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Ventricular longitudinal function by cardiovascular magnetic resonance predicts cardiovascular morbidity in HFrEF patients

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Abstract

Aims Ventricular longitudinal function measured as basal-apical atrioventricular plane displacement (AVPD) or global longitudinal strain (GLS) is a potent predictor of mortality and could potentially be a predictor of heart failure-associated morbidity. We hypothesized that low AVPD and GLS are associated with the combined endpoint of cardiovascular mortality and heart failure-associated morbidity.

Methods and results Two hundred eighty-seven patients (age 62 ± 12 years, 78% male) with heart failure with reduced (≤40%) ejection fraction (HFrEF) referred to a cardiovascular magnetic resonance exam were included. Ventricular longitudinal function, ventricular volume, and myocardial fibrosis or infarction were analysed from cine and late gadolinium enhancement images. National registries provided data on causes of cardiovascular hospitalizations and cardiovascular mortality for the combined endpoint. Time-to-event analysis capable of including reoccurring events was employed with a 5-year follow-up. HFrEF patients had EF 26.5 ± 8.0%, AVPD 7.8 ± 2.4 mm, and GLS −7.5 ± 3.0%. In contrast, ventricular longitudinal function was approximately twice as large in an age-matched control group (AVPD 15.3 ± 1.6 mm; GLS −20.6 ± 2.0%; $P < 0.001$ for both). There were 578 events in total, and the majority were HF hospitalizations ($n = 418$). Other major events were revascularizations ($n = 64$), cardiovascular deaths ($n = 40$), and myocardial infarctions ($n = 21$). One hundred fifty-five (54%) patients experienced at least one event (mean 2.0, range 0–64). Of these patients, 119 (71%) had three events or fewer, and the first three events comprised 51% of all events (295 events). Patients in the bottom AVPD or GLS tertile (<6.8 mm or $>−6.1$%) overall experienced more than 3 times as many events as the top tertile (>8.8 mm or $<−8.4$%; $P < 0.001$). Patients in this tertile also faced more cardiovascular deaths ($P < 0.05$), HF hospitalizations ($P = 0.001$), myocardial infarctions (only GLS: $P = 0.032$), and accumulated longer in-hospital length-of-stay overall (AVPD 20.9 vs. 9.1 days; GLS 22.4 vs. 6.5 days; $P = 0.001$ for both), and from HF hospitalizations (AVPD 19.3 vs. 8.3 days; GLS 19.3 vs. 5.4 days; $P = 0.001$ for both). In multivariate analysis adjusted for significant covariates, AVPD and GLS remained independent predictors of events (hazard ratio 1.12 per-mm-decrease and 1.13 per-%-increase) alongside hyponatremia (<135 mmol/L), aetiology of HF, and LV end-diastolic volume index.

Conclusions Low ventricular longitudinal function is associated with an increase in number of events as well as longer in-hospital stay from cardiovascular causes. In addition, AVPD and GLS have independent prognostic value for cardiovascular mortality and morbidity in HFrEF patients.

Introduction

Heart failure (HF) is a worldwide major healthcare challenge with increasing prevalence, especially in the elderly population.[1] It accounts for an estimated 1–2% of the total healthcare budget in some European countries,[2,3] with hospitalizations being the predominant cost. Alongside debilitating symptoms HF patients suffer from high morbidity and premature mortality. HF readmissions and reoccurring events are common,[4] and excessive hospitalizations have a detrimental impact on quality of life.[5]

The basis of HF is often an impairment of left ventricular (LV) function, with systolic and diastolic dysfunction of either ischaemic or non-ischaemic aetiology. The major contributor, both systolic and diastolic cardiac pumping, is ventricular longitudinal function, which can be quantified as the basal-apical atrioventricular plane displacement (AVPD), also called mitral annular plane systolic excursion (MAPSE).[6] Longitudinal function can also be quantified as global longitudinal strain (GLS) - a measure of myocardial deformation in the basal-apical direction. HF patients with an ejection fraction ≤40% are given the diagnosis 'heart failure with reduced ejection fraction' (HFrEF) and have over 40% higher mortality than other forms of HF.[7] As expected, patients with HFrEF have low AVPD and GLS.[8,9] Furthermore, echocardiographic studies have shown GLS to correlate with exercise capacity[10] and predict outcomes in HFrEF using standard survival analyses.[11,12]

We have previously shown that ventricular longitudinal function can predict cardiovascular and all-cause death.[13] This is in addition to several echocardiography and cardiovascular magnetic resonance (CMR) studies showing similar prediction of patient outcome in several other patient groups.[14–16] Predicting which patients are at high risk of death is undeniably important but morbidity in HF patients is arguably equally important due to the reduced quality of life. The European Society of Cardiology guidelines point to existing gaps in evidence regarding imaging biomarkers and their connection to outcomes in HF.[1] Therefore, the specific goals were to determine if AVPD or GLS can predict the combined endpoint of cardiovascular mortality and morbidity in HFrEF patients and to investigate the relationship of AVPD and GLS with the number of and length of HF-associated events.

Methods

Study population

Two hundred eighty-seven patients with HFrEF that underwent CMR were included and have been previously described.[13] All patients gave informed written consent to participate in a study of outcomes linked to their CMR findings prior to inclusion, and the study was approved by the Regional Ethical Review Board in Lund, Sweden, and the Swedish National Board of Health and Welfare. Indications for the CMR scans were clinical assessment for ventricular function, infarct, fibrosis, or pre-implantation investigation prior to primary cardioverter-defibrillator therapy or cardio-resynchronizing therapy in patients with reduced ejection fraction (EF). Exclusion criteria were EF above 40%, significant valve pathology, or insufficient image quality for ventricular longitudinal measurements.

