

ORIGINAL ARTICLE

Myocardial Contraction Fraction for Risk Stratification in Low-Gradient Aortic Stenosis With Preserved Ejection Fraction

Dan Rusinaru, MD, PhD; Yohann Bohbot, MD; Maciej Kubala, MD, PhD; Momar Diouf, PhD; Alexandre Altes, MD; Agnès Pasquet, MD, PhD; Sylvestre Maréchaux^{id}, MD, PhD; Jean-Louis Vanoverschelde, MD, PhD; Christophe Tribouilloy^{id}, MD, PhD

BACKGROUND: Myocardial contraction fraction (MCF) is a volumetric measure of myocardial shortening independent of left ventricular size and geometry. This multicenter study investigates the usefulness of MCF for risk stratification in low-gradient severe aortic stenosis with preserved ejection fraction.

METHODS: We included 643 consecutive patients with low-gradient severe aortic stenosis with preserved ejection fraction in whom MCF was computed at baseline and analyzed mortality during follow-up.

RESULTS: Throughout follow-up with medical and surgical management (34.9 [16.1–65.3] months), lower MCF tertiles had higher mortality than the highest tertile. Eighty-month survival was 56±4% for MCF>41%, 41±4% for MCF 30% to 41%, and 40±4% for MCF<30% ($P<0.001$). After comprehensive adjustment, mortality risk remained high for MCF 30% to 41% (adjusted hazard ratio, 1.53 [1.08–2.18]) and for MCF<30% (adjusted hazard ratio, 1.82 [1.24–2.66]) versus MCF>41%. The optimal MCF cutoff point for mortality prediction was 41%. Age, body mass index, Charlson index, peak aortic velocity, and ejection fraction were independently associated with mortality. MCF (χ^2 to improve 10.39; $P=0.001$), provided greater additional prognostic value over the baseline parameters than stroke volume (SV) index (χ^2 to improve 5.41; $P=0.042$), left ventricular mass index (χ^2 to improve 2.15; $P=0.137$), or global longitudinal strain (χ^2 to improve 3.67; $P=0.061$). MCF outperformed ejection fraction for mortality prediction. When patients were classified by SV index and MCF, mortality risk was low when SV index was ≥ 30 mL/m² and MCF>41%, higher for patients with SV index ≥ 30 mL/m² and MCF $\leq$ 41% (adjusted hazard ratio, 1.47 [1.05–2.07]) and extremely high for patients with SV index <30 mL/m² (adjusted hazard ratio, 2.29 [1.45–3.62]).

CONCLUSIONS: MCF is a valuable marker of risk in low-gradient severe aortic stenosis with preserved ejection fraction and could improve decision-making, especially in normal-flow low-gradient severe aortic stenosis with preserved ejection fraction.

Key Words: aortic valve stenosis ■ echocardiography ■ mortality ■ myocardial contraction ■ stroke volume

See Editorial by Gillam and Mediratta

Low-gradient severe aortic stenosis with preserved left ventricular ejection fraction (LGSAS-PEF) is a heterogeneous clinical entity. In severe AS (aortic valve area [AVA] ≤ 1 cm²) with preserved ($\geq 50\%$) left ventricular (LV) ejection fraction (EF), low (<40 mmHg) mean gradients are often interpreted as the

consequence of a paradoxical low-flow (LF) state but may also be observed in cases with normal (≥ 35 mL/m²) stroke volume (SV) index. Guidelines recommend aortic valve replacement (AVR) for symptomatic LF/LGSAS-PEF after careful clinical and imaging work-up.^{1,2} However, the management of patients with normal flow (NF)/

Correspondence to: Christophe Tribouilloy, MD, PhD, Department of Cardiology, University Hospital Amiens, 80054 Amiens Cedex 1, France. Email tribouilloy.christophe@chu-amiens.fr

The Data Supplement is available at <https://www.ahajournals.org/doi/suppl/10.1161/CIRCIMAGING.120.012257>.

For Sources of Funding and Disclosures, see page 796.

© 2021 American Heart Association, Inc.

Circulation: Cardiovascular Imaging is available at www.ahajournals.org/journal/circimaging

CLINICAL PERSPECTIVE

Myocardial contraction fraction (MCF), the ratio of stroke volume (SV) to myocardial volume, is a volumetric measure of myocardial shortening and thickening independent of left ventricular size and geometry. This multicenter study investigates the usefulness of MCF for risk stratification in a large cohort of patients with low-gradient severe aortic stenosis and preserved left ventricular ejection fraction. MCF is a strong independent predictor of mortality, and patients with $MCF \leq 41\%$ have $>50\%$ increase in mortality risk during follow-up. MCF has significant additional prognostic value for mortality when added to a baseline multivariable model and outperforms ejection fraction and transvalvular aortic flow rate. Our findings lead to a novel appraisal of risk in low-gradient severe aortic stenosis with preserved ejection fraction based on the previously reported 30 mL/m^2 SV index cutoff and on the 41% MCF cut point. In patients with aortic stenosis with valve area $\leq 1 \text{ cm}^2$, low-gradient, and normal ejection fraction, the detection of an SV index below 30 mL/m^2 is a marker of high mortality risk, and in the presence of symptoms should lead to aortic valve replacement. For such patients, MCF has little additive value because in the majority of cases it is $\leq 41\%$. Conversely, in patients with low-gradient severe aortic stenosis with preserved ejection fraction and SV index $\geq 30 \text{ mL/m}^2$, the calculation of MCF is of importance as it refines risk prediction. Patients with normal flow and $MCF \leq 41\%$ have increased risk of mortality during follow-up while with $MCF > 41\%$ the risk of death is relatively low. These patients with normal flow and $MCF \leq 41\%$ might presumably benefit from surgical or transcatheter aortic valve replacement.

Nonstandard Abbreviations and Acronyms

AS	aortic stenosis
AVA	aortic valve area
AVR	aortic valve replacement
EF	ejection fraction
FR	flow rate
GLS	global longitudinal strain
HR	hazard ratio
LF	low flow
LGSAS-PEF	low-gradient severe aortic stenosis with preserved ejection fraction
LV	left ventricle
MCF	myocardial contraction fraction
MESA	Multi-Ethnic Study of Atherosclerosis
NF	normal flow
SV	stroke volume

LGSAS-PEF remains elusive and highly debated.^{3–7} We recently reported that when the 35 mL/m^2 cutoff is used to define LF, almost 40% of normal individuals are in an LF state.⁸ Hence, SV index $<30 \text{ mL/m}^2$ seems a more appropriate cut point in terms of outcome prediction and should be used to define LF in clinical practice.^{8,9} While this lowered cut point represents a clarification for paradoxical LF/LGSAS-PEF, it increases the prevalence of NF/LGSAS-PEF. Therefore, there is an ongoing search for markers of risk during follow-up that would be more sensitive and incremental to SV index, especially for patients with NF/LGSAS-PEF.¹⁰

Myocardial contraction fraction (MCF) is the ratio of SV to myocardial volume and represents a volumetric measure of the shortening and thickening of the myocardium, which is not influenced by LV size and geometry.¹¹ MCF measured by echocardiography or by magnetic resonance imaging is predictive of cardiovascular events and mortality in healthy adults^{12,13} but also in heart failure and in cardiomyopathies.^{14–16} MCF was linked to greater mortality risk following transcatheter AVR in a small series of patients with severe AS with PEF.¹⁷ To our knowledge, the prognostic usefulness of MCF in LGSAS-PEF has not been investigated.

