Ratio of Transmitral Early Filling Velocity to Early Diastolic Strain Rate as a Predictor of Cardiovascular Morbidity and Mortality Following Acute Coronary Syndrome

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The ratio of early mitral inflow velocity (E) to early diastolic strain rate (E/e'sr) is a significant predictor of cardiac outcomes in various patient populations. This study aims to evaluate the predictive value of E/e'sr for heart failure, acute myocardial infarction, and death due to cardiovascular disease following acute coronary syndrome (ACS). In total, 432 ACS patients underwent echocardiography following percutaneous coronary intervention. The end point was the composite of heart failure, acute myocardial infarction, and death due to cardiovascular disease. Median follow-up was 4.4 (interquartile range 0.2 to 6.3) years. During the follow-up period, 199 (46.1%) met the composite outcome. Mean value of E/e'sr in patients was 0.70 ± 0.37 m. In univariable Cox regression, E/e'sr was a predictor of the composite outcome (hazard ratio [HR] 1.05 95% confidence interval [CI] 1.03 to 1.07, p <0.001, per 0.10 m increase). After multivariable adjustment for demographic and clinical parameters, E/e'sr remained an independent predictor (HR 1.03; 95% CI 1.01 to 1.06; p = 0.013, per 0.10 m increase). Global longitudinal strain (GLS) modified the relation between E/e'sr and outcome (p value for interaction = 0.011). In ACS patients with a relatively preserved systolic function assessed by GLS (GLS ≥ 13.2%), E/e'sr showed to be a significant predictor (HR 1.20; 95% CI 1.06 to 1.36; p = 0.005, per 0.10 m increase). In contrast, E/e'sr was not a significant predictor in ACS patients with impaired systolic function (GLS < 13.2%; HR 1.02; 95% CI 0.99 to 1.04; p = 0.28). In conclusion, E/e'sr provides important prognostic information regarding cardiovascular morbidity and mortality in ACS patients. However, E/e'sr was not an independent predictor over that of echocardiographic parameters. Furthermore, E/e'sr is a stronger prognosticator in patients with relatively preserved systolic function as opposed to patients with impaired systolic function. **(Am J Cardiol 2019;123:1776−1782)**

Serious adverse complications are observed in patients with acute coronary syndrome (ACS) including heart failure (HF) and acute myocardial infarction (AMI), both being associated with increased morbidity and mortality.[1] In order to improve the prognosis for ACS patients, it is important to identify high-risk patients to intervene with treatment and close monitoring at an early point. Early in the pathogenesis of HF, patients can develop asymptomatic left ventricular (LV) dysfunction caused by structural and/or functional cardiac abnormalities which act as precursors of HF.[2−5] E/e' as a measure of LV filling pressure has been used to evaluate diastolic dysfunction and has proved to be an important predictor of major adverse events in various populations.[6−8]

However, E/e' is subject to certain technical limitations.[9] Ratio of transmitral early filling velocity (E) to early diastolic strain rate (E/e'sr) has been suggested as a novel measure of LV filling pressure.[10−13] Previous studies have shown a strong correlation between E/e'sr and invasively measured LV filling pressure.[10−12] We have previously found E/e'sr to be a stronger predictor of cardiovascular morbidity and mortality in subjects with preserved systolic function as assessed by global longitudinal strain (GLS) as opposed to subjects with reduced GLS in a large general population study.[13] The purpose of this study was to investigate the prognostic importance of E/e'sr in a large cohort of patients suffering from ACS.

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Methods

This was a retrospective study based on 580 consecutive ACS patients (ST-segment elevation myocardial infarction [STEMI], non-ST-segment elevation myocardial infarction [NSTEMI], or unstable angina pectoris [UAP]) admitted to Copenhagen University Hospital Gentofte, Denmark, for percutaneous coronary intervention (PCI) from January 2003 to November 2008 and included in a clinical registry. All patients with an echocardiogram available were qualified to enter the study. The included 580 patients underwent an extensive echocardiogram performed (median: 2 days [1 to 3days]) after the PCI procedure. A more detailed description is available in the Supplementary material page 2. Of the 580 patients, 120 were excluded due to nonsinus rhythm or missing images or missing Doppler measurements. An additional 28 were excluded due to inadequate image quality for speckle tracking leaving 432 to be included in this study.

