A Validated Echocardiographic Risk Model for Predicting Outcome Following ST-segment Elevation Myocardial Infarction

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Many echocardiographic measures have been proposed as potential predictors of outcome following ST-elevation myocardial infarction (STEMI). We hypothesized that combining multiple echocardiographic measures in a risk model provides more prognostic information than individual echocardiographic measures. We prospectively included 373 STEMI patients which constituted our derivation cohort. We also identified 298 STEMI patients from a clinical registry that constituted our validation cohort. Echocardiogram was performed at a median of 2 days after infarction. The echocardiogram consisted of conventional and advanced measures. The end point was a composite of heart failure and/or cardiovascular death. During a median follow-up of 5.4 years, we observed 80 events in our derivation cohort. A stepwise backward Cox regression including all echocardiographic parameters identified global longitudinal strain, wall motion score index (WMSI), E/e', and E/global strain rate e (E/GLSRe) as significant predictors of outcome. A Classification and Regression Tree analysis outlined a risk model with WMSI, GLSRe, and E/e' as key echocardiographic parameters. Patients with WMSI ≥ 2.22 were at high risk, patients with WMSI < 2.22, GLSRe < 0.82s^{-1} and E/e'≥7.6 at intermediate risk, and patients with WMSI < 2.22 and GLSRe ≥ 0.82s^{-1} or GLSRe < 0.82s^{-1} and E/e' < 7.6 at low risk of heart failure and/or cardiovascular death. When compared with the low-risk group, an incremental risk was observed (intermediate group: HR = 2.52 [1.24;5.11], p = 0.011; high-risk group: HR = 4.37 [1.40;13.66], p = 0.011). The risk model was validated in the validation cohort (C-statistic: 0.71). In conclusion, we devised an echocardiographic risk model for STEMI patients suggesting advanced and conventional measures of systolic function and filling pressures to be important for the prognosis. **(Am J Cardiol 2020;125:1461−1470)**

Myocardial infarction (MI) is associated with a wide range of long-term complications including heart failure (HF) and cardiovascular death (CVD).[1,2] Early recognition of impending HF could allow for timely management and thereby improve overall prognosis, which is otherwise poor in patients with MI and systolic dysfunction.[3,4] Left ventricular ejection fraction (LVEF) by echocardiography is the gold standard to evaluate prognosis in patients with ST-segment elevation MI (STEMI).[2] However, increasing evidence suggests that systolic dysfunction which goes unrecognized by the LVEF can be detected by advanced echocardiographic measures of systolic function.[5] Furthermore, assessing LVEF provides an unbalanced view of cardiac function as patients may suffer from diastolic dysfunction or pulmonary hypertension, both of which increase the risk of HF.[6,7] Consequently, many studies have investigated the prognostic impact of associated cardiac dysfunction and suggest potential value of both conventional and advanced echocardiographic markers of systolic and diastolic function.[8] These measures have however not been tested in the same cohort, and the evidence has not been able to translate into clinical practice. We hypothesized that combining multiple echocardiographic measures in a risk model would provide more prognostic information than individually proposed echocardiographic measures.[5,6,9] By extension, we wanted to devise an echocardiographic risk model, which would provide an overview of how to clinically approach the post-MI risk stratification. Lastly, we sought to validate our proposed risk model in an external cohort of STEMI patients.

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See page 1469 for disclosure information.

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Methods

Details on the population used as the derivation cohort have previously been described in depth.[10] Briefly, this was a prospective study including patients admitted with STEMI treated with primary percutaneous coronary intervention (PCI) at Gentofte Hospital, University of Copenhagen, Denmark, from September 2006 to December 2008. A total of 391 patients were included. All patients underwent an echocardiographic examination prior to discharge and at a median of 2 days after PCI. Of these, 14 patients were excluded due to atrial fibrillation rhythm during the echocardiogram, and 4 patients were excluded since no echocardiographic measures could be performed. Data on baseline characteristics were retrieved upon inclusion in the study.

