate, whereas if the AVA remains <1 cm^2 with AVMG <40 mm Hg, the AS severity remains indeterminate.[3,4] It is also stated that even if AVA is ≥1 cm^2 when AVMG exceeds 40 mm Hg (in the absence of reversible high-flow situations like anemia), AS is considered severe.[3] Thus, some also consider this as criterion for severe AS during LDDSE.

It has previously been shown that AVA <1 cm^2 in the presence of a transaortic flow rate (FR) ≥210 mL/s identified severe AS at rest and can also risk stratify patients as FR is also a marker of LV function.[5–9] Thus we aimed to assess the value of stress FR in LGAS patients with reduced LVEF for the diagnosis of severity of AS and presence of flow reserve on the basis of the prediction of mortality.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Population

Between July 2002 and December 2018, 379 consecutive patients with AVA <1 cm^2 and AVMG <40 mm Hg from 22 centers in Canada, Europe, the United States, and the United Kingdom underwent LDDSE. The time span of the trial data for each country has been different, which explains the overall long time frame of data collection. All eligible patients from each center were included in this study. Of the 379 patients with discordant AS, 287 patients had reduced LVEF <50% and were the population studied. The general indications for LDDSE were to identify the severity of AS and the presence of flow reserve. This project was granted approval by the local research and development departments of the participating centers, which waived the requirement for informed consent.

Stress Echocardiography Protocol and Interpretation

The low-dose dobutamine protocol was similar for all centers and followed contemporary guidelines for conducting the test. For the purpose of the study, only the rest and peak Doppler acquisitions were used.

All echocardiographic data were prospectively collected and analyzed at the respective centers. The baseline echocardiographic images were acquired, and measurements were performed during the stress echo study. The left ventricular outflow tract (LVOT) diameter was measured as per international recommendations.[4] For the calculation of AVA, the continuity equation was used. The SV was derived as LVOT velocity time integral×LVOT area, whereas the left ventricular ejection time (LVET) was measured from the LVOT or AV Doppler. The FR was calculated as SV divided by LVET (Figure 1). The interobserver variability of measurements of LVET, LVOT velocity time integral, and LVOT diameter (related to FR calculation), from the United Kingdom centers that participated in this study, was good.[6] Further analysis between the UK center (which acted as the reference) and the center that provided the largest number of patients (132) in 10 random studies has shown good reproducibility for both LVOT diameter (interclass correlation coefficient, 0.89 [95% CI, 0.55–0.97]) and LVET (interclass correlation coefficient, 0.96 [95% CI, 0.83–0.99]).

For the diagnosis of severe AS during LDDSE, 3 definitions were assessed: (1) the ACC/EACVI definition (AVA <1 cm^2 and AVMG ≥40 mm Hg for severe, and AVA >1 cm^2 for moderate AS). AVA <1 cm^2 and AVMG ≥40 mm Hg henceforth will be referred to as guideline-defined severe AS; (2) the stress AVMG ≥40 mm Hg regardless of AVA; and (3) stress AVA <1 cm^2 at a normalized transaortic flow (the cutoff of transaortic flow was assessed with survival analysis).

Clinical Data and Outcomes

Clinical information was collected from the different centers participating in this study and included patients' age, sex, body surface area, history of hypertension (patients receiving antihypertensive medications or having known hypertension [blood pressure, ≥140/90 mm Hg], diabetes, chronic kidney disease [eGFR, <60 mL/min per 1.73 m^2 for ≥3 months]), hyperlipidemia, atrial fibrillation, coronary artery disease (history of myocardial infarction or coronary intervention [percutaneous coronary intervention or bypass surgery] or coronary artery stenosis ≥50%), and the presence of heart failure symptoms (New York Heart Association class ≥II).

Patients were treated at the respective centers at their treating physician's discretion, informed by guidelines and aware of the results of stress echocardiography. However, the analysis related to transaortic FR presented in this study was not available at the time, and as FR was not in the guidelines, it was not used in the clinical management of the study patients. The outcome assessed was all-cause mortality. The local hospital databases were used to check the occurrence and date of death and aortic valve intervention. Patients were also contacted by phone when required to identify aortic valve intervention performed in different hospitals.

Statistical Analysis

Categorical variables are expressed as percentages and continuous variables as means with SD or medians with interquartile range. Variables were compared with the use of χ^2 test and the paired samples *t* test. Kaplan-Meier survival curves, univariable and multivariable Cox regression analysis were performed to assess predictors of mortality. Variables with $P<0.10$ from the univariable analysis were used in the multivariable model. For the assessment of the stress flow parameters and the stress criteria of aortic stenosis and to avoid the theoretical risk of colinearity, these were entered in separate multivariable models—if the *P* was significant, these were further compared with net reclassification index. A simple hierarchical Cox regression model was formed to assess the incremental prognostic value of an individual variable to the baseline model. To assess possible interplay between different variables, their interaction was assessed in Cox regression analysis. To address the impact on outcome based on the possible variable practice of each center, adjustment was performed based on 4 broad practice groups (TOPAS [Truly or Pseudo-Severe Aortic Stenosis] group, UK, Poland, and Portugal practice groups). Furthermore, to exclude possible immortal-time bias related to aortic valve intervention a time-dependent Cox regression analysis was also performed.

Finally, the receiver operator characteristic curve and the Delong test were used to compare the areas under the curve between stress flow parameters and identify the best cutoff value of stress FR. A sensitivity analysis was performed to identify the minimum stress FR value that could predict survival. Overall, in 4 patients, one of the rest AVA, rest SV/FR, stress AVA, or stress SV/FR could not be determined; the default listwise deletion analysis was used. For all tests, $P<0.05$ was considered to be statistically significant. Hazard ratios (HRs) with 95% CIs were estimated.