The Danish National Board of Health's National Patient Registry was used to obtain information regarding outcomes (development of HF and AMI) using International Classification of Diseases (ICD) 10 codes. Information regarding mortality outcomes was obtained from the Danish Register of Causes of Death. These registers have previously been found to be very reliable for outcome ascertainment.[14] Additionally, information regarding coronary revascularization was obtained to differentiate it from the composite outcome of the study. Patients were censored at the time of meeting the first event. Follow-up was 100%. Competing-risks regression models were used to account for noncardiovascular death as a competing risk to the composite outcome (our event of interest).

Conventional echocardiography and color TDI were performed as has been previously described.[15] A detailed description is available in the Supplementary material, page 2.

Two-dimensional speckle tracking was performed in the 4-,2-, and apical long-axis projections with the highest available frame rate. A semiautomatic function was used to make the region of interest cover the thickness of the myocardial wall. The region of interest was adjusted manually by the investigator in cases of inaccurate tracing. A total of 18 segments, 6 from each projection were included. Global values were calculated as the mean of all segments. Segments could be excluded if considered untraceable. Global longitudinal systolic strain was expressed as an absolute value. Global e'sr was calculated as the mean of all segments and E/e'sr was calculated as E velocity (m/s) divided by e'sr (s − 1). We were able to show good intra- and interobserver variability of both E/e'sr and E/e' with a small bias (E/e'sr: mean difference ± 1.96 SDs was 0.04 ± 0.23 for the intraobserver analysis and 0.06 ± 0.37 for the interobserver analysis, and E/e': mean difference ± 1.96 SDs was −0.02 ± 0.25 for the intraobserver analysis and 0.04 ± 0.31 for the interobserver analysis).

Statistical significance was defined as a two-tailed $p \leq 0.05$. Baseline demographic, clinical, and echocardiographic data were compared with trend tests using linear regression for continuous Gaussian distributed variables. An extension of the Wilcoxon rank-sum test[16] was used for non-Gaussian distributed continuous variables. Chi-square test for trend for proportions was used for categorical variables. Rates of events were calculated as the number of events divided by person-time at risk. Differences in variables stratified according to the outcome are shown in Supplementary Table 1. Estimated incidence rates were constructed with a Poisson model. The association between the predictor of interest (E/e'sr) and the composite outcome was examined using restricted cubic splines with a best fit with 2 knots. Uni- and multivariable Cox proportional hazard models were used to investigate associations between baseline, clinical, and echocardiographic variables with the risk of meeting the composite outcome. TAPSE was missing in 58 (12%) of the patients and was therefore excluded as a variable in the multivariable Cox regressions model. Kaplan-Meier curves were created for the cohort stratified according to tertiles of E/e'sr. Harrell's C-statistics was used to investigate the incremental value of E/e'sr when added to a model containing demographical, clinical, and echocardiographic variables. Analyses were performed using STATA Statistical Software, Release 13 (College Station, TX: StataCorp LP).