Twenty age-matched healthy controls without a history of, presence of, or medication for cardiovascular disease, diabetes, hypertension (blood pressure >140/90 mmHg), or other systemic disease, as well as absence of pathology on electrocardiography or CMR, were included for comparisons.

Study design and endpoints

This study was a predictive cohort study using a time-to-event analysis capable of including reoccurring events with a maximum of a 5-year follow-up. Dependent variables of interest were measurements of LV longitudinal function, specifically peak systolic AVPD and GLS, but also maximum atrioventricular plane velocities measured in systole, early diastole and during atrial contraction.

The primary endpoint was the composite of the following events: cardiovascular death, hospitalizations from HF, acute myocardial infarction (AMI), revascularization with percutaneous coronary intervention or coronary artery bypass surgery, heart transplantation, LV assist device implantation, hospitalization from cardiac arrest, sustained ventricular arrythmia or lung oedema. The secondary endpoint was defined as the number of events and accumulated length of hospital stay from events. The tertiary endpoint was the number of and accumulated length of hospital stay for HF hospitalizations.

Data acquisition

Cardiovascular magnetic resonance imaging was performed using three different clinical MRI-scanners: 1.5T Philips Achieva (Best, the Netherlands) (*n* = 276), 3T Philips Achieva (Best, the Netherlands) (*n* = 6) and 1.5T Siemens Aera (Erlangen, Germany) (*n* = 5).

Standard long-axis and short-axis cine images were acquired using steady-state free precession sequences which were used to measure ventricular longitudinal function variables and ventricular volumes. Late gadolinium enhancement (LGE) sequences for infarct and fibrosis assessments were used according to the clinical protocol.

Patients' data and biochemical laboratory results from 2003 to 2019 were gathered from electronic medical journals

and were collected as close to the CMR scan as possible although not longer than ±1 year from the CMR examination. Data on in-patient admissions, diagnoses and deaths were obtained from the Swedish National Board of Health and Welfare's Hospital and Cause of Death Registries. Events were recorded through algorithmic processing of all available in-patient admissions from pre-defined international classification of disease (ICD)-10 codes. The Appendix A provides a description of the algorithm used and Supporting Information, *Table S1* shows all ICD-10 codes.

Analyses of ventricular longitudinal function

Left ventricular volumes and longitudinal measurements were analyzed from cine images using the imaging analysis software Segment 2.2 (http://segment.heiberg.se).[17]

The ventricular longitudinal function variables consisted of three categories: GLS, AVPD and valve plane velocities. GLS was calculated using feature tracking in the long-axis images, with myocardial end-diastolic delineations as manual inputs.[18] The strain tracking was visually checked and reiterated after adjustment if incorrect. AVPD was measured in each long-axis image in a temporally-resolved manner using a semi-automatic tracking algorithm[19] with a previously described methodology.[6] In short, annotation points were placed at the highest myocardial point in each long-axis image yielding in total six positions around the atrioventricular plane. The maximum valve plane velocities were obtained from a velocity curve derived from the time-resolved atrioventricular plane curve at the following three cardiac phases: systole (LV s$\prime$), early ventricular filling (LV e$\prime$) and atrial systole (LV a$\prime$).

Statistical analysis

Normality of variables was visually assessed by histograms and descriptive statistics. Continuous data are presented as mean ± standard deviation or median and interquartile range. Categorical variables are presented with absolute numbers and valid percentages. Comparisons between groups were performed with student's t-test or ANOVA (least significant difference post-hoc test) for normally distributed variables and Mann–Whitney U or Kruskal–Wallis test for non-normally distributed variables. Categorical values were compared using the χ^2 test. Cumulative event probability curves are shown as Kaplan–Meier plots with the log-rank test for assessing differences stratified by tertiles. To display differences between groups with reoccurring event data we used the mean cumulative function (MCF),[20,21] which shows the mean number of events that patients in each group experienced at each point in time since the start of follow-up. The Wald statistic (β/standard error)^2 was used for dimensionless comparison between variables. To determine the prognostic relevance of different variables in univariate and multivariate analyses we used the Prentice, William & Peterson-Total time (PWP-tt) model.[22] PWP-tt is an extension of the standard Cox proportional hazards model that incorporates reoccurring events. Appendix A provides further statistical details. Statistical analyses were performed using SPSS v.27.0 (IBM Corporation, Armonk, NY, USA) and R v.4.0.3.

Results

Baseline characteristics of the study population

We identified 295 patients with HFrEF that underwent CMR. Eight patients were excluded from AVPD measurement due to poor image quality, resulting in 287 patients for the final analysis. Of these, we identified 4 cases of insufficient image quality for GLS measurements resulting in 283 patients for GLS measurements. The mean age was 62 years, 78% were male and mean LV EF was 26.5% (*Table 1*). The cause of heart failure was mostly ischaemic (59%) and 47% had a functional status of New York Heart Association classification (NYHA) III. The most common co-morbidities were presence or treatment for hypertension (37%), diabetes (23%) and history of atrial fibrillation or flutter (20%) as well as history of revascularization (39%), AMI (34%) or stroke (5%). Most patients (92%) were medicated with beta-blockers and renin-angiotensin-aldosterone-system inhibitors and 52% received specific aldosterone inhibitors.