Statistical analysis was performed with SPSS, version 26.0 (SPSS, Inc, Chicago, IL).

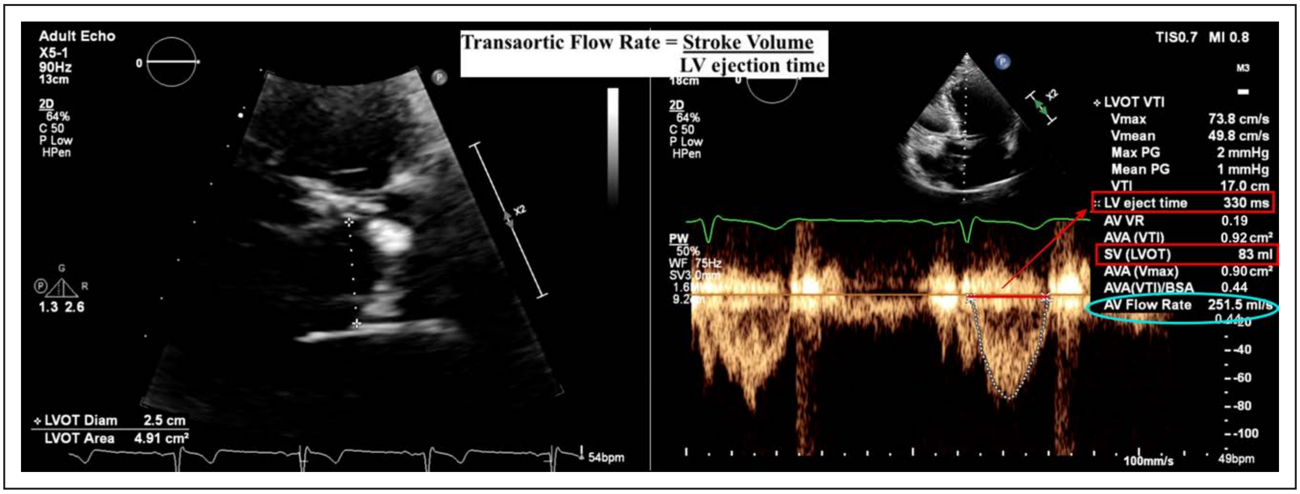

Figure 1. Calculation of flow rate from echocardiography (Echo) in patients with aortic stenosis.
Left ventricular outflow tract (LVOT) velocity time integral (VTI) and LVOT diameter are used for the calculation of stroke volume (SV), which is then divided by the left ventricular (LV) ejection time. 2D indicates 2 dimensional; AVA, aortic valve area; AV VR, aortic valve velocity ratio; BSA, body surface area; MI, mechanical index; PG, peak gradient; PW, pulsed wave; and TIS, thermal index for soft tissue.

RESULTS

Clinical Characteristics and LDDSE Echocardiographic Parameters

Two hundred eighty-seven patients (mean LVEF, 31±10%) underwent stress echocardiography (Tables 1 and 2). The mean patient age was 75±10 years, and 71% were men. At rest, the mean gradient was 25±7 mm Hg, the mean AVA was 0.77±0.14 cm^2, and the mean FR and SV index (SVi) were 179±47 mL/s and 29±8 mL/m^2, respectively, reflecting a population of discordant AS in the presence of low flow.

The median maximum dobutamine-infused dose was 20 (interquartile range, 15–20) µg/kg per minute. The heart rate increased by 22±17 bpm, representing a 30% increase from baseline.

Outcomes

Over the mean follow-up period of 24±30 months (median, 12.6 [interquartile range, 4.9–33.3] months), there were 127 (44.3%) deaths, and 147 (51.2%) patients underwent aortic valve intervention. Forty-nine (17.1%) patients died post-aortic valve intervention and 78 (27.2%) in the medical management group.

Stress FR for the Prediction of Mortality

In the multivariable model, higher stress FR was an independent predictor of reduced mortality (per 10 mL/s: HR, 0.97 [95% CI, 0.94–0.99]; *P*=0.01; Table 3). The exclusion of patients who underwent balloon valvuloplasty or addition of coronary artery bypass grafting in the multivariable model did not change the above findings. There was no significant difference in mortality between those undergoing surgical aortic valve replacement versus transcatheter valve intervention (log-rank *P*=0.32). Hence, further multivariable analysis was not performed. Following further adjustment to the time to aortic valve intervention using a time-dependent Cox regression analysis, higher stress FR remained significant (per 10 mL/s: HR, 0.97 [95% CI, 0.94–0.99]; *P*=0.01).

The addition of stress FR to a model containing rest FR provided incremental prognostic value (*P*=0.01; Figure I in the Supplemental Material). Additionally, higher stress FR in this model was an independent predictor of reduced mortality (per 10 mL/s: HR, 0.96 [95% CI, 0.93–0.99]; *P*=0.01), whereas higher rest FR was not (per 10 mL/s: HR, 1.00 [95% CI, 0.95–1.10]; *P*=0.85).