For the validation cohort, 298 STEMI patients were included as part of a clinical registry including patients admitted with acute coronary syndrome to Gentofte Hospital from January 2003 to November 2008, which served as an invasive center for primary PCI for 10 other hospitals. The study design and population have previously been described in depth.[11] Of 580 patients identified with transthoracic echocardiography, patients with poor image quality, nonsinus rhythm during the echocardiogram were excluded (n = 113), and so were patients with any missing value of the components in the proposed risk model (n = 67), and finally only patients with STEMI were included. All underwent primary PCI and echocardiography was performed at a median of 2 days after PCI. Baseline data were included upon admission. Patients for the derivation cohort were included as part of a prospective study which started in 2006, whereas patients in the validation cohort were included as part of a clinical registry. The inclusion period for the 2 cohorts overlap from 2006 to 2008, however, none of the patients appeared in both cohorts. The patients included in the derivation cohort were selected at the discretion of the PCI operator, meaning that the inclusion of patients for the prospective study differed by which PCI operator was on call at the patients' admission. This explains the selection of the 2 different cohorts within the same time frame of 2006 to 2008.

EchoPac version 113 (GE Healthcare, Norway) was used for analyses in the validation cohort. Patients in the validation cohort had their echocardiograms performed median 2 (IQR 1-3) days after PCI. Of the 298 STEMI patients, 127 experienced the outcome of HF/CVD during a median follow-up of 3.5 years.

The study was approved by a regional scientific ethics committee and the Danish Data Protection Agency and complied with the second declaration of Helsinki.

The culprit lesion was determined by coronary angiography, and multivessel disease was defined as more than 1 obstructed coronary artery. All patients were treated with primary PCI according to contemporary guidelines. Patients received loading doses of 300 mg acetylsalicylic acid, 600 mg clopidogrel, and 10,000 units of unfractionated heparin prior to PCI. The PCI operator decided whether patients should receive additional treatment in the form of glycoprotein inhibitors. In accordance with contemporary guidelines, patients were subsequently started in a relevant post-MI regimen including antithrombotic drugs, cholesterol-lowering drugs, and β-antagonists.

The primary end point was a composite of HF hospitalization and/or CVD (HF/CVD). We used time to first event analysis. Data on HF hospitalization were obtained through ICD-10 diagnostic codes from the Danish Board of Health's National Patient Registry. Data on CVD were retrieved from the Danish Mortality Registry.

All echocardiograms were performed by either experienced clinicians or sonographers with a standardized protocol. The examinations were performed on GE Vivid 7 ultrasound machines using a 3.5 MHz probe. The echocardiograms were analyzed offline (EchoPac BT 112, GE Healthcare, Horten, Norway) by an investigator in a blinded manner.

LV dimensions were measured in the parasternal long-axis view at the base of the ventricle in end-diastole with an angle perpendicular to the given structures. These dimensions were used for calculation of the LV mass index by Deveraux's formula. The Simpson's biplane method was used for measuring the LVEF. Wall motion score index (WMSI) was estimated by the 16-segment international model.[12] The left atrial volume (LAV) was measured at end-systole by the biplane area-length method and indexed to body surface area. Transmitral inflow patterns were measured by pulsed-wave Doppler imaging in the apical 4-chamber view with the sample placed at the tip of the mitral valve leaflets. This provided the E (early diastolic filling), A (late diastolic filling), E/A-ratio and the E-wave deceleration time (DT). Pulsed-wave tissue Doppler imaging was sampled at the mitral annulus in the septal and lateral wall in the apical 4-chamber view to obtain the early ventricular myocardial relaxation velocity (PW-e'). Indexation with E-wave velocity by transmitral inflow was performed to calculate the E/e' as an estimate of LV filling pressure. Patients were grouped by diastolic dysfunction grades based on PW-e', E/A-ratio, E/e' and DT according to the 2009 diastolic dysfunction guidelines.[13]

