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ORIGINAL ARTICLE

Independent Prognostic Value of Stroke Volume Index in Patients With Immunoglobulin Light Chain Amyloidosis

See editorial by Siddiqi et al

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BACKGROUND: Heart involvement is the most important prognostic determinant in AL amyloidosis patients. Echocardiography is a cornerstone for the diagnosis and provides important prognostic information.

METHODS AND RESULTS: We studied 754 patients with AL amyloidosis who underwent echocardiographic assessment at the Mayo Clinic, including a Doppler-derived measurement of stroke volume (SV) within 30 days of their diagnosis to explore the prognostic role of echocardiographic variables in the context of a well-established soluble cardiac biomarker staging system. Reproducibility of SV, myocardial contraction fraction, and left ventricular strain was assessed in a separate, yet comparable, study cohort of 150 patients from the Pavia Amyloidosis Center. The echocardiographic measures most predictive for overall survival were SV index <33 mL/min, myocardial contraction fraction <34%, and cardiac index <2.4 L/min/m^2 with respective hazard ratios (95% confidence intervals) of 2.95 (2.37–3.66), 2.36 (1.96–2.85), and 2.32 (1.91–2.80). For the subset that had left ventricular strain performed, the prognostic cut point was −14% (hazard ratios, 2.70; 95% confidence intervals, 1.84–3.96). Each parameter was independent of systolic blood pressure, Mayo staging system (NT-proBNP [N-terminal pro-B-type natriuretic peptide] and troponin), and ejection fraction on multivariable analysis. Simple predictive models for survival, including biomarker staging along with SV index or left ventricular strain, were generated.

CONCLUSIONS: SV index prognostic performance was similar to left ventricular strain in predicting survival in AL amyloidosis, independently of biomarker staging. Because SV index is routinely calculated and widely available, it could serve as the preferred echocardiographic measure to predict outcomes in AL amyloidosis patients.

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Key Words: amyloidosis ■ echocardiography ■ patients ■ prognosis ■ stroke volume

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CLINICAL PERSPECTIVE

Cardiac involvement is the major prognostic determinant in immunoglobulin light chain amyloidosis patients. In this large cohort of patients, we showed that a stroke volume index <33 mL/min is associated with more than a doubling of the risk of death. The prognostic role of stroke volume index resulted, independent from cardiac biomarkers staging systems. The application of stroke volume index should be possible in almost any echocardiographic system with a good reproducibility. This measure could also play an important role in patient stratification in interventional trials.

The systemic amyloidoses are disorders of protein conformation and metabolism that result in tissue deposition of insoluble fibrils, organ dysfunction, and death. In light chain amyloidosis, fibrils are composed mainly by the N terminus of a monoclonal immunoglobulin light chain (AL).[1] AL amyloidosis is a systemic disease, and most patients have clinical involvement of >1 organ at diagnosis. Heart involvement is present in almost two-thirds of patients with this disease, representing the most common cause of death.[2,3]

Cardiac amyloidosis typically causes a restrictive cardiomyopathy,[4] in which the deposition of misfolded amyloid proteins in the myocardium causes structural alterations, whereas cardiotoxic light chains cause myocardial dysfunction,[5,6] eventually leading to heart failure. Despite the progression of the disease, ejection fraction (EF) often remains within the normal or preserved range, and a reduced EF is a sign of late or end-stage disease.[7,8] More subtle echocardiographic parameters, such as increased left ventricular (LV) wall thickness and decreased fractional shortening, which have been found to be independent predictors of cardiac mortality in AL amyloidosis,[7,9] are often overlooked. Myocardial strain imaging[10–14] and mid-wall fractional shortening are useful for diagnosis and prognostication of survival among patients with cardiac amyloidosis[15–18] but are not routinely performed. Myocardial strain imaging is limited by technical challenges in acquisition and vendor-specific variation in calculated results. The myocardial contraction fraction (MCF), which is defined as the ratio of stroke volume (SV) to myocardial volume (MV), was proposed by King et al[19] as a novel index of myocardial function, being a volumetric measure of myocardial shortening, which differentiates myocardial performance in patients with pathological versus physiological hypertrophy. In a recent article of 34 patients, MCF was found to be superior to EF in predicting overall survival among AL amyloidosis patients.[20] NT-proBNP (N-terminal pro-B-type natriuretic peptide)[21] and cardiac troponins[22–24] are currently the most important markers for the assessment of prognosis in AL amyloidosis and are combined in different staging systems.[25–27] Unfortunately, the general cardiologist often overlooks the prognostic implications of these variables, and they are tests that are ordered only after an index of suspicion for AL amyloidosis has been raised. We, therefore, set out to assess the potential prognostic value of widely accessible echocardiographic variables in a larger cohort of AL amyloidosis patients.

METHODS

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. The study included 754 patients who underwent hematologic assessment, as well as complete echocardiographic evaluation at Mayo Clinic, Rochester, MN, within 30 days of their AL amyloidosis diagnosis. Patients were diagnosed from January 1, 1996, to February 1, 2015. The diagnosis of AL amyloidosis was predicated on the presence of organ involvement as previously defined[28] and a tissue biopsy specimen that stained positive with Congo red and exhibited green birefringence under polarized light. The diagnosis of AL amyloidosis was confirmed by tissue typing with immunohistochemistry, immunofluorescence, or laser-microdissection mass spectrometry according to the technique available at the time of diagnosis.[29,30] The Mayo Foundation institutional review board approved the study, and all patients consented to have their medical records reviewed according to institutional review board practices.

Echocardiography

Because the study covered a 19-year period, clinical echocardiography protocols varied, with more of an emphasis on 2-dimensional (2D) measurements. Patients were evaluated with standard echocardiographic protocols used in the Mayo Clinic Echocardiography Laboratory at the time of diagnosis. Measurements of diastolic thickness of the interventricular septum and LV posterior wall, end-systolic and end-diastolic LV diameters 2D techniques, LV mass, EF, left atrial volume, and Doppler evaluation of diastolic function and SV were performed as previously described.[31,32] MCF was calculated as LV SV (obtained from a Doppler-derived method) divided by LV MV, which is defined as LV mass divided by the mean density of myocardium (1.05 g/mL).[19] Using a previously validated technique, LV end-diastolic and end-systolic volumes were calculated from 2D echo-guided M-mode echocardiographic dimensions as previously reported.[33–35] In addition, a subset of 238 patients had measurement of LV global peak longitudinal strain (LV strain) using speckle-tracking as previously described.[36] Sonographers with experience in obtaining two dimensional speckle tracking echocardiography performed the echocardiographic studies using a Vivid 7 or E9 GE Medical System with a 2.5 to 4.0 MHz transducer in accordance with the guidelines of the American Society of Echocardiography.[31] LV strain measurements were performed during the echocardiographic examination with dedicated vendor-specific software (EchoPAC PC version 6.0; GE Healthcare, Co).