Left-ventricular longitudinal function in HFrEF patients was low, as AVPD and GLS were approximately half the values of the age-matched control group (AVPD 7.8 ± 2.4 mm vs 15.3 ± 1.6 mm; GLS −7.5 ± 3.0% vs. −20.6 ± 2.0%; $P < 0.001$ for both), and correlated only moderately with EF (r = 0.65–0.66, *Figure 1*). Valve plane velocities in patients (LV s$\prime$ −3.5 ± 1.0 cm/s; LV e$\prime$ 3.6 ± 1.5 cm/s; LV a$\prime$ 3.3 ± 1.8 cm/s) were also lower than in healthy controls (LV s$\prime$ −6.2 ± 0.7 cm/s; LV e$\prime$ 6.4 ± 1.3 cm/s; LV a$\prime$ 5.2 ± 1.0 cm/s; $P < 0.001$).

Patients that experienced events had a higher degree of HF with ischaemic aetiology (Δ23%, $P < 0.001$) and more often presence of LGE (Δ11%, $P = 0.03$). They had more often prior AMIs (Δ19%, $P = 0.001$), larger left ventricles (increased EDV index Δ11 mL/m^2, $P = 0.02$; ESV index Δ15 mL/m^2, $P = 0.004$) and worse systolic function (lower EF Δ3.5%; LV s$\prime$ Δ0.4 cm/s; AVPD Δ1.2 mm and higher GLS Δ2%; $P < 0.004$ for all).

Number and length of events

There were 578 events in total for the 5-year follow-up and the majority were HF hospitalizations (n = 418). Other major events were revascularizations (n = 64), cardiovascular deaths

Table 1 Baseline characteristics for 287 HFrEF patients and CMR results

Baseline characteristics		No events (N = 132)	With events (N = 155)	P-value
Sex	Male	100 (76%)	125 (81%)	0.39
Age, years	Mean (SD)	61.4 (12.3)	61.9 (12.7)	0.77
Smoking (n = 255)	Yes	18 (15%)	27 (20%)	0.38
Aetiology of heart failure	ICM	61 (46%)	107 (69%)	**<0.001**
LGE presence	Yes	93 (71%)	127 (82%)	**0.03**
Hypertension	Yes	51 (39%)	54 (35%)	0.59
Diabetes	Yes	23 (17%)	43 (28%)	0.05
History of atrial fib. or flutter	Yes	23 (17%)	35 (23%)	0.35
NYHA class (n = 216)	NYHA I	10 (10%)	10 (9%)	0.26
	NYHA II	36 (35%)	27 (24%)	
	NYHA III	45 (44%)	56 (50%)	
	NYHA IV	12 (11%)	20 (17%)	
Prior stroke	Yes	6 (5%)	7 (5%)	0.99
Prior revascularization	Yes	49 (37%)	62 (40%)	0.71
Prior AMI	Yes	31 (24%)	66 (43%)	**0.001**
RAAS inhibitor (n = 261)	Yes	111 (92%)	125 (89%)	0.65
Beta-blocker (n = 261)	Yes	109 (90%)	132 (94%)	0.30
Aldosterone inhibitor (n = 258)	Yes	65 (54%)	68 (49%)	0.51
Diuretics (n = 261)	Yes	79 (65%)	93 (66%)	0.95
Device, ICD or CRT	Yes	81 (61%)	80 (52%)	0.12
NT-proBNP, ng/L (n = 170)	Median [IQR]	1010 [503–2200]	2210 [1180–4110]	0.13
eGFR, mL/min/1.73 m^2 (n = 254)	Mean (SD)	68.7 (18.4)	68.6 (22.0)	0.96
EDV index, mL/m^2	Mean (SD)	144 (44.0)	156 (42.4)	**0.02**
ESV index, mL/m^2	Mean (SD)	105 (41.4)	120 (41.8)	**0.004**
SV index, mL/m^2	Mean (SD)	38.7 (10.6)	36.9 (9.94)	0.15
Cardiac index, L/min/m^2	Mean (SD)	2.37 (0.85)	2.34 (0.64)	0.81
Ejection fraction, %	Mean (SD)	28.3 (7.78)	24.8 (7.93)	**<0.001**
GLS, % (n = 283)	Mean (SD)	−8.57 (3.25)	−6.60 (2.49)	**<0.001**
LV AVPD, mm	Mean (SD)	8.37 (2.55)	7.23 (2.20)	**<0.001**
LV sʹ, cm/s	Mean (SD)	−3.65 (1.01)	−3.30 (0.99)	**0.004**
LV eʹ, cm/s	Mean (SD)	3.73 (1.56)	3.42 (1.49)	0.09
LV aʹ, cm/s	Mean (SD)	3.46 (1.78)	3.23 (1.76)	0.27

Number of patients with available data are shown in parentheses, and bold numbers indicate statistical significance.
ICM, ischaemic cardiomyopathy; NICM, non-ischaemic cardiomyopathy; LGE, late gadolinium enhancement; NYHA, New York Heart Association; AMI, acute myocardial infarction; RAAS, renin angiotensin aldosterone system; ICD, implantable cardioverter-defibrillator; CRT, cardiac resynchronizing therapy; NT-proBNP, n-terminal pro brain natriuretic peptide; IQR, interquartile range; eGFR, estimated glomerular filtration rate; EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume; GLS, global longitudinal strain; LV, left-ventricular; AVPD, atrioventricular plane displacement.