A curved M-mode line was placed through the mitral leaflets coaptation point in the apical 4-chamber view to obtain a color-coded M-mode diagram. This was used to place the cardiac time intervals and calculate the isovolumetric contraction time, ejection time, isovolumetric relaxation time, and the myocardial performance index.[9] The 3 apical projections were used for obtaining peak longitudinal myocardial velocities (systolic: global s'; early diastolic: global e', late diastolic: global a') with samples placed in the mitral annulus in all 6 myocardial walls and global measures were calculated as averages from the 6 regions. Longitudinal displacement (LD) was measured with the same samples by the use of tissue tracking modality

Speckle tracking was performed from the 3 apical projections by a semiautomatic technique. The investigator could modify the region of interest to properly cover all 3 layers of the LV wall. Segments could be excluded at the discretion of the investigator. The software calculated and provided an estimate of the global longitudinal strain (GLS) for each projection. The 3 projections were then averaged to obtain an overall GLS. The same was the case for global longitudinal strain rates (global systolic strain rate: GLSRs; global early diastolic strain rate: GLSRe). The GLSRe was indexed to the E-wave to obtain the E/GLSRe.

Statistics were performed with STATA SE v. 13.1 (StataCorp LP, College Station, Texas). A p value <0.05 was

considered statistically significant in all analyses. Categorical variables were compared between outcome groups by X^2 test and expressed as percentages. Continuous variables exhibiting Gaussian distribution were compared by Student's t-test and expressed as means ± standard deviation (SD), whereas variables not showing Gaussian distribution were compared by Wilcoxon signed-rank test and expressed as medians with interquartile ranges [IQR].

All echocardiographic parameters (LVEF, WMSI, E/A, DT, E/e', PW-e', LAV, diastolic dysfunction grade, GLS, GLSRs, GLSRe, E/GLSRe, global s', global e', global a', global LD, isovolumetric contraction time, isovolumetric relaxation time, ejection time) were incorporated in a stepwise backward Cox proportional hazards regression to identify the most influential echocardiographic predictors of outcome. Echocardiographic and clinical predictors were incorporated in a multivariable Cox regression model to account for potential confounders and to obtain adjusted hazard ratios (HR). We tested for collinearity by calculating variation inflation factor (VIF) with a VIF threshold of 5.

Harrell's C-statistics were calculated from univariable Cox regression models for the univariable echocardiographic predictors of outcome.

The same echocardiographic parameters which were included in the stepwise backward Cox regression were also included in a classification and regression tree analysis (CART) to obtain the optimal risk stratification scheme (Figure 1). CART analysis performs continuous dichotomous partitioning of variables based on their best predictive ability. It starts with 1 variable being split up into 2 overall risk categories. The model then continues by applying a secondary parameter to the split variables from the initial parameter, and this secondary parameter is also partitioned based on its predictive ability. This algorithm continues until a stop code is assigned. This results in a binary decision tree.

Clinical and echocardiographic characteristics were also determined with patients stratified by the risk groups determined by the CART analysis and p for trend across categories was tested. The risk groups were incorporated in the same multivariable Cox regression as for the echocardiographic predictors. Kaplan-Meier curves were constructed for the population stratified by the risk categories obtained by the CART analysis, and the differences in outcome between the groups were tested with the log-rank test (Figure 2).

We used Grønnesby-Borgan X^2 to test how well our risk model calibrated with respect to predicting HF/CVD in our derivation cohort (Figure 3) and in the external validation cohort (Figure 4). C-statistics were calculated for our risk model in both our derivation cohort and in the external validation cohort to assess the discrimination. Secondly, we applied our risk model in the validation cohort and visually displayed the predictive capability by Kaplan-Meier curves stratified by the 3 risk categories obtained from the cut-off-values derived from the CART analysis (Figure 5). Differences in outcome were tested with the log-rank test.