Reproducibility of SV, MCF, and LV strain was assessed in a separate, yet comparable, study cohort from the Pavia Amyloidosis Center. Briefly, echo data from 150 consecutive patients with AL amyloidosis were analyzed twice by the same observer, allowing a 2-week time interval between 2 blinded measurements. This allowed assessing the intraobserver reproducibility of the different measures. A second observer repeated the same measures independently to assess interobserver reproducibility. Reproducibility was assessed in terms of coefficients of variation and percentage difference, which is defined as the absolute difference between 2 paired values divided by the average of the 2 values and expressed as a percentage.

Biomarkers

In all patients, blood was collected at the time of diagnosis. Creatinine, glomerular filtration rate, alkaline phosphatase, albumin, and 24-hour protein loss were measured at the time of the diagnosis in all the patients. Since 2004, measurements of NT-proBNP, cardiac troponin T, and free light chain were added to the routine panel. The cardiac biomarkers NT-proBNP (cutoff 1800 ng/L) and troponin T (cutoff 0.025 μg/L) and difference between amyloidogenic and nonamyloidogenic free light chain (cutoff 180 mg/L) were combined into the Mayo 2012 cardiac staging system.[26] Stage I patients have all markers below the cutoffs, stage II patients have only 1 marker above the cutoff, stage III patients have 3 markers above the cutoffs, and stage IV patients have all markers above the cutoffs.

Statistical Analysis

Continuous variables were expressed as median values and interquartile range and categorical variables as frequencies and percentages. Correlation among variables was summarized using Pearson correlation coefficient. Survival was analyzed using the Kaplan–Meier method to estimate the distribution of survival as a function of the follow-up duration, while censoring those not known to be deceased at last known follow-up. The best cutoffs of all the variables were evaluated using the Contal and O'Quigley method. Using these cutoffs, sensitivity and specificity were calculated based on 2-year mortality. Hazard ratios (HR) and corresponding 95% confidence intervals (CI) were estimated using Cox proportional hazards. When analyzing continuous variables, HR are reported per 1 SD in each variable to allow comparability between variables with different scales. In the subset of patients assessable for cardiac biomarkers, Harrell's survival C statistics were calculated to assess the discriminatory ability of the models and compare different models for predicting overall mortality.[37] Comparisons among C statistics were computed using the SE derived from 1000 bootstrap samples. Survival curves were plotted according to the Kaplan–Meier method, and differences in survival were tested using the log-rank test. All analyses were performed using SAS software V.9.4 and JMP 10.0 (Cary, NC). All *P* values were 2-sided, and $P \leq 0.05$ was considered to be statistically significant.

RESULTS

The study population was composed of 754 patients with a biopsy-proven AL amyloidosis diagnosis. A total of 495 (66%) patients had a positive biopsy of the abdominal fat aspirate and 80 (10%) had a positive endomyocardial biopsy; 465 (61%) had amyloid deposits in the bone marrow biopsy. In Figure 1, we defined how the patient population was divided according to the time of diagnosis. Patient characteristics are shown in Table I in the Data Supplement. Median age was 64 years, and 65% were male. A total of 591 (78%) patients were considered to have cardiac amyloidosis based on diagnostic criteria (intraventricular septum >12 mm in the absence of other cardiac causes and an elevated NT-proBNP [>332 ng/L]).[28,38] During a median follow-up of living patients of 40.8 months (interquartile range, 19–72 months), 480 (63%) have died. Standard 2D echocardiographic parameters, SV index (SVI), LV strain, and MCF are illustrated in Table II in the Data Supplement along with their impacts on the risk of death expressed by HR. In particular, an SVI below the cutoff of 33 mL/m^2 was able to significantly predict overall survival (HR, 2.95; 95% CI, 2.37–3.66; $P<0.001$). In addition, MCF <34% significantly predicted survival (HR, 2.36; 95% CI, 1.96–2.85). The measures of MCF, SVI, and cardiac index were associated with a reduced survival (Figure 2A through 2C). These cutoffs were able to discriminate the overall survival if the study population was divided into different cohorts according to the time of diagnosis, that had a different outcome as previously described by our group.[39] In particular, in Figure I in the Data Supplement, we reported the outcome of patients in the cohort of 2005 to 2009 (Figure IA and IB in the Data Supplement) and in the cohort 2010 to 2015 (Figure IC and ID in the Data Supplement) for both SVI and MCF. It is also shown the effect of circulating cardiac biomarkers, assessed by

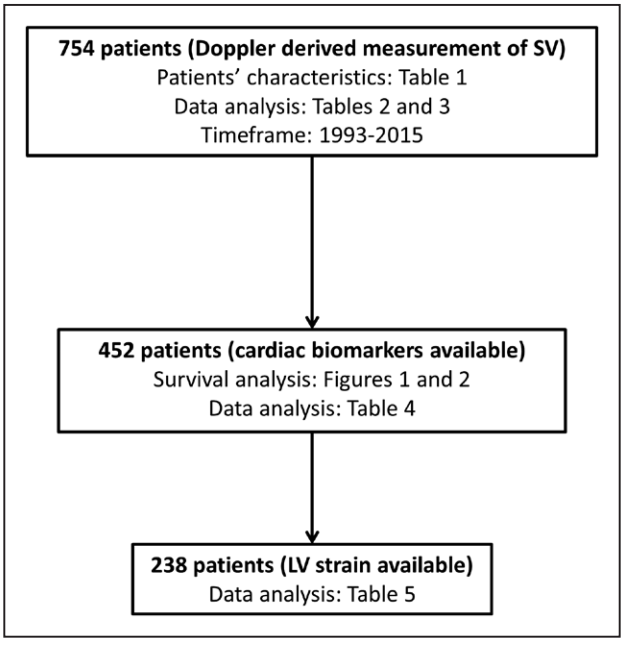

Figure 1. Consort diagram of the study population. LV indicates left ventricular; and SV, stroke volume.

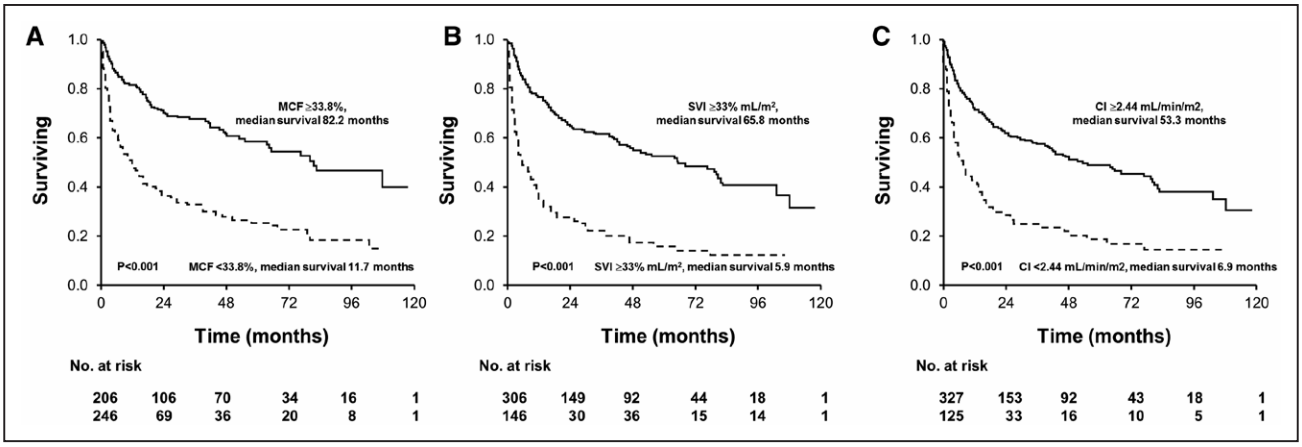

Figure 2. Overall survival (OS) according to echocardiographic variables (N=452).
A, OS according to myocardial contraction fraction (MCF). **B**, OS according to stroke volume index (SVI). **C**, OS according to cardiac index (CI).

the prognostic impact of the cardiac biomarker staging system (Figure II in the Data Supplement). Sensitivity and specificity data of the different cutoffs are reported in Table III in the Data Supplement.