(n = 40) and myocardial infarctions (n = 21). Out of all HFrEF patients, 155 (54%) experienced at least one event (mean 2 events, range 0–64). Of these patients, 119 (71%) had 3 events or fewer and the first three events comprised 51% of all events (295 events). By only the first event, patients in tertiles with the lowest AVPD or GLS had significantly higher probability of experiencing events (*Figure 2*). By the first three events, the MCF stratified by AVPD and GLS tertiles showed that patients in the bottom tertile (<6.8 mm or >−6.1%) experienced on average over 3 times as many events in a five-year period as patients in the top tertile (>8.8 mm or <−8.4%, P < 0.001) (*Figure 3*). More specifically, patients in the lowest tertiles of AVPD and GLS suffered more cardiovascular deaths (P < 0.05), HF hospitalizations (P = 0.001), and AMIs (only GLS, P = 0.032) (Supporting Information, *Table S2A,B*), and accumulated longer in-hospital length-of-stay (AVPD 20.9 vs. 9.1 days; GLS 22.4 vs. 6.5 days; P = 0.001 for both) and HF hospitalizations (AVPD 19.3 vs.

8.3 days; GLS 19.3 vs. 5.4 days; P = 0.001 for both) than those in the highest tertiles (Supporting Information, *Table S3A,B*).

Univariate predictors of events

The first three reoccurring events were analyzed with PWP-tt. Predictors with the highest univariate prognostic relevance were ventricular longitudinal function variables (AVPD hazard ratio (HR) 1.14 per-mm-decrease; GLS HR 1.14 per-%-increase; LV sʹ HR 1.3 per-cm/s-decrease) and EF (HR 1.18 per-5%-decrease) (*Table 2*). Other important predictors associated with higher incidence of events were higher LV end-systolic and end-diastolic volume index, hyponatremia (<135 mmol/L), higher NYHA classification, ischaemic aetiology, presence of LGE, higher levels of N-terminal pro brain natriuretic peptide, and male sex.

Figure 1 Plot showing moderate to good (*r* = 0.65–66) correlations between ventricular longitudinal function measurements [atrioventricular plane displacement (AVPD), global longitudinal strain (GLS)] and ejection fraction (EF). The correlation between AVPD and GLS was stronger at *r* = −0.76.
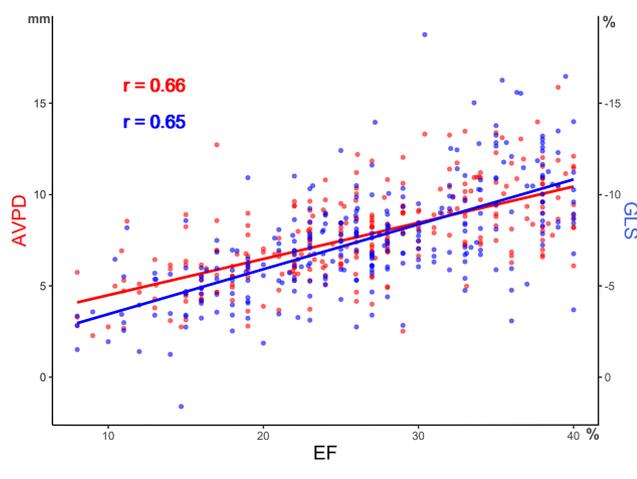
Multivariate predictors of events

Both AVPD and GLS remained in their final multivariate models after the variable selection process, establishing their independence as relevant predictors for the combined endpoint with hazard rate ratios of 1.12 per-mm-decrease for AVPD and 1.13 per-%-increase for GLS. For AVPD, final covariates were hyponatremia (<135 mmol/L), aetiology of HF and LV end-diastolic volume index. Final covariates along with GLS were hyponatremia and aetiology of HF (*Table 3*). Inclusion of AVPD and GLS in the final models yielded incremental predictive value compared with reduced models (likelihood ratio test: AVPD $\chi^2(1)$ = 16.8; GLS $\chi^2(1)$ = 30.6, both $P < 0.001$) but only GLS displayed significant discriminatory value assessed with concordance index [AVPD 0.60 (95% CI 0.56–0.64) to 0.62 (95% CI 0.58–0.66); GLS 0.58 (95% CI 0.54–0.62) to 0.63 (95% CI 0.59–0.67)] (*Table 4*).

Discussion

This study shows that ventricular longitudinal function measured as AVPD or GLS with CMR has independent prognostic value for cardiovascular mortality and morbidity in a HFrEF population. AVPD and GLS are associated with increased number of HF-associated events as well increased length of hospital stay. The outcome is primarily driven by HF hospitalizations. The use of longitudinal functional measures such as AVPD or GLS is thus of value even in patients with severely reduced EF.

Prognostic importance of ventricular longitudinal function

Several prior studies have shown that ventricular longitudinal function assessed by echocardiography or CMR can predict adverse outcome in broad patient populations[12,14–16] as well as in specific non-HFrEF patient groups—for example, idiopathic heart failure,[23] acute heart failure,[24] hypertension,[25] in individuals without current, or history of, heart disease,[26] and in the general population.[27] The novelty of the present study is that we demonstrate the strong prognostic values to predict mortality and morbidity for AVPD and GLS in patients with HFrEF and use a statistical method that takes into account reoccurring events. Unlike mortality which is a clearly defined endpoint, morbidity is not. Nonetheless, morbidity is an important aspect of the cumulative burden of heart failure and contributes greatly to the reduction of patient quality of life and has significant health care costs. We therefore included more diagnoses than the common triplet of cardiovascular adverse events: death, HF hospitalization, and AMI (see Appendix A for full list).