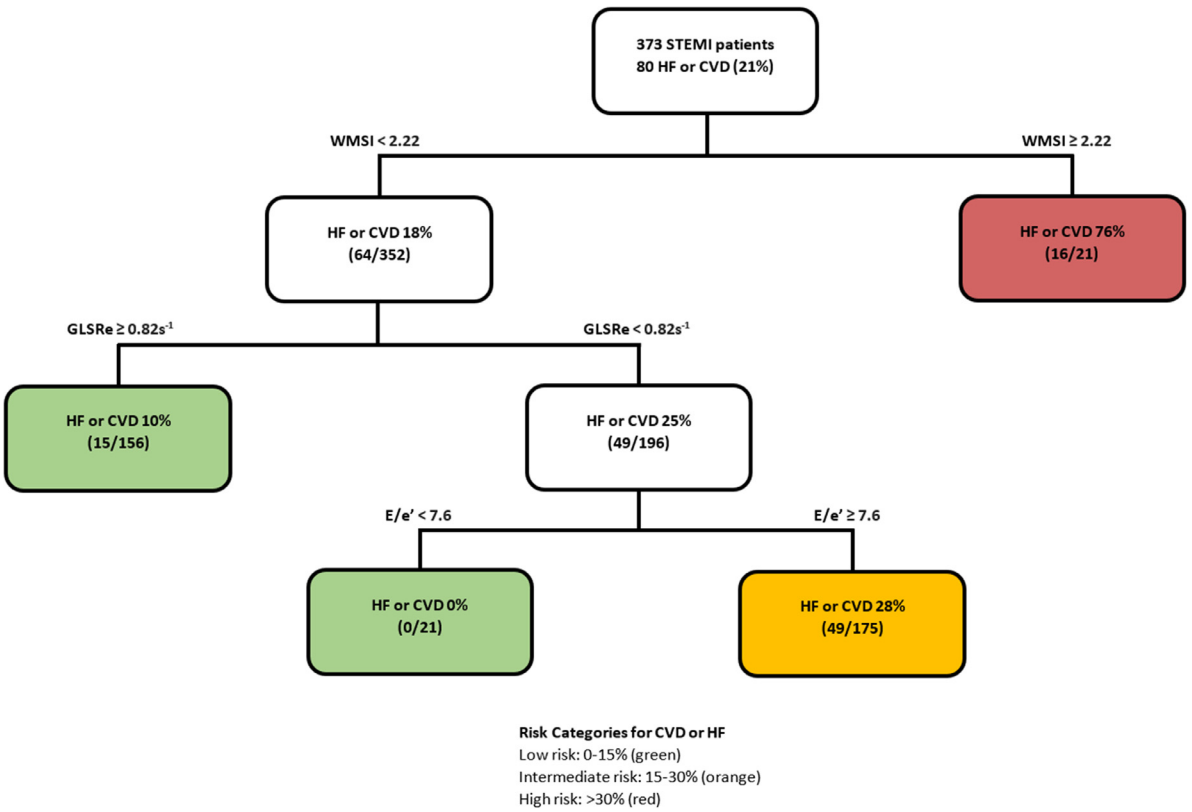

Figure 1. Risk stratification model

The CART analysis initially included all echocardiographic predictors but selected 3 parameters to stratify patients with regards to the risk of heart failure and/or cardiovascular death. CART = classification and regression tree; CVD = cardiovascular death; GLSRe = global longitudinal early diastolic strain rate; HF = heart failure; STEMI = ST-elevation myocardial infarction; WMSI = wall motion score index.