In the 754 patients evaluable for MCF, SVI, and cardiac index, incremental multivariable modeling was performed to assess the association of echocardiographic variables with risk of death, excluding LV strain because of the limited number of patients with available strain measurements. Because MCF, SVI, and cardiac index all contain SV as part of their calculation, separate models were generated for each of them (Table 1). The 3 variables (MCF, SVI, and cardiac index) were independent predictors of survival along with EF, systolic blood pressure, and type of first-line therapy (autologous stem cell transplant). Other echocardiographic parameters, such as intraventricular septum and posterior wall, and the presence of pericardial effusion were not independent of MCF, but intraventricular septum remained an independent predictor in the models with SVI and cardiac index (Table 1).

Additional analysis was performed using the subset of 452 patients with available circulating cardiac biomarkers. This subgroup could be stratified with the use of the Mayo 2012 cardiac biomarker staging that identified 4 stages with significantly different overall survival (Figure II in the Data Supplement). A significant worsening of the echocardiographic parameters according to the different biomarkers staging was noted (Table IV in the Data Supplement). In particular, while the median EF in stage IV resulted still >50%, MCF, SVI, and LV strain were significantly reduced compared with the median value. MCF, SVI, and cardiac index each retained prognostic value on addition of cardiac biomarkers staging (Mayo 2012 stage III and IV) to the models shown in Table 2. Results were similar when staging was analyzed across 4 levels rather than combined, although MCF was only of borderline significance (Table V in the Data Supplement). Other useful echocardiographic variables that were significant predictors of survival at univariate analysis were tested in a stepwise multivariate approach. In particular, intraventricular septum, posterior wall, deceleration time, and relative wall thickness were added to the analyses, but none of these variables were prognostic in the models with SVI in addition to cardiac biomarker staging. To identify the model most predictive of survival, we compared the 3 systems containing the prognostic variables (SVI, MCF, and cardiac index) using the survival C statistic. A baseline model of EF, systolic blood pressure, and biomarker staging had a C statistics of 0.70; 95% CI, 0.67–0.74. The addition of SVI—but not MCF or cardiac index—added prognostic

Table 1. Multivariable Proportional Hazards Model for Risk of Death Using Echocardiographic Parameters Only (n=754)

	MCF <33.6% Model		SVI <33 mL/m² Model		Cardiac Index <2.44 Model	
Variable	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
MCF, SVI, or CI	1.72 (1.39–2.13)	<0.001	1.90 (1.47–2.46)	<0.001	1.50 (1.20–1.87)	<0.001
EF <55%	1.73 (1.40–2.14)	<0.001	1.60 (1.24–2.06)	<0.001	1.73 (1.39–2.16)	<0.001
SBP <95 mm Hg	1.44 (1.16–1.81)	0.001	1.47 (1.13–1.90)	0.004	1.42 (1.14–1.78)	0.002
IVS >12 mm	Not included		1.44 (1.07–1.93)	0.02	1.48 (1.17–1.86)	0.001
ASCT	0.57 (0.43–0.76)	<0.001	0.50(0.35–0.72)	<0.001	0.56 (0.42–0.74)	<0.001

ASCT indicates autologous stem cell transplant; CI, confidence interval; EF, ejection fraction; HR, hazard ratio; IVS, intraventricular septum; MCF, myocardial contraction fraction; SBP, systolic blood pressure; and SVI, stroke volume index.

Table 2. Multivariable Proportional Hazards Model for Risk of Death Incorporating Circulating Cardiac Biomarkers (n=452)

	MCF <33.6% Model		SVI <33 mL/m² Model		Cardiac Index <2.44 Model	
Variable	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
MCF, SVI, or CI	1.54 (1.11–2.14)	0.009	1.92 (1.42–2.60)	<0.001	1.48 (1.10–1.99)	0.01
EF <55%	1.59 (1.20–2.10)	0.001	1.41 (1.05–1.88)	0.02	1.58 (1.19–2.10)	0.002
SBP <95 mm Hg	1.51 (1.13–2.02)	0.006	1.40 (1.04–1.88)	0.03	1.50 (1.11–2.01)	0.007
Stage III and IV	1.83 (1.30–2.58)	<0.001	1.89 (1.36–2.63)	<0.001	2.07 (1.50–2.86)	<0.001
ASCT	0.62 (0.40–0.95)	0.03	0.61 (0.40–0.94)	0.02	0.65 (0.42–0.99)	0.05
C statistic	0.70 (0.67–0.74)		0.72 (0.68–0.75)		0.70 (0.67–0.74)	

ASCT indicates autologous stem cell transplant; CI, confidence interval; EF, ejection fraction; HR, hazard ratio; MCF, myocardial contraction fraction; SBP, systolic blood pressure; and SVI, stroke volume index.

power to the basal model (Table 2) with respective C statistics of 0.72; 95% CI, 0.68–0.75; *P*=0.010. To further validate these analyses, a second method of measuring SV, the Simpson method incorporating 2D data, was used to calculate MCF and SVI; MCF was no longer independently prognostic but SVI was (Table VI in the Data Supplement).

To evaluate the contribution of LV strain, the 238 patients who had baseline LV global peak systolic strain assessment were included. The optimal cutoff of LV strain predicting mortality at 2 years was ≥–14% (sensitivity, 86.2%; specificity, 57.1%) and was able to sharply discriminate the overall survival of patients (Figure IIIA in the Data Supplement). Of note, MCF was highly correlated with LV strain (*r*=–0.85; *P*<0.001; Figure IIIB in the Data Supplement). The correlation between LV strain and SVI was less strong (*r*=–0.70; *P*<0.001, not shown). When LV strain was added to EF, systolic blood pressure, and cardiac biomarker stages III and IV, LV strain was found to be an independent risk factor (Table 3, model A); however, the addition of SVI to model A drove LV strain from the model (Table 3, models B and C). This analysis led us to investigate a simplified model containing circulating biomarker stage and each of the most powerful cardiac measures in the group of patients evaluable for cardiac biomarkers (Table VII in the Data Supplement). The addition of SVI to biomarker staging system had the higher C statistics as compared with the biomarkers alone. In the subset of patients with advanced cardiac stages (stage III and IV and cardiac stage IIIa and IIIb, according to Wechalekar et al[27]), SVI was able to identify a subgroup of patients with a significantly better overall survival (Figure 3).