The assessment of SV flow reserve (increase in SV by 20%) or as continuous variable during stress was not a predictor of mortality in the univariable analysis (*P*=0.64 and *P*=0.27, respectively). When receiver operating characteristic curves for stress SVi and stress FR were constructed for the prediction of mortality at 4 years, stress FR had a statistically higher area under the curve value, compared with stress SVi (FR: area under the curve, 0.69 [95% CI, 0.58–0.80]; *P*=0.001 and SVi: area under the curve, 0.61 [95% CI, 0.50–0.72]; *P*=0.055, with *Z* score of 2.07, *P*=0.04). When stress SVi was added in the multivariable model instead of stress FR, higher stress SVi was a significant independent predictor of reduced mortality (HR, 0.98 [95% CI, 0.96–0.997]; *P*=0.02). However, comparison of the model containing stress SVi with the baseline model using net reclassification index showed insignificant

Table 1. Baseline Clinical Characteristics (n=287)

Age, y	75±10
Male sex, n (%)	203 (70.7)
Body surface area, m^2	1.86±0.20
Hypertension, n (%)	202 (70.3)
Diabetes, n (%)	126 (43.9)
Hyperlipidemia, n (%)	112 (39.0)
Coronary artery disease, n (%)	201 (70.0)
Atrial fibrillation, n (%)	69 (24.0)
Chronic kidney disease, n (%)	103 (35.9)
NYHA, %	
Class I	19 (6.6)
Class II	101 (35.2)
Class III	142 (49.5)
Class IV	20 (7.0)
Aortic valve intervention, n (%)	147 (51.2)
Surgical AVR, n (%)	78 (27.2)
TAVI, n (%)	65 (22.6)
BAV, n (%)	4 (1.4)

AVR indicates aortic valve replacement; BAV, balloon aortic valvuloplasty; NYHA, New York Heart Association; and TAVI, transcatheter aortic valve intervention.

Table 2. Patient Echocardiographic Characteristics at Rest and Peak Stress (n=287)

	Rest	Stress	*P* value
Heart rate, bpm	73±13	95±20	<0.001
SBP, mm Hg	121±20	128±25	<0.001
DBP, mm Hg	72±11	71±13	0.25
LVEF, %	31±10	42±14	<0.001
AVA, cm^2	0.77±0.14	0.89±0.23	<0.001
AVAi, cm^2/m^2	0.42±0.09	0.48±0.13	<0.001
Dimensionless index	0.22±0.06	0.26±0.07	<0.001
Aortic mean gradient, mm Hg	25±7	36±12	<0.001
Aortic peak gradient, mm Hg	42±13	59±18	<0.001
Stroke volume, mL	54±14	67±21	<0.001
Stroke volume index, mL/m^2	29±8	36±11	<0.001
LV ejection time, ms	318±190	268±58	<0.001
Flow rate, mL/s	179±47	255±79	<0.001

AVA indicates aortic valve area; AVAi, indexed aortic valve area; DBP, diastolic blood pressure; LV, left ventricle; LVEF, left ventricular ejection fraction; and SBP, systolic blood pressure.

Table 3. Univariable and Multivariable Analysis for Prediction of All-Cause Mortality (n=287)

	Univariable analysis			Multivariable analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age, y	1.03	1.01–1.04	0.01	1.01	0.99–1.03	0.16
Male sex	0.90	0.62–1.31	0.59			
Body surface area (by 1m² increase)	0.71	0.32–1.56	0.39			
Hypertension	1.12	0.77–1.64	0.55			
Diabetes	1.34	0.94–1.90	0.11			
Chronic kidney disease	1.92	1.35–2.74	<0.001	1.5	1.05–2.20	0.03
Hyperlipidemia	1.17	0.82–1.68	0.38			
Atrial fibrillation	1.10	0.70–1.66	0.73			
Coronary artery disease	1.36	0.89–2.10	0.15			
Aortic valve intervention	0.35	0.24–0.51	<0.001	0.4	0.27–0.60	<0.001
Presence of symptoms (NYHA II-IV)	2.47	0.91–6.71	0.08	2.14	0.77–5.94	0.14
Different practice groups	0.95	0.82–1.1	0.47			
Rest LVEF (by 5% increase)	0.84	0.77–0.93	<0.001	0.89	0.81–0.98	0.02
Stress LVEF (by 5% increase)	0.95	0.89–1.01	0.11			
Severe AS (stress AVMG ≥40mmHg with stress AVA <1cm²)	0.85	0.48–1.48	0.56			
Stroke volume flow reserve	0.92	0.65–1.30	0.64			
Stress flow rate (by 10 mL/s increase)	0.95	0.93–0.97	<0.001	0.97	0.94–0.99	0.01

AS indicates aortic stenosis; AVA, aortic valve area; AVMG, aortic valve mean gradient; HR, hazard ratio; LVEF, left ventricular ejection fraction; and NYHA, New York Heart Association.

reduction of risk classification ability by 2.9% (*P*=0.41), whereas for stress FR, there was improvement by 7.7% (*P*=0.03), and addition of stress FR to the model containing stress SVi showed improvement by 7% (*P*=0.03; thresholds of 50% and 75% for probability of death over 4 years were used to determine lower, intermediate, and higher risk groups).

In view of the above findings, stress FR was considered as a better marker of transaortic flow compared with stress SVi in this study. A cutoff value of stress FR 257 mL/s provided optimum prediction of mortality (log-rank *P*<0.001). A sensitivity analysis identified a minimum stress FR cutoff of 210 mL/s for the discrimination of outcome (Table I in the Supplemental Material). The Kaplan-Meier survival curve for stress FR cutoff 210 mL/s is shown in Figure 2 (log-rank *P*<0.001). This cutoff remained significant after adjusting for age, chronic kidney disease, stress LVEF, aortic valve intervention, and the presence of heart failure symptoms (New York Heart Association II–IV; HR, 1.55 [95% CI, 1.10–2.30]; *P*=0.03). In patients with low FR at rest (FR <200 mL/s), which is the majority of the population, stress FR <210 mL/s remained significant for the prediction of mortality (log-rank *P*=0.01; Figure II in the Supplemental Material).