Our concordance indices are consistent with the average number of 0.63 found in a systematic review of predictive models in HF.[28] This number is only moderately successful but ventricular longitudinal function variables were the most valuable predictors among the other well-known risk factors. AVPD and GLS are therefore likely valuable tools for the prediction of outcome throughout the HF spectrum.

The predictive ability of valve plane velocities from standard cine images was moderate as they only univariately predicted outcome. Patients with events had lower maximum systolic velocities but no difference could be seen between the diastolic estimates. The HFrEF patients in our study are likely better separated with systolic measurements because systolic dysfunction is their primary cause of HF and morbidity. However, valve plane velocity measurements from CMR may have beneficial contributions in HF with preserved EF, where diastolic dysfunction is an important part of the pathophysiology. The prognostic implications of measuring valve velocities may also be greater when using CMR techniques with higher frame rate closer to tissue Doppler echocardiography.[29]

Echocardiography remains the primary imaging method for assessing heart failure, and choosing the right patients for CMR is important. The 2021 ESC guideline gives a Class I recommendation to investigate ventricular function by CMR in patients with poor acoustic windows or need of tissue characterization in infiltrative or inflammatory cardiomyopathies.[30] CMR is also recommended (Class IIa) to distinguish between ischaemic and non-ischaemic myocardial damage, as carried out in the current study.

Figure 2 Cumulative event plot according to Kaplan–Meier of AVPD (A) and GLS (B) tertiles, generated from only the first event. There was a higher probability of experiencing an event for patients in tertiles with the lowest ventricular longitudinal function (AVPD, *P* = 0.01; GLS, *P* < 0.0001). The number of patients in each tertile still remaining in the study for each year is shown as 'Number at risk'.
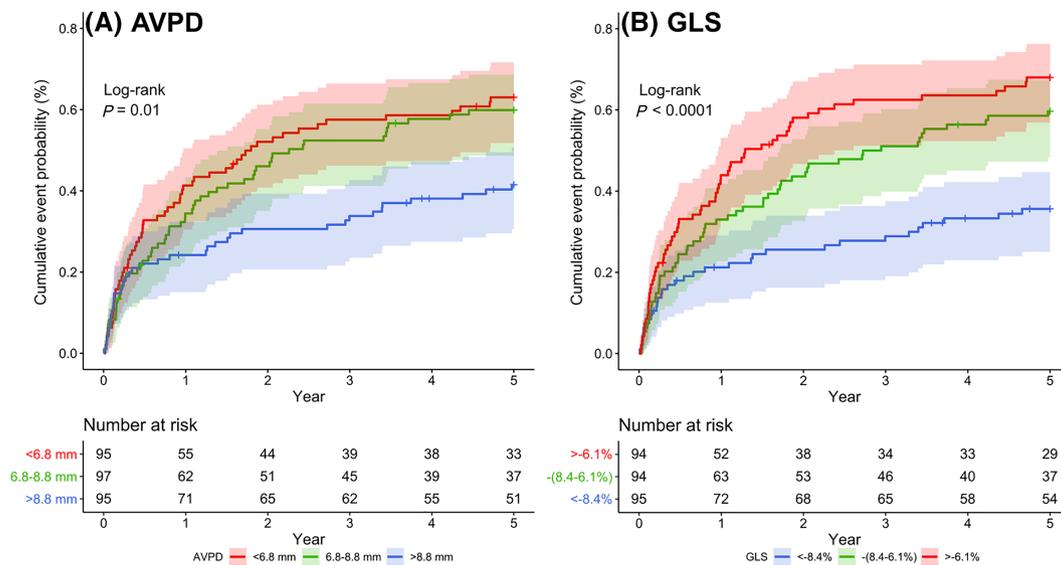

Figure 3 Mean cumulative function (MCF) of events by tertiles of (A) atrioventricular plane displacement (AVPD) and (B) global longitudinal strain (GLS). The horizontal axes show the time since the study entry and the vertical axes show the average number of events an individual had experienced during follow-up. Each colour displays the MCF and predicted confidence intervals for each tertile. On average, a patient in the lowest tertile of ventricular longitudinal function (red) had over 3 times as many events during follow up compared with the highest tertile (blue). *Two-sample pseudo-score test, variance estimator: Poisson.
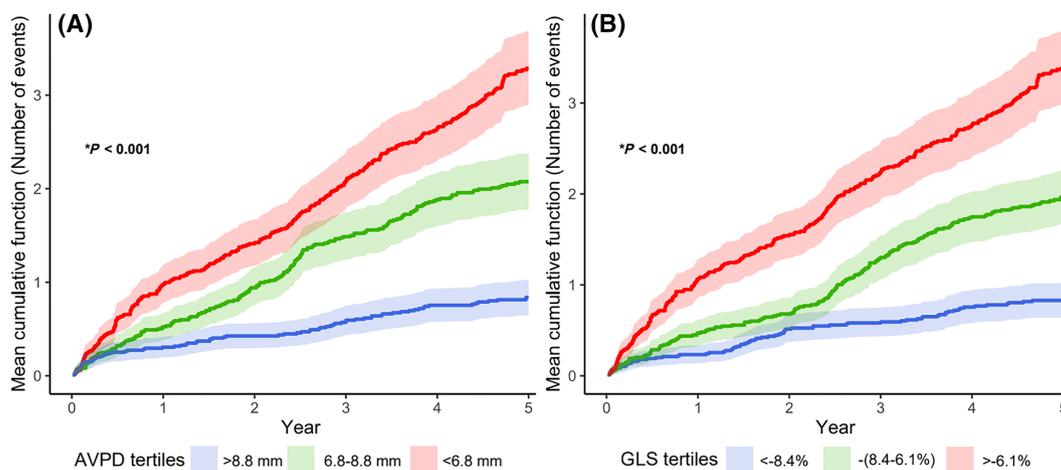
Ventricular longitudinal function in heart failure