The intraobserver and interobserver coefficients of variations were, respectively, 0.4% and 0.7% for LV end-diastolic diameter, 3.0% and 3.4% for septal wall thickness, 2.9% and 3.2% for posterior wall LV thickness. As to LV strain data, intraobserver and interobserver percentage difference were 5±4% (*r*=0.98; 95% CI limits of agreements [LOA], 2.38%–0.99%) and 6±4% (*r*=0.96; 95% CI LOA, 3.02%–1.39%), respectively. MCF and SV showed slightly worse reproducibility. Intraobserver and interobserver percentage difference were 8±5% (*r*=0.86; 95% CI LOA, 5.22%–2.99%) and 9±6% (*r*=0.82; 95% CI LOA, 5.99%–3.23%) for MCF and 8±5% (*r*=0.84; 95% CI LOA, 5.44%–2.89%) and 10±6% (*r*=0.78; 95% CI LOA, 6.66%–3.43%) for SV.

DISCUSSION

Understanding outcomes in patients with AL is essential given the heterogeneity of the disease. Echocardiography was one of the first and most important diagnostic and prognostic tools for cardiac assessment among patients with AL.[40] In terms of prognosis, soluble cardiac biomarkers have largely supplanted echocardiog-

Table 3. Multivariable Proportional Hazards Models for Risk of Death Incorporating LV Strain and SVI (n=238)

	Model A		Model B		Model C	
Variable	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
LV strain ≥–14%	1.95 (1.04–3.66)	0.04	1.75 (0.93–3.33)	0.08	Not included	
EF <55%	1.26 (0.81–1.97)	0.31	1.02 (0.64–1.64)	0.92	1.16 (0.73–1.84)	0.54
SBP <95 mm Hg	1.60 (1.01–2.52)	0.04	1.38 (0.86–2.20)	0.18	1.36 (0.85–2.18)	0.20
Stage III and IV	2.69 (1.44–5.01)	0.002	2.51 (1.34–4.70)	0.004	3.11 (1.73–5.59)	<0.001
SVI <33 mL/m²	Not included		2.00 (1.24–3.23)	0.004	2.14 (1.32–3.47)	0.002
ASCT	0.34 (0.12–0.96)	0.04	0.37 (0.13–1.05)	0.06	0.36 (0.13–1.02)	0.05
C statistic	0.75 (0.70–0.80)		0.76 (0.72–0.81)		0.75 (0.70–0.80)	

ASCT indicates autologous stem cell transplant; CI, confidence interval; EF, ejection fraction; HR, hazard ratio; LV, left ventricular; SBP, systolic blood pressure; and SVI, stroke volume index.

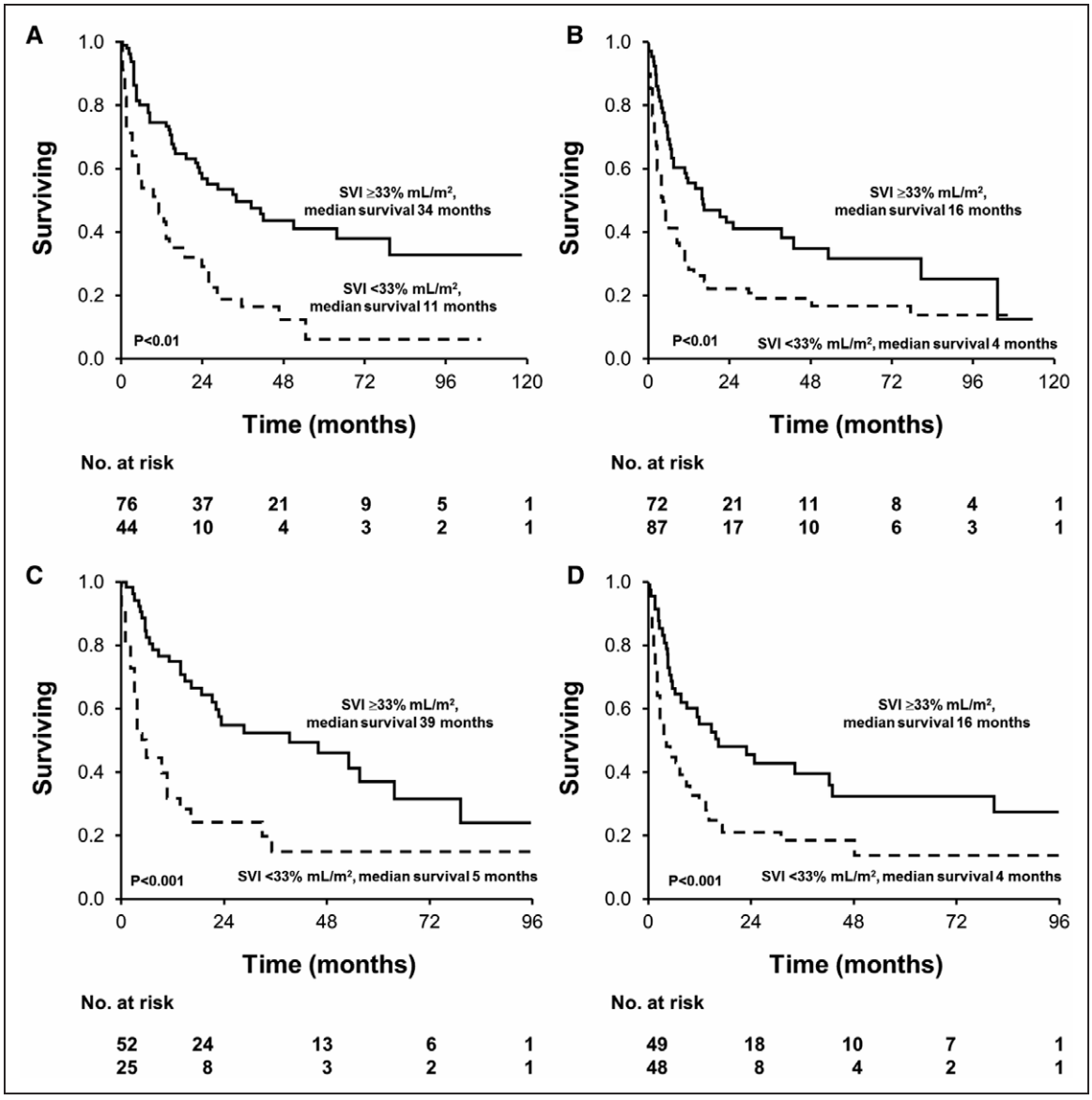

Figure 3. Overall survival (OS) according to stroke volume index (SVI) in different biomarker stagings (N=452). **A**, OS according to SVI in Mayo 2012 stage III. **B**, OS according to SVI in Mayo 2012 stage IV. **C**, OS according to SVI in stage IIIa. **D**, OS according to SVI in stage IIIb.