Results

Baseline data stratified by tertiles of E/e'sr are presented in Table 1. Mean age of the study sample was 65.5 ± 12.1 years, and 73.8% were male (Table 1). During a median follow-up time of 4.4 (interquartile range 0.2 to 6.3) years, 160 patients were admitted due to HF, 52 were admitted due to AMI, and/or 30 died due to CVD. A total of 199 patients (46.1%) met the composite outcome. The mean E/e'sr ratio was 0.70 ± 0.37 m. In univariable Cox regression analysis, E/e'sr was a significant predictor of the composite outcome (hazard ratio [HR] 1.04; 95% confidence interval [CI] 1.03 to 1.07; $p < 0.001$, per 0.10 m increase; Table 2). This was also the case for E/e' (HR 1.06; 95% CI 1.03 to 1.09; $p < 0.001$, per 1 unit increase). A decrease of event-free survival was observed with increasing tertiles of E/e'sr (Figure 1). After multivariable adjustment for demographic and clinical parameters, age, gender, BMI, previous CVD, family history of CVD, diabetes mellitus, smoking status, hypercholesterolemia, systolic and diastolic blood pressure, heart rate, previous STEMI, multivessel disease, LAD occlusion, and left main stem coronary artery occlusion, E/e'sr remained an independent predictor of the composite outcome (HR 1.03; 95% CI 1.01 to 1.06; $p = 0.013$). This was also true for E/e' (HR 1.04; 95% CI 1.00 to 1.08; $p = 0.037$). In competing risks regression analysis with noncardiovascular death as the competing event, similar results were found (Supplementary Table 2). However, when other echocardiographic predictors (LVEF, LVMI, DT) were included in the model, neither E/e'sr nor E/e' remained as significant predictors of the composite outcome (E/e'sr: HR 0.99; 95% CI 0.95 to 1.04; $p = 0.79$) and (E/e': HR 0.99; 95% CI 0.95 to 1.05; $p = 0.99$).

GLS significantly modified the relation between E/e'sr and outcome (p for interaction = 0.011; Figure 2). In patients with high GLS (GLS ≥ 13.2%; patients with GLS values above the median of the population) E/e'sr was a strong predictor of the composite outcome in a univariable