Ventricular shortening and lengthening are reflected in both the amplitude and velocity of AVPD and GLS. The fundamental difference between the two is that GLS is a measure of myocardial deformation in the longitudinal direction while AVPD is a measure of the results of myocardial deformation on the atrioventricular plane. Both of these parameters are directly linked to both systolic and diastolic performance.[31] Decreased systolic and diastolic function cause HF, through decreased cardiac output and myocardial stretch leading to neurohormonal activation and pulmonary congestion which are sources of clinical symptoms and deterioration. This can explain why longitudinal pumping in HFrEF has prognostic

Table 2 Univariate analysis according to PWP-tt (up to third event, 295 events in total)

Variables	HR	95% CI	Wald	*P*-value
LGE presence	1.56	1.14–2.13	7.82	0.005
Aetiology of heart failure, ICM	1.54	1.19–1.98	9.99	0.002
Sex, male	1.56	1.15–2.11	8.33	0.004
NYHA	1.33	1.12–1.57	11.14	0.001
Prior stroke	1.33	0.76–2.33	1	0.317
Prior revascularization	1.14	0.89–1.47	1.05	0.305
Atrial fib or flutter	1.23	0.92–1.65	1.95	0.162
Hypertension	0.92	0.71–1.19	0.38	0.538
Diabetes	1.37	1.04–1.79	5.1	0.024
Smoking	0.78	0.57–1.06	2.54	0.111
Hyponatremia, <135 mmol/L	1.88	1.34–2.65	13.15	<0.001
Age, 10 years	1.08	0.97–1.2	2.04	0.153
NT-proBNP, log (ng/L)	1.72	1.22–2.43	9.46	0.002
eGFR, mL/1.73m^2	0.98	0.91–1.05	0.42	0.517
LV EDV index, 10 mL/m^2	1.05	1.02–1.08	10.97	0.001
LV ESV index, 10 mL/m^2	1.06	1.03–1.09	14.19	<0.001
LV SV index, 10 mL/m^2	0.94	0.82–1.07	1.01	0.316
Cardiac index, L/min/m^2	0.97	0.75–1.26	0.05	0.821
Ejection fraction, 5%	1.18	1.1–1.27	19.07	<0.001
LV AVPD, mm	1.14	1.09–1.21	24.92	<0.001
GLS, %	1.14	1.1–1.19	38.54	<0.001
LV s*ı*, cm/s	1.3	1.13–1.49	14.23	<0.001
LV e*ı*, cm/s	0.86	0.79–0.95	9.84	0.002
LV a*ı*, cm/s	0.9	0.84–0.97	7.64	0.006
BMI	0.98	0.96–1.01	1.54	0.215

LGE, late gadolinium enhancement; ICM, ischaemic cardiomyopathy; NYHA, New York Heart Association; NT-proBNP, N-terminal pro brain natriuretic peptide; eGFR, estimated glomerular filtration rate; LV, left-ventricular; EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume; GLS, global longitudinal strain; AVPD, atrioventricular plane displacement; BMI, body mass index.

Table 3 Multivariate analysis according to PWP-tt (forward selection)—up to the third event

| Variables | Multivariate stepwise | | | |
	HR	95% CI	Wald	*P*-value
GLS				
LV GLS, %	1.13	1.09–1.18	32.96	<0.001
Hyponatremia, <135 mmol/L	1.8	1.28–2.53	11.59	0.001
Aetiology of heart failure, ICM	1.51	1.17–1.95	8.51	0.004
AVPD				
LV AVPD, mm	1.12	1.06–1.18	15.28	<0.001
Hyponatremia, <135 mmol/L	2.01	1.48–2.72	20.03	<0.001
Aetiology of heart failure, ICM	1.73	1.34–2.26	14.19	<0.001
LV EDV index, 10 mL/m^2	1.05	1.01–1.08	8.42	0.004

GLS, global longitudinal strain; ICM, ischaemic cardiomyopathy; AVPD, atrioventricular plane displacement; LV, left-ventricular; EDV, end-diastolic volume.

implications for cardiovascular mortality and morbidity measured as increased rate and occurrence of events, as well as longer hospital stay.