To address the possible interplay between aortic valve intervention and the guideline-defined severe AS, which could influence the outcome of the patients in the latter group, their interaction was assessed, which was not significant (HR, 1.52 [95% CI, 0.47–4.89]; *P*=0.49).

Association of Different Criteria of Diagnosis of Severe AS With Mortality

When the three different definitions of severe AS (guideline-defined AS, versus stress AVMG ≥40 mm Hg, versus AVA <1 cm² at stress FR ≥210 mL/s) were entered into the multivariable model, AVA <1 cm² at stress FR ≥210 mL/s was a significant independent predictor of mortality (HR, 1.72 [95% CI, 1.05–2.82]; *P*=0.03). However, the guideline-defined severe AS (HR, 1.19 [95% CI, 0.64–2.19]; *P*=0.59) or stress AVMG ≥40 mm Hg (HR, 0.63 [95% CI, 0.40–1.00]; *P*=0.05) were not associated with increased risk of mortality (Table 4). The adjusted survival curves for stress AVA <1 cm² at the normalized stress FR ≥210 mL/s versus stress AVA >1 cm² at FR ≥210 mL/s (HR, 1.7 [95% CI, 1.10–2.82]; *P*=0.03) are shown in Figure III in the Supplemental Material.

Prevalence of Severe AS According to the Different Criteria

Diagnosis of severe AS based on guideline-defined criteria during LDDSE was present in 83 (29%) patients, versus 104 (36%) patients if a definition of stress AVMG ≥40 mm Hg (regardless of AVA) was used and 127 (45%) if the stress AVA <1 cm² at stress FR ≥210 mL/s was used as the criterion of severe AS (*P*<0.001; Figure 3).

When stress AVA ≥1 cm² at stress FR ≥210 mL/s was considered as moderate AS, 75 patients were identified.

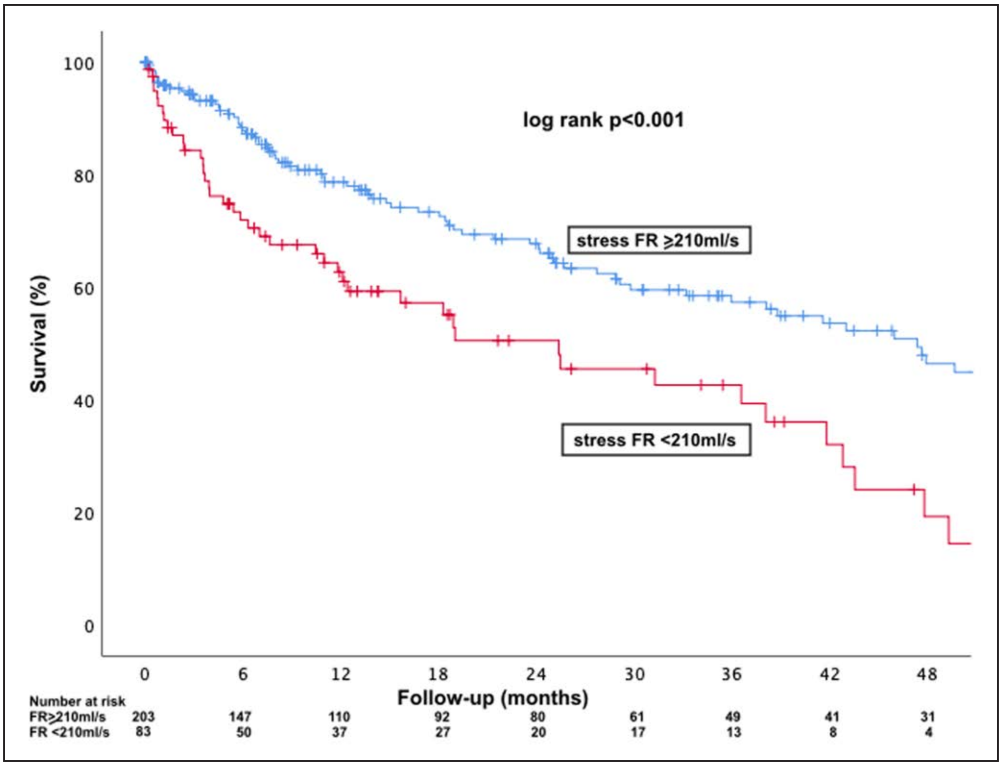

Figure 2. Prognostic value of normalized stress flow rate (FR).
Kaplan-Meier survival curves demonstrate that stress FR with cutoff value of 210 mL/s predicted outcome in patients with reduced left ventricular ejection fraction low-gradient aortic stenosis (log-rank $P<0.001$).

Thus, the diagnostic yield of AS severity (severe and moderate AS) when using the AVA cutoff 1 cm^2 at FR ≥210 mL/s was 202 patients (71%) versus 164 (57%) patients when the guideline definition of severity of AS is used ($P<0.001$).

Of the 78 patients who underwent medical management and died, severe AS was present in 10 (13%), 10 (13%), and 27 (35%; $P=0.03$) as diagnosed by guideline-based criteria, by the criteria of stress AVMG ≥40 mm Hg and by stress AVA <1 cm^2 at stress FR ≥210 mL/s, respectively (Figure 3).