This study merges the consecutive experience with LGSAS-PEF of 3 expert centers for the diagnosis and management of valvular heart diseases and aims to investigate whether MCF assessed by echocardiography-Doppler (1) predicts mortality during follow-up in LGSAS-PEF and (2) allows stratification of mortality risk in each of the flow-patterns (LF and NF).

METHODS

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

Patient Population

The study consists of consecutive patients aged ≥ 18 years diagnosed with severe ($AVA \leq 1 \text{ cm}^2$) AS and low ($<40 \text{ mm Hg}$) mean pressure gradient at the echocardiography laboratories of 2 French (Amiens and Lille) and one Belgian center (Bruxelles) between 2000 and 2017 and included in an electronic database at the time of the index echocardiography.¹⁸ Patients with $>$ mild aortic and mitral regurgitation, prosthetic valves, congenital heart disease, supra- or subvalvular AS, dynamic LV outflow tract obstruction, mitral stenosis, $EF < 50\%$, and patients who refused to participate in the study were excluded. Six hundred ninety-eight patients with LGSAS-PEF were initially enrolled. The study sample comprised 643 patients after exclusion of 55 patients because of missing data. Baseline characteristics were collected at inclusion. We obtained institutional review board authorizations before conducting the study and subjects gave informed consent for research participation. The study was conducted in accordance with institutional policies, national legislation, and the revised Helsinki declaration.

Echocardiography

All patients underwent a comprehensive Doppler-echocardiography study, using commercially available systems (Sonos 5500, IE33, EPIQ5, EPIQ7; Philips Healthcare, Andover, MA and Vivid-7, Vivid-9; GE Healthcare, Milwaukee, WI).⁸ SV was calculated by multiplying the LV outflow tract area by the LV outflow tract time-velocity integral¹⁹ and was indexed to body surface area. LF was defined by SV index <30 mL/m² as previously stated.⁸ Otherwise, patients were considered to have NF/LGSAS-PEF. MCF was computed as the ratio of SV to myocardial volume.¹¹ Myocardial volume was defined as LV mass divided by the mean density of the myocardium (1.05 g/mL). LV mass was calculated according to a validated linear method.²⁰ The measure of LV diameters and wall thickness was performed as recommended by the American Society of Echocardiography.²⁰ In patients with septal bulges, the LV diastolic dimension was measured by M-mode echocardiography (or 2-dimensional echocardiography in case of suboptimal alignment) in the parasternal long-axis view below the septal bulge.²¹ EF was measured by the Simpson biplane method. LV global longitudinal strain (GLS) was measured using the Echopac software (GE Vivid 9, General Electric Ultrasound). Transvalvular aortic flow rate (FR) was computed directly as the ratio of SV to ejection time or estimated from the product of the AVA and the mean linear transvalvular flow velocity (Data Supplement).

Management and Follow-Up

Patients were followed at the outpatient clinics of the enrolling centers or at public hospitals and private practices by referring cardiologists working in collaboration with the centers. Information on follow-up was retrospectively obtained by direct patient interview or follow-up letters to physicians, patients and (if necessary) next of kin. The end point of the study was survival after diagnosis encompassing medical and surgical management. Median overall follow-up was 34.9 (16.1–65.3) months. Follow-up was complete until death or the end of the study for 95% of patients. Clinical decisions regarding medical management and indications for AVR were made by the heart team with the approval of the patient's referring cardiologist in accordance with guideline recommendations.

Statistical Analysis

Continuous variables were expressed as mean value $\pm$ 1 SD or median (25th and 75th percentiles), as appropriate. Categorical variables were displayed as frequency percentages and counts. The relationship between baseline continuous variables and MCF tertiles was explored using 1-way ANOVA tests or Kruskal-Wallis tests. Pearson χ^2 statistic or Fisher exact test were used to examine the association between the MCF tertiles and baseline categorical variables. The significance between the highest tertile and the others was examined if there was a significant difference across tertiles. Individual differences were compared with Mann-Whitney *U* tests (with Bonferroni correction for multiple comparisons) and Tukey tests for normally distributed data.

The analysis of mortality encompassed the entire follow-up irrespective if AVR was performed or not. The survival time of patients lost to follow-up was censored at the date of the last

contact. Estimated survival rates $\pm$ 1 SE were determined using the Kaplan-Meier estimator and compared by 2-sided log-rank tests. Analyses of all-cause mortality were performed using Cox proportional hazards models. Multivariable Cox models were adjusted for covariates selected a priori, considered of potential prognostic impact on the basis of previous studies and clinical judgment (age, sex, body mass index, symptoms, hypertension, coronary artery disease, history of atrial fibrillation, Charlson comorbidity index, peak aortic jet velocity [Vmax], AVA, and EF). Additionally, we tested the field center effect by adding dummy variables to the multivariable model. The effect of AVR on outcome was analyzed as a time-dependent covariate. The proportionality assumption was tested using the test by Grambsch and Therneau.²²

A stepwise backward model including the above covariates was used to construct a baseline model predicting mortality during follow-up. To assess the potential additive prognostic value of MCF and other parameters, we evaluated the ability of each of these parameters to improve the prediction of death by comparing the additional increase of the χ^2 value of the combined model over the baseline model. Additionally, we determined the optimal cutoff values of MCF and other parameters for survival by the Contal and O'Quigley method, which is based on the concept of maximizing the log-rank statistic²³ and computed incremental χ^2 values over the baseline model. Models were compared using likelihood tests. Data were analyzed with SPSS (v 18.0; IBM Corp, Armonk, NY) and SAS (version 9.4, SAS Institute Inc, Cary, NC).

RESULTS

Baseline Characteristics

Baseline characteristics of the study patients (median age 81 years, 63% women) are presented in Table 1. With lower MCF, the frequency of male sex increased, patients were more often symptomatic, had greater body surface area, higher comorbidity index, and more often atrial fibrillation. Patients with lower MCF had smaller AVA, greater LV diameters, LV mass index, and left atrial volume index. SV index and EF were lower in patients with lower MCF while systolic pulmonary artery pressure increased with lower MCF.