raphy. We set out to assess how measures like MCF,[20] LV strain,[15] SVI, and cardiac index held up against other simple prognostic measures like troponin T, NT-proBNP,[26] and systolic blood pressure.[27] Using one of the largest cohorts of subjects with AL amyloidosis with echocardiographic assessment and soluble cardiac biomarkers, we found that MCF correlated well with LV strain and that it was prognostic for overall survival even in the context of cardiac biomarkers. The prognostic impact of these variables was also independent of the type of therapy. The echocardiographic variables reported in our article are similar to those previously reported by others.[15,16,20] In addition, SVI was able to identify a subset of patients with a better prognosis, even in the context of patients with severe cardiac involvement according to the cardiac biomarker staging systems. Therefore, we observed that SVI performed, as well as MCF and LV strain, in survival models, leading us to think that this simple measure, SVI, is the favored echocardiographic parameter to predict outcomes among patients with AL amyloidosis. Interestingly, a similar cutoff of SVI (35 mL/m^2) has been found to be a useful prognostic marker in patients with aortic stenosis with preserved EF.[41] An advantage of SVI is that it is routinely calculated as part of a standard echocardiographic study, requires little time, does not require additional calculations or analysis, and is not limited by the challenges in determining LV mass as is required for MCF or those of LV strain (2D image quality, sonographer expertise, and vendor and software variations). We did show, however, that LV strain when using

the same vendor and software data was slightly more reproducible than MCF and SV (that are measured by manual tracing and hence more operator-dependent).

Because the published data on MCF[20] was compelling, we speculated that SVI might be as useful and more readily available in a busy cardiology practice because MCF is defined as the ratio between SV and MV. The MCF evaluates shortening in relation to the degree of amyloid infiltration (as inferred from the myocardial chamber volume) and quantitates the effect of amyloid infiltration in the myocardium. Progressive amyloid deposition in the myocardium causes an increase in LV MV, concomitant with a decline in SV, which is indicated by declining MCF.[20] It is important to note that, in those echocardiographic laboratories in which the LV strain is not yet (or readily) available, the measure of MCF seems to be a reasonable substitute for patients with AL amyloidosis, serving as the poor man's LV strain. Similar to EF, the MCF is dependent on afterload,[19] but in contradistinction to EF in AL amyloid in which SV and end diastolic volume show parallel declines (and hence no change in EF), the MCF declines because increases in MV (because of amyloid deposition) are accompanied by SV reduction. Thus, in the setting of amyloid-induced LV mass increase (that can also be viewed as amyloid-induced LV hypertrophy), MCF is reduced, analogous to mid-wall fractional shortening.[42] Although MCF does not require specific software or a specific training because it is calculated from conventional echocardiographic measures, it is not automatically calculated by standard package software. In addition, the measurements that are needed for the calculation of LV mass and MV are hampered by possible errors. To limit these, we focused only on 2D-derived data, excluding from the study all the subjects that had only M-mode–based measurements of LV chamber size. However, the prognostic ability of MCF was limited, if the SV was calculated by only 2D measurement. Another important limitation of MCF is that the measurement of MV assumes a constant myocardial density (1.05 g/mL) irrespective of the underlying pathology, which presumes that there is no difference between myocardial tissue and amyloid tissue density. Previous data have shown that myocardial density varies in several conditions, such as cardiac infarction.[43] Moreover, a recent study with cardiac magnetic resonance documented a different degree of extracellular volume expansion in the main types of cardiac amyloidosis.[44] The use of SVI as a prognostic marker could overcome this assumption and the different limitations highlighted for MCF. LV strain is a powerful tool with the ability to promote early diagnosis by detection of subtle abnormalities in ventricular function and recognition of the characteristic pattern of apical sparing. However, unlike SVI, LV strain requires specific vendor-dependent software, expertise, and time and is not available in all centers. In addition, the results are not standardized across ultrasound systems, leading to a recommendation that serial studies be performed on the same machine. Recognizing the role of inter- and intraobserver variability in any measurement as a potential limitation, we integrated our data with an evaluation of reproducibility on a comparable patients' cohort. The reasonable reproducibility of Doppler-derived measurement of SV reinforces the role of our new proposed approach. Indeed, we documented a high prognostic role of this measurement in a real-world data setting, encompassing several years in a referral echocardiographic laboratory. In addition, a validation analysis confirmed our results by assessing the prognostic role of 2D-derived SVI. Unfortunately, a limitation of our study is that only few patients had cardiac magnetic resonance data and 3D echocardiographic data available. Therefore, no comparison with this method was possible. In addition, in this series, we did not have a correlation with electrocardiogram data. Further studies in large series are warranted to assess the prognostic impact of SVI in the setting of cardiac biomarkers.

In conclusion, SVI is a simple, powerful, independent predictor of survival in patients with AL amyloidosis. In particular, the prognostic role of SVI was independent of EF, blood pressure, the cardiac biomarkers staging, and LV strain. SVI performed at least, as well as LV strain for predicting survival in AL, independent of biomarker staging. Because SVI is routinely calculated and widely available, it could serve as the preferred echocardiographic measure to predict outcomes in AL amyloidosis patients.

ARTICLE INFORMATION

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Independent Prognostic Value of Stroke Volume Index in Patients With Immunoglobulin Light Chain Amyloidosis

Paolo Milani, Angela Dispenzieri, Christopher G. Scott, Morie A. Gertz, Stefano Perlini, Roberta Mussinelli, Martha Q. Lacy, Francis K. Buadi, Shaji Kumar, Mathew S. Maurer, Giampaolo Merlini, Suzanne R. Hayman, Nelson Leung, David Dingli, Kyle W. Klarich, John A. Lust, Yi Lin, Prashant Kapoor, Ronald S. Go, Patricia A. Pellikka, Yi L. Hwa, Stephen R. Zeldenrust, Robert A. Kyle, S. Vincent Rajkumar and Martha Grogan

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Supplemental materials.

Supplemental Table 1. Characteristics of 754 patients with AL amyloidosis.

Variable	Median (interquartile range) - Number (%)
Diagnosis periods: 1996-2002 / 2002-2008 / 2008-2015	29 (4) / 303 (40) / 422 (56)
Age, years	64 (56-72)
Sex: male	493 (65)
Body mass index, Kg/m^2	25 (23,28)
NT-proBNP, ng/L (613 patients)	2896 (708, 7757)
Troponin T, mcg/L (732 patients)	0.03 (0.01, 0.09)
dFLC*, mg/L (763 p)	288 (100, 700)
Mayo Stage 2012[†] (452 patients) Stage: I / II / III / IV	86 (19) / 87 (19) / 120 (27) / 159 (35)
Mayo Stage 2004[§] (512 patients) Stage: I / II / IIIa / IIIb	77 (15) / 198 (39) / 132 (26) / 105 (20)
Bone marrow plasma cells (%)	10 (5, 20)
Creatinine, mg/dL	1.2 (0.9, 1.6)
eGFR[II], mL/min	48 (44, 78)
Urine total protein, g/24h	0.72 (0.16, 3.96)
Renal Stage[#] Stage: I / II / III	354 (54) / 251 (39) / 46 (7)
Alkaline phosphatase, U/L	98 (72, 171)
First line treatment, n (%) Mel-Dex Bortezomib-based ASCT Other Missing	 197 (26.1) 145 (19.2) 116 (15.4) 228 (30.2) 68 (9.0)