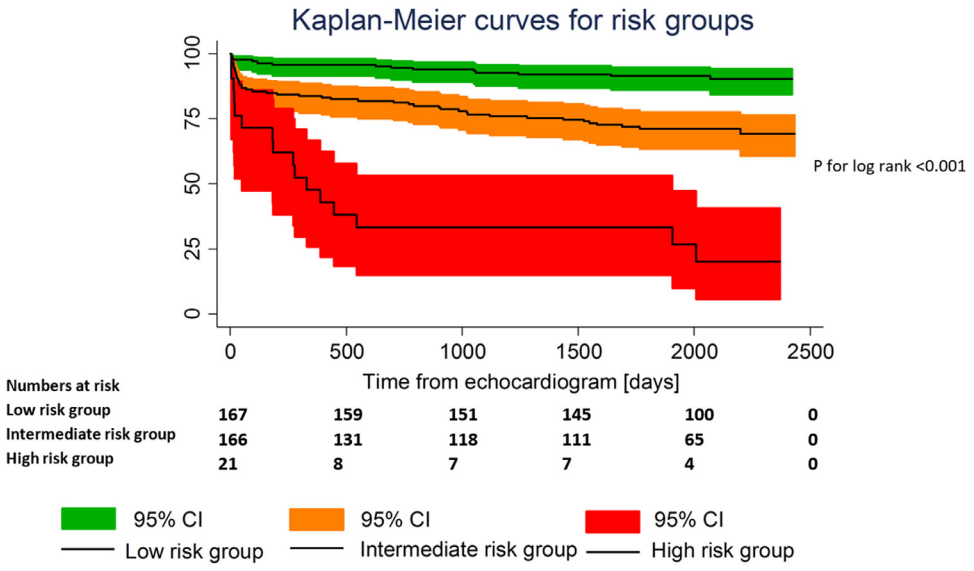

Figure 2. Kaplan-Meier curves for risk groups
Patients are stratified and plotted by risk groups defined by the classification and regression tree analysis. The curves show an incremental increase in the probability of heart failure hospitalization and/or cardiovascular death with increasing risk group assignment.

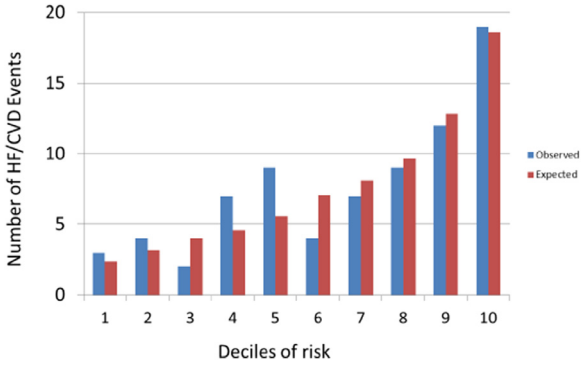

Figure 3. Internal calibration between observed and predicted events
X-axis represents the population split into deciles of risk of events. HF/CVD events are shown on the y-axis. Red bars represent the expected number of events in the cohort and blue bars represent the number of events predicted by our risk model. HF/CVD = heart failure/cardiovascular death.

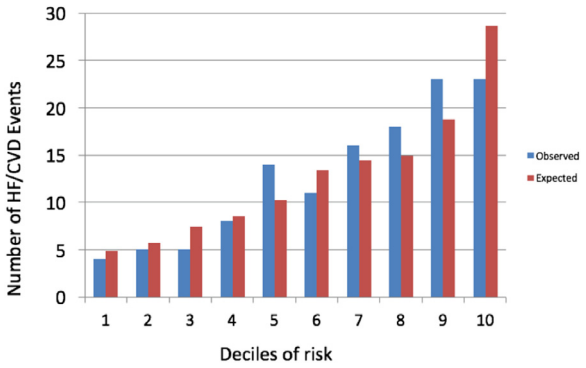

Figure 4. External calibration between observed and predicted events
X-axis represents the population split into deciles of risk of events. HF/CVD events are shown on the y-axis. Red bars represent the expected number of events in the cohort and blue bars represent the number of events predicted by our risk model. HF/CVD = heart failure/cardiovascular death.