Statistical considerations for outcome studies in heart failure

Standard survival analyses ignore data beyond the first event. In patients with HF however there is a large difference in morbidity between a patient with only one hospitalization and a patient having reoccurring frequent hospitalizations. Therefore, it could be misleading to use conventional survival analyses methods to analyses diseases where non-fatal events such as HF and hospitalizations are common. More research including reoccurring events in HF is warranted, as stated by the Heart Failure Association of the European Society of Cardiology.[32] An additional benefit of including more than one event is increased statistical power, resulting in substantially lower sample size needed compared with conventional 'time to first event' analyses. Several methods for analyzing reoccurring events have been proposed.[33,34] We used the PWP-tt model (Appendix A) that allows the baseline hazard to change between events, which is advantageous because (i) the risk of mortality increases by every hospitalization in HF[35]; (ii) the sequence of events is taken into consideration; and (iii) there are similarities in interpretation with the standard Cox proportional hazards model (unlike

Table 4 PWP-tt – model fit – (forward selection)—up to the third event

	Likelihood ratio test		Concordance index (95% CI)
	χ^2	*P*-value	
AVPD			
Model without AVPD	Reference	Reference	0.60 (0.56–0.64)
AVPD	16.83	<0.001	0.62 (0.58–0.66)
GLS			
Model without GLS	Reference	Reference	0.58 (0.54–0.62)
GLS	30.6	<0.001	0.63 (0.59–0.67)

AVPD, atrioventricular plane displacement; GLS, global longitudinal strain.

count regressions and more advanced methods such as multi-state models). By using a reoccurring event analysis, the number of events included in the analysis increased from 155 in a standard Cox proportional hazards model to 295 events for our analysis.

We ascribed the same value to cardiovascular death as any other event in our composite endpoint. This is definitely an erroneous assumption but is also the case when using the standard Cox PH model and not isolated to PWP-tt. Another side-effect of analyzing reoccurring events in combination with a terminal event such as cardiovascular death is that such occurrence stops the counting process. Thus, a patient that experiences an early terminal event may experience fewer events in total. This is likely to have a small effect on our results as only 27 out of 295 (9%) events for the three strata comprised cardiovascular deaths.

Non-cardiovascular predictor of outcome

Hyponatremia (serum sodium <135 mmol/L) independently predicted events in our study. Hyponatremia is the most common electrolyte abnormality in HF and it marks the dilution of sodium from excessive water retention.[36] Our finding is in line with a review of 117 predictive heart failure models including 249 variables, where the most frequently used variables with the highest predictive values (Odds ratios or Hazard ratios) were sodium and blood urea nitrogen.[28]

Study considerations and limitations

We employed a feature-tracking algorithm to calculate GLS from standard cine images. Other ways of measuring strain with CMR such as tagging,[37] displacement encoding with stimulated echoes 'DENSE',[38] strain-encoding 'SENC'[39] and most recently fast-SENC 'fSENC'[40] require specialized pulse sequences. These methods are probably more accurate and precise than strain from feature-tracking, especially for segmental values, but it appears that feature-tracking is adequate for assessment of global strain values[41] and is therefore more widely used. On the other hand, AVPD can be quantified even more easily without specialized analysis software and can be applied to essentially all sequences and mo-

dalities with cine imaging of a heartbeat in the longitudinal axis. Most importantly, this study shows that measuring the excursion of the basal portion of the ventricle as a proxy for global longitudinal function has a similar predictive ability as GLS for morbidity.

It has been shown that GLS by echocardiography has prognostic merit in HFrEF patients.[11,12] However, it is not clear that measuring ventricular longitudinal function by one modality has a better predictive value over the other. Unfortunately, we do not have sufficient data to perform a comparative analysis between CMR and echocardiography. However, we find it unlikely that adding GLS by CMR would add prognostic value to a GLS measured prior on an echocardiography examination with adequate image quality.

The role of AVPD/MAPSE in echocardiography has been replaced by GLS partly because the reproducibility of MAPSE has been questioned. Using CMR we found a lower intra and interobserver variability of AVPD [intra class correlation (ICC): 0.95–92; coefficient of variation (CoV): 10–13%] compared with GLS (ICC 0.90, CoV: 19%).[13] Recently, an artificial intelligence approach to automated measurements of CMR AVPD showed higher reproducibility and prognostic value than manual GLS.[42] This could accelerate the clinical adoption of ventricular longitudinal function measurements henceforth.

Selection and referral bias
Because subjects were included from patients referred for CMR, we have limited knowledge of the referral bias. This may limit the generalizability of the results to the general HFrEF patient population, particularly regarding atrial fibrillation, renal failure, and implanted devices. This may partly explain why these variables do not predict events in our study.

Medication
Our study participants were included prior to widespread use of sodium-glucose co-transporter-2 'SGLT2' inhibitors and neprilysin inhibitors that have been effective in reducing hospitalizations and mortality in HF patients.[1] Potentially, the number of events would have been lower in our cohort with these medications. Also, we did not take into account possible changes in prescribed medications during the follow-up period which may alter the course of disease. However, our patient cohort did have a high degree of guideline indicated medication and device implantation for HF with no difference

between patients with and without events. This suggests that most patients already were on appropriate HF therapy and substantial changes are therefore less likely.

Conclusions

Atrioventricular plane displacement and GLS are independent predictors of cardiovascular morbidity and mortality. Furthermore, low ventricular longitudinal function is associated with an increased number of events as well as longer in-hospital stay. We suggest that ventricular longitudinal function is a valuable measure in HFrEF patients to predict patients at higher risk of cardiovascular mortality and morbidity.