Impact of Aortic Valve Intervention on Survival Using Different Definitions of Severe Aortic Stenosis

In patients with severe AS defined by the novel criterion of stress AVA <1 cm^2 at stress FR ≥210 mL/s, aortic valve intervention was associated with reduced mortality (HR, 0.29 [95% CI, 0.15–0.54]; $P<0.001$; Figure 4A). The impact of aortic valve intervention on survival when the other two definitions were used was not significant (for the guideline definition, $P=0.05$ and for stress AVMG ≥40 mm Hg, $P=0.21$; Figure 4B and 4C). Projected AVA <1 cm^2 had been previously shown as a criterion of severe AS and was associated with increased mortality in medically treated patients.[10–12] Projected AVA <1 cm^2 showed similar prognostic value to that of AVA <1 cm^2 at stress FR ≥210 mL/s for the prediction of reduced mortality in the aortic valve intervention versus medical groups (HR, 0.36 [95% CI, 0.22–0.60]; $P<0.001$; Figure 4D). When the above analysis was also adjusted to SV-defined flow reserve or to the time to aortic valve intervention, the above results did not change significantly.

Patients with moderate AS defined by AVA ≥1 cm^2 at FR ≥210 mL/s during stress did not derive any benefit from aortic valve intervention versus medical therapy ($P=0.11$; Figure IVA in the Supplemental Material). This was also true when moderate AS was defined by the projected AVA ($P=0.10$; Figure IVB in the Supplemental Material).

DISCUSSION

Our study showed that (1) in patients with symptomatic low-flow LGAS and reduced LVEF who underwent LDDSE, lower stress FR predicted mortality irrespective of aortic valve intervention; (2) among the definitions of severe AS during stress, AVA <1 cm^2 at FR ≥210 mL/s was the best predictor of mortality, compared with the guideline-defined severe AS or stress AVMG ≥40 mm Hg (regardless of AVA). Moreover, with this criterion (stress AVA <1 cm^2 at stress FR ≥210 mL/s), the highest yield of severe AS was obtained compared with the other two criteria and indeterminate studies were low (≈30%); (3) SV flow reserve, the guideline-directed measure of flow

Table 4. Multivariable Analysis for Prediction of All-Cause Mortality (n=287) by the Different Definitions of Severe Aortic Stenosis

	Stress AVA <1 cm² with stress AVMG ≥40 mm Hg			Stress AVMG ≥40 mm Hg			Stress AVA <1 cm² at stress FR ≥210 mL/s		
	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
Age, y	1.00	0.99–1.06	0.15	1.00	0.99–1.03	0.17	1.00	0.98–1.03	0.68
Chronic kidney disease	1.53	0.86–2.75	0.15	1.61	1.12–2.3	0.01	1.82	0.13–3.00	0.01
Aortic valve intervention	0.32	0.17–0.61	0.001	0.41	0.27–0.61	<0.001	0.32	0.20–0.53	<0.001
Presence of symptoms (NYHA II–IV)	2.04	0.61–6.82	0.25	2.10	0.75–5.8	0.16	2.25	0.80–6.33	0.12
Rest LVEF (by 5% increase)	0.89	0.76–1.03	0.11	0.89	0.8–0.98	0.02	0.86	0.75–0.98	0.02
Severe AS	1.19	0.64–2.19	0.59	0.63	0.4–1	0.05	1.70	1.10–2.80	0.03

AS indicates aortic stenosis; AVA, aortic valve area; AVMG, aortic valve mean gradient; HR, hazard ratio; LVEF, left ventricular ejection fraction; and NYHA, New York Heart Association.

reserve, was not associated with mortality[3]; (4) finally and most importantly, patients with stress AVA <1 cm² at stress FR ≥210 mL/s but not those with the guideline-defined severe AS or stress AVMG ≥40 mm Hg had improved outcome following aortic valve intervention.

Concept of Transaortic FR for the Assessment of AS

We have previously demonstrated that in patients with LGAS, an AVA <1 cm² at a transaortic FR of 200 mL/s was indicative of severe AS.[5] This was based on the concept that the valve in severe AS is to a large degree noncompliant, as demonstrated although in a rigid valve model with pulsatile FR alteration. In this experiment, AVA increased in all grades of AS severity with increasing transaortic FR up to 200 mL/s, considered as normal flow at rest, but further improvement of the AVA in severe AS was minimal, unlike milder stenosis where the AVA continued to increase.[8]

Prognostic Value of FR

The prognostic value of rest FR in symptomatic patients with LGAS was first demonstrated in a relatively small population who all underwent aortic valve intervention.[6] This was then confirmed in a large study consisting of patients with AVA<1 cm², irrespective of gradient status, who also all underwent aortic valve intervention.[13] In these studies, the lowest cutoff of FR which predicted mortality was 200 to 210 mL/s. These studies indicated that FR is a marker of LV function independent of LVEF and SVi.