Results

Of the 373 patients in our derivation cohort, 80 experienced HF (n = 70), CVD (n = 13), or both (n = 3) over a median follow-up period of 5.4 years (IQR: 4.1; 6.0 years; follow-up rate, 100%). Baseline characteristics for the derivation cohort and stratified by the outcome are presented in Table 1.

In brief, the mean age of the entire population was 62 years, there was a higher proportion of men, a third of patients had hypertension, and half of the patients were smokers, but aside from this, risk factors were not common. The mean LVEF for the entire population was 46% and diastolic dysfunction was prevalent in 75%. Those who developed HF/CVD more often had diabetes, more were nonsmokers, had higher peak troponin, and more had the LAD as the culprit lesion compared with those free of events. They also had more impaired systolic function and more extensive diastolic dysfunction.

When all echocardiographic measures were included in a backward stepwise Cox regression, only 4 parameters were determined as significant predictors of outcome: GLS (HR = 1.15 (1.03-1.28), p = 0.01, per 1% decrease), WMSI (HR = 2.28 (1.01-5.14), p = 0.046, per 1 increase), E/e' (HR = 1.06 (1.01-1.12), p = 0.020, per 1 increase), E/GLSRe (HR = 1.62 (1.01-2.59), p = 0.044, per 1 increase). When these were included in a multivariable Cox regression, which also encompassed potential clinical and biochemical confounders (age, diabetes, eGFR, troponin I, smoking status, and systolic blood pressure) only WMSI remained an independent significant predictor of outcome (HR = 3.23 (1.56-6.70), p = 0.002, per 1 increase). We did not observe any collinearity in this model (VIF<5 for all measures). Of all echocardiographic parameters, WMSI also provided the highest C-statistics, followed closely by LVEF and GLS. Among the diastolic measures, GLSRe provided the highest C-statistics (c-stat = 0.648), followed by the E/GLSRe (c-stat = 0.626) and PW-e' (c-stat = 0.612).

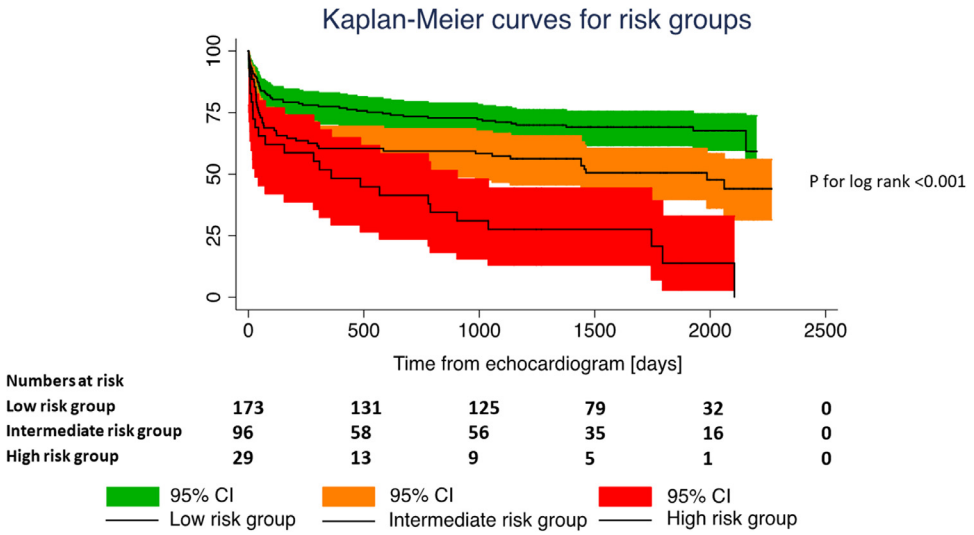

Figure 5. Kaplan-Meier curves for risk groups in the validation cohort
Patients are stratified and plotted by risk groups defined by the classification and regression tree analysis. The curves show an incremental increase in the probability of heart failure hospitalization and/or cardiovascular death with increasing risk group assignment.