Table 1
Baseline data

Variable	Tertile			
E/e'sr (m)	All 0.70 ± 0.37	1st <0.54	2nd 0.54-0.73	3rd >0.73	p Value
	(n = 432)	(n = 144)	(n = 144)	(n = 144)	
Age (years)	65.5 ± 12.1	61.9 ± 11.2	64.3 ± 11.5	70.1 ± 12.3	<0.001
Male gender	319 (73.8%)	115 (79.9%)	107 (74.3%)	97 (67.4%)	0.054
Systolic Blood Pressure (mm Hg)	138 ± 26	137 ± 24	135 ± 27	141 ± 26	0.11
Diastolic blood pressure (mm Hg)	82 ± 16	82 ± 16	81 ± 18	82 ± 15	0.97
Heart Rate (beats per minute)	74 ± 15	72 ± 13	74 ± 14	76 ± 17	0.027
BMI (kg/m^2)	26.5 ± 4.3	25.7 ± 3.9	26.8 ± 4.1	27.1 ± 4.8	0.012
Body surface area, (m^2)	2.0 ± 0.2	2.0 ± 0.2	2.0 ± 0.3	1.9 ± 0.2	0.90
Hypertension	184 (42.6%)	56 (38.9%)	62 (43.1%)	66 (45.8%)	0.49
Diabetes	41 (9.5%)	8 (5.6%)	13 (9.0%)	20 (13.9%)	0.053
Family history of heart disease	130 (30.1%)	50 (34.7%)	40 (27.8%)	40 (27.8%)	0.33
Prior cardiovascular disease	42 (9.7%)	7 (4.9%)	16 (11.1%)	19 (13.2%)	0.046
Current smokers	199 (46.1%)	75 (52.1%)	64 (44.4%)	60 (41.7%)	0.19
Hypercholesterolemia	106 (24.5%)	22 (15.3%)	50 (34.7%)	34 ± (23.6%)	<0.001
Acute coronary syndrome					
STEMI	323 (74.8%)	103 (71.5%)	112 (77.8%)	108 (75.0%)	0.47
NSTEMI and/or UAP	109 (25.2%)	41 (28.5%)	32 (22.2%)	36 (25.0%)	0.47
Multivessel lesion	28 (6.5%)	8 (5.6%)	12 (8.3%)	8 (5.6%)	0.54
Culprit lesion:					
Left anterior descending	216 (50.0%)	81 (56.2%)	55 (38.2%)	80 (55.6%)	0.002
Circumflexa	60 (13.9%)	16 (11.1%)	24 (16.7%)	20 (13.9%)	0.39
Right coronary artery	154 (35.6%)	47 (32.6%)	64 (44.4%)	43 (29.9%)	0.023
Left main stem	2 (0.5%)	0 (0%)	1 (0.7%)	1 (0.7%)	0.61
Echocardiography					
Interventricular septal thickness (cm)	1.1 ± 0.2	1.0 ± 0.2	1.0 ± 0.2	1.1 ± 0.2	0.017
Left ventricular internal diameter (cm)	4.9 ± 0.6	4.8 ± 0.4	4.9 ± 0.6	5.0 ± 0.6	0.097
Left ventricular posterior wall thickness(cm)	1.0 ± 0.2	0.9 ± 0.2	1.0 ± 0.2	1.0 ± 0.2	0.001
Left ventricular mass index (g/m^2)	90.1 [76.6-106.2]	85.0 [72.3-96.6]	89.9 [76.1-108.9]	98.0 [84.6-111.8]	<0.001
Left ventricular ejection fraction (%)	41.3 ± 11.5	45.0 ± 10.0	43.0 ± 10.6	36.0 ± 12.0	<0.001
E/A-ratio	1.1 ± 0.4	1.0 ± 0.3	1.1 ± 0.4	1.1 ± 0.5	0.004
Deceleration time (ms)	170.9 ± 46.2	177.1 ± 45.7	170.9 ± 42.4	164.6 ± 50.0	0.071
e' (cm/s)	7.5 ± 2.3	8.0 ± 2.4	7.8 ± 2.4	6.6 ± 2.0	<0.001
E/e'	9.7 [7.8-12.3]	8.1 [6.5-9.5]	9.7 [7.9-12.1]	12.4 [10.2-15.9]	<0.001
Tricuspid annular plane systolic excursion (cm)	1.9 ± 0.4	2.0 ± 0.3	1.9 ± 0.4	1.8 ± 0.5	0.005
Left atrial volume index (mL/m^2)	26.0 ± 9.0	24.0 ± 7.8	26.4 ± 8.4	27.4 ± 10.1	0.014
Global longitudinal strain (%)	13.0 ± 3.6	14.5 ± 3.0	13.4 ± 3.4	11.0 ± 3.6	<0.001

E/e'sr = (ratio of transmitral early filling velocity to early diastolic strain rate).

Table 2
E/e'sr as a predictor of long-term outcome in ACS patients with preserved systolic function (GLS ≥ 13.2%) or impaired systolic function (GLS < 13.2%)

			Left ventricular systolic function			
			Preserved		Impaired	
Variable	All		(GLS ≥ 13.2%)		(GLS < 13.2%)	
Number of patients	432		221		211	
Number of events	199		61		138	
	Hazard ratio (95% CI)	p Value	Hazard ratio (95% CI)	p Value	Hazard ratio (95% CI)	p Value
Unadjusted						
E/e'sr per 0.10 m increase	1.05 [1.03-1.07] C-stat 0.63	<0.001	1.20 [1.06-1.36] C-stat 0.60	0.005	1.02 [0.99-1.04] C-stat 0.55	0.28
Adjusted*						
E/e'sr per 0.10 m increase	1.01 [0.98-1.03]	0.60	1.17 [1.01-1.36]	0.049	0.99 [0.94-1.05]	0.80

CI = confidence interval; C-stat = Harrel's C-statistics; DT = mitral valve deceleration time; E/e'sr = ratio of transmitral early filling velocity to early diastolic strain rate; GLS = global longitudinal strain; LVMI = left ventricular mass index.

* Adjusted for age, gender, smoking status, hypercholesterolemia, DT, LVMI, and left ventricular ejection fraction.