*dFLC, difference between involved and un-involved free-light chain; [Y]eGFR, estimated glomerular filtration rate; [†]Mayo stage 2012[1]: based on NT-proBNP (cutoff 1800 ng/L), troponin T (cutoff 0.025 mcg/L) and dFLC (cutoff 180 mg/L). Stage I patients have all markers below the cutoffs, stage II only one marker above the cutoffs, stage III patients three markers above the cutoffs and stage IV all markers above the cutoff; [§]Mayo Stage 2004[2, 3]: based on NT-proBNP (cutoff 332 ng/L), troponin T (cutoff 0.025

mcg/L) Stage I patients have all markers below the cutoffs, stage II only one marker above the cutoffs, stage IIIa patients with both markers above the cutoff and NT-proBNP <8500 ng/L, Stage IIIb patients with both markers above the cutoff and NT-proBNP >8500 ng/L; [II]eGFR, estimated glomerular filtration rate; [#]Renal Stage[4]: Stage I: both proteinuria ≤5g/24h and eGFR ≥50 mL/min per 1.73 m^2; stage II: either proteinuria >5g/24h or eGFR <50 mL/min per 1.73 m^2; stage III: both proteinuria >5g/24h and eGFR <50 mL/min per 1.73 m^2; Mel-Dex, melphalan and dexamethasone; ASCT, autologous stem cell transplant.

Supplemental Table 2. Echocardiographic patients' characteristics and univariate proportional hazards models (n=754).

		Dichotomous variables			Continuous variables		
Variable	Cut-point	Pts at risk/tot	HR[*] (95% CI)	P	Median (IQR)	HR[†] (95% CI)	P
IVS[‡], mm	≥12 mm	559/754	1.84 (1.48, 2.30)	<0.001	14 (11, 16)	1.34 (1.24, 1.46)	<0.001
PW[II], mm	≥14 mm	335/754	1.67 (1.39, 2.00)	<0.001	13 (11, 15)	1.34 (1.23, 1.46)	<0.001
EF, %	<55%	219/754	2.46 (2.04, 2.97)	<0.001	61 (52, 67)	0.64 (0.59, 0.70)	<0.001
Dec.-time, ms	<166 ms	372/754	1.88 (1.54, 2.30)	<0.001	177 (149, 213)	0.99 (0.99, 0.99)	<0.001
Relative wall thickness	>0.84	425/754	1.72 (1.41, 2.12)	<0.001	0.91 (0.76, 1.12)	2.08 (1.55, 2.77)	<0.001
LV-strain, %	≥-14%	152/299	2.70 (1.84, 3.96)	<0.001	-13 (-18, -10)	2.02 (1.65, 2.46)	<0.001
SV, mL	<62 ml	250/754	2.84 (2.36, 3.41)	<0.001	72 (55, 87)	0.59 (0.53, 0.65)	<0.001
SVI, mL/m^2	<33 mL/m^2	190/592	2.95 (2.37, 3.66)	<0.001	39 (29, 46)	0.58 (0.51, 0.65)	<0.001
CI, L/min/m^2	<2.44 L/min/m^2	206/750	2.32 (1.91, 2.80)	<0.001	2.8 (2.4, 3.5)	0.71 (0.65, 0.79)	<0.001
CO, L/min	<5.26 L/min	346/751	1.96 (1.63, 2.34)	<0.001	5.5 (4.4, 6.6)	0.69 (0.62, 0.76)	<0.001
LV mass index[§], g/m^2	≥111 g/m^2	446/754	1.63 (1.35, 1.97)	<0.001	120 (97, 147)	1.00 (1.00, 1.01)	<0.001
MCF[zz], %	<33.6%	400/754	2.36 (1.96, 2.85)	<0.001	32 (23, 48)	0.62 (0.55, 0.69)	<0.001
Mayo 2012 stage	III and IV	303/452	2.99 (2.27, 3.95)	<0.001	-	-	-
Pericardial effusion	Present	137/718	1.77 (1.42, 2.22)	<0.001	-	-	-
SBP[#], mmHg	<95 mmHg	139/743	1.85 (1.49, 2.31)	<0.001	110 (98, 121)	0.84 (0.77, 0.92)	<0.001
SBP[#], mmHg	<100 mmHg	194/743	1.62 (1.32, 1.97)	<0.001	-	-	-

[*]HR, hazard ratio, [†]HR reported per 1 SD increase in each variable; [‡]IVS, interventricular septum thickness; [§]LV mass, left ventricular mass; [II]PW, posterior wall thickness; [#]SBP, systolic blood pressure.

Supplemental Table 3. Evaluation of cutoffs using method of Contal and O'Quigley (sensitivity and specificity calculated with mortality at 2 years) (number of patients: 452).

Variable	Cutoff [N(%)]	Sensitivity, % (95% CI)	Specificity, % (95% CI)
IVS, mm	≥15 [194 (43%)]	57.0 (49.8, 64.0)	71.0 (62.4, 78.6)
PW, mm	≥13 [269 (60%)]	74.5 (67.9, 80.4)	55.7 (46.8, 64.4)
LV mass, g	≥208 [280 (62%)]	70.5 (63.7, 76.7)	48.1 (39.3, 57.0)
LV mass indexed	≥110 [279 (62%)]	70.5 (63.7, 76.7)	48.1 (39.3, 57.0)
EF, %	<55 [154(34%)]	47.0 (39.9, 54.2)	80.9 (73.1, 87.3)
SBP, mmHg	<95 [93 (21%)]	29.0 (22.8, 35.8)	89.3 (82.7, 94.0)
SV, mL	<62 [146 (32%)]	49.0 (41.9, 56.1)	84.7 (77.4, 90.4)
SVI, mL/m^2	<33 [146 (32%)]	50.0 (42.9, 57.1)	86.3 (79.2, 91.6)
CO, L/min	<5.26 [210 (46%)]	60.5 (53.4, 67.3)	67.2 (58.4, 75.1)
CI, $L/min/m^2$	<2.44 [125 (28%)]	41.5 (34.6, 48.7)	87.8 (80.9, 92.9)
MCF, %	<33.6 [246 (54%)]	72.5 (65.8, 78.6)	64.1 (55.3, 72.3)
LV-strain, % (N=238)	≥-14 [145 (61%)]	86.2 (76.7, 92.9)	57.1 (45.4, 68.4)

CI, left ventricular cardiac index; CO, left ventricular cardiac output; EF, ejection fraction; HR, relative risk, IVS, interventricular septum thickness; LV mass, left ventricular mass; LV-strain, left ventricular global peak longitudinal strain; MCF, myocardial contraction fraction; PW, posterior wall thickness; SBP, systolic blood pressure; SVI, stroke volume index.

Supplemental Table 4. Echocardiographic data according to cardiac stages.