The CART analysis revealed WMSI, E/e', GLSRe as the most important variables in a risk stratification scheme (Figure 1). It designated patients with WMSI ≥ 2.22 as high risk subjects, patients with WMSI < 2.22, GLSRe < 0.82, and E/e' ≥ 7.6 as intermediate risk subjects, and patients with either WMSI < 2.22 and GLSRe ≥ 0.82 or WMSI < 2.22, GLSRe < 0.82, and E/e' < 7.6 as low risk subjects. There was not collinearity between these selected variables (VIF<5 for all measures).

With the patients stratified based on the risk groups proposed by the CART analysis (Table 2), it became apparent that patients in the high-risk group did not represent the oldest patients, and did not contain the majority of hypertensives. However, the high-risk group contained relatively more diabetics, had more extensive MI, and less successful reperfusion. The high-risk group also had more LV dilatation compared to the other risk groups and more pronounced LV mass. Particularly diastolic dysfunction differed markedly between the three risk groups, and the high-risk group also had significantly worse systolic function. Incidence rates revealed an increased risk of outcome across all risk groups (Table 2). The univariable Cox regression showed the intermediate and high-risk categorizations were significant predictors of outcome compared with the low-risk group, which was consistent after multivariable adjustment (Table 3). None of the echocardiographic predictors remained independent predictors of the outcome when included in this multivariable model with the risk groups. We did not observe any collinearity in this model (VIF < 5 for all measures).

The incremental risk of experiencing the outcome when stratified by the risk groups was visually displayed from the Kaplan-Meier curves (Figure 2).

Our calibration test showed that our risk model calibrated well to predict outcome in our derivation cohort as shown by a nonsignificant difference in predicted and observed number of events in the different risk categories (Grønnesby-Borgan X^2 statistic of 7.6, p = 0.58, see Figure 3). C-statistic for discrimination was: 0.69

Baseline characteristics for the validation cohort are shown in supplemental Table 1.

Our calibration test showed that our risk model calibrated well to predict HF/CVD in the independent validation cohort of STEMI patients as determined by a nonsignificant difference between predicted and observed number of HF/CVD outcomes (Grønnesby-Borgan X^2 statistic of 6.5, p = 0.69, see Figure 4). When we applied the risk model in the external validation cohort, we observed a risk stratification similar to the one observed in the derivation cohort with an incremental risk of HF/CVD with increasing risk group assignment (Figure 5). C-statistic for discrimination was 0.71.

Discussion

Several individual echocardiographic measures have been established as predictors of outcome, but to our knowledge, this is the first study to create and validate an echocardiographic risk model based on comprehensive echocardiographic analyses. The identified predictors confirm findings from previous studies, whereas the novelty of this study lies in terms of how to approach this clinically by the use of an echocardiographic risk model. This was emphasized in our CART analysis, which yielded a very simple algorithm with proposed cut-off values, and thus comprehensible to clinicians.

Although we now preside over a wide list of known echocardiographic predictors of outcome following acute MI, clinical guidelines rely on LVEF as the only echocardiographic marker in terms of risk prediction,[2] indicating that the accumulating evidence on echocardiographic risk markers has not yet seen fit to translate into practice. The consequence is that the risk stratification process relies on the individual judgment of the clinician, and although the use of many echocardiographic variables is theoretically feasible, a dedicated risk algorithm could be a time-efficient tool that may ease and streamline the clinical practice.

Table 1
Derivation cohort: Baseline characteristics

Variable	All n = 373	No HF and/or CVD n = 293	HF and/or CVD n = 80	p value
Age (years)	62 ± 11	62 ± 11	64 ± 12	0.11
Men	280 (75%)	217 (74%)	63 (79%)	0.39
Prior myocardial infarctoin	17 (5%)	12 (4%)	5 (6%)	0.41
Hypertension	119 (32%)	98 (33%)	21 (26%)	0.22
Hypercholesterolemia	62 (17