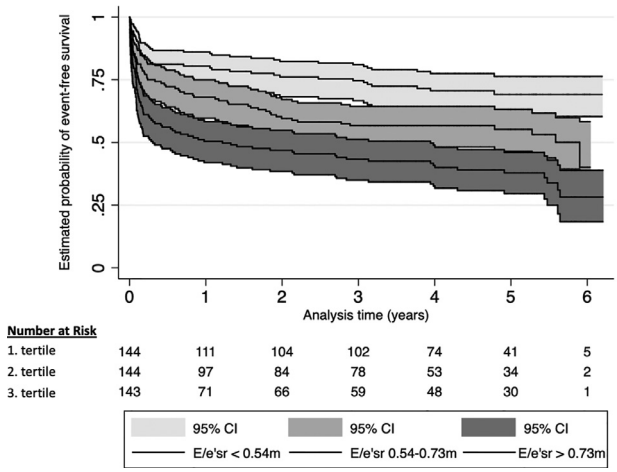

Figure 1. Kaplan-Meier curves stratified according to tertiles of E/e'sr in patients with high and low GLS. Kaplan-Meier survival estimates stratified according to tertiles of E/e'sr (with 95% confidence intervals). CI = confidence interval, E/e'sr = ratio of transmitral early filling velocity to early diastolic strain rate.

model (HR 1.20; 95% CI 1.06 to 1.36; p = 0.005, pr 0.10 m increase). This was not the case for patients with low

GLS (<13.2%) as E/e'sr was not a significant predictor (HR 1.02; 95% CI 0.99 to 1.04; p = 0.28, per 0.10 m increase; Table 2). E/e'sr remained an independent predictor even after adjusting for age, gender, smoking status, hypercholesterolemia, DT, LVMI, and LVEF in the high GLS group (HR 1.17; 95% CI 1.01 to 1.36; p = 0.049, per 0.10 m increase). E/e' did, however, not remain significant in the high GLS group after multivariable adjustments for the same variables (HR: 1.02; 95% CI 0.92-1.13; p = 0.69, per 1 unit increase).

To assess the incremental value of E/e'sr in ACS patients with impaired/relatively preserved GLS, we added the measurement to a model including demographic, clinical, and echocardiographic variables: age, gender, smoking status, hypercholesterolemia, and LVEF.

Adding E/e'sr to the model in the group with impaired strain did not result in a significant increase of Harrell's C-statistics (0.68 [0.65 to 0.72] vs 0.68 [0.64 to 0.72], p = 0.36). However, in the group with relatively preserved GLS a significant increase was found (0.59 [0.55 to 0.63] vs 0.63 [0.59 to 0.67], p = 0.002; Figure 3). To investigate the additive prognostic value of E/e'sr to E/e' in our study population, E/e'sr was added to a univariable Cox model including E/e'. The addition of E/e'sr resulted in a significant increase of Harrell's C-statistics (0.57 [0.53 to 0.62] vs 0.60 [0.56-0.65], p <0.001). The opposite was not true, as adding E/e' to a univariable Cox model including E/e'sr did not result in a significant increase (0.63 [0.59 to 0.67] vs 0.60 [0.56 to 0.65], p = 0.078).