Variable	Mayo Stage I 86 patients Median (range)	Mayo Stage II 87 patients Median (range)	Mayo Stage III 120 patients Median (range)	Mayo Stage IV 159 patients Median (range)
IVS, mm	11 (10-13)	13 (11-15)	14 (13-16)	16 (14-18)
PW, mm	11 (9-12)	11 (10-14)	14 (12-15)	15 (13-17)
EF, %	67 (63-69)	65 (59-69)	60 (50-66)	55 (42-64)
SV, mL	66 (57.9-74.2)	64.2 (53-76.1)	55.3 (45.7-68)	48.4 (38.8-59.1)
SVI, mL/m^2	45 (40-53)	42 (36-49)	36 (29-45)	30 (25-39)
LV mass, mL	181 (152-224)	208 (163-265)	240 (196-318)	266 (216-322)
LV-strain	-19 (-20;-15)	-16 (-18;-12)	-11 (-14;-9)	-10 (-12;-7)
LV CI, L/min/m^2	3.28 (2.78-3.72)	3.21 (2.69-3.85)	2.68 (2.37-3.32)	2.52 (1.95-2.94)
LV CO, L/min	6.35 (5.36-7.20)	5.98 (5.18-7.23)	5.19 (4.31-6.34)	4.81 (3.80-6.60)
MCF, %	52.2 (43.8-62.4)	41.4 (30.5-53.6)	29.3 (21.4-38.2)	23.1 (18.1-30.8)
Type of 1st line therapy				
ASCT	30 (35%)	23 (27%)	9 (8%)	9 (6%)
Bortezomib-based	17 (20%)	24 (28%)	35 (29%)	48 (30%)
Melphalan-Dex	15 (17%)	19 (22%)	49 (41%)	64 (40%)
Other	17 (20%)	17 (19%)	22 (18%)	27 (17%)
Missing	7 (8%)	4 (4%)	5 (4%)	11 (7%)

CI, left ventricular cardiac index; CO, left ventricular cardiac output; EF, ejection fraction; HR, relative risk, IVS, interventricular septum thickness; LV mass, left ventricular mass; LV-strain, left ventricular global peak longitudinal strain; MCF, myocardial contraction fraction; PW, posterior wall thickness; SBP, systolic blood pressure; SVI, stroke volume index; ASCT, autologous stem cell transplant.

Supplemental Table 5. Multi-variable proportional hazards model for risk of death incorporating circulating cardiac biomarkers stages (n=452).

	MCF <33.6% model		SVI <33 mL/m^2 model	
Variable	HR (95% CI)	P	HR (95% CI)	P
MCF, SVI	1.36 (0.98, 1.90)	0.065	1.73 (1.28, 2.34)	<0.001
EF <55%	1.84 (1.39, 2.44)	<0.001	1.65 (1.23, 2.21)	<0.001
SBP <95 mmHg	1.46 (1.08, 1.95)	0.013	1.37 (1.01, 1.83)	0.041
Mayo staging 2012				
II vs I	1.60 (0.94, 2.78)	0.082	1.68 (0.99, 2.90)	0.058
III vs I	2.39 (1.45, 4.06)	<0.001	2.51 (1.56, 4.19)	<0.001
IV vs I	3.00 (1.81, 5.16)	<0.001	3.04 (1.89, 5.09)	<0.001

Supplemental Table 6. Multi-variable proportional hazards model for risk of death incorporating circulating cardiac biomarkers and using 2D measurement (Simpson method) to calculate stroke volume (n=452).

	MCF 2D <33.6% model		SVI 2D <33 mL/m^2 model	
Variable	HR (95% CI)	P	HR (95% CI)	P
MCF or SVI	1.02 (0.64, 1.72)	0.905	1.45 (1.07, 1.97)	0.013
EF <55%	2.13 (1.61, 2.81)	<0.001	2.00 (1.51, 2.64)	<0.001
SBP <95 mmHg	1.56 (1.59, 2.98)	<0.001	1.51 (1.10, 2.04)	0.010
Stage III and IV	1.57 (1.14, 2.11)	0.005	1.99 (1.46, 2.74)	<0.001

HR, relative risk; EF, ejection fraction; SBP, systolic blood pressure; MCF, myocardial contraction fraction; SVI, stroke volume index.

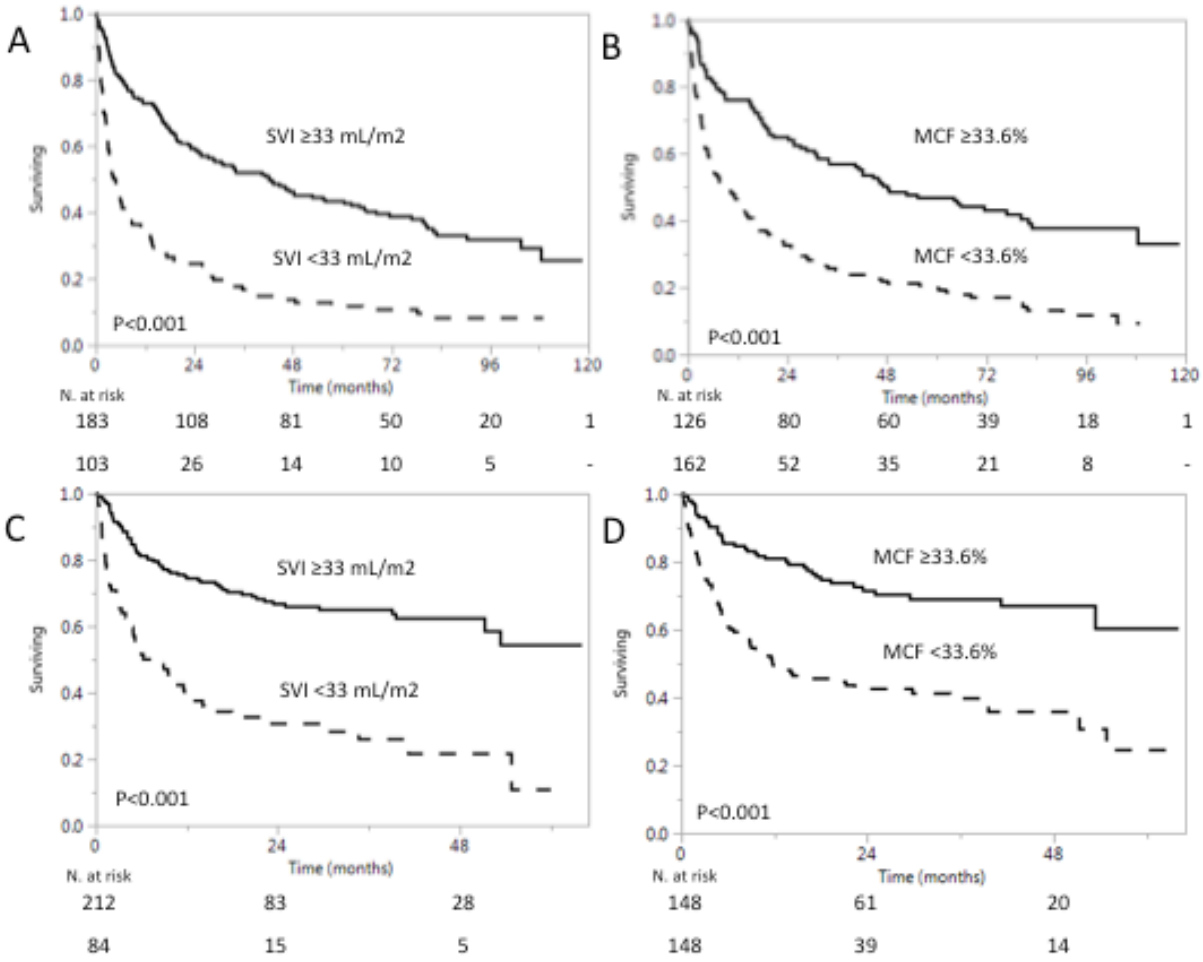
Supplemental Table 7. Simplified multi-variable proportional hazards models using circulating cardiac biomarkers, LV-strain, MCF, and SVI (n= 238).