However, the concept that AVA <1 cm² at normal FR identified severe AS and, therefore, these patients should benefit from aortic valve intervention led to a propensity-matched analysis in patients who underwent aortic valve intervention versus conservative management.[14] This showed mortality benefit of such patients following valve intervention. Subsequently, a large study of patients with various grades of AS showed that AVA <1 cm² at resting FR of ≥210 mL/s was associated with increased mortality,

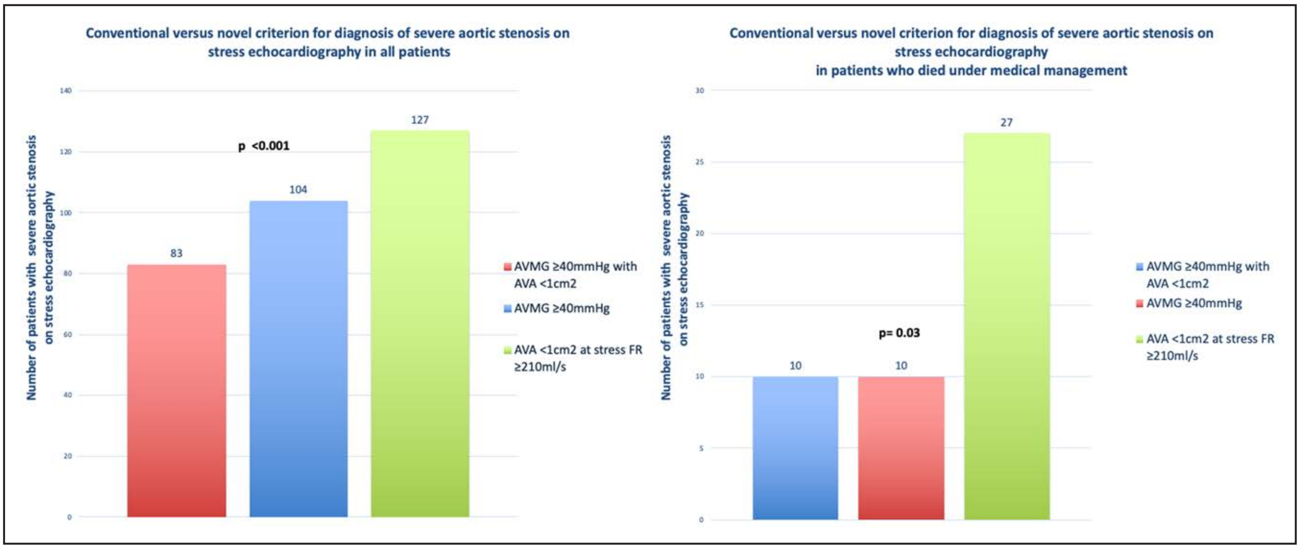

Figure 3. Diagnostic yield of severe aortic stenosis (AS) in patients with reduced left ventricular ejection fraction (LVEF) low-gradient AS by different definitions.

Significantly more patients were diagnosed with severe AS, in the whole population but also in the population of patients with medical management who died, when the novel criterion of stress aortic valve area (AVA) <1 cm² at stress flow rate (FR) ≥210 mL/s was used compared with the guideline definition of severe AS, or stress aortic valve mean gradient (AVMG) ≥40 mm Hg (P<0.001 and P=0.03, respectively).