MCF and Mortality

During follow-up 311 patients died. AVR was performed in 256 patients (74 [34.6%] in the low MCF tertile, 87 [40.5%] in the intermediate MCF tertile, and 95 [44.4%] in the high MCF tertile; $P=0.115$) by surgical (75.4%) or percutaneous techniques (24.6%). Management was solely conservative in 387 patients. Forty-seven percent ($n=75$) of patients in New York Heart Association class III and IV underwent surgical or transcatheter AVR during follow-up (Data Supplement). Eighty-month actuarial survival was $56\pm4\%$ for MCF $>41\%$, $41\pm4\%$ for MCF 30% to 41%, and $40\pm4\%$ for MCF $<30\%$ ($P<0.001$ for MCF $>41\%$ versus MCF 30%–41%, $P<0.001$ for MCF $>41\%$ versus MCF $<30\%$, $P=0.562$ for MCF 30%

Table 1. Baseline Characteristics, Overall and According to Tertiles of MCF

Variable	All patients (n=643)	MCF<30% (n=214)	MCF 30%–41% (n=215)	MCF>41% (n=214)	P value
Age, y	81.0 (75.0 to 86.4)	81.8 (74.9 to 87.0)	81.6 (75.0 to 86.0)	80.2 (75.6 to 86.2)	0.443
Male sex, % (n)	37.0% (238)	43.9% (94)	34.0% (73)	33.2% (71)	0.037
Body surface area, m ²	1.78±0.22	1.80±0.22*	1.78±0.23	1.75±0.20	0.016
Body mass index, kg/m ²	25.9 (22.9 to 29.5)	26.9 (23.5 to 29.9)	25.9 (22.9 to 29.5)	25.4 (22.6 to 29.3)	0.127
Systolic blood pressure, mm Hg	140.0 (120.0 to 150.0)	140.0 (120.0 to 160.0)	140.0 (124.5 to 150.0)	140.0 (125.0 to 150.0)	0.673
Symptoms, % (n)	74.2% (477)	80.4% (172)	72.6% (156)	69.6% (149)	0.032
NYHA class, % (n)					0.164
I–II	75.1% (483)	72.0% (154)	75.8% (163)	77.6% (166)	
III–IV	27.9% (160)	28.0% (60)	24.2% (52)	22.4% (48)	
Hypertension, % (n)	75.6% (486)	74.3% (159)	79.5% (171)	72.9% (156)	0.238
Diabetes, % (n)	32.3% (208)	34.6% (74)	31.2% (67)	31.3% (67)	0.693
Coronary artery disease, % (n)	42.5% (273)	46.3% (99)	42.8% (92)	38.3% (82)	0.247
History of atrial fibrillation, % (n)	38.1% (245)	47.2% (101)	36.3% (78)	30.8% (66)	0.002
Chronic kidney disease, % (n)	26.0% (167)	35.5% (76)†	26.0% (56)†	16.4% (35)	<0.001
Charlson comorbidity index	2.0 (1.0 to 4.0)	3.0 (1.0 to 4.0)*	2.0 (1.0 to 4.0)	2.0 (1.0 to 3.5)	0.034
Aortic valve area, cm ²	0.84 (0.72 to 0.94)	0.79 (0.67 to 0.89)†	0.86 (0.72 to 0.94)*	0.88 (0.80 to 0.97)	<0.001
Aortic valve area index, cm ² /m ²	0.46±0.09	0.43±0.09†	0.47±0.08†	0.49±0.08	<0.001
Peak aortic jet velocity, m/s	3.5 (3.2 to 3.8)	3.4 (3.0 to 3.8)*	3.6 (3.2 to 3.8)	3.6 (3.3 to 3.8)	0.010
Transaortic mean gradient, mm Hg	30.0 (24.0 to 35.0)	29.0 (23.0 to 35.0)	30.0 (24.0 to 35.0)	29.0 (24.0 to 35.0)	0.511
LVOT diameter, mm	21.0 (20.0 to 22.0)	20.0 (19.0 to 21.5)†	21.0 (20.5 to 22.0)†	22.0 (20.5 to 23.0)	<0.001
LVOT time-velocity integral, cm	19.0 (17.0 to 22.0)	18.0 (16.0 to 20.0)†	19.0 (17 to 21)†	20.0 (19.0 to 22.0)	<0.001
LV end-diastolic diameter, mm	46.4±7.1	49.1±7.7†	45.9±6.3	44.3±6.2	<0.001
LV end-systolic diameter, mm	29.0 (25.0 to 33.0)	32.0 (27.0 to 36.0)†	29.0 (26.0 to 32.3)*	27.0 (22.0 to 30.5)	<0.001
LV end-diastolic volume, mL	101.0 (80.0 to 130.0)	106.0 (82.2 to 145.8)	102.0 (79.0 to 124.0)	98.0 (80.5 to 123.5)	0.107
LV end-systolic volume, mL	37.0 (27.0 to 52.0)	43.0 (30.0 to 62.0)†	38.0 (28.0 to 51.0)	34.0 (25.0 to 44.0)	<0.001
Ejection fraction (%)	63.6 (57.0 to 68.0)	60.0 (55.0 to 65.0)†	63.0 (57.0 to 68.0)†	65.0 (60.9 to 70.2)	<0.001
Stroke volume, mL	65.9±17.1	57.2±14.5†	67.1±16.4†	73.3±16.3	<0.001
Stroke volume index, mL/m ²	37.2±9.3	31.7±7.5†	37.7±8.3†	42.1±8.9	<0.001
LV mass index, g/m ²	107.7 (86.1 to 133.8)	136.8 (112.7 to 159.5)†	110.5 (92.3 to 126.8)†	82.0 (69.1 to 97.4)	<0.001
Transvalvular aortic flow rate, mL/s	239±76	212±72†	246±74†	261±75	<0.001
Left atrial volume index, mL/m ² ‡	45.0 (34.7 to 59.5)	47.5 (36.9 to 64.2)*	44.4 (35.0 to 60.9)	41.0 (28.0 to 51.3)	0.001
Systolic pulmonary artery pressure, mm Hg§	34.0 (28.0 to 43.0)	35.0 (29.0 to 49.0)*	35.0 (28.0 to 44.8)	32.0 (25.5 to 39.5)	0.007
LV global longitudinal strain (%)	−13.2 (−16.2 to −10.2)	−10.9 (−13.8 to −7.5)†	−13.4 (−15.9 to −10.2)†	−15.2 (−18.4 to −12.9)	<0.001

LV indicates left ventricular; LVOT, left ventricular outflow tract; MCF, myocardial contraction fraction; and NYHA, New York Heart Association.

* $P<0.050$ individual category vs MCF>41%.

† $P<0.001$ individual category vs MCF>41%.