	LV-strain >=-14%		MCF <33.6%		SVI <33 mL/min	
Variable	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
LVS/MCF/SVI	2.27 (1.25, 4.12)	0.007	1.78 (1.06, 3.00)	0.03	2.55 (1.65, 3.94)	<0.001
Stage III and IV	3.38 (1.83, 6.23)	<0.001	3.75 (2.03, 6.94)	<0.001	3.82 (2.16, 6.76)	<0.001
c-Statistic	0.71 (0.66, 0.75)		0.70 (0.66, 0.75)		0.74 (0.69. 0.78)	

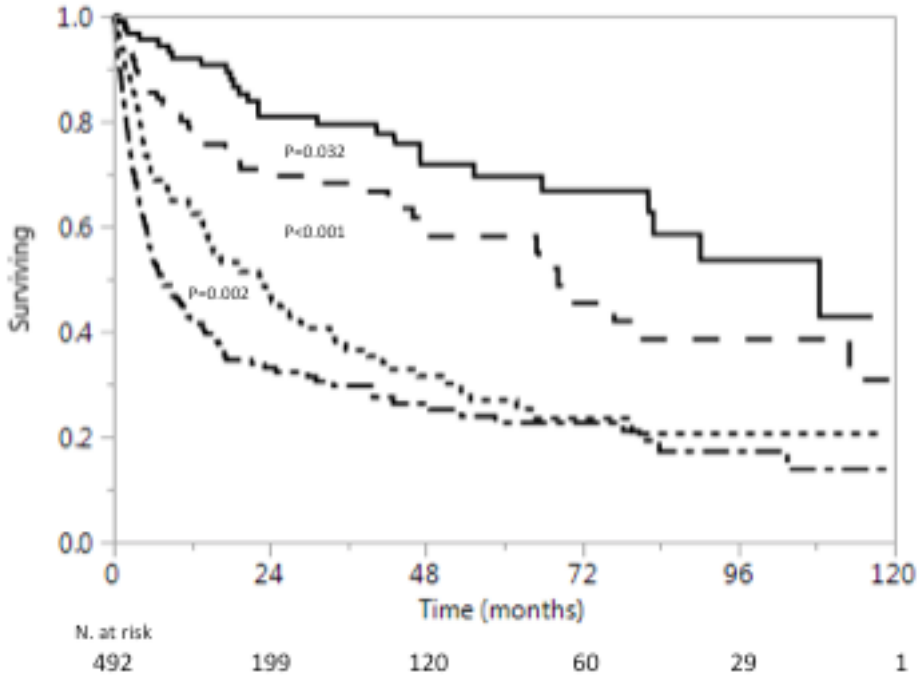
HR, relative risk; LV-strain, left ventricular global peak longitudinal strain; MCF, myocardial contraction fraction; SVI, stroke volume index.

Supplemental Figure 1. Overall survival according to SVI and MCF in different timeframes.

A. Years of diagnosis (2005-2009). Full line SVI ≥33 mL/m^2, median survival 42.1 months. Dotted line SVI <33 mL/m^2, median survival 4.5 months.
B. Years of diagnosis (2005-2009). Full line MCF ≥33.8%, median survival 48.2 months, dotted line MCF <33.8%, median survival 8.8 months.
C. Years of diagnosis (2010-2015). Full line SVI ≥33 mL/m^2, median survival not reached. Dotted line SVI <33 mL/m^2, median survival 8.1 months.
D. Years of diagnosis (2010-2015). Full line MCF ≥33.8%, median survival not reached, dotted line MCF <33.8%, median survival 11.1 months.

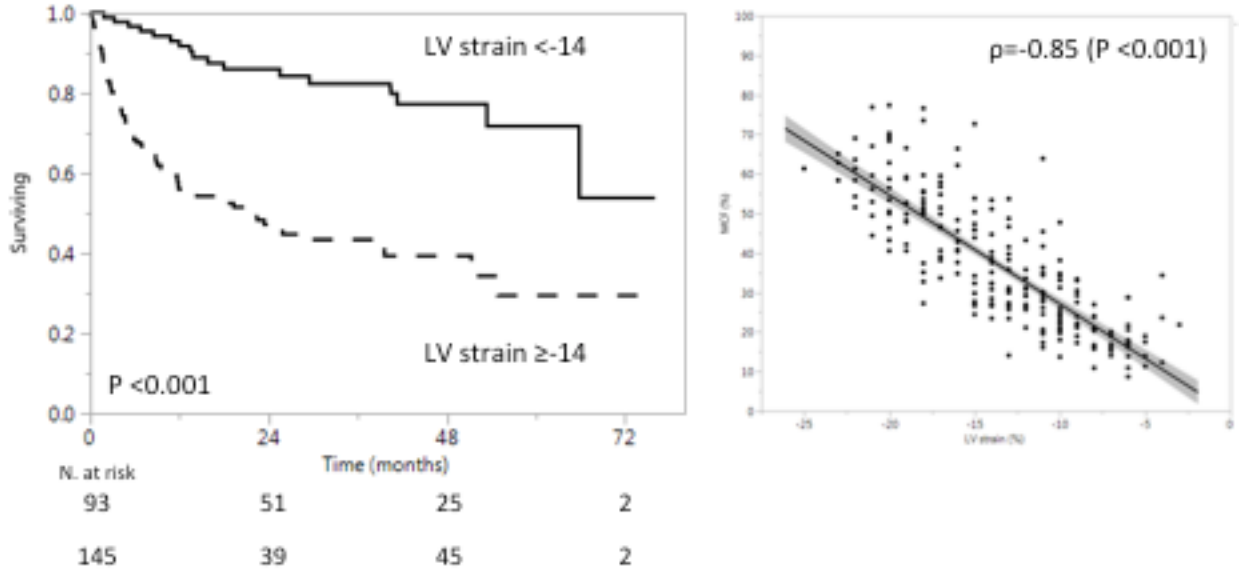


Supplemental Figure 2. Overall survival according to the Mayo 2012 cardiac biomarker staging in the subgroup of patients assessable for cardiac biomarkers (N=452), P<0.001.
Cutoffs values: NT-proBNP (1800 ng/L), troponin T (0.025 ng/mL) and difference between amyloidogenic and non-amyloidogenic free light chain (dFLC, 180 mg/L). Stage I patients have all markers below the cutoffs, stage II only one marker above the cutoffs, stage III patients three markers above the cutoffs and stage IV all markers above the cutoff.



Supplemental Figure 3. The performance of mean longitudinal LV-strain

A. Overall survival according to LV-strain. Full line LV-strain <-14%, median survival not reached. Dotted line LV-strain ≥-14%, median survival 22.3 months.
B. Correlation between LV-strain and MCF.



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