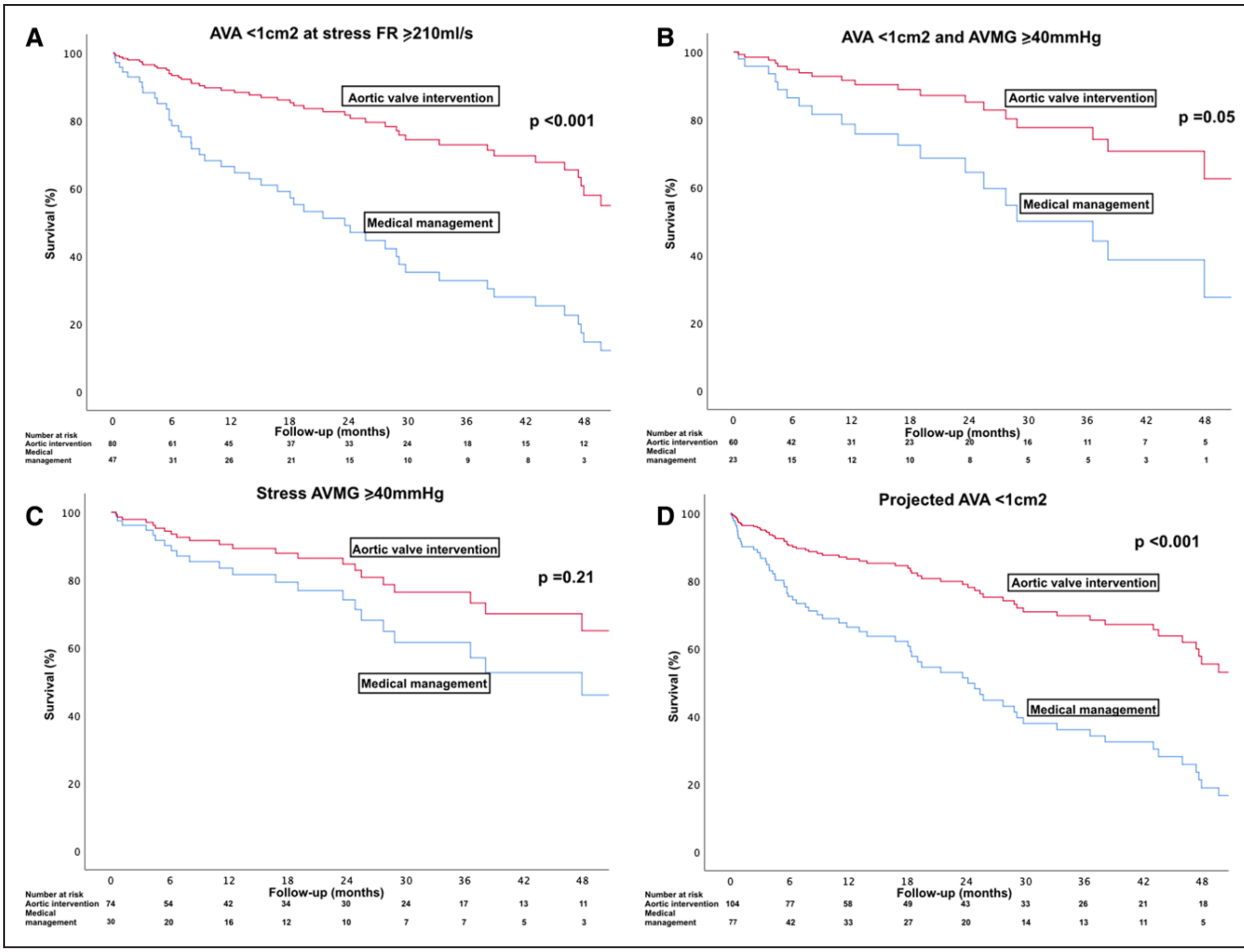

Figure 4. Impact of aortic valve intervention on mortality by different definitions of severe aortic stenosis (AS).
Survival curves adjusted to age, chronic kidney disease, presence of symptoms, rest, and stress left ventricular ejection fraction demonstrate mortality in patients with aortic valve intervention vs medical therapy according to the different AS criteria during low-dose dobutamine stress echocardiography. **A**, Patients with stress aortic valve area (AVA) <1 cm^2 at stress flow rate (FR) ≥210 mL/s had improved survival with aortic valve intervention. Patients with (**B**) the guideline definition (stress AVA <1 cm^2 and stress aortic valve mean gradient [AVMG] ≥40 mm Hg) or (**C**) stress AVMG ≥40 mm Hg did not demonstrate improved outcome. Projected AVA <1 cm^2 at 250 mL/s demonstrated benefit with aortic valve intervention (**D**).

which suggested that these patients had severe AS.[9] In this study, the authors also validated the prognostic impact of this criterion of AS in a separate large population.

The present study highlights the prognostic value of stress FR during LDDSE in patients with LGAS and reduced LVEF. The ability of the left ventricle to normalize the low transaortic flow during LDDSE suggests the presence of flow reserve. Stress FR also reflects the degree of recruitable myocardium (contractile reserve), increase in LVOT velocity, which is a major component of FR-suggested improved myocardial contractility. The latter, which is a marker of contractile reserve, is particularly relevant in these patients with compromised baseline left ventricular systolic function. Higher stress FR was associated with reduced risk of mortality independent of stress LVEF. The conventional marker of flow reserve, SV-derived flow reserve, was not associated with mortality. This is largely the case because during LDDSE, the heart rate increases significantly, which may result in either no change or even a reduction in SV because of an attenuation of left ventricular filling volume due to shortening of the filling time.[15] Under these circumstances, SV-derived flow reserve will change only marginally despite the improvement in myocardial contractility. Its lack of prognostic value has also been shown previously in patients with LGAS who underwent transcatheter aortic valve implantation.[16] Although it was not assessed in this study, LV strain may complement the assessment of contractile function.[17,18] In this study, lower stress SVi was associated to a lesser degree with an increased risk of mortality than stress FR. The likely explanation is that SVi represents volume and not flow and like SV-derived flow reserve is subject to the same limitations.

Lack of Prognostic Power of Guideline-Defined AS

This study also showed that patients in whom AVA remained <1 cm^2 at a normalized FR had a higher mortality versus those in whom AVA exceeded 1 cm^2, independent of aortic valve intervention, which suggests that FR ≥210 mL/s discriminated patients with severe versus nonsevere AS. AVA remaining below 1 cm^2, despite normalization of FR, implies a noncompliant aortic valve, which is the hallmark of severe AS. Diagnostic results were achieved in ≈70% of patients. In the conservative arm, which reflected the natural course of the aortic valve disease, survival was worst in the FR-determined criterion of severe AS compared with the guideline-defined criterion for severe AS or stress AVMG ≥40 mm Hg. Furthermore, the latter criteria were neither associated with mortality nor imparted survival benefit with aortic valve intervention, which the FR-determined criterion of severe AS did. Thus guideline-directed criteria are not optimal for the identification of AS severity, although there is a suggestion that patients with moderate AS in the presence of LV dysfunction may also be at increased risk and benefit from aortic valve intervention.[19]

A previously published elegant study in low-flow LGAS with reduced LVEF has shown that stress AVMG had low while stress AVA had high sensitivities for the detection of severe AS. The combined criteria had low sensitivity but high specificity. This study further showed that the guideline-defined criteria lacked prognostic power.[12] The aforementioned study also showed that when the projected AVA was calculated at an FR of 250 mL/s, this criterion detected more patients with severe AS compared with guideline-defined severe AS and was associated with increased mortality. In the present study, projected AVA showed similar mortality benefit when such patients underwent aortic valve intervention versus medical therapy, compared with stress AVA <1 cm^2 at stress FR ≥210 mL/s. However, projected AVA requires relatively cumbersome calculation for every patient and furthermore is only valid in those who achieved >15% FR change. On the contrary, the novel criterion proposed by this study does not require any such calculation and is an online, real-time assessment of AVA when stress FR 210 mL/s is reached. However, in 30% of our patients, stress FR ≥210 mL/s was not achieved. Projected AVA (excluding patients with <15% FR change) or computed tomography aortic valve calcium score may then be used to assess the prognostic significance of AS[10,11] (Figure 5).