‡123 missing data.

§215 missing data.

||424 missing data.

to 41% versus MCF<30%, Figure 1A). On multivariable analysis, lower MCF tertiles had increased mortality risk compared with the highest tertile (Table 2). Adjustment for AVR (as time-dependent variable) did not modify the excess risk of death of lower MCF tertiles compared with the highest tertile (adjusted hazard ratio [HR], 1.53 [1.08–2.18] for MCF 30% to 41% versus MCF>41%, adjusted HR, 1.82 [1.24–2.66] for MCF<30% versus MCF>41%; Table 2, Figure 1B). The prognostic value of low MCF remained powerful after further adjustment for FR (adjusted HR, 1.57 [1.09–2.24] for MCF 30%–41%

versus MCF>41%, adjusted HR, 1.80 [1.22–2.69] for MCF<30% versus MCF>41%). In the subgroup of patients in whom left atrial volume index was available, the relation between MCF tertiles and outcome was unchanged (adjusted HR, 1.47 [1.01–2.14] for MCF 30% to 41% versus MCF>41%, adjusted HR, 1.68 [1.13–2.50] for MCF<30% versus MCF>41%).

The baseline multivariable model for mortality including clinical (age, sex, body mass index, symptoms, hypertension, coronary artery disease, history of atrial fibrillation, and Charlson comorbidity index) and

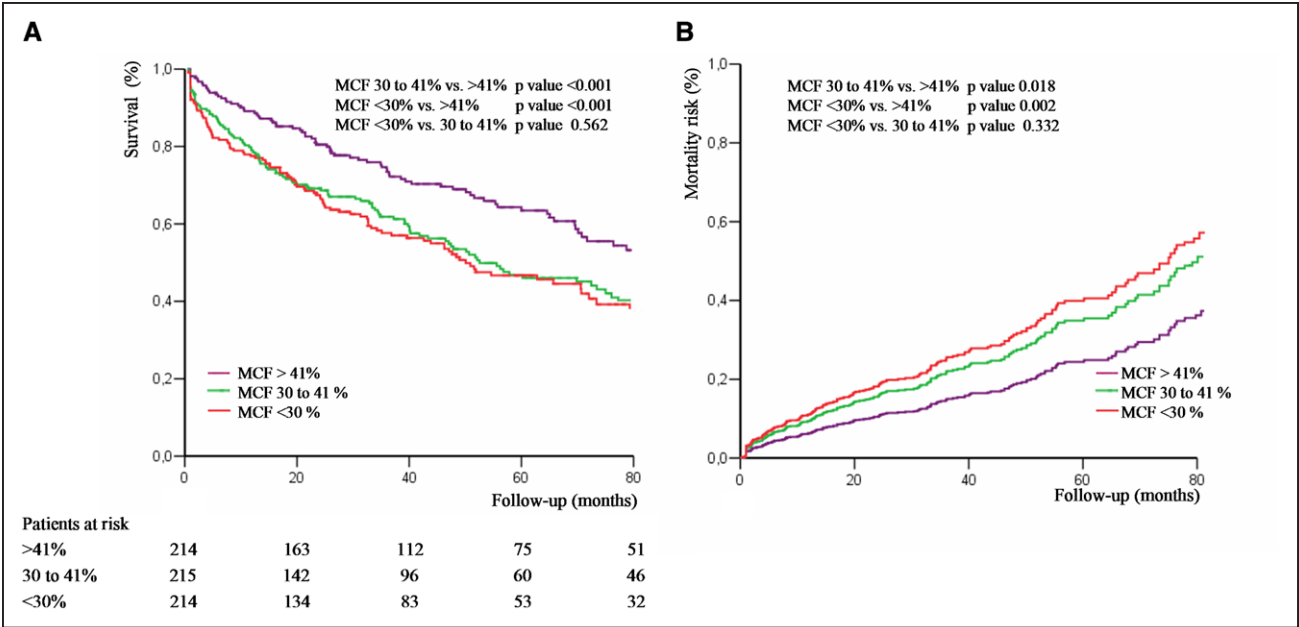


Figure 1. Outcome according to myocardial contraction fraction (MCF) tertiles.
A, Kaplan-Meier survival curves. **B**, Adjusted mortality curves (covariates for adjustment are from Model 3, Table 2).

echocardiography-Doppler variables (Vmax, AVA, and EF) is presented in Table 3. Age, body mass index, Charlson comorbidity index, Vmax, and EF were independent predictors of death during follow-up. On multivariable analysis,

Table 2. Relative Risk of All-Cause Mortality Associated With MCF

Model	Overall death	
	HR (95% CI)	P value
Unadjusted		
>41%	Referent	
30%–41%	1.42 (1.08–1.88)	0.014
<30%	1.67 (1.26–2.20)	<0.001
Multivariable model 1*		
>41%	Referent	
30%–41%	1.52 (1.08–2.14)	0.017
<30%	1.63 (1.15–2.31)	0.006
Multivariable model 2†		
>41%	Referent	
30%–41%	1.50 (1.06–2.13)	0.022
<30%	1.68 (1.15–2.45)	0.007
Multivariable model 3‡		
>41%	Referent	
30%–41%	1.53 (1.08–2.18)	0.018
<30%	1.82 (1.24–2.66)	0.002

AVA indicates aortic valve area; AVR, aortic valve replacement; CAD, coronary artery disease; EF, ejection fraction; HR, hazard ratio; MCF, myocardial contraction fraction; and Vmax, peak aortic jet velocity.
*Model 1 is adjusted for age, sex, body mass index, symptoms, hypertension, CAD, history of atrial fibrillation, and comorbidity index.
†Model 2 includes variables in model 1 and Vmax, AVA, and EF.
‡Model 3 includes variables in model 2 and AVR as time-dependent covariate.

the field center effect was not significant ($P=0.531$ and $P=0.238$, respectively). Although MCF, SV index, and FR were found to have significant additional prognostic value for mortality over the baseline model (Table 3), the predictive value of MCF was greater than that of SV index or FR. On multivariable analysis, MCF (adjusted HR, 0.97 [0.96–0.98], $P<0.001$ per 1% MCF increment) outperformed EF ($P=0.388$) for mortality prediction. In the subgroup of patients in whom LV GLS was available ($n=219$) MCF was a better predictor of mortality (adjusted HR, 0.97 [0.97–0.99], $P<0.001$ per 1% MCF increment) than EF ($P=0.928$) or LV GLS ($P=0.492$). The optimal MCF cutoff point for the prediction of all-cause mortality was 41.0% by the Contal and O’Quigley method (log-rank statistic =38.16, Q-statistic =2.51, $P<0.001$; Figure 1 in the [Data Supplement](#)). Similar optimal cutoff points were 31.6 mL/m² for SV index, −14.2% for LV GLS, 96.1 g/m² for LV mass index, and 198 mL/s for FR. MCF<41% showed higher incremental predictive value over the baseline model compared with SV index <31.6 mL/m² or LV GLS >−14.2% (additional value of the χ^2 of the model: 11.69 for MCF≤41%, $P=0.001$; 9.13 for SV index <31.2 mL/m², $P=0.003$; 3.52 for LV GLS >−14.2%, $P=0.045$). LV mass index >96.1 g/m² and FR <198 mL/s did not significantly improve the baseline model.

Subgroup Analysis

Subgroups by SV Index

Among patients with LF ($n=141$), MCF was ≤41% in 90.1% of cases ($n=127$). MCF≤41% was associated with poorer 80-month actuarial survival compared with MCF>41% (27±5% versus 52±15%), but the difference

Table 3. Multivariate Analysis of the Prediction of All-Cause Mortality

Variable	Partial hazard ratio (95% CI)	χ^2	P value	χ^2 to improve	Partial hazard ratio (95% CI)	P value
Baseline model						
Age (per 1-year increase)	1.08 (1.06–1.10)	31.25	<0.001			
Body mass index (per 1 kg/m ² increase)	0.96 (0.93–0.98)	6.89	0.004			
Charlson comorbidity index (per 1 unit increase)	1.10 (1.04–1.19)	9.71	0.002			
Vmax (per 1 m/s increase)	0.67 (0.50–0.91)	6.82	0.009			
LV ejection fraction (per 1% increase)	0.98 (0.96–1.00)	3.09	0.062			
		127.56*	<0.001			
Additional variables†						
Stroke volume index (per 1 mL/m ² increase)				5.41	0.98 (0.97–0.99)	0.042
LV mass index (per 1 g/m ² increase)				2.15	1.002 (0.99–1.01)	0.137
LV global longitudinal strain (per 1% increase) ‡				3.67	1.05 (0.99–1.12)	0.061
Transvalvular aortic flow rate (per mL/s decrease)				4.54	0.99 (0.99–1.00)	0.034
MCF (per 1% increase)§				10.39	0.96 (0.94–0.99)	0.001

Baseline model is a Cox multivariable model for all-cause mortality (model 2, Table 2). LV indicates left ventricular; MCF, myocardial contraction fraction; and Vmax, peak aortic jet velocity.

* χ^2 of the baseline model.

†Additional variables were added each on top of the baseline model and the χ^2 to improve the baseline model for each variable is presented.

‡Available in 219 patients.

§ $P < 0.010$ MCF vs stroke volume index, MCF vs LV global longitudinal strain, and MCF vs transvalvular aortic flow rate.

was not statistically significant ($P=0.112$). After covariate adjustment MCF $\leq 41\%$ was still not significantly associated with mortality (adjusted HR, 3.53 [0.74–16.8]). In the group of patients with NF ($n=502$), 59.9% ($n=301$) had MCF $\leq 41\%$ and 40.1% ($n=201$) had MCF $> 41\%$. MCF $\leq 41\%$ was associated with lower 80-month actuarial survival compared with MCF $> 41\%$ ($44\pm 4\%$ versus $54\pm 4\%$, $P=0.021$). On multivariable analysis, the excess mortality risk associated with MCF $\leq 41\%$ was confirmed (adjusted HR, 1.41 [1.01–1.97]).

When patients were divided in 3 groups according to SV index and MCF, both flow and MCF strongly influenced outcome. Estimated survival was the highest for NF with MCF $> 41\%$, lower for NF with MCF $\leq 41\%$ and very poor for the LF subgroup (Figure 2A). On multivariable analysis, compared with the reference group (NF with MCF $> 41\%$) mortality risk was increased for NF with MCF $\leq 41\%$ (adjusted HR, 1.47 [1.05–2.07]) and was very high for LF (adjusted HR, 2.29 [1.45–3.62]; Figure 2B).

When SV index subgroups were delineated by the 35 mL/m² threshold,^{1,2} or by sex-specific cut points,²⁴ the results remained essentially unchanged (Data Supplement).

Subgroups by Symptomatic Status

MCF $\leq 41\%$ was associated with poorer 80-month survival than MCF $> 41\%$ in asymptomatic ($44\pm 7\%$ versus $62\pm 9\%$; $P=0.012$) and symptomatic patients ($38\pm 4\%$ versus $49\pm 5\%$; $P=0.008$). On multivariable analysis, MCF $\leq 41\%$ was independently predictive of mortality in both subgroups (adjusted HR, 3.46 [1.51–7.96] for asymptomatic patients and adjusted HR, 1.49

[1.04–2.14] for symptomatic patients, P for interaction 0.184).

DISCUSSION

We report herein the value of MCF for long-term mortality risk assessment in a large cohort of patients with LGSAS-PEF. MCF is a strong independent predictor of mortality in LGSAS-PEF after adjustment for factors known as major determinants of prognosis. MCF below the 41% cutoff is associated with $> 50\%$ increase in the risk of death during follow-up. Furthermore, MCF has significant additional prognostic value for mortality when added to a baseline multivariable model, including demographic, clinical, and echocardiography-Doppler variables. Finally, long-term outcome is impacted by both flow and MCF with acceptable mortality for patients with NF and normal MCF, intermediate risk for patients with NF and low MCF, and dismal prognosis for patients with LF.

LGSAS-PEF is a heterogeneous clinical entity in regard to the severity of the valvular obstacle and the function of the LV. Based on the 35 mL/m² SV index cut point,²⁵ LGSAS-PEF is classically dichotomized in LF/ and, respectively, NF/LGSAS-PEF. NF/LGSAS-PEF represents more than half of all diagnosed LGSAS cases with preserved and with reduced EF. While AVR is currently recommended after careful clinical and imaging work-up for patients with LF/LGSAS-PEF presenting with symptoms related to the valvular obstacle,^{2,3} the management of NF/LGSAS-PEF remains unclear and difficult. Studies investigating outcomes of patients with NF/LGSAS-PEF have led to conflicting results. We have

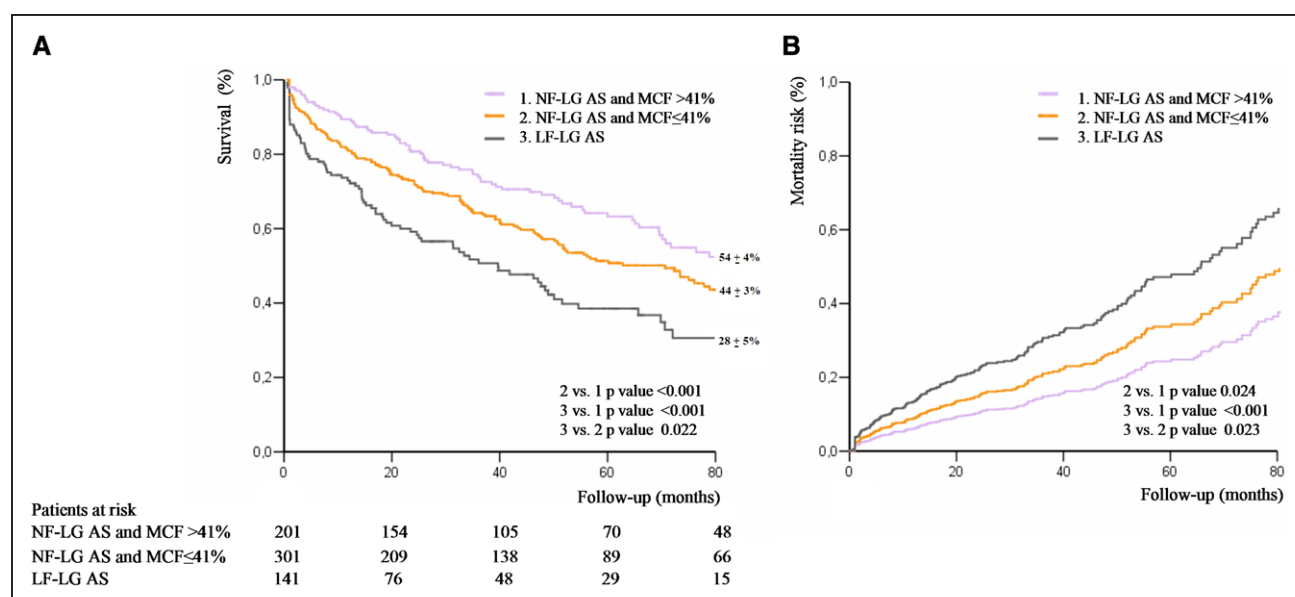


Figure 2. Subgroup analysis according to stroke volume (SV) index and myocardial contraction fraction (MCF).

A, Kaplan-Meier actuarial survival; **B**, Adjusted mortality curves. For adjustment covariates, see Figure 1B. AS indicates aortic stenosis; LF, low flow; LG, low gradient; and NF, normal flow.

reported that NF/LGSAS-PEF has a comparable outcome to moderate AS⁷ while others have suggested that patients NF/LGSAS-PEF benefit from AVR compared with medical management.^{3,4} Apart from methodological differences, patient heterogeneity might explain these discordant results. Moreover, recent outcome studies of patients with AS^{8,9} supported by echocardiography-Doppler data in normal individuals^{24,26} have lowered to 30 mL/m² the LF cut point in severe AS with PEF. LF/LGSAS-PEF thus defined displays dismal outcome. Conversely, this lowered cut point increases the prevalence of NF/LGSAS. Therefore, markers of risk that would be more sensitive and incremental to SV index, especially for NF/LGSAS-PEF, are urgently needed. In this regard, the sole parameter that has been investigated for diagnostic and prognostic purposes is FR. Low-dose dobutamine stress echocardiography or preload stress echocardiography can be used in patients with NF/LGSAS and FR <200 mL/s to rule out severe AS. Our results confirm the 200 mL/s FR cut point and show that MCF retains independent prognostic value after adjustment for FR.

MCF is a volumetric expression of the shortening and thickening of the myocardium during systole that is independent of the size and the geometry of the LV.¹¹ In the report by King et al,¹¹ MCF assessed by 3-dimensional transthoracic echocardiography successfully distinguished patients with heart failure with preserved EF from healthy athletes with LV hypertrophy and normal controls. Low MCF by cardiovascular magnetic resonance imaging was associated with an increased risk of cardiovascular disease in the Framingham Heart Study Offspring cohort study¹² and more recently in the MESA study (Multi-Ethnic Study of Atherosclerosis).²⁷ In the

Cardiovascular Health Study, MCF by 2-dimensional echocardiography guided M-mode was inversely associated with adverse cardiovascular outcomes and mortality.¹³ Moreover, reduced MCF predicted adverse events in patients with nonischemic dilated cardiomyopathies,¹⁴ transthyretin amyloidosis,¹⁵ and hypertrophic cardiomyopathy with normal EF.¹⁶ The prognostic usefulness of MCF in patients with AS has not been established. To the best of our knowledge, only one single-center retrospective study of 126 patients with severe AS referred for transcatheter AVR reported that preoperative MCF ≤30% was predictive of increased 1-year mortality.¹⁷ The present study identified a higher MCF cut point for mortality prediction. This discrepancy may be explained by differences in the studied populations and the use by Romeo et al¹⁷ of a different method (classical receiver-operating curve) for cut point identification in outcome analyses.

According to the results of the present study, MCF effectively stratifies risk in LGSAS-PEF, especially for patients in whom flow across the aortic valve is normal. As for other pathological forms of LV hypertrophy,¹⁵ we show that MCF is superior to EF for outcome prediction in LGSAS-PEF. Flow across the aortic valve^{8,24,25} dichotomizes LGSAS-PEF and, in spite of some data suggesting progressive incremental mortality risk with lower SV index,²⁸ cannot further refine risk prediction. Recently, concentric remodeling patterns have been identified as markers of risk in severe AS with PEF.²⁹ By integrating LV remodeling and LV systolic function, MCF is an interesting prognostic marker in AS with normal EF. From a physiological perspective, MCF can be understood as the amount by which the myocardium shortens and thickens in systole relative to the total volume

of the LV myocardium.¹¹ However, from a mathematical point of view, MCF is the inverse of LV concentricity from which the ratio of LV end-systolic volume to LV mass is subtracted.¹² This suggests that reductions in MCF are proportional with LV concentricity but further influenced by larger LV end-systolic volumes. Our findings lead to a novel appraisal of risk in LGSAS-PEF based on the previously reported 30 mL/m² SV index cutoff^{8,24,26} and on the 41% MCF cut point found predictive of increased mortality risk in the present analysis. In patients with aortic valve stenosis with AVA $\leq$ 1 cm² by continuity equation, low-gradient, and normal EF, the detection of an SV index by Doppler-echocardiography below 30 mL/m² is a marker of high mortality risk, and in the presence of symptoms related to the valvular obstacle should lead to AVR as conservative management is associated with unacceptable mortality in this situation. For such patients, MCF has little additive value because in the vast majority of cases it is $\leq$ 41%. However, a small group of patients (10%) with SV index $<$ 30 mL/m² and MCF $>$ 41% has low mortality during follow-up, although the present study could not demonstrate that this apparently better outcome is statistically significant. Larger cohorts are, therefore, needed to clarify the prognosis of this small group. Conversely, in patients with LGSAS-PEF and SV index $\geq$ 30 mL/m², the calculation of MCF is of importance as it refines risk prediction. Patients with NF/LGSAS-PEF and MCF $\leq$ 41% have increased risk of mortality during follow-up while with MCF $>$ 41% the risk of death is relatively low. These patients with NF/LGSAS-PEF and MCF $\leq$ 41% might presumably benefit from surgical or transcatheter AVR.

Limitations

Contrary to the original description of MCF,¹¹ we assessed SV by Doppler-echocardiography at the aortic annulus as this measurement is part of any routine echocardiographic examination and, in patients with AS, is systematically used to calculate the AVA. Other imaging modalities such as magnetic resonance imaging and computed tomography provide estimates of SV and LV mass but are more costly, time consuming and not always available in routine practice. Furthermore, Doppler-derived SV values are lower compared with SV assessed by magnetic resonance imaging translating into different SV cut points associated with mortality. This study also shows that LV GLS is not superior to MCF for outcome prediction purposes. LV GLS was not available for all patients included in this study and, therefore, results involving this parameter should be interpreted as hypothesis generating and require further validation. Biomarkers of myocardial stress/injury or diastolic overload and parameters of LV diastolic function were not available. Although the linear estimation of LV mass was not developed and validated in AS, it is the most

frequently used method for LV mass calculation in clinical practice and in scientific reports. We acknowledge that transthyretin cardiac amyloidosis is prevalent in patients with severe LF/LG AS and interacts with natural history outcomes.³⁰ We cannot investigate the link between concurrent cardiac amyloidosis and outcomes in this cohort as the presence of amyloidosis was not systematically investigated in our patients.

Conclusions

MCF is a unitless volumetric ratio of the systolic shortening and thickening of the myocardium easily obtainable by routine Doppler-echocardiography. In LGSAS-PEF, MCF is superior to EF for the prediction of long-term mortality. Baseline MCF $<$ 41% is associated with $>$ 50% increase in the risk of death during follow-up. MCF $<$ 41% is a marker of risk in LGSAS-PEF, especially in patients with NF in whom therapy is still highly debated. MCF might therefore improve the understanding of NF/LGSAS-PEF and guide decision-making. Further studies are needed to compare the relative value of MCF and LV GLS in LGSAS-PEF.

ARTICLE INFORMATION

Received December 2, 2020; accepted May 25, 2021.

Affiliations

Pôle Coeur-Thorax-Vaisseaux, Department of Cardiology (D.R., Y.B., M.K., C.T.) and Division of Clinical Research and Innovation (M.D.), University Hospital Amiens, France. Centre Universitaire de Recherche en Santé, Laboratoire MP3CV - EA 7517, Université de Picardie, Amiens, France (D.R., Y.B., S.M., C.T.). Groupement des Hôpitaux de l'Institut Catholique de Lille/Faculté libre de médecine, Université Lille Nord de France (A.A., S.M.). Pôle de Recherche Cardiovasculaire, Institut de Recherche Expérimentale et Clinique, Université Catholique de Louvain, Brussels, Belgium (A.P., J.-L.V.). Division of Cardiology, Cliniques Universitaires Saint-Luc, Brussels, Belgium (A.P., J.-L.V.).

Sources of Funding

None.

Disclosures

None.

Supplemental Materials

Supplemental Methods
Supplemental Results
Supplemental Figure 1
References 31, 32

REFERENCES

1. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, et al; ACC/AHA Task Force Members. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. *Circulation*. 2014;129:e521–e643. doi: 10.1161/CIR.0000000000000031
2. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Jung B, Lancellotti P, Lansac E, Rodriguez Muñoz D, et al; ESC Scientific Document Group. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J*. 2017;38:2739–2791. doi: 10.1093/eurheartj/ehx391
3. Zusman O, Pressman GS, Banai S, Finkelstein A, Topilsky Y. Intervention versus observation in symptomatic patients with normal flow low gradient

- severe aortic stenosis. *JACC Cardiovasc Imaging*. 2018;11:1225–1232. doi: 10.1016/j.jcmg.2017.07.020
4. Saeed S, Vamvakidou A, Seifert R, Khattar R, Li W, Senior R. The impact of aortic valve replacement on survival in patients with normal flow low gradient severe aortic stenosis: a propensity-matched comparison. *Eur Heart J Cardiovasc Imaging*. 2019;20:1094–1101. doi: 10.1093/ehjci/jez191
 5. Mehrotra P, Jansen K, Flynn AW, Tan TC, Elmariah S, Picard MH, Hung J. Differential left ventricular remodelling and longitudinal function distinguishes low flow from normal-flow preserved ejection fraction low-gradient severe aortic stenosis. *Eur Heart J*. 2013;34:1906–1914. doi: 10.1093/eurheartj/ehy094
 6. Kang DH, Jang JY, Park SJ, Kim DH, Yun SC, Song JM, Park SW, Chung CH, Song JK, Lee JW. Watchful observation versus early aortic valve replacement for symptomatic patients with normal flow, low-gradient severe aortic stenosis. *Heart*. 2015;101:1375–1381. doi: 10.1136/heartjnl-2015-307528
 7. Chadha G, Bohbot Y, Rusinaru D, Maréchaux S, Tribouilloy C. Outcome of normal-flow low-gradient severe aortic stenosis with preserved left ventricular ejection fraction: a propensity-matched study. *J Am Heart Assoc*. 2019;8:e012301. doi: 10.1161/JAHA.119.012301
 8. Rusinaru D, Bohbot Y, Ringle A, Maréchaux S, Diouf M, Tribouilloy C. Impact of low stroke volume on mortality in patients with severe aortic stenosis and preserved left ventricular ejection fraction. *Eur Heart J*. 2018;39:1992–1999. doi: 10.1093/eurheartj/ehy123
 9. Tastet L, Tribouilloy C, Maréchaux S, Vollema EM, Delgado V, Salaun E, Shen M, Capoulade R, Clavel MA, Arsenault M, et al. Staging cardiac damage in patients with asymptomatic aortic valve stenosis. *J Am Coll Cardiol*. 2019;74:550–563. doi: 10.1016/j.jacc.2019.04.065
 10. Chahal NS, Drakopoulou M, Gonzalez-Gonzalez AM, Manivarmane R, Khattar R, Senior R. Resting aortic valve area at normal transaortic flow rate reflects true valve area in suspected low-gradient severe aortic stenosis. *JACC Cardiovasc Imaging*. 2015;8:1133–1139. doi: 10.1016/j.jcmg.2015.04.021
 11. King DL, El-Khoury Coffin L, Maurer MS. Myocardial contraction fraction: a volumetric index of myocardial shortening by freehand three-dimensional echocardiography. *J Am Coll Cardiol*. 2002;40:325–329. doi: 10.1016/s0735-1097(02)01944-7
 12. Chuang ML, Gona P, Salton CJ, Yeon SB, Kissinger KV, Blease SJ, Levy D, O'Donnell CJ, Manning WJ. Usefulness of the left ventricular myocardial contraction fraction in healthy men and women to predict cardiovascular morbidity and mortality. *Am J Cardiol*. 2012;109:1454–1458. doi: 10.1016/j.amjcard.2012.01.357
 13. Maurer MS, Koh WJ, Bartz TM, Vullaganti S, Barasch E, Gardin JM, Gottdiener JS, Psaty BM, Kizer JR. Relation of the myocardial contraction fraction, as calculated from M-mode echocardiography, with incident heart failure, atherosclerotic cardiovascular disease and mortality (results from the cardiovascular health study). *Am J Cardiol*. 2017;119:923–928. doi: 10.1016/j.amjcard.2016.11.048
 14. Arenja N, Riffel JH, Fritz T, André F, Aus dem Siepen F, Mueller-Hennessen M, Giannitsis E, Katus HA, Friedrich MG, Buss SJ. Diagnostic and prognostic value of long-axis strain and myocardial contraction fraction using standard cardiovascular MR imaging in patients with nonischemic dilated cardiomyopathies. *Radiology*. 2017;283:681–691. doi: 10.1148/radiol.2016161184
 15. Rubin J, Steidley DE, Carlsson M, Ong ML, Maurer MS. Myocardial contraction fraction by M-mode echocardiography is superior to ejection fraction in predicting mortality in transthyretin amyloidosis. *J Card Fail*. 2018;24:504–511. doi: 10.1016/j.cardfail.2018.07.001
 16. Shimada YJ, Hoeger CW, Latif F, Takayama H, Ginns J, Maurer MS. Myocardial contraction fraction predicts cardiovascular events in patients with hypertrophic cardiomyopathy and normal ejection fraction. *J Card Fail*. 2019;25:450–456. doi: 10.1016/j.cardfail.2019.03.016
 17. Romeo FJ, Seropian IM, Arora S, Vavalle JP, Falconi M, Oberpi R, Kotowicz V, Agatiello CR, Berrocal DH. Prognostic impact of myocardial contraction fraction in patients undergoing transcatheter aortic valve replacement for aortic stenosis. *Cardiovasc Diagn Ther*. 2020;10:12–23. doi: 10.21037/cdt.2019.05.02
 18. Tribouilloy C, Rusinaru D, Maréchaux S, Castel AL, Debry N, Maizel J, Mentaverri R, Kamel S, Slama M, Lévy F. Low-gradient, low-flow severe aortic stenosis with preserved left ventricular ejection fraction: characteristics, outcome, and implications for surgery. *J Am Coll Cardiol*. 2015;65:55–66. doi: 10.1016/j.jacc.2014.09.080
 19. Quiñones MA, Otto CM, Stoddard M, Waggoner A, Zoghbi WA; Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2002;15:167–184. doi: 10.1067/mje.2002.120202
 20. Lang RM, Badano LP, Mor-Avi V, Afila J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015;28:1–39.e14. doi: 10.1016/j.echo.2014.10.003
 21. Mitchell C, Rahko PS, Blauwet LA, Canaday B, Finstuen JA, Foster MC, Horton K, Ogunyankin KO, Palma RA, Velazquez EJ. Guidelines for performing a comprehensive transthoracic echocardiographic examination in adults: recommendations from the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2019;32:1–64. doi: 10.1016/j.echo.2018.06.004
 22. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika*. 1994;81:515–526. doi: 10.1093/biomet/81.3.515
 23. Contal C, O'Quigley J. An application of changepoint methods in studying the effect of age on survival in breast cancer. *Comput Stat Data Anal*. 1999;30:253–270. doi: 10.1016/S0167-9473(98)00096-6
 24. Rusinaru D, Rietzschel ER, Bohbot Y, De Buyzere ML, Buiciuc O, Maréchaux S, Gillebert TC, Tribouilloy C. Allometric versus ratiometric normalization of left ventricular stroke volume by Doppler-echocardiography for outcome prediction in severe aortic stenosis with preserved ejection fraction. *Int J Cardiol*. 2020;301:235–241. doi: 10.1016/j.ijcard.2019.09.056
 25. Hachicha Z, Dumesnil JG, Bogaty P, Pibarot P. Paradoxical low-flow, low-gradient severe aortic stenosis despite preserved ejection fraction is associated with higher afterload and reduced survival. *Circulation*. 2007;115:2856–2864. doi: 10.1161/CIRCULATIONAHA.106.668681
 26. Rusinaru D, Bohbot Y, Djelaili F, Delpierre Q, Altes A, Serbout S, Kubala M, Maréchaux S, Tribouilloy C. Normative reference values of cardiac output by pulsed-wave doppler echocardiography in adults. *Am J Cardiol*. 2021;140:128–133. doi: 10.1016/j.amjcard.2020.10.046
 27. Abdalla M, Akwo EA, Bluemke DA, Lima JAC, Shimbo D, Maurer MS, Bertoni AG. Association between reduced myocardial contraction fraction and cardiovascular disease outcomes: the multi-ethnic study of atherosclerosis. *Int J Cardiol*. 2019;293:10–16. doi: 10.1016/j.ijcard.2019.07.040
 28. Eleid MF, Sorajja P, Michelena HI, Malouf JF, Scott CG, Pellikka PA. Survival by stroke volume index in patients with low-gradient normal EF severe aortic stenosis. *Heart*. 2015;101:23–29. doi: 10.1136/heartjnl-2014-306151
 29. Capoulade R, Clavel MA, Le Ven F, Dahou A, Thébaud C, Tastet L, Shen M, Arsenault M, Bédard É, Beaudoin J, et al. Impact of left ventricular remodelling patterns on outcomes in patients with aortic stenosis. *Eur Heart J Cardiovasc Imaging*. 2017;18:1378–1387. doi: 10.1093/ehjci/jeu288
 30. Castaño A, Narotsky DL, Hamid N, Khalique OK, Morgenstern R, DeLuca A, Rubin J, Chiuzaan C, Nazif T, Vahl T, et al. Unveiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. *Eur Heart J*. 2017;38:2879–2887. doi: 10.1093/eurheartj/ehx350
 31. Namasivayam M, He W, Churchill TW, Capoulade R, Liu S, Lee H, Danik JS, Picard MH, Pibarot P, Levine RA, et al. Transvalvular flow rate determines prognostic value of aortic valve area in aortic stenosis. *J Am Coll Cardiol*. 2020;75:1758–1769. doi: 10.1016/j.jacc.2020.02.046
 32. Zhang Y, Nitter-Hauge S. Determination of the mean pressure gradient in aortic stenosis by Doppler echocardiography. *Eur Heart J*. 1985;6:999–1005. doi: 10.1093/oxfordjournals.eurheartj.a061821