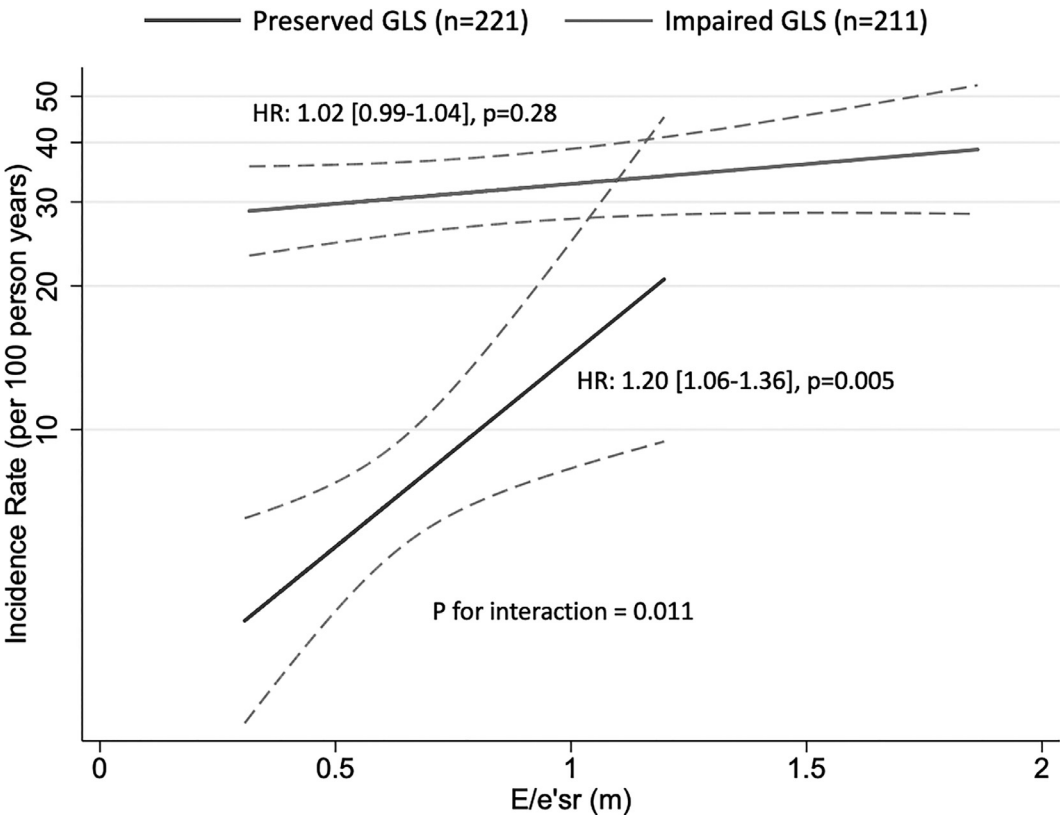

Figure 2. Incidence rate of heart failure, acute myocardial infarction, or cardiovascular mortality according to E/e'sr and high/impaired GLS groups. Displaying the unadjusted incidence rate of heart failure, acute myocardial infarction, or cardiovascular mortality (with 95% confidence intervals) per 1,000 person-years for the population according to high/impaired GLS. A significant linear association was found between E/e'sr and the composite outcome in participants with both high/impaired GLS, p <0.001 for both. HRs are calculated per 10 cm increase of E/e'sr. E/e'sr = ratio of transmitral early filling velocity to early diastolic strain rate; GLS = global longitudinal strain, HR = hazard ratio.

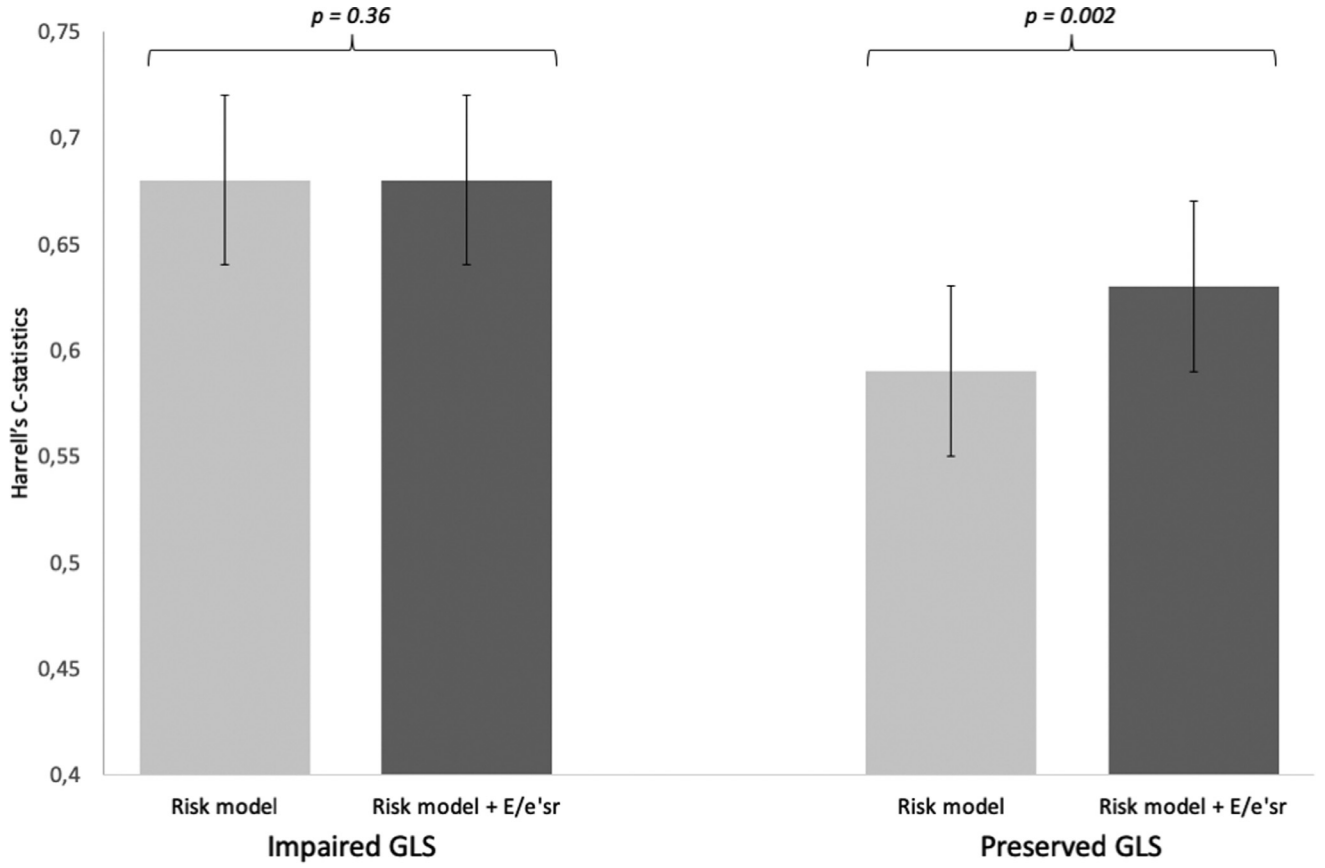

Figure 3. Differences in Harrell's C-statistics stratified according to impaired/preserved GLS. Harrel's C-statistics for risk model including age, gender, smoking status, hypercholesterolemia, and LVEF with/without the addition of E/e'sr in ACS patients with impaired and preserved systolic function as assessed by the median of GLS in this cohort (13.2%). Confidence intervals (95%) are displayed as capped bars. E/e'sr = Ratio of transmitral early filling velocity to early diastolic strain ratio; GLS = global longitudinal strain.

Discussion

In this retrospective study of a cohort of ACS patients who underwent transthoracic echocardiography with 2-dimensional speckle tracking echocardiography and long-term outcome assessment, we demonstrated that: (1) LV filling pressure measured as E/e'sr was a significant predictor of the composite outcome, AMI, HF, and/or CVD death, (2) E/e'sr was a stronger predictor of the composite outcome in patients with preserved systolic function, as assessed by GLS, as opposed to patients with more impaired systolic function, (3) E/e'sr provided incremental prognostic value in predicting the composite cardiovascular outcome in ACS patients with preserved GLS, and (4) E/e'sr was a superior predictor of cardiovascular morbidity and mortality in patients with preserved GLS when compared with E/e'.

Annular myocardial velocities obtained by TDI was initially used to assess regional diastolic function but its ability to estimate global diastolic function has been found to be limited.[17] Several known limitations of Doppler-based methods, such as angle dependency with angulations >20°, may limit e' from truly capturing early diastolic impairment.[9] Furthermore, regional wall motion abnormalities near the mitral annulus of the left ventricle may give lower values of regional e' measurements resulting in a decreased overall e' despite global normal LV relaxation.[18]

In contrast, e'sr, derived from 2-dimensional speckle tracking echocardiography, was recently introduced as a measure that could overcome these limitations and more accurately reflect the global LV relaxation.[10] As this technique angle-independently discriminates between active and passive myocardial motion it more precisely reflects regional and global diastolic function of the LV compared with E/e'. Longitudinal strain rate was used as it has previously been found that longitudinal strain had better reproducibility than circumferential strain. Previous studies have demonstrated that E/e'sr is more accurately associated with invasively measured filling pressure compared with E/e'.[10–12] Additionally, E/e'sr has been found to be a strong predictor of adverse cardiac events in various patient populations. In both an atrial fibrillation population and in a separate systolic HF population, E/e'sr was found to be superior to E/e' as a predictor of adverse cardiac outcomes.[19,20] Ersbøll et al[18] investigated the prognostic value of E/e'sr in a large STEMI cohort. They found E/e'sr to be superior to both LVEF, E/e', and GLS as a prognosticator. We did not find E/e'sr to be superior to LVEF and GLS in our cohort of ACS patients. However, the mean LVEF in Ersbøll et al's cohort was above 50%, so their STEMI population had a relatively preserved systolic function compared with our cohort with a mean LVEF of 41.3 ± 11.5%. In our study, we found that when examining ACS patients with impaired systolic function as

assessed by GLS < 13.2%, E/e'sr was not a better prognosticator than measures of systolic function. In contrast, we found that E/e'sr proved to be a strong predictor in patients with relatively preserved systolic function as assessed by GLS > 13.2%. We have previously found similar results in a large general population study.[13] This may be due to its quality as an early marker of cardiac pathology as the slowly progressing impairment of diastolic active relaxation takes place in early pathogenesis. Subtle changes to the active relaxation probably affect diastolic function before systolic function is affected. So, E/e'sr may be a superior predictor early in the cardiac pathology before systolic function is significantly affected. However, as cardiac disease progresses and starts to severely affect systolic function, systolic measures such as GLS and LVEF become superior prognosticators.

Similar results were found in another study of STEMI patients which did not find E/e'sr to provide incremental information above that of LV systolic parameters.[21] It is not that the prognostic value of E/e'sr is poor in ACS patients with impaired systolic function but rather that E/e'sr does not provide additional benefit to systolic measurements such as GLS. It is of utmost importance to be able to identify high-risk patients with otherwise preserved systolic function to improve risk stratification and initiate early intervention to reduce progression of early cardiac dysfunction.[22]

As this is an observational study, residual confounders may exist. However, the analysis was based on consecutive patients from a well-defined registry. Furthermore, only patients who had an echocardiogram performed 2 days following their PCI were included. Additionally, we did not have information regarding the no-reflow phenomenon which could have impacted prognosis. Technical challenges to strain rate including concerns regarding reproducibility and accessibility have been discussed in the literature. However, we found the reproducibility to be good strain rate measurements were obtainable in a large number of the included patients.

In conclusion, E/e'sr is an independent predictor of cardiovascular morbidity and mortality in ACS patients who underwent PCI and had an echocardiography performed 1 to 3 days after the procedure. However, E/e'sr did not remain an independent predictor when systolic echocardiographic parameters were included in the model. E/e'sr provides incremental prognostic information over and above demographic and clinical factors but not over echocardiographic parameters. Furthermore, it seems that E/e'sr is a stronger prognosticator in patients with preserved cardiac function as opposed to patients with impaired cardiac function. In addition, E/e'sr showed to be a stronger predictor of cardiac events than E/e' in patients with preserved cardiac function.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.amjcard.2019.03.004.

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