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Conflict of interest

J. Berg and K. Solem are employees of Syntach AB. Dr. Carlsson contributed to this article as an employee of Lund University. The views expressed are his own and do not necessarily represent the views of the National Institutes of Health or the United States Government.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. shows all ICD-10 codes generating events and co-morbidities.
Table S2A. Number of events - AVPD tertiles.
Table S2B. Number of events - GLS tertiles.
Table S3A. Length of Stay (days) – AVPD tertiles.
Table S3B. Length of Stay (days) – GLS tertiles.

Appendix A.

A.1 Statistical details

Prentice, William & Peterson—total time (PWP-tt) is an extension of the standard Cox proportional hazards model to incorporate reoccurring events by stratifying the model with an event sequence indicator and connecting patients in different strata using a cluster parameter. The risk set is constructed such that an individual is only under risk for event number 'k' after having experienced event 'k-1'. In most cases, the number of individuals and events in subsequent stratum reduces significantly with increasing number of strata. As the statistical power predominantly is coupled to the number of events in each stratum, there is often a need for truncation of the dataset to mitigate this risk. The number of strata should be chosen specifically for each study with this in consideration. We chose to truncate our data to the first three events to avoid inflating the risk of type-II error.

Differences between mean cumulative function (MCF) curves were tested with two-sample pseudo-score tests (variance estimator: Poisson). Multicollinearity between variables was assessed with Pearson's linear regression coefficients with a cut-off value for inclusion to final multivariate models chosen as <0.8. Variables with missing values $>5\%$ were omitted from multivariate models due to the depleting effect on sample size.

After the initial tests, three steps were taken to arrive at multivariate models. First, univariate hazard ratios (HR) of the association between dependent variables, covariates and events were calculated. Second, two separate multivariate models were produced using forward selection for (i) atrioventricular plane displacement (AVPD), and (ii) global longitudinal strain (GLS), starting with the variable with maximum Wald statistic and adding all univariate predictors of events with a P-value <0.1 in a stepwise manner ranked by the Wald statistic, keeping only the variables that remained significant after inclusion ($P < 0.05$). Third, proportional hazards assumptions were assessed with the scaled Schoenfeld residuals. The final predictive models were compared with nested models without AVPD and GLS, respectively, via the likelihood ratio test. Lastly, the final models' discriminatory abilities were assessed with the concordance index.

A.2 On selecting a reoccurring event model

Survival analyses are important tools for evaluating therapies, effect of exposures and biomarkers alike. Survival data is rarely normally distributed and needs special consideration to appropriately deal with individuals that have not had an

event, that is, censoring, because these individuals have an unknown time-to-event. Analysis if survival and time-to-event data has become synonymous with Kaplan–Meier and Cox-regression PH 'semi-parametric' model. While widely used and useful, they were developed to deal with a single event and are most suitable for the analysis of terminal events. When a patient experiences a non-terminal event, such as HF hospitalization, they are not considered at risk for any additional event and data beyond that event is ignored.

Balancing the number of strata and events: PWP-tt can be seen as an extension of the standard Cox PH model stratified according to an event sequence indicator. Because the PWP-tt model tries to fit the best estimates of covariates along all strata, it is necessary to have sufficient numbers of patients, events and ultimately statistical power in the final few strata to avoid inaccurate models. While PWP-tt is a promising tool for assessing the repeated nature of certain types of diseases by allowing the baseline hazard to change with sequential events and returning event-specific hazard rate ratios of covariates, the full potential of this approach is even better appreciated with a higher number of events and patients.

Inclusion bias in outcome studies: Outcome studies using non-terminal events, including within the imaging research field, are often subject to a stochastic inclusion pattern. More concretely, a patient's inclusion may not be tied to a particular stage in the disease progression but to a relatively random referral process. Following this, patient A might not have had a hospitalization for years and patient B might just have been discharged from the hospital, two completely separate underlying risk scenarios. This effect is averaged out by an increasing number of patients and events. Reoccurring event analysis can mitigate this effect by increasing the number of events and by better temporal matching between patients' events, yielding more accurate hazard estimates.

A.3 Registry data analysis

The Swedish National Board of Health and Welfare's Hospital Registry and Cause of Death Registry offers detailed data on outcomes. To handle the large number of data entries, we developed an algorithm for data extraction in MATLAB (R2019a. Natick, Massachusetts: The MathWorks Inc. United States). The working principle of the algorithm was to search through each patient's available hospital admissions spanning the available years (2003–2018), and extract the information of interest within the timespan between the date of the CMR exam and the 5-year follow-up end date. The CMR acquisition dates are used as a starting date for each patient. A list of the event categories and associated ICD-10 codes are used by the algorithm for finding events and categorizing them into one of the subcategories. Heart failure morbidity is made up of several categories of cardiovascular diagnoses and procedures associated with heart failure (Supporting Information, *Table S1*). Each category's events are collated with the main diagnosis, time-to-event and the total accumulated days of hospital length of stay. The event data used for time-to-event analyses are selected from the earliest event encountered in the different categories. Special considerations were taken with adjacent hospitalizations. Namely, when two or more hospitalizations are immediately adjacent (the end of the first event is within a day of the beginning of the second event), they are combined. Otherwise, a new event would be created if a patient is transferred from one hospital facility to another. Without combing adjacent hospitalizations, the algorithm which has the aim of only counting unique events, would falsely count several events instead of one even if the main diagnoses were the same. The end of follow-up was five years after CMR at which the patients that had not yet encountered an event were right-censored. Data on co-morbidities were searched for in all available hospitalizations prior to the CMR date, and dichotomized.

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