Study Limitations

This study is a multicentre study and although the echocardiographic data were prospectively collected, the outcome data were collected retrospectively in some of the centers. Furthermore, the study is observational in nature, and, therefore, selection and other biases may be present. Although concurrent coronary artery bypass grafting

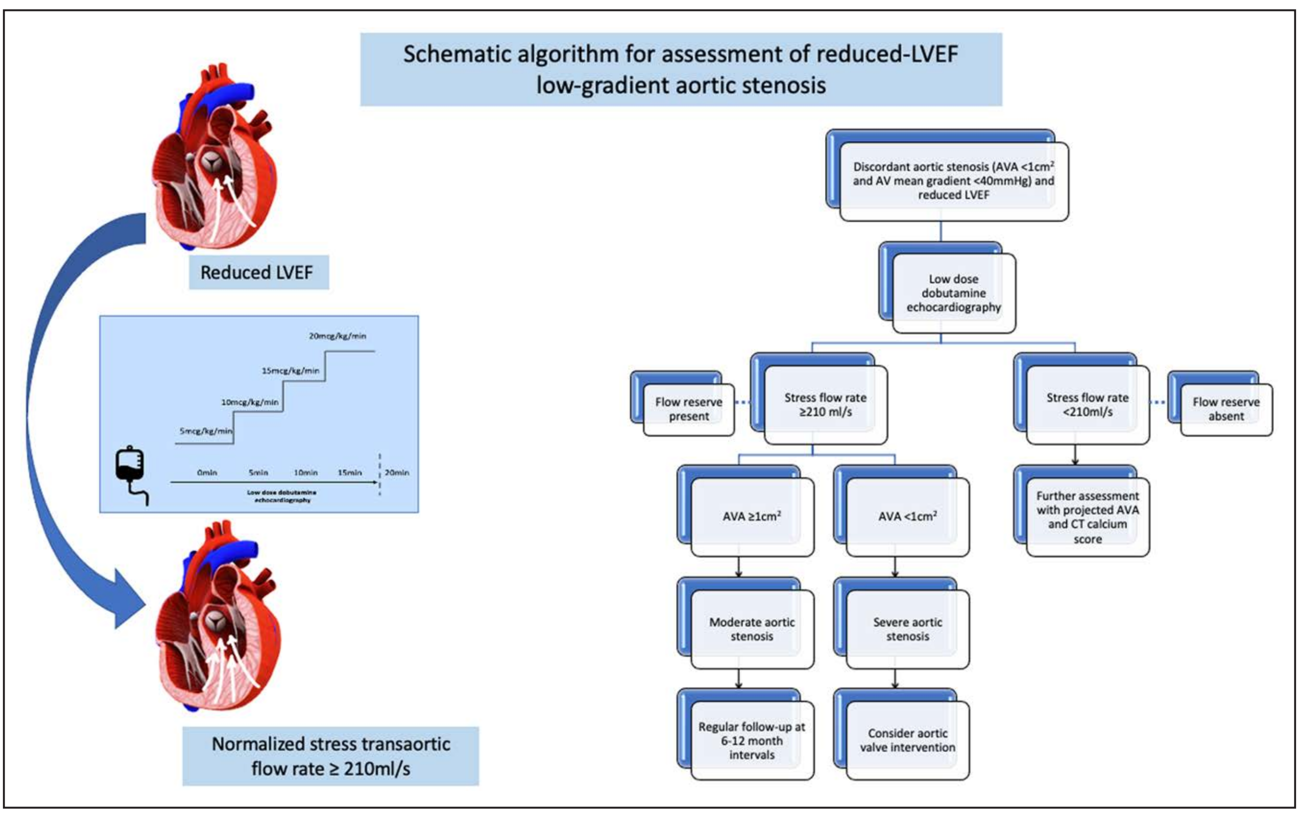

Figure 5. Schematic algorithm for assessment of reduced left ventricular ejection fraction (LVEF) low-gradient aortic stenosis (AS) with low-dose dobutamine stress echocardiography.
When the stress flow rate was ≥210 mL/s, stress aortic valve area (AVA) reflected the underlying AS severity. When there is absence of flow reserve, further assessment with computed tomography (CT) calcium score and projected AVA may be required. AV indicates aortic valve.

and left bundle branch block data were not available for analysis and may have influenced results through the revascularization effect and prolongation of LVET, respectively, from this and previous studies, these did not influence the outcome.[6] No external validation using valve calcium score or macroscopic assessment during aortic valve surgery was performed. There may have also been heterogeneity in clinical practice among the different centers, although adjustments for the possible different practices did not alter our results notwithstanding this is a real-life multicentre study, with a large number of patients and events (both death and aortic valve intervention), which means that the results would be applicable to a wide range of patients.

Conclusions

In a large population of patients with LGAS and reduced LVEF, lower stress FR, but not SV-derived flow reserve, was an independent predictor of mortality. Attainment of a stress AVA <1 cm^2 at a normalized stress FR ≥210 mL/s during LDDSE was the best determinant of severity of AS compared with guideline-defined AS, and patients with severe AS based on the novel FR criterion showed improved outcome with aortic valve intervention compared with medical therapy. This benefit was not evident when other guideline definitions were applied. Therefore, the assessment of stress FR and stress AVA during LDDSE is important for the evaluation of AS severity and the presence of flow reserve and can provide valuable information for guiding management of these patients.

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Supplemental Materials

Supplemental Figures I–IV
Supplemental Table I

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