Prognostic Value and Interplay Between Myocardial Tissue Velocities in Patients Undergoing Coronary Artery Bypass Grafting

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Early diastolic tissue velocity (e') by tissue Doppler imaging represents an early marker of left ventricular (LV) dysfunction in ischemic heart disease. We assessed the value of e' for predicting mortality in patients undergoing coronary artery bypass grafting (CABG). We retrospectively investigated patients treated with CABG between 2006-2011. Before surgery, all patients underwent an echocardiogram with tissue Doppler imaging to measure tissue velocities: systolic (s'), e', and late diastolic (a'). The primary outcome was all-cause mortality. Survival analysis was applied. Improvement of EuroSCORE-II was assessed by net reclassification index. Of 660 patients, 72 (11%) died during a median follow-up time of 3.8 years. Mean age was 68 years, LVEF 50%, and 84% were men. All tissue velocities showed a significant negative association with outcome and e' provided highest Harrell's C-statistics (c-stat=0.68). After multivariable adjustment for EuroSCORE-II, LV hypertrophy, LV internal diameter, and global longitudinal strain, declining e' was associated with a higher risk of mortality (HR=1.35 (1.12 to 1.61), p = 0.001, per 1cm/s absolute decrease). LVEF≤40% modified the relationship between both s' and e' and outcome (p for interaction=0.021 and 0.024, respectively), such that neither predicted mortality when LVEF was ≤40%. In patients with LVEF>40%, only e' remained a predictor after multivariable adjustments (HR=1.36 (1.10 to 1.69), p = 0.005, per 1cm/s absolute decrease). A net reclassification index improvement of 0.14 was observed when adding global e' to the EuroSCORE-II. In conclusion, e' is an independent predictor of all-cause mortality in patients undergoing CABG, especially in patients with LVEF>40%, and improves the predictive value of EuroSCORE-II. **(Am J Cardiol 2021;144:37−45)**

Patients undergoing coronary artery bypass grafting (CABG) are at increased mortality risk due to the prevalence of cardiovascular risk factors,[1] coronary artery disease,[2] and the possibility of surgical complications.[3] Identifying patients at risk is important to customize the observation and management of these patients to improve prognosis. Echocardiography is an integral part of the preoperative evaluation.[4,5] The left ventricular ejection fraction (LVEF) is an established predictor of outcome following CABG,[6] and the only echocardiographic parameter included in the established prediction model; EuroSCORE II.[7] However, several studies have revealed that tissue Doppler imaging (TDI) can identify signs of left ventricular (LV) dysfunction in patients with a normal echocardiogram.[8,9] Furthermore, studies have revealed a specific progression of myocardial dysfunction assessed by myocardial tissue velocities in ischemic heart disease.[10,11] Impaired relaxation appears to be the first blow in the ischemic cascade, followed by a decrease in systolic tissue function. First hereafter does LVEF become abnormal. By extension, studies have revealed that specific tissue velocity patterns, representative of systolic and diastolic function, are capable of predicting outcomes in patients with acute myocardial infarction (MI).[12] However, the clinical value of myocardial tissue velocities and patterns have not been examined in patients undergoing CABG. We hypothesized that (1) dysfunction of myocardial relaxation (e') by TDI is associated with outcome in patients undergoing CABG and (2) e' adds additional value to EuroSCORE II. Furthermore, we hypothesized (3) that e' is associated with outcome specifically in patients with preserved ejection fraction (LVEF>40%) as a sign of preclinical LV dysfunction. Finally, we sought to explore the association between specific tissue velocities patterns and outcome.

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Methods

We performed a retrospective study of patients who were treated with isolated CABG at Gentofte Hospital in Denmark, from January 2006-May 2011 (n=782). We excluded patients who had CABG performed as rescue treatment, patients who did not have an echocardiogram available, and patients who had significant valvular disease (moderate-severe mitral or aortic valve dysfunction), leaving 730 patients for inclusion. We furthermore excluded patients with poor imaging quality (n=21), patients who did not have an echocardiogram with color TDI (n=22), and patients with atrial fibrillation or atrial flutter during the echocardiogram (n=27). In total, 660 patients were included.

The study was approved by the Danish Health Authorities and the Danish Data Protection Agency. Retrospective studies, like this one, do not need approval by an ethics committee in Denmark.

The primary end point was all-cause mortality, which was obtained from the National Causes of Death Registry. The secondary end points were cardiovascular death and incident heart failure. Information on cardiovascular death was also derived from the National Causes of Death Registry whereas details on diagnosis of heart failure were extracted from the National Patient Registry.

Laboratory samples were collected upon admission, including a routine panel of blood samples: C-reactive protein (CRP), hemoglobin, leukocytes, thrombocytes, and creatinine, all assayed by standard laboratory methods. Creatine-kinase MB was measured within 2 days following surgery.

The echocardiographic examinations were performed prior to CABG, at a median of 15 days (9 to 33 days) before surgery. All examinations were performed using a Vivid Dimension (GE Healthcare; Horten, Norway) with a 3.5-MHz transducer. Images were digitally transferred to a remote digital image archive. All analyses were performed offline as post-processing analyses (EchoPAC BT 11.1.0, GE Vingmed Ultrasound AS) by a single experienced operator blinded to follow-up information. All analyses were performed in accordance with European Association of Echocardiography and American Society of Echocardiography recommendations.[13] Details on these analyses are provided in supplemental material.

Myocardial tissue velocities were measured from color-coded TDI in the apical 4-chamber, 2-chamber, and apical longitudinal long-axis view. Sample volumes were placed at all six LV walls at the level of the mitral annulus. These were used to measure the systolic (s'), early diastolic (e'), and late diastolic (a') tissue velocities (Figure 1). Global values (global s', e', a) were measured as averages from all the walls. Descriptions of high vs. low values refer to the numeric values for tissue velocities, and associations refer to absolute decreases in tissue velocities. Categories of high-low global s', global e', global a' were created from the numeric mean value in the population and patients were divided into 8 patterns of different combinations.

Patients were stratified by tertiles of global e' and p for trend for across groups were tested. Continuous variables showing Gaussian-distribution are shown as mean ± SD and variables not showing Gaussian-distribution are shown as median with interquartile ranges. Categorical variables are shown as numbers and percentages. Fisher's exact test was performed when expected number of observations was below 5 within a group, otherwise the Chi^2 test was used.

Association between myocardial tissue velocities were assessed with scatter plots and Pearson's correlation coefficient (r).

Univariable Cox proportional hazards regression were tested for known predictors of all-cause mortality and potential confounders identified from groupwise comparison across tertiles of global e'. E/e' was included as a categorical variable (E/e'>14) as an estimate of elevated filling pressure in accordance with diastolic function guidelines.[14] Proportional hazards were tested by Schoenfeld residuals. Interactions for tissue velocities were tested against LVEF<40%.

The discriminative value of myocardial tissue velocities was quantified using Harrell's C-statistic.[15] The performance was internally validated using bootstrapping methods. To account for the optimism associated with evaluating a marker in the sample from which it is derived, we calculated the optimism-corrected C statistic for global e' using 100 bootstrap samples.[16]

Multivariable Cox proportional hazards regression models were performed in 2 models to control for confounders and to obtain adjusted hazard ratios (HR). Model 1 included: EuroSCORE II, LV internal diameter, LV hypertrophy, and global longitudinal strain (GLS). Model 2 included: age, gender, hypertension, prior MI, hemoglobin, CRP, LV internal diameter, LV hypertrophy, and GLS. Continuous net reclassification index (NRI) was performed to investigate the added value of tissue velocities to the EuroSCORE II.[7]

The continuous associations between tissue velocities and all-cause death were assessed through restricted cubic spline curves constructed by Poisson regression. The number of knots which provided the lowest Akaike information criterion was chosen. Kaplan-Meier curves for all-cause death were created for tissue velocities stratified into high versus low categories by the numeric mean values and the log-rank test was used to test for equality between groups. Cox proportional hazards regression was also performed for tissue velocities stratified by LVEF subgroups (cutoff: 40%). Finally, Cox proportional hazards regression was performed for myocardial tissue patterns to identify specific patterns associated with outcome, and adjustments were made for only the EuroSCORE II due to the low number of events.

A p-value <0.05 was considered significant in all analyses.

Statistical analyses were performed using STATA version 15 (StataCorp LP, College Station, Texas). Kaplan-Meier curves were created using R Studio (version 3.6.0)

Results

During a median follow-up period of 3.8 years (interquartile ranges: 2.8;4.9y), 72 (11%) of 660 patients died. Of these, 40 were cardiovascular deaths. Furthermore, 33 were diagnosed with heart failure during follow-up. Follow-up was complete. Baseline characteristics for the overall

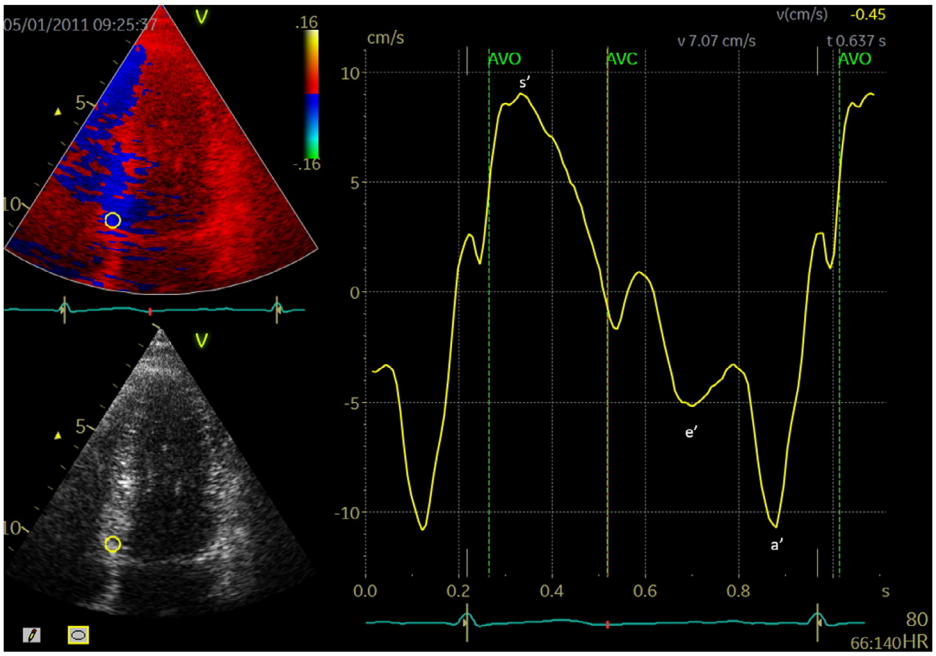

Figure 1. Myocardial tissue velocities by color tissue Doppler echocardiography. The figure shows an example of a typical profile of a myocardial velocity curve with a sample placed at the base of the septal wall. There is a peak systolic tissue velocity (s'), and 2 peak velocities −early (e') and late (a') − in diastole. AVC: aortic valve closure AVO: aortic valve opening.

population and stratified by tertiles of global e' are shown in Table 1. Decreasing global e' was associated with older age, a higher proportion of men, hypertension, prior MI, increasing CRP, decreasing hemoglobin, and alterations in nearly all echocardiographic variables except for tricuspid regurgitant gradient and LAVI.

Patients who died at follow-up were older (72 vs 67y), had a higher prevalence of diabetes (35 vs 23%), peripheral artery disease (24 vs 10%), renal dysfunction, higher CCS class, and lower hemoglobin. Furthermore, patients who died more frequently presented with left main stenosis and were unstable upon operation. Of echocardiographic variables, those who died had more often had LV hypertrophy (35% vs 23%), lower LVEF (46 vs 51%), reduced GLS (-12 vs -14%), higher filling pressure (E/e' 12 vs 10), and impaired myocardial tissue velocities.

Univariable and multivariable Cox regressions for all-cause death are shown in Table 2. Of conventional echocardiographic variables, only LVEF and E/e'>14 were associated with mortality in univariable analyses, whereas advanced echocardiographic analyses revealed GLS and all myocardial tissue velocities to be associated with mortality. In multivariable Cox regression, the global e' was the only myocardial tissue velocity that remained independently associated with outcome after adjusting for the EuroSCORE II, LV internal diameter, LV hypertrophy, and GLS, and this was consistent after further adjustments (model 2). The risk of mortality increased linearly with decreasing absolute values of global s' (Figure 2) and global e' (Figure 2), whereas the association was biphasic for global a' with high risk for those with the highest absolute value of global a', decreasing risk with intermediate values, and then showing high risk again for those with lowest values (Figure 2).

Harrell's C-statistics revealed that global e' was the echocardiographic parameter that provided the highest discrimination (Table 2). The internal validation revealed an optimism-corrected C-statistic of 0.69 (0.63 to 0.75). Of all tissue velocities, only global e' improved NRI when added to EuroSCORE II (continuous increase in NRI: global s': 0.08 (-0.06, 0.19); global e': 0.14 (0.04, 0.26); global a': 0.03 (-0.07, 0.20)).

By grouping patients into high vs low values of tissue velocities, we found that a low global s' (<5.27 cm/s) did not confer a significantly increased risk of death compared with patients with high global s' (unadjusted HR: 1.54 (0.96 to 2.47), p = 0.07), Figure 3. For global e', patients with a low value (<5.06 cm/s) had a 3-fold increased risk of outcome (unadjusted HR: 3.02 (1.77 to 5.15), p <0.001), Figure 3. For global a', patients with a low value (<7.09 cm/s) did not have a significantly increased risk of death compared with high values (HR: 1.51 (0.95 to 2.40), p = 0.08, Figure 3).

Impaired systolic function (LVEF≤40%) significantly modified the relationship between global s' and mortality (p for interaction=0.021) as well as global e' and mortality (p for interaction=0.024). When patients were stratified by LVEF categories, it became apparent that none of the myocardial tissue velocities were associated with outcome in patients with depressed LVEF (n=105, deaths=20). However, both global s' and e' were associated with outcome in univariable Cox regression in patients with preserved LVEF (n=555, deaths=52): global s': HR=1.52 (1.15 to 2.01), p = 0.001; global e': HR=1.65 (1.35 to 2.02), p<0.001, per 1cm/s absolute decrease. After multivariable adjustment for model 1 variables, only e' remained independently associated with mortality (HR=1.36 (1.10 to 1.69), p = 0.005, per 1cm/s absolute decrease), and the same was the case when applying the second multivariable

Table 1
Baseline characteristics

	All n=660	Global e' (cm/s)			p-value
		< −5.7	−5.7 to −4.2	> −4.2	
Variable					
Age (years)	68±9	64±9	67±8	71±8	*<0.001*
Men	555 (84%)	197 (90%)	183 (83%)	175 (80%)	*0.015*
Hypertension	447 (68%)	133 (61%)	151 (69%)	163 (74%)	*0.009*
Diabetes mellitus	160 (24%)	47 (21%)	52 (24%)	61 (28%)	*0.29*
Smoking status					*0.36*
Current	136 (21%)	42 (19%)	45 (21%)	49 (22%)	
Former	324 (49%)	102 (46%)	107 (49%)	115 (52%)	
Never	200 (30%)	76 (35%)	68 (31%)	56 (26%)	
Previous myocardial infarction	158 (24%)	48 (22%)	40 (18%)	70 (32%)	*0.002*
Previous stroke	70 (11%)	17 (8%)	26 (12%)	27 (12%)	*0.23*
Peripheral artery disease	77 (12%)	25 (11%)	25 (11%)	27 (12%)	*0.94*
Canadian Cardiovascular Society class					*0.12*
1	56 (9%)	27 (12%)	15 (7%)	14 (6%)	
2	511 (77%)	171 (77%)	170 (77%)	170 (77%)	
3	87 (13%)	21 (10%)	33 (15%)	33 (15%)	
4	6 (1%)	1 (1%)	2 (1%)	3 (1%)	
Heart rate (beats per minute)	70±13	69±12	71±14	71±13	*0.10*
Body mass index (kg/m^2)	27±4	27±4	27±4	27±4	*0.20*
Indication for surgery					*0.10*
- Stable angina pectoris	336 (51%)	125 (57%)	105 (48%)	106 (48%)	
- Acute coronary syndrome	324 (49%)	95 (43%)	115 (52%)	114 (52%)	
Number of narrowed coronary arteries					*0.74*
1	5 (1%)	2 (1%)	2 (1%)	1 (1%)	
2	135 (21%)	51 (23%)	42 (19%)	42 (19%)	
3	520 (79%)	167 (76%)	176 (80%)	177 (81%)	
Left main stenosis	243 (37%)	90 (41%)	74 (34%)	79 (36%)	*0.27*
Unstable up to operation	31 (5%)	11 (5%)	10 (5%)	10 (5%)	*0.97*
Extra-corporal-circulation-time (minutes)	81±24	78±22	83±23	83±27	*0.13*
Peak creatine kinase-muscle/brain (μg/L)	27 [20;39]	26 [20;39]	26 [19;36]	29 [22;40]	*0.20*
C-reactive peptide (mg/L)	4 [2;9]	2 [2;7]	5 [2;10]	4 [2;9]	*0.029*
Creatinine (μmol/L)	96 [82;108]	95 [83;106]	94 [82;109]	99 [83;113]	*0.21*
Hemoglobin (mmol/L)	8.4±0.9	8.6±0.8	8.3±0.8	8.3±0.9	*0.002*
Leukocytes (10^9/L)	8.1 [6.9;9.5]	8.0 [6.9;9.5]	8.1 [7.0;9.6]	8.2 [7.0;9.6]	*0.50*
Trombocytes (10^9/L)	264 [221;315]	260 [215;301]	263 [224;323]	268 [226;321]	*0.07*
Left ventricular ejection fraction (%)	50±11	55±8	52±10	45±13	*<0.001*
Global longitudinal strain (%)	−13±4	−15±3	−14±4	−11±4	<0.001
Tricuspid annular plane systolic excursion (cm)	2.4±0.4	2.5±0.4	2.4±0.6	2.3±0.4	<0.001
Tricuspid regurgitant gradient (mmHg)	25±8	24±7	24±9	25±9	0.94
Left ventricular internal diameter (cm)	4.96±0.67	4.84±0.58	4.94±0.61	5.09±0.78	*<0.001*
Left ventricular hypertrophy	158 (24%)	25 (11%)	48 (22%)	85 (39%)	<0.001
Left atrial volume index (mL/m^2)	25±9	24±9	25±9	26±10	*0.07*
E/A	0.89 [0.72;1.14]	1.07 [0.88;1.27]	0.86 [0.76;1.06]	0.73 [0.62;0.96]	*<0.001*
E/e'	10 [8;13]	9 [7;10]	10 [8;12]	12 [9;15]	*<0.001*
E-wave deceleration time (ms)	225±69	219±56	222±58	235±88	0.040
Global s' (cm/s)	5.3±1.2	6.0±0.9	5.3±1.0	4.5±1.1	<0.001
Global e' (cm/s)	−5.1±1.6	−6.9±0.9	−5.0±0.4	−3.3±0.7	<0.001
Global a' (cm/s)	−7.1±1.8	−7.2±1.6	−7.3±1.8	−6.8±1.9	0.012

The more negative values of e' the better. Thus the third column shows the patients with best e' and the fifth column shows the patients with the worst e'.
E/A: ratio of early to late transmitral filling velocities; E/e': ratio of early transmitral filling to early relaxation velocity; s': systolic tissue velocity; e': early diastolic tissue velocity; a': late diastolic tissue velocity.

model of confounders identified within the cohort (HR=1.37 (1.09 to 1.72), p = 0.007, per 1cm/s absolute decrease).

The association between tissue velocities and the secondary outcomes of cardiovascular death and heart failure are shown in Supplemental Table 1. In brief, all tissue velocities were significantly associated with both outcomes in unadjusted analyses, but no tissue velocities remained associated with any of these outcomes after further multivariable adjustment (model 2). We observed that LVEF modified the association between global e' and both secondary outcomes (p for interaction <0.05 for both outcomes), but not for the other tissue velocities. Analyses restricted to patients with preserved LVEF revealed similar findings as for the overall population (Supplemental Table 2).

Table 2
Cox proportional hazards regressions

Variable	Univariable model			Multivariable model 1*		Multivariable model 2†	
	HR (95% CI)	p-value	c-stat	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (per 1y increase)	1.06 (1.03-1.10)	<0.001	0.65				
Male gender	0.70 (0.49-1.25)	0.23	0.53				
Diabetes mellitus	1.71 (1.05-2.78)	0.030	0.55				
Peripheral artery disease	2.56 (1.49-4.41)	0.001	0.56				
Creatinine (per 1 μmol/L increase)	1.01 (1.01-1.02)	<0.001	0.59				
Haemoglobin (per 1mmol/L decrease)	2.15 (1.65-2.81)	<0.001	0.69				
Left main occlusion	1.72 (1.09-2.74)	0.021	0.56				
Unstable at operation	2.53 (1.26-5.09)	0.009	0.53				
Surgical indication: acute coronary syndrome	1.91 (1.18-3.09)	0.009	0.58				
Left ventricular hypertrophy	1.59 (0.98-2.58)	0.06	0.56				
Left ventricular ejection fraction (per 1% decrease)	1.03 (1.01-1.05)	<0.001	0.61	1.00 (0.97-1.03)	0.85	1.01 (0.98-1.04)	0.59
Global longitudinal strain (per 1% absolute decrease)	1.11 (1.05-1.18)	<0.001	0.64				
E/e'>14	2.27 (1.37-3.75)	0.001	0.58	1.96 (1.15-3.32)	0.013	1.65 (0.96-2.87)	0.07
Global s' (per 1 cm/s decrease)	1.38 (1.13-1.69)	0.002	0.60	1.05 (0.82-1.36)	0.69	0.98 (0.75-1.28)	0.90
Global e' (per 1cm/s absolute decrease)	1.52 (1.30-1.79)	<0.001	0.68	1.35 (1.12-1.61)	0.001	1.26 (1.04-1.52)	0.020
Global a' (per 1cm/s absolute decrease)	1.14 (1.01-1.30)	0.036	0.56	0.99 (0.85-1.15)	0.88	0.99 (0.86-1.14)	0.93

E/e': ratio of transmitral early filling velocity to early diastolic relaxation velocity; s': systolic tissue velocity; e': early diastolic tissue velocity; a' late diastolic tissue velocity.

* Model 1: adjusted for EuroSCORE II, left ventricular internal diameter, left ventricular hypertrophy, and global longitudinal strain.

† Model 2: adjusted for age, gender, hypertension, prior myocardial infarction, C-reactive peptide, hemoglobin, left ventricular internal diameter, left ventricular hypertrophy, and global longitudinal strain.

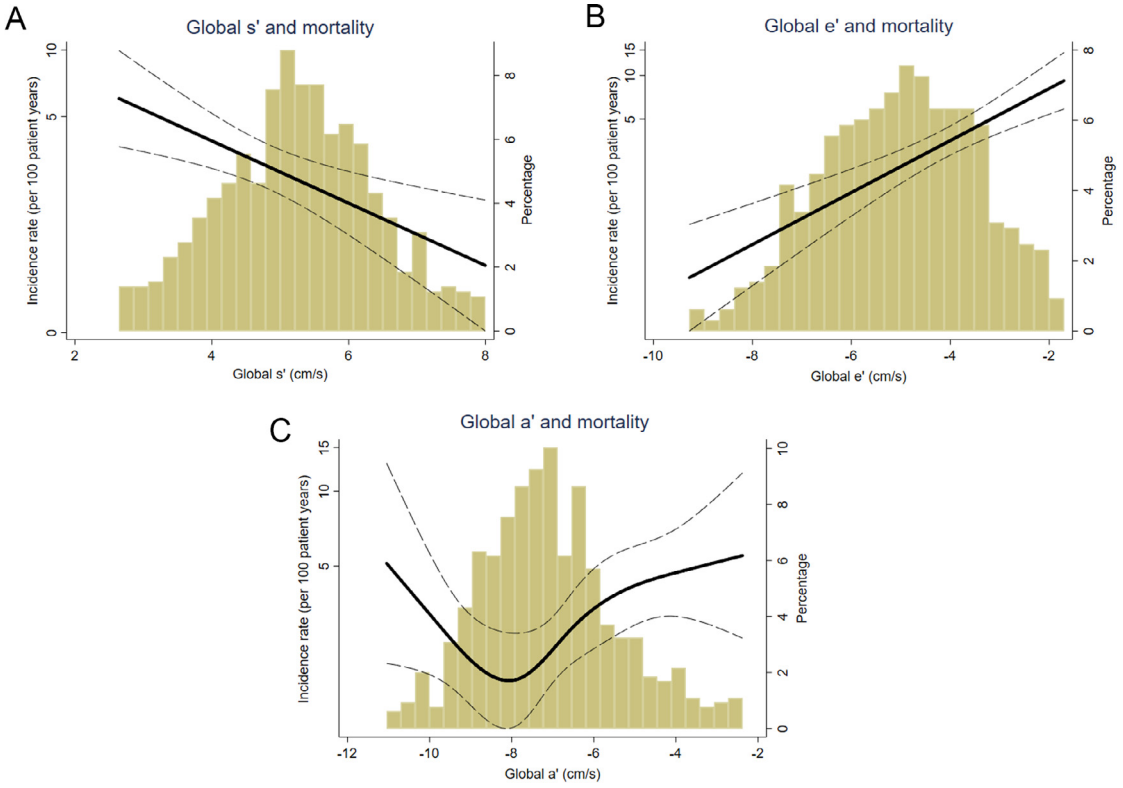

Figure 2. Restricted cubic spline curves for mortality by tissue velocities. X-axis represents the value of the tissue velocities and y-axis to the left shows the incidence rate and to the right the percentages in the histogram. Figure 2A shows the linearly increased risk of mortality associated with decreasing global s', Figure 2B shows the linearly increased risk of mortality associated with increasing global e', and Figure 2C shows the increased risk of mortality associated with decreasing global a' in a biphasic manner, with high risk with lowest global a' values, lower risk with intermediate values and then highest risk with highest values.

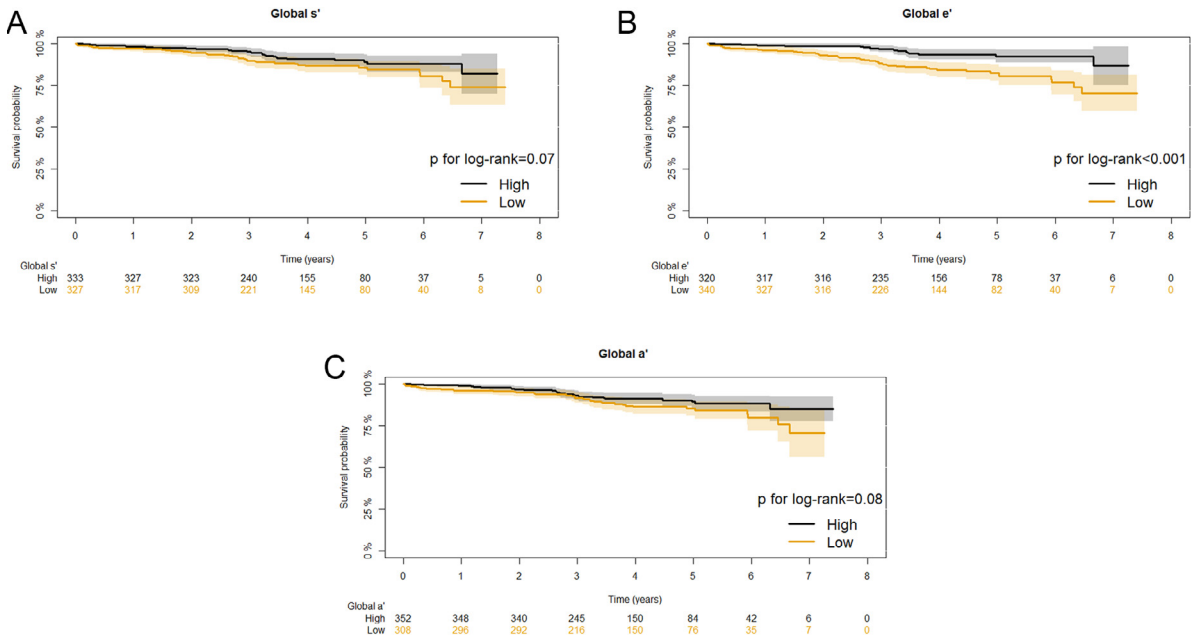

Figure 3. Kaplan-Meier curves for tissue velocities. The graph shows the risk of event-free survival (y-axis) during follow-up (x-axis) for patients stratified by high vs low s' by the mean value of 5.27 cm/s (Figure 3A), for patients stratified by high vs low e' by the numeric mean value of 5.06 cm/s (Figure 3B), and for patients stratified by high vs low a' by the numeric mean value of 7.09 cm/s (Figure 3C).

Pearson's correlations coefficients revealed moderate linear correlations between systolic tissue velocity and the diastolic velocities: global s' and global e' (r=-0.58, p<0.001); global s' and global a' (r=-0.55, p <0.001); however, only a weak correlation between the diastolic velocities of global e' and global a' (r=0.08, p = 0.046).

In 8 different categories of combinations of tissue velocities we observed the following patterns to be associated with outcome: pattern 3 (high global s', low global e', high global a'); pattern 4 (high global s', low global e', low global a'); pattern 7 (low global s', low global e', high global a'); and pattern 8 (low global s', low global e', low global a') (Table 3). These findings were consistent after adjustment for the EuroSCORE II.

Discussion

The main finding of the present study was that early myocardial relaxation velocity by TDI was associated with outcome even after adjustments for clinical risk tools (EuroSCORE II) and key echocardiographic variables. Furthermore, it provided the highest discriminative value of any echocardiographic variable as evidenced by a C-statistic of 0.68 and improved the predictive value of EuroSCORE II. The findings seemed to be driven by those with preserved LVEF. Furthermore, we observed that the other tissue velocities did not add value when analyzed separately but could be valuable when interpreted in specific patterns. As this was a single-center retrospective study, our findings are primarily hypothesis-generating. Even though we validated our findings internally using Bootstrapping methods, our findings still need to be validated in an external cohort.

Several possible reasons may explain our primary finding regarding the value of e'. First of all, it may in part be a reflection of the TDI modality in general as TDI solely investigates longitudinal LV function.[17] Additionally, e' has been shown to correlate with end-diastolic stiffness in patients undergoing CABG,[18] which may be another explanation for its association to outcome. Finally, longitudinal function is most prone to ischemia since ischemia primarily affects subendocardial fibers which largely controls longitudinal function. This level of dysfunction would go unrecognized by the LVEF as it first starts to decrease when both longitudinal and circumferential function is lost.[19] To that end, the e' seems to be the first blow in the ischemic cascade as outlined previously, and therefore be more sensitive than the other tissue velocities for detecting preclinical LV dysfunction. This is supported by population-based studies showing the e' to be capable of predicting acute MI,[8] and studies showing its predictive value in patients with cardiovascular risk factors and various cardiac diseases.[20,21]

For patients with impaired LVEF, none of the tissue velocities were associated with outcome, suggesting that the primary value of tissue velocities lies in the detection of preclinical LV dysfunction. An exception to this is that a' has been shown to predict outcome in patients with heart failure with reduced LVEF as it associates with pulmonary capillary wedge pressure and may thus indicate pulmonary congestion.[11]

Although none of the tissue velocities were found to be independently associated with incident heart failure nor cardiovascular death, this may rely on the few events, which runs a risk of type II errors. By extension, we also have to recognize that the lacking association for s' and a' with outcomes may also be due to low statistical power, and the same applies to our pattern analyses. Apart from this, our pattern analyses did show some intriguing findings

Table 3
Cox proportional hazards regressions by myocardial tissue patterns

	Patterns			Univariable regression		Multivariable regression**	
Group	Global s'	Global e'	Global a'	HR (95% CI)	P-value	HR (95% CI)	P-value
Group 1 n=156	↑	↑	↑	Reference group	-	Reference group	-
Group 2 n=76	↑	↑	↓	1.99 (0.70-5.67)	0.20	1.98 (0.69-5.65)	0.20
Group 3 n=80	↑	↓	↑	2.97 (1.15-7.66)	0.024	2.87 (1.11-7.40)	0.029
Group 4 n=21	↑	↓	↓	4.60 (1.34-15.71)	0.015	4.22 (1.24-14.44)	0.022
Group 5 n=27*	↓	↑	↑	-	-	-	-
Group 6 n=61	↓	↑	↓	1.31 (0.38-4.46)	0.67	1.23 (0.36-4.21)	0.74
Group 7 n=89	↓	↓	↑	3.42 (1.37-8.58)	0.009	3.15 (1.26-7.91)	0.014
Group 8 n=150	↓	↓	↓	4.07 (1.76-9.37)	0.001	3.06 (1.29-7.23)	0.011

s': systolic tissue velocity; e': early diastolic tissue velocity; a': late diastolic tissue velocity.
Arrows denote high and low values (according to the numeric mean values below)
s' mean value = 5.27 cm/s
e' numeric mean value = 5.06 cm/s
a' numeric mean value = 7.09 cm/s
* no events in this group
**Adjusted for the EuroSCORE II.

suggesting that if we interpret all tissue velocities collectively, we may be able to get an understanding of where patients are located on the stage of progressive LV dysfunction, which is in line with previous findings from patients with acute MI.[12]

Even though the LVEF is incorporated in the EuroSCORE II, we found that tissue velocities can detect patients at risk of mortality even in patients with preserved LVEF. Furthermore, the e' increased the NRI for EuroSCORE II suggesting that a refinement of these prediction models with more advanced echocardiographic measures is possible. This is particularly important for patients with preserved LVEF, who may be deemed low-risk and not followed as closely in the clinic. In this population, we observed that 9% of patients with preserved LVEF (LVEF>40%) died during follow-up, which suggests that there is still a need for refining risk assessment in these patients to optimize prognosis even further. Furthermore, the strength of tissue velocities, and specifically the e', is that it is already incorporated in the standard echocardiogram, making it a readily applied parameter for predicting outcome.

Detection of preoperative LV dysfunction for identifying patients at risk as in our study is important, however, Diller et al have also examined whether CABG improves cardiac function and found that e' transiently increased until 18 months after CABG.[22] Whether a postoperative echocardiogram showing persistently low e' would identify patients at even higher mortality risk is unknown, although this could be intriguing to investigate.

Since the study was of retrospective design, we could not obtain detailed information on medication and cannot exclude the possibility of uncontrolled confounding. We also excluded patients with atrial fibrillation and/or flutter, since these patients often have variable pre- and afterload conditions, which requires multiple cycles or advanced indexing methods to assess LV function.[23] Additionally, even though we performed an internal validation, the study is limited by the lack of an external validation cohort. We focused on the preoperative echocardiographic information and did not include after operative echocardiographic information, which also provides important insights in terms of prognosis. Our findings may be influenced by low statistical

power, which increases our likelihood of making type II errors, particularly in the extended multivariable models which may suffer from overfitting. This could also explain some of the findings, including the nonsignificant association between global s' and a' and all-cause death and the nonsignificant association between tissue velocities and secondary outcomes after multivariable adjustments. Finally, the EuroSCORE II model was not originally designed for the prediction of long-term mortality but rather in-hospital mortality but it has shown to be capable of predicting this outcome as well.[24]

In conclusion, early myocardial relaxation velocity was associated with all-cause mortality in patients undergoing CABG and improved the clinical value of the EuroSCORE II. The findings were driven by patients with preserved ejection fraction. Specific patterns of isolated diastolic dysfunction or combined systolic and diastolic dysfunction identify patients at particularly high risk of mortality. The findings provide new insights on how to interpret and use tissue velocities in clinical practice, specifically for outcome prediction.

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Disclosures

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.12.058.

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