Global Longitudinal Strain and Left Atrial Volume Index Provide Incremental Prognostic Value in Patients With Hypertrophic Cardiomyopathy

Yasmine L. Hiemstra, MD; Philippe Debonnaire, MD, PhD; Marianne Bootsma, MD, PhD; Erik W. van Zwet, MD, PhD; Victoria Delgado, MD, PhD; Martin J. Schalij, MD, PhD; Douwe E. Atsma, MD, PhD; Jeroen J. Bax, MD, PhD; Nina Ajmone Marsan, MD, PhD

Background—Current methods for predicting adverse events in patients with hypertrophic cardiomyopathy are still limited. Left ventricular global longitudinal strain (GLS) and left atrial volume index (LAVI) have been recently proposed as novel prognostic factors in several cardiovascular diseases. The objective of this study was to evaluate the prognostic value of GLS and LAVI in patients with hypertrophic cardiomyopathy.

Methods and Results—Two-dimensional echocardiography was performed in 427 patients with hypertrophic cardiomyopathy (66% men, age 52±15 years), and LAVI and GLS were assessed. During follow-up, the primary end point of all-cause mortality, heart transplantation, sudden cardiac death, and appropriate implantable cardioverter defibrillator therapy was noted. A total of 103 patients reached the primary end point during a follow-up of 6.7 (interquartile range, 3.3–10.0) years. Multivariable Cox regression analysis revealed GLS and LAVI to be independently associated with the primary end point (hazard ratio GLS, 1.10 [1.03–1.19], P=0.007; hazard ratio LAVI, 4.27 [2.35–7.74], P<0.001) after correcting for other clinical variables. When applying the pre-specified cut-off values of 34 mL/m^2 for LAVI and −15% for GLS, Kaplan–Meier survival curves showed significant better survival for patients with LAVI <34 mL/m^2 (P<0.001) and GLS <−15% (P<0.001) as compared with their counterparts. The likelihood ratio test showed a significant incremental prognostic value of LAVI and GLS (P<0.001) as compared with a model with clinical and standard echocardiographic risk factors. The C-statistic for this model increased from 0.68 to 0.73 when adding GLS and LAVI.

Conclusions—GLS and LAVI are independently associated with adverse outcome in patients with hypertrophic cardiomyopathy and may help to optimize risk stratification in these patients. (***Circ Cardiovasc Imaging*. 2017;10:e005706. DOI: 10.1161/CIRCIMAGING.116.005706.)**

Key Words: cardiomyopathy, hypertrophic ■ death, sudden, cardiac ■ echocardiography ■ heart transplantation ■ prognosis

Hypertrophic cardiomyopathy (HCM) is the most prevalent inherited cardiomyopathy and is associated with increased cardiovascular morbidity and mortality. Particularly, patients with HCM experience more frequent sudden cardiac death (SCD) and death because of heart failure and show an increased risk of stroke-related mortality due to high prevalence of atrial fibrillation.[1,2] However, risk stratification in patients with HCM remains challenging, mainly because of a large heterogeneity of phenotypes with different prognosis, varying from asymptomatic mild cardiomyopathy throughout life to the occurrence of SCD at young age. Current approach for risk stratification in patients with HCM is mainly focused on SCD and advocates for combination of clinical and echocardiographic parameters.[3,4] However, those parameters are known to have limited sensitivity and specificity, particularly, in predicting cardiovascular events other than SCD.[5] Therefore, research has focused on identifying potential additional prognosticators to optimize HCM patient management.[6–11]

See Editorial by Maron
See Clinical Perspective

Two-dimensional speckle tracking strain analysis has been recently proposed as a new method to improve assessment of left ventricular (LV) function as compared with conventional echocardiography. In patients with HCM, in whom LV ejection fraction is mostly within the normal ranges, global longitudinal strain (GLS) has shown to be able to detect subtle myocardial systolic dysfunction, and initial studies have proposed this parameter as a potential novel prognostic factor.[12–16] Similarly, left atrial volume index (LAVI) has been

Received September 20, 2016; accepted May 9, 2017.

From the Departments of Cardiology (Y.L.H., P.D., M.B., V.D., M.J.S., D.E.A., J.J.B., N.A.M.) and Medical Statistics (E.W.v.Z.), Leiden University Medical Center, The Netherlands.

The Data Supplement is available at http://circimaging.ahajournals.org/lookup/suppl/doi:10.1161/CIRCIMAGING.116.005706/-/DC1.

Correspondence to Nina Ajmone Marsan, MD, PhD, Department of Cardiology, Leiden University Medical Centre, Albinusdreef 2, 2333 ZA Leiden, The Netherlands. E-mail n.ajmone@lumc.nl

shown to be associated with specific clinical outcomes, such as new onset of atrial fibrillation and SCD, probably reflecting not only LV diastolic dysfunction but also LV outflow tract (LVOT) obstruction, mitral regurgitation, and intrinsic atrial myopathy.[17–19] However, the prognostic value of the combination of GLS and LAVI has not been investigated thoroughly. Therefore, the objective of this study was to evaluate the incremental prognostic value of GLS and LAVI for hard adverse clinical outcomes in a large cohort of patients with HCM and with a long-term follow-up.

Methods

Patient Population

The population consisted of patients with HCM, defined according to current guidelines: a maximal LV hypertrophy (LVH) ≥15 mm, in absence of any other cardiac or systemic disease that could cause a similar degree of LVH.[3] Patients were identified from an ongoing clinical registry and excluded if age was <16 years. Patient data were prospectively collected in the departmental cardiology information system (EPD-Vision; Leiden University Medical Center, Leiden, The Netherlands) and included the following information: demographic characteristics, New York Heart Association functional class, use of medications, comorbidities, and the currently adopted SCD risk factors, such as unexplained syncope, nonsustained ventricular tachycardia (nsVT) on 24 hours electrocardiographic Holter monitoring (≥3 beats at ≥120 bpm), and positive family history for SCD at young age (<50 years) in first- or second-degree relatives. Furthermore, an ECG and echocardiogram were performed in all patients at the moment of the first visit at the outpatient clinic. Interventions, such as percutaneous revascularization, septal alcohol ablation, myectomy, or other cardiac surgery during follow-up or before the first outpatient visit, were also recorded. The study complies with the Declaration of Helsinki and was approved by the institutional review board. Because of the retrospective design of this study, the Medical Ethical Committee waived the need of written informed consent.

Echocardiography

Standard transthoracic 2-dimensional echocardiographic studies were performed using commercially available ultrasound machines (Vivid 5, Vivid 7, and E9, GE-Vingmed, Milwaukee, WI). Images were digitally stored and analyzed offline (EchoPAC, version 112, GE Medical Systems, Horten, Norway). LV end-diastolic and end-systolic diameters were measured from the parasternal long-axis view. LV volumes, LV ejection fraction, and left atrial (LA) volumes were measured using Simpson method and indexed for body surface area.[20] LA volume was calculated at end systole, tracing the LA endocardium in the 4- and 2-chamber views. Measurements of septal and posterior wall thickness were obtained in the parasternal long-axis from an M-mode acquisition while maximal LV wall thickness was assessed from a short-axis view at 3 different levels (basal, mid, and apical). LV diastolic function was assessed mainly using the mitral inflow peak velocities of E divided by the peak early diastolic velocity (E′) of the lateral mitral annulus by tissue Doppler imaging, obtaining the E/E′ ratio.[21] Assessment of the presence of systolic anterior movement of the mitral valve was performed from a parasternal long-axis view and from apical 3- and 5-chamber views. LVOT resting peak gradient was quantified by continuous wave Doppler. The presence and grade of mitral regurgitation were assessed according to a multiparametric approach as recommended.[22]

GLS was measured using speckle tracking analysis on standard apical views (2-, 3-, and 4-chamber views), acquired with a frame rate of 40 to 90 Hz (mean, 60 fps). The region of interest was automatically created and manually adjusted when necessary to fit the entire wall thickness. GLS was then calculated by averaging the peak longitudinal strain in 17 segments from the 3 different views.

Clinical Outcome

The primary end point was a combined end point of all-cause mortality, heart transplantation, aborted SCD, and appropriate implantable cardioverter defibrillator (ICD) therapy. Aborted SCD was defined as a successful resuscitation from cardiac arrest with documented ventricular tachycardia and ventricular fibrillation. Appropriate ICD therapy was defined as antitachycardia pacing and shock for ventricular tachycardia or ventricular fibrillation. The occurrence of events during follow-up was obtained by medical charts review, retrieval of survival status through the municipal civil registries, and by contact with the general practitioner of the patient. The secondary end point included (aborted) SCD and appropriate ICD therapy.

Statistical Analysis

Continuous variables are expressed as mean±SD, when normally distributed, and as median (interquartile range), when not normally distributed. Categorical variables are presented as absolute numbers and percentages. Differences in baseline characteristics between patients with and without the primary end point were assessed using Student *t* test, Mann–Whitney *U* test, or χ^2 when appropriate. Univariable Cox regression analysis was performed for all clinical and echocardiographic variables, and the variables with a $P<0.10$ were included in a multivariable Cox regression analysis (selecting among the ones highly correlated with each other) to identify independent predictors of the primary and secondary end points: hazard ratio (HR) and 95% confidence intervals were calculated. Kaplan–Meier curves were constructed to estimate the cumulative event-free survival for the primary end point and compared by the log-rank test. Cut-off value for LAVI (34 mL/m^2) was defined based on guidelines recommendations, whereas for GLS (−15%) it was chosen based on the median value of GLS in the current population and on previously suggested cut-off value from the literature in patients with HCM.[12,14,15] To evaluate the incremental value of GLS and LAVI on top of clinical and standard echocardiographic parameters, likelihood ratio testing was performed, as well as calculation of the overall C-statistic as proposed by Harrell et al[23] as an analogue of the area under the receiver operating characteristic curve for survival analysis for both primary and secondary end points. Furthermore, we assessed the impact of adding GLS and LAVI to a basic model using the continuous net reclassification improvement. A $P<0.05$ was considered significant. Statistical analysis was performed with the SPSS software package and the R-package survINDRI (version 20, IBM Corp, Armonk, NY).

Results

Patient Population

A total of 427 patients with HCM (52±15 years, 66% men) were included (Table 1). A pathogenic or likely pathogenic gene mutation was found in 167 (63%) of the patients who underwent genetic testing (n=264). Mean LV ejection fraction was normal in this HCM patient population (65±9%), but mean GLS was impaired (−15±4%) and median LAVI was increased (36 [28–47] mL/m^2).

Long-Term Clinical Outcome

During a median follow-up of 6.7 (interquartile range, 3.3–10.0) years, 103 patients reached the primary end point: 53 patients experienced aborted SCD or appropriate ICD therapy, 2 patients underwent heart transplantation, and 48 patients died. Cause of death was of cardiac origin in 22 patients (11 heart failure, 10 SCD, and 1 other cardiovascular cause), noncardiac in 10 patients (3 sepsis, 6 malignancy, and 1 suicide), and unknown in 16 patients. As shown in Table 1, there were no significant differences in demographics, cardiovascular risk factors, and symptoms between patients who reached the

Table 1. Clinical and Echocardiographic Characteristics of the Total Patient Population and Dichotomized for Patients Who Reached the Primary End Point vs Those Who Did Not

	Overall n=427	End Point No, n=324	End Point Yes, n=103	*P* Value
Clinical characteristics				
Age, y	52±15	51±15	53±15	0.347
Men, n (%)	282 (66)	214 (66)	68 (66)	1.000
Hypertension, n (%)	151 (35)	126 (40)	33 (33)	0.239
Previous AF, n (%)	61 (14)	35 (11)	26 (25)	<0.001
Diabetes mellitus, n (%)	30 (7)	19 (6)	11 (11)	0.116
NYHA class, n (%)				0.066
I	333 (80)	258 (82)	75 (73)	
II	69 (17)	49 (15)	20 (20)	
III	15 (3)	8 (3)	7 (7)	
Genetic mutation HCM, n (%)*	167 (63)	131 (63)	36 (70)	0.192
Septal intervention	56 (13)	34 (11)	22 (21)	0.007
Patients with ICD	150 (35)	86 (27)	64 (62)	<0.001
Medication use, n (%)				
β-Blockers	167 (39)	117 (36)	50 (49)	0.028
Calcium antagonist	93 (22)	66 (21)	27 (27)	0.273
Diuretics	59 (14)	40 (13)	19 (19)	0.142
SCD risk factors				
Family history of SCD, n (%)	178 (42)	135 (42)	43 (42)	1.000
Unexplained syncope, n (%)	38 (9)	26 (8)	12 (12)	0.320
Prior nsVT, n (%)	110 (26)	70 (22)	40 (39)	0.001
Echocardiography				
LA diameter	41±7	40±7	44±8	<0.001
LVEDD, mm	44±7	44±6	44±7	0.398
LVEF, %	65±9	66±9	63±11	0.012
E/E′	10 (8–16)	12 (7–15)	17 (9–25)	<0.001
IVS, mm	19±5	19±5	21±6	<0.001
PW, mm	13±3	12±3	13±4	0.019
Max LVH, mm	21±6	21±5	23±7	<0.001
LVOT gradient, mm Hg	9 (6–19)	19 (6–16)	26 (5–34)	0.555
MR >grade 2, n (%)	89 (21)	59 (19)	30 (33)	0.010
SAM, n (%)	154 (36)	107 (33)	47 (46)	0.024
GLS, %†	−15±4	−16±4	−13±4	<0.001
LAVI, mL/m²‡	36 (28–47)	37 (26–43)	51 (35–65)	<0.001

Primary end point: all-cause mortality, heart transplantation, aborted sudden cardiac death, or appropriate ICD therapy.

AF indicates atrial fibrillation; GLS, global longitudinal strain; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter defibrillator; IVS, interventricular septum; LA, left atrial; LAVI, left atrial volume index; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LVOT, left ventricular outflow tract; MR, mitral regurgitation; nsVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association; PW, posterior wall; SAM, systolic anterior movement, and SCD sudden cardiac death.

*Only genetically tested patients (n=264).

†Missing data for 35 of 427 patients.

‡Missing data for 20 of 427 patients.

primary end point and those who did not. However, patients who reached the primary end point were more likely to undergo a septal intervention, used more frequently β-blockers, and showed a higher incidence of nsVT at 24-hour ECG Holter monitoring. Furthermore, patients who reached the primary end point had a significantly larger maximum wall thickness, worse LV diastolic function (E/E′), more prevalence of systolic anterior movement, more impaired (less negative) GLS, and a larger LAVI (Table 1).

The secondary end point included 63 events, of which 53 aborted SCD or appropriate ICD therapy and 10 SCD.

Survival Analysis

Univariable Cox proportional hazard regression analysis showed that atrial fibrillation, New York Heart Association class, nsVT on 24-hour Holter monitoring, use of β-blockers, GLS, LV ejection fraction, LAVI, maximal LVH, E/E′, LA diameter, LVOT resting peak gradient, systolic anterior movement, mitral regurgitation >2, and septal intervention during follow-up all had a significant association with the primary end point. However, multivariable analysis for the primary end point revealed only GLS (HR, 1.10 [1.03–1.19]; *P*=0.007) and LAVI (HR, 4.27 [2.35–7.74]; *P*<0.001) as independent predictors (Table 2).

Table 2. Univariable and Multivariable Cox Proportional Hazard Regression Analysis to Identify Independent Predictors of the Primary End Point

Parameter	Univariable HR (95% CI)	*P* Value	Multivariable HR (95% CI)	*P* Value
Age	1.01 (0.99–1.03)	0.081	1.00 (0.98–1.01)	0.750
Men	0.97 (0.64–1.45)	0.863		
NYHA class ≥2	1.72 (1.11–2.68)	0.016	0.61 (0.30–1.21)	0.261
Previous AF	2.38 (1.52–3.72)	<0.001	1.17 (0.61–2.24)	0.638
Septal intervention	1.82 (1.13–2.94)	0.013	1.79 (0.96–3.35)	0.067
β-Blocker	1.58 (1.07–2.32)	0.021		
Family SCD	1.02 (0.69–1.51)	0.928		
Syncope	1.28 (0.70–2.35)	0.417		
nsVT	1.89 (1.27–2.82)	0.002	1.44 (0.87–2.40)	0.156
LA diameter	1.05 (1.03–1.08)	<0.001		
LVEF	0.97 (0.96–0.99)	0.008		
E/E′	2.03 (1.43–2.91)	<0.001	1.38 (0.90–2.12)	0.142
Max LVH	1.04 (1.01–1.07)	0.007	1.00 (0.95–1.05)	0.909
LVOT gradient	1.22 (1.01–1.48)	0.047		
MR grade ≥2	1.81 (1.17–2.80)	0.008		
SAM	1.79 (1.21–2.64)	0.003	1.18 (0.66–2.08)	0.582
GLS	1.13 (1.08–1.19)	<0.001	1.10 (1.03–1.19)	0.007
LAVI	4.23 (2.83–6.31)	<0.001	4.27 (2.35–7.74)	<0.001

AF indicates atrial fibrillation; CI, confidence interval; GLS, global longitudinal strain; HR, hazard ratio; LA, left atrial; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LVOT, left ventricular outflow tract; MR, mitral regurgitation; nsVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association; SAM, systolic anterior movement; and SCD sudden cardiac death.

When dividing the population according to the pre-specified cut-off value of LAVI, patients with LAVI ≥34 mL/m^2 had worse outcome as compared with patients with LAVI <34 mL/m^2. The cumulative event-free survival at, respectively, 2 and 6 years was 98% and 93% versus 94% and 81%, respectively (log-rank, 19.7; *P*<0.001; Figure 1A). When dividing the population according to the pre-specified cut-off value of GLS, patients with GLS ≥−15% had worse outcome as compared with patients with GLS <−15% (Figure 1B). The cumulative event-free survival at, respectively, 2 and 6 years was 98% and 91% versus 92% and 76%, respectively (log-rank, 27.1; *P*<0.001).

When dividing the population in 4 groups based on the pre-specified GLS and LAVI cut-off values, the group of patients with both GLS <−15% and LAVI <34 mL/m^2 had the best outcome, whereas patients with both GLS ≥−15% and LAVI ≥34 mL/m^2 had the worst outcome. The cumulative event-free survival at 6 years was 99% for GLS <−15% and LAVI <34 mL/m^2 versus 63% for patients with GLS ≥−15% and LAVI ≥34 mL/m^2 (log-rank, 49.3; *P*<0.001; Figure 2).

When considering the secondary end point, GLS and LAVI showed a significant association with this outcome (HR, 1.12 [1.06–1.19]; *P*<0.001 for GLS and HR, 3.94 [2.33–6.66]; *P*<0.001 for LAVI) together with sex, nsVT, LA diameter, and maximum LVH at the univariable analysis. When corrected for sex, LVH, and nsVT, GLS and LAVI remained independently associated with the secondary end point at multivariable analysis (HR, 1.08 [1.01–1.16]; *P*=0.023 for GLS and HR, 3.70 [2.08–6.60]; *P*<0.001 for LAVI).

Incremental Value of GLS and LAVI

Figure 3 shows the results of the likelihood ratio test and the Harrell C-statistic for LAVI and GLS on top of clinical and standard echocardiographic parameters associated with the primary end point at the univariable Cox regression analysis. The addition of LAVI ≥34 mL/m^2 to a basic model provided a significant improvement (*P*<0.001) with an increase of the C-statistic from 0.68 to 0.71. The sequential addition of GLS ≥−15% further improved the model (likelihood ratio test *P*=0.008). Overall, the combined

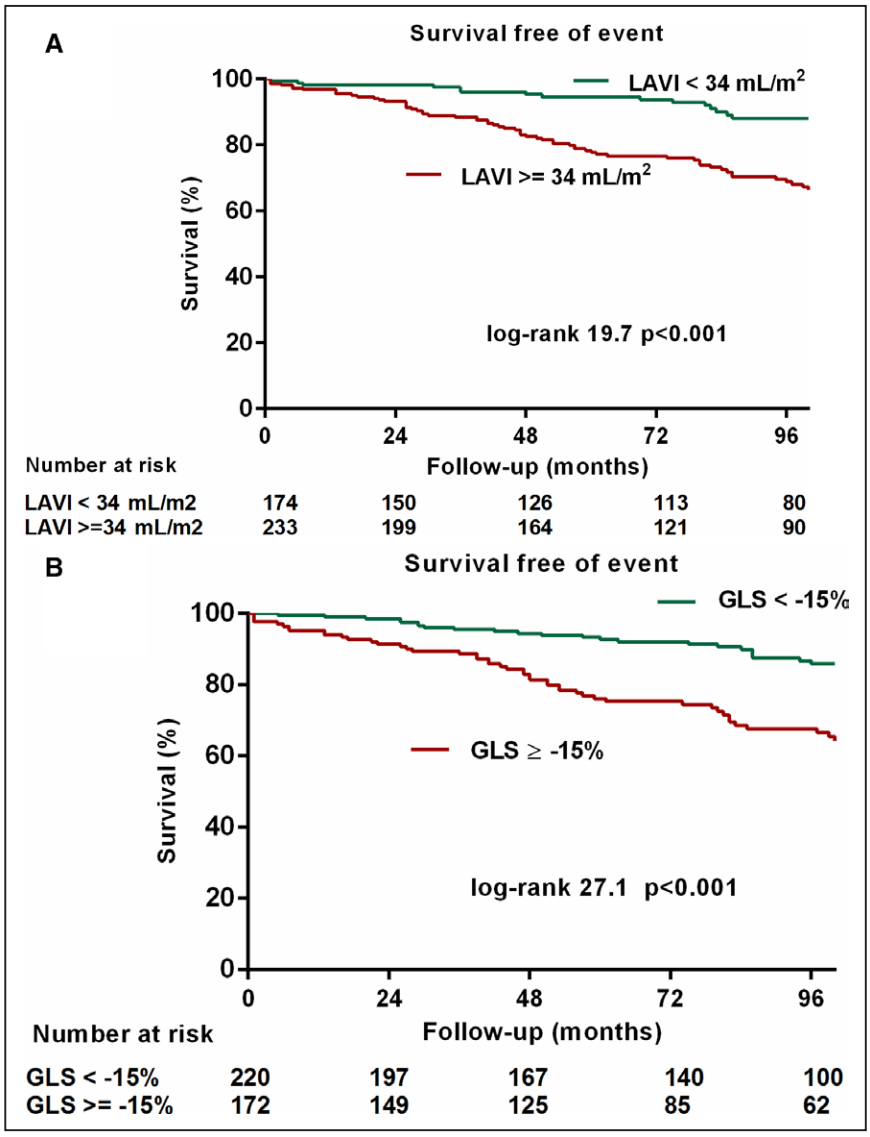

Figure 1. Kaplan–Meier analysis to evaluate the survival free of the primary end point of all-cause mortality, heart transplantation, aborted sudden cardiac death, or appropriate implantable cardioverter defibrillator therapy. **A**, Left atrial volume index (LAVI). **B**, Global longitudinal strain (GLS).

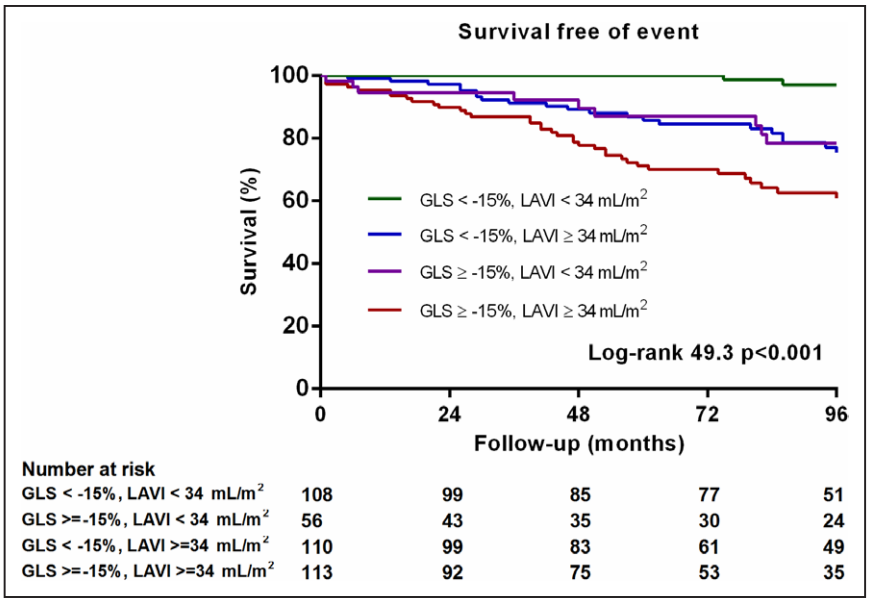

Figure 2. Kaplan–Meier analysis to evaluate the survival free of experiencing the primary end point (all-cause mortality, heart transplantation, aborted SCD, or appropriate implantable cardioverter defibrillator therapy) when combining assessment of global longitudinal strain (GLS) and left atrial volume index (LAVI). Model 1: age, New York Heart Association class ≥2, previous atrial fibrillation, nonsustained ventricular tachycardia at Holter monitoring, maximum left ventricular wall thickness, maximum left ventricular outflow tract gradient, E/E′, and systolic anterior movement.

addition of LAVI and GLS to the clinical and standard echocardiographic risk factors provided the best model (likelihood ratio test $P<0.001$, C-statistic=0.73). The incremental value of this model was also demonstrated by a net reclassification improvement of 0.30 (95% confidence interval, 0.15–0.42; $P<0.001$).

Similarly, when considering the secondary end point, the addition of LAVI ≥34 mL/m^2 and GLS ≥−15% to a basic model, including sex, nsVT, and maximum LVH, also provided incremental prognostic value: χ^2 increased from 25 to 29 adding GLS ($P=0.046$) with an improvement of C-statistic from 0.68 to 0.70. More importantly, adding LAVI increased the χ^2 to 39 ($P<0.001$) with an improvement of C-statistic to 0.79. The net reclassification improvement was 0.26 (95% confidence interval, 0.11–0.41; $P<0.001$).

Inter- and Intraobserver Variability

Interobserver reproducibility for GLS and LAVI was assessed by 2 independent operators in 15 randomly selected patients. The intraclass correlation coefficient between 2 observers was 0.94 ($P<0.001$) for LAVI and 0.94 ($P<0.001$) for GLS. The intraclass correlation coefficient for intraobserver agreement was 0.95 ($P<0.001$) for LAVI and 0.91 ($P<0.001$) for GLS.

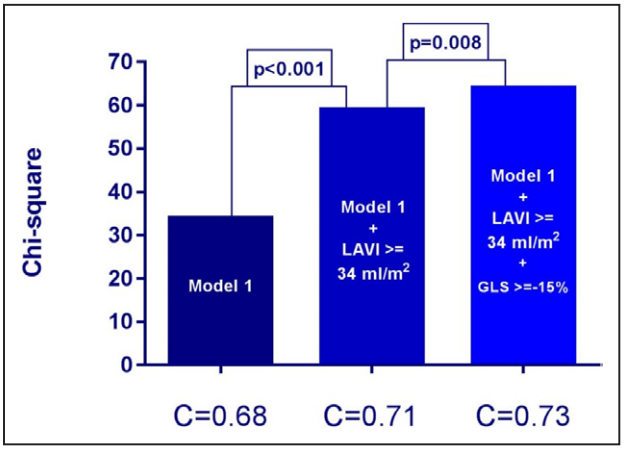

Figure 3. Likelihood ratio test. The bar graphs show the incremental value of global longitudinal strain and left atrial volume index (LAVI) on top other important clinical risk factors for predicting the primary end point. Harrell C-statistic represents overall adequacy of the risk prediction.

Discussion

The main findings of the current study can be summarized as follows: (1) in a large cohort of patients with HCM, GLS and LAVI demonstrated to be independently associated with the primary end point of all-cause mortality, heart transplantation, and aborted SCD, as well as with the secondary end point of (aborted) SCD or appropriate ICD therapy; (2) the presence of both preserved GLS and LAVI showed the highest cumulative event-free survival as compared with patients with impaired GLS or LAVI; and (3) the addition of GLS and LAVI provided incremental prognostic value on top of other clinical and standard echocardiographic parameters.

Risk Stratification in HCM

In patients with HCM, risk stratification is a clinical challenge and has been mainly focused on prevention of SCD, for which several risk markers have been proposed, such as family history for SCD, unexplained syncope, nsVT, LV thickness, and LVOT gradient.[24] Recently, O'Mahony et al[4] developed a new risk prediction model to predict SCD in patients with HCM, which included the use of continuous variables instead of dichotomized variables and which was implemented in the current European Society of Cardiology guidelines.[3] Although the new risk model improves risk stratification for SCD and subsequently identification of patients who can benefit from an ICD,[25,26] there are no recommendations in current guidelines for risk stratification for other adverse events, such as heart failure–related mortality and other cardiovascular deaths that may occur in patients with HCM.[27] Therefore, several studies have tried

to identify additional prognostic markers to optimize clinical management of patients with HCM.

Among these, N-terminal pro-B-type natriuretic peptide, atrial fibrillation, New York Heart Association class, and functional exercise capacity were shown to be associated with worse overall prognosis in patients with HCM.[9–11] Furthermore, the presence of myocardial fibrosis, as assessed by cardiovascular magnetic imaging with late gadolinium enhancement, has been proposed as an important risk marker and showed to be associated not only with SCD but also with adverse cardiovascular events in patients with HCM .[6–8,28] However, in clinical practice, ideal prognosticators would be simple and readily available parameters, which should reflect structural abnormalities, such as myocardial fibrosis together with myocardial systolic and diastolic dysfunctions.

GLS as Risk Marker

Several studies have shown that GLS, measured by speckle tracking echocardiography, is able to detect subtle myocardial dysfunction in patients with HCM probably reflecting the characteristics myocardial fiber disarray, myocardial fibrosis, and microvascular dysfunction.[16] A study of Serri et al[29] showed that GLS can be measured with good reproducibility and is significantly impaired in patients with HCM as compared with healthy controls. In a cohort of 32 patients with HCM who underwent septal myectomy, GLS significantly correlated with fibrosis in the myocardium samples and could predict arrhythmias better than cardiovascular magnetic imaging with late gadolinium enhancement.[30]

Initial studies have also assessed the value of GLS to predict adverse events in patients with HCM.[12–15] Hartlage et al,[12] using a cut-off value for GLS of −16% in 79 patients with HCM, found an abnormal GLS to be predictive for a combined end point of heart failure hospitalizations, sustained ventricular arrhythmias, and all-cause mortality. In a population of 92 high-risk patients with HCM who received an ICD, Debonnaire et al[14] demonstrated the value of GLS (with a cut-off of −14%) as potential marker in the prediction of appropriate ICD therapy, which is confirmed for a larger and more heterogeneous HCM population by the current study. Recently, a study by Reant et al[15] showed the association between GLS and the combined end point of cardiac death, heart failure admission, and appropriate ICD therapy in a large cohort of 472 patients with HCM where patients with atrial fibrillation were excluded. Particularly, patients with a GLS >−15.6% showed to have higher risk for cardiac events. In the present study with a similarly large patient population, the prognostic value of GLS was also demonstrated for the hard end point of all-cause mortality and appropriate ICD therapy. Particularly, the same cut-off value of −15% for GLS showed significant incremental value over clinical and standard echocardiographic parameters. Furthermore, in the current study, patients in atrial fibrillation were not excluded and the multivariable Cox regression analysis corrected for atrial fibrillation, increasing the clinical application of these results considering the potential prognostic value of atrial fibrillation in

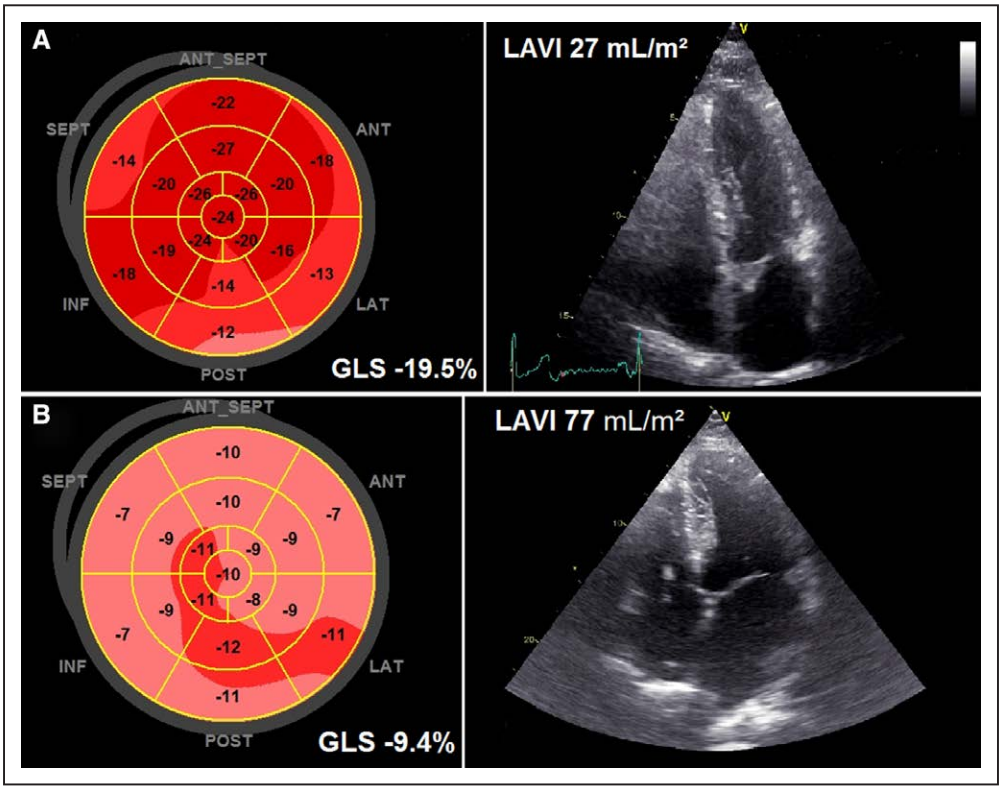

Figure 4. Examples of global longitudinal strain (GLS) displayed in a bull's eye for the 17 left ventricular segments (color coded from dark red, as preserved GLS, to pink as impaired GLS) and left atrial volume index (LAVI) assessment. **A**, A 55-year-old patient with normal GLS and LAVI who did not experience an event during 7.5 years of follow-up. **B**, A 42-year-old patient with both abnormal GLS and LAVI who experienced appropriate implantable cardioverter defibrillator therapy 2.5 years after baseline echocardiography.

patients with HCM.[31] Finally, the current study evaluated the prognostic value of GLS in combination with LAVI, another potentially important prognosticator.

LAVI as Risk Marker

Enlargement of LA occurs frequently in patients with HCM, reflecting significant LV diastolic dysfunction, LVOT obstruction, presence of mitral regurgitation, and intrinsic atrial myopathy.[32] Increased LA diameter is currently implemented in the HCM risk model for SCD.[4] However, LAVI is considered superior as an estimate of LA size[17] and was suggested by initial studies to be of prognostic value for general risk stratification in patients with HCM.[18,19] In the study performed by Yang et al,[18] LAVI was found to be an independent predictor of cardiovascular events in a population of 81 patients with nonapical HCM. Similar results were presented by Losi et al,[19] who evaluated LAVI in 140 patients with HCM at baseline and during follow-up and showed worse prognosis in patients with an enlarged LAVI or a rapid increase in LAVI during follow-up. Debonnaire et al[14] showed that LAVI (with a cut-off of 34 mL/m^2) was independently associated with appropriate ICD therapy. Our study not only confirms the association of LAVI with the risk of appropriate ICD therapy or SCD but also shows for the first time the prognostic value of LAVI for a hard mortality outcome, including a large HCM population and with long-term follow-up.

Clinical Implications

The present study demonstrated that the combination of GLS and LAVI may improve risk stratification of patients with HCM; for SCD or appropriate ICD therapy, but also for the more general end point of all-cause mortality. The prediction model, including clinical and standard echocardiographic risk factors, showed a C-statistic of 0.68, which is in line with previous literature[26]; the addition of GLS and LAVI increased the C-statistics to 0.73 for the primary end point and to 0.79 for the secondary end point, suggesting the improvement in predictive value. Such parameters, readily available from a standard echocardiographic screening, might, therefore, be of great value to improve risk stratification and, therefore, potentially to be included in future studies for a more comprehensive risk score for all-cause mortality on top of conventional parameters.

Although the identification of strict cut-off values for these parameters might be debatable, clinical application of GLS and LAVI in the standard management of patients with HCM might be stimulated by showing the clinicians how specific values perform in predicting the outcome. In this cohort, a cumulative event-free survival of 99% after 6 years was demonstrated for patients with both preserved GLS and LAVI (as defined using −15% and 34 mL/m^2),[12–15,18] whereas event-free survival was only 63% after 6 years in patients with impaired GLS and LAVI (Figure 4). Therefore, the identification of patients who are considered at low risk could be improved using GLS and LAVI, with important implications for the timing of starting medical therapy, planning follow-up of outpatient visits, and SCD screening, as well as decision making over ICD implantation.

Limitations

This study has several limitations that should be mentioned. In this single-center study, only echocardiographic equipment of GE was used; therefore, the results (and the cut-off value proposed) should be interpreted with caution when compared with other vendors. The European Association of CardioVascular Imaging and the American Society of Echocardiography recently set up a task force to evaluate the intervendor variability. From this evaluation, GLS showed a variability <10% between different vendors, which is comparable to standard echocardiographic measurements currently used.[33] Furthermore, it is known that in patients with HCM, appropriate ICD therapy may overestimate the event rate when antitachycardia pacing for ventricular tachycardia that could have been self-terminating are included. In the Data Supplement, the results of the Cox analysis are provided when antitachycardia pacing was removed as an outcome, which showed similar results (Tables I and II in the Data Supplement). Other potential prognostic markers, such as cardiovascular magnetic imaging with late gadolinium enhancement or NT-pro-BNP, were not systematically assessed. Importantly, further prospective studies in large patient population are needed to validate these data, especially to determine the most appropriate cut-off value for GLS in patients with HCM and how these measurements could be implemented in daily clinical practice.

Conclusions

GLS and LAVI are both independently associated with adverse outcome in patients with HCM. The combination of these 2 parameters has incremental value on top of standard clinical and echocardiographic parameters for predicting adverse events and could be considered in a more comprehensive risk score assessment.

Sources of Funding

Dr Delgado received consulting fees from Abbott Vascular. The Department of Cardiology of Leiden University Medical Centre received research grants from Biotronik, Medtronic, Boston Scientific, and Edwards Lifesciences.

Disclosures

None.

References

1. Klues HG, Schiffers A, Maron BJ. Phenotypic spectrum and patterns of left ventricular hypertrophy in hypertrophic cardiomyopathy: morphologic observations and significance as assessed by two-dimensional echocardiography in 600 patients. *J Am Coll Cardiol*. 1995;26:1699–1708. doi: 10.1016/0735-1097(95)00390-8.
2. Olivotto I, Cecchi F, Casey SA, Dolara A, Traverse JH, Maron BJ. Impact of atrial fibrillation on the clinical course of hypertrophic cardiomyopathy. *Circulation*. 2001;104:2517–2524.
3. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, Hagege AA, Lafont A, Limongelli G, Mahrholdt H, McKenna WJ, Mogensen J, Nihoyannopoulos P, Nistri S, Pieper PG, Pieske B, Rapezzi C, Rutten FH, Tillmanns C, Watkins H. 2014 ESC guidelines on diagnosis and management of hypertrophic cardiomyopathy: the task force for the diagnosis and management of hypertrophic cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J*. 2014;35:2733–2779.
4. O'Mahony C, Jichi F, Pavlou M, Monserrat L, Anastasakis A, Rapezzi C, Biagini E, Gimeno JR, Limongelli G, McKenna WJ, Omar RZ, Elliott PM; Hypertrophic Cardiomyopathy Outcomes Investigators. A novel clinical risk prediction model for sudden cardiac death in hypertrophic

cardiomyopathy (HCM risk-SCD). *Eur Heart J*. 2014;35:2010–2020. doi: 10.1093/eurheartj/eht439.
5. Maron BJ, Casey SA, Chan RH, Garberich RF, Rowin EJ, Maron MS. Independent assessment of the European Society of Cardiology sudden death risk model for hypertrophic cardiomyopathy. *Am J Cardiol*. 2015;116:757–764. doi: 10.1016/j.amjcard.2015.05.047.
6. Chan RH, Maron BJ, Olivotto I, Pencina MJ, Assenza GE, Haas T, Lesser JR, Gruner C, Crean AM, Rakowski H, Udelson JE, Rowin E, Lombardi M, Cecchi F, Tomberli B, Spirito P, Formisano F, Biagini E, Rapezzi C, De Cecco CN, Autore C, Cook EF, Hong SN, Gibson CM, Manning WJ, Appelbaum E, Maron MS. Prognostic value of quantitative contrast-enhanced cardiovascular magnetic resonance for the evaluation of sudden death risk in patients with hypertrophic cardiomyopathy. *Circulation*. 2014;130:484–495. doi: 10.1161/CIRCULATIONAHA.113.007094.
7. Bruder O, Wagner A, Jensen CJ, Schneider S, Ong P, Kispert EM, Nassenstein K, Schlosser T, Sabin GV, Sechtem U, Mahrholdt H. Myocardial scar visualized by cardiovascular magnetic resonance imaging predicts major adverse events in patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2010;56:875–887. doi: 10.1016/j.jacc.2010.05.007.
8. Ismail TF, Jabbour A, Gulati A, Mallorie A, Raza S, Cowling TE, Das B, Khwaja J, Alpendurada FD, Wage R, Roughton M, McKenna WJ, Moon JC, Varnava A, Shakespeare C, Cowie MR, Cook SA, Elliott P, O'Hanlon R, Pennell DJ, Prasad SK. Role of late gadolinium enhancement cardiovascular magnetic resonance in the risk stratification of hypertrophic cardiomyopathy. *Heart*. 2014;100:1851–1858. doi: 10.1136/heartjnl-2013-305471.
9. D'Amato R, Tomberli B, Castelli G, Spoladore R, Girolami F, Fornaro A, Caldini A, Torricelli F, Camici P, Gensini GF, Cecchi F, Olivotto I. Prognostic value of N-terminal pro-brain natriuretic peptide in outpatients with hypertrophic cardiomyopathy. *Am J Cardiol*. 2013;112:1190–1196. doi: 10.1016/j.amjcard.2013.06.018.
10. Coats CJ, Gallagher MJ, Foley M, O'Mahony C, Critoph C, Gimeno J, Dawnay A, McKenna WJ, Elliott PM. Relation between serum N-terminal pro-brain natriuretic peptide and prognosis in patients with hypertrophic cardiomyopathy. *Eur Heart J*. 2013;34:2529–2537. doi: 10.1093/eurheartj/eht070.
11. Desai MY, Bhonsale A, Patel P, Naji P, Smedira NG, Thamilarasan M, Lytle BW, Lever HM. Exercise echocardiography in asymptomatic HCM: exercise capacity, and not LV outflow tract gradient predicts long-term outcomes. *JACC Cardiovasc Imaging*. 2014;7:26–36. doi: 10.1016/j.jcmg.2013.08.010.
12. Hartlage GR, Kim JH, Strickland PT, Cheng AC, Ghasemzadeh N, Pernetz MA, Clements SD, Williams BR 3rd. The prognostic value of standardized reference values for speckle-tracking global longitudinal strain in hypertrophic cardiomyopathy. *Int J Cardiovasc Imaging*. 2015;31:557–565. doi: 10.1007/s10554-015-0590-5.
13. Reant P, Reynaud A, Pillois X, Dijos M, Arsac F, Touche C, Landelle M, Rooryck C, Roudaut R, Lafitte S. Comparison of resting and exercise echocardiographic parameters as indicators of outcomes in hypertrophic cardiomyopathy. *J Am Soc Echocardiogr*. 2015;28:194–203. doi: 10.1016/j.echo.2014.10.001.
14. Debonnaire P, Thijssen J, Leong DP, Joyce E, Katsanos S, Hoogslag GE, Schalij MJ, Atsma DE, Bax JJ, Delgado V, Marsan NA. Global longitudinal strain and left atrial volume index improve prediction of appropriate implantable cardioverter defibrillator therapy in hypertrophic cardiomyopathy patients. *Int J Cardiovasc Imaging*. 2014;30:549–558. doi: 10.1007/s10554-014-0378-z.
15. Reant P, Mirabel M, Lloyd G, Peyrou J, Lopez Ayala JM, Dickie S, Bulluck H, Captur G, Rosmini S, Guttmann O, Demetrescu C, Pantazis A, Tome-Esteban M, Moon JC, Lafitte S, McKenna WJ. Global longitudinal strain is associated with heart failure outcomes in hypertrophic cardiomyopathy. *Heart*. 2016;102:741–747. doi: 10.1136/heartjnl-2015-308576.
16. Saito M, Okayama H, Yoshii T, Higashi H, Morioka H, Hiasa G, Sumimoto T, Inaba S, Nishimura K, Inoue K, Ogimoto A, Shigematsu Y, Hamada M, Higaki J. Clinical significance of global two-dimensional strain as a surrogate parameter of myocardial fibrosis and cardiac events in patients with hypertrophic cardiomyopathy. *Eur Heart J Cardiovasc Imaging*. 2012;13:617–623. doi: 10.1093/ejechocard/jer318.
17. Tsang TS, Abhayaratna WP, Barnes ME, Miyasaka Y, Gersh BJ, Bailey KR, Cha SS, Seward JB. Prediction of cardiovascular outcomes with left atrial size: is volume superior to area or diameter? *J Am Coll Cardiol*. 2006;47:1018–1023. doi: 10.1016/j.jacc.2005.08.077.
18. Yang WI, Shim CY, Kim YJ, Kim SA, Rhee SJ, Choi EY, Choi D, Jang Y, Chung N, Cho SY, Ha JW. Left atrial volume index: a predictor of adverse outcome in patients with hypertrophic cardiomyopathy. *J Am Soc Echocardiogr*. 2009;22:1338–1343. doi: 10.1016/j.echo.2009.09.016.
19. Losi MA, Betocchi S, Barbati G, Parisi V, Tocchetti CG, Pastore F, Migliore T, Contaldi C, Caputi A, Romano R, Chiariello M. Prognostic significance of left atrial volume dilatation in patients with hypertrophic cardiomyopathy. *J Am Soc Echocardiogr*. 2009;22:76–81. doi: 10.1016/j.echo.2008.11.001.
20. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. 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. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK, Popescu BA, Waggoner AD. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2016;29:277–314. doi: 10.1016/j.echo.2016.01.011.
22. Lancellotti P, Tribouilloy C, Hagendorff A, Popescu BA, Edvardsen T, Pierard LA, Badano L, Zamorano JL; Scientific Document Committee of the European Association of Cardiovascular Imaging. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2013;14:611–644. doi: 10.1093/ehjci/jet105.
23. Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med*. 1996;15:361–387. doi: 10.1002/(SICI)1097-0258(19960229)15:4<361::AID-SIM168>3.0.CO;2-4.
24. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, Naidu SS, Nishimura RA, Ommen SR, Rakowski H, Seidman CE, Towbin JA, Udelson JE, Yancy CW; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines; American Association for Thoracic Surgery; American Society of Echocardiography; American Society of Nuclear Cardiology; Heart Failure Society of America; Heart Rhythm Society; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2011;124:e783–e831. doi: 10.1161/CIR.0b013e318223e2bd.
25. Ruiz-Salas A, García-Pinilla JM, Cabrera-Bueno F, Fernández-Pastor J, Peña-Hernández J, Medina-Palomo C, Barrera-Cordero A, De Teresa E, Alzueta J. Comparison of the new risk prediction model (HCM Risk-SCD) and classic risk factors for sudden death in patients with hypertrophic cardiomyopathy and defibrillator. *Europace*. 2016;18:773–777. doi: 10.1093/europace/euv079.
26. Vriesendorp PA, Schinkel AF, Liebregts M, Theuns DA, van Cleemput J, Ten Cate FJ, Willems R, Michels M. Validation of the 2014 European Society of Cardiology guidelines risk prediction model for the primary prevention of sudden cardiac death in hypertrophic cardiomyopathy. *Circ Arrhythm Electrophysiol*. 2015;8:829–835. doi: 10.1161/CIRCEP.114.002553.
27. Magnusson P, Gadler F, Liv P, Mörner S. Causes of death and mortality in hypertrophic cardiomyopathy patients with implantable defibrillators in Sweden. *J Cardiovasc Med (Hagerstown)*. 2016;17:478–484. doi: 10.2459/JCM.0000000000000359.
28. O'Hanlon R, Grasso A, Roughton M, Moon JC, Clark S, Wage R, Webb J, Kulkarni M, Dawson D, Sulaibeekh L, Chandrasekaran B, Bucciarelli-Ducci C, Pasquale F, Cowie MR, McKenna WJ, Sheppard MN, Elliott PM, Pennell DJ, Prasad SK. Prognostic significance of myocardial fibrosis in hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2010;56:867–874. doi: 10.1016/j.jacc.2010.05.010.
29. Serri K, Reant P, Lafitte M, Berhouet M, Le Bouffos V, Roudaut R, Lafitte S. Global and regional myocardial function quantification by two-dimensional strain: application in hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2006;47:1175–1181. doi: 10.1016/j.jacc.2005.10.061.
30. Almaas VM, Haugaa KH, Strøm EH, Scott H, Smith HJ, Dahl CP, Geiran OR, Endresen K, Aakhus S, Amlie JP, Edvardsen T. Noninvasive assessment of myocardial fibrosis in patients with obstructive

hypertrophic cardiomyopathy. *Heart*. 2014;100:631–638. doi: 10.1136/heartjnl-2013-304923.
31. Siontis KC, Geske JB, Ong K, Nishimura RA, Ommen SR, Gersh BJ. Atrial fibrillation in hypertrophic cardiomyopathy: prevalence, clinical correlations, and mortality in a large high-risk population. *J Am Heart Assoc*. 2014;3:e001002. doi: 10.1161/JAHA.114.001002.
32. Abhayaratna WP, Seward JB, Appleton CP, Douglas PS, Oh JK, Tajik AJ, Tsang TS. Left atrial size: physiologic determinants and clinical applications. *J Am Coll Cardiol*. 2006;47:2357–2363. doi: 10.1016/j.jacc.2006.02.048.
33. D'hooge J, Barbosa D, Gao H, Claus P, Prater D, Hamilton J, Lysyansky P, Abe Y, Ito Y, Houle H, Pedri S, Baumann R, Thomas J, Badano LP; EACVI/ASE/Industry Task Force to Standardize Deformation Imaging. Two-dimensional speckle tracking echocardiography: standardization efforts based on synthetic ultrasound data. *Eur Heart J Cardiovasc Imaging*. 2016;17:693–701. doi: 10.1093/ehjci/jev197.

CLINICAL PERSPECTIVE

Risk stratification in patients with hypertrophic cardiomyopathy remains a clinical challenge and, although sudden cardiac death risk factors have been identified, little is known on which parameters might be used to predict overall mortality in this population. Current study explored potential association between clinical and echocardiographic parameters with the combined end point of all-cause mortality, heart transplantation, and aborted sudden cardiac death in a large cohort of patients with hypertrophic cardiomyopathy. Global longitudinal strain and left atrial volume index, which are easy to obtain and widely available measures, showed to be independently associated with the outcome and with a high negative predictive value. Although these results must be confirmed in prospective studies, these novel echocardiographic indices seem promising for application in the clinical practice where clinicians might implement them for risk stratification (namely identifying low-risk patients) and therefore to optimize patient management and monitoring.

Circulation
Cardiovascular Imaging

Global Longitudinal Strain and Left Atrial Volume Index Provide Incremental Prognostic Value in Patients With Hypertrophic Cardiomyopathy

Yasmine L. Hiemstra, Philippe Debonnaire,, Marianne Bootsma, Erik W. van Zwet,, Victoria Delgado,, Martin J. Schalij, Douwe E. Atsma, Jeroen J. Bax and Nina Ajmone Marsan

Circ Cardiovasc Imaging. 2017;10:
doi: 10.1161/CIRCIMAGING.116.005706
Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1941-9651. Online ISSN: 1942-0080

Supplement: results without ATP as an outcome

Table 1. Baseline characteristics of patient population, dichotomized for patients that did and did not reach the endpoint.

	Overall N=427	Event No N=338	Event Yes N=89	P value
Clinical characteristics				
Age (years)	52±15	51±14	53±15	0.233
Men [n(%)]	282 (66)	226 (67)	56 (63)	0.530
Hypertension [n(%)]	151 (35)	131 (40)	28 (33)	0.263
Sinus rhythm [n(%)]	371 (87)	297 (88)	74 (83)	0.216
Genetic mutation HCM gene[n(%)]*	167 (63)	136 (63)	31 (66)	0.236
Septal intervention	56 (13)	38 (11)	18 (20)	0.033
Patients with ICD at baseline	91 (21)	63 (19)	28 (31)	0.013
**only genetically tested patients (N=264)*				
Medication use [n(%)]				
Beta-blockers	167 (39)	125 (37)	42 (47)	0.088
Calcium-antagonist	93 (22)	71 (22)	22 (25)	0.474
Diuretics	59 (14)	41 (12)	18 (21)	0.060
Risk factors				
Family history of SCD [n(%)]	178 (42)	144 (43)	34 (38)	0.470
Unexplained syncope [n(%)]	38 (9)	28 (8)	10 (11)	0.0404
Prior NSVT [n(%)]	110 (26)	78 (24)	32 (36)	0.020
Echocardiography				
LA diameter	41 ±7	40±7	44±8	<0.001
MR > grade 2 [n(%)]	89 (21)	60 (19)	29 (36)	0.001
SAM [n(%)]	154 (36)	114 (34)	49 (46)	0.047
LVEDD (mm)	44 ±7	44±6	44±7	0.580
LVEF (%)	65 ±9	66±9	63±12	0.013
E/E’	10 (8-16)	9 (7-15)	15 (9-25)	<0.001
IVS (mm)	19 ±5	19 ±5	21±6	<0.001
PW (mm)	13 ±3	12±3	13±4	0.015
Max LVH (mm)	21 ±6	21±6	23±7	0.004
LVOT gradient (mmHg)	9 (6-19)	9 (6-17)	8 (5-34)	0.794
GLS (%)	-15 ±4	-16±4	-13±4	<0.001
LAVI (mL/m²)	36 (28-47)	34 (27-44)	48 (35-66)	<0.001

GLS global longitudinal strain, HCM hypertrophic cardiomyopathy, IVS interventricular septum, LAVI left atrial volume index, LVEDD left ventricular end diastolic diameter, LVEF left ventricular ejection fraction, LVH left ventricular hypertrophy, LVOT left ventricular outflow tract, MR mitral regurgitation, NSVT non-sustained ventricular tachycardia, PW posterior wall, SAM systolic anterior movement, SCD sudden cardiac death

Table 2. Univariate and multivariate Cox proportional hazard regression analysis to identify independent predictors of outcome.

Parameter	**Univariate HR (95% CI)**	**P-value**	**Multivariate HR (95% CI)**	**P-value**
Age	1.02 (1.00-1.03)	0.052	0.99 (0.97-1.02)	0.623
Gender	0.82 (0.53-1.26)	0.367		
NYHA class ≥ 2	3.50 (1.60-7.66)	0.002	1.78 (0.63-5.03)	0.275
Previous AF	2.13 (1.44-3.13)	<0.001	1.22 (0.63-2.39)	0.559
Septal intervention	1.64 (0.97-2.76)	0.064	1.42 (0.73-2.75)	0.303
B-blocker	1.44 (0.95-2.19)	0.085		
Family SCD	0.85 (0.56-1.31)	0.468		
Syncope	1.20 (0.62-2.32)	0.589		
nsVT	1.58 (1.02-2.44)	0.039	1.54 (0.89-2.66)	0.122
LA diameter	1.05 (1.03-1.08)	<0.001		
LVEF	0.97 (0.95-0.99)	0.002		
E/E’	2.37-(1.64-3.42)	<0.001	1.80 (1.16-2.79)	0.009
E/A ratio	1.57 (1.24-1.98)	<0.001		
Max LVH	1.03 (1.00-1.06)	0.058	1.01 (0.96-1.06)	0.659
LVOT gradient	1.19 (0.96-1.46)	0.117		
MR grade ≥ 2	2.18 (1.38-3.44)	0.001		
SAM	1.70 (1.12-2.59)	0.013	0.99 (0.54-1.80)	0.964
GLS	1.15 (1.10-1.21)	<0.001	1.08 (1.01-1.17)	0.036
LAVI	4.67 (3.05-7.15)	<0.001	5.10 (2.66-9.77)	<0.001

CI confidence interval, GLS global longitudinal strain, HR hazard ratio, IVPG intraventricular peak gradient, LA left atrium, LAVI left atrial volume index, LVEF left ventricular ejection fraction, LVH left ventricular hypertrophy, MR mitral regurgitation, nsVT non-sustained ventricular tachycardia, SAM systolic anterior movement, SCD sudden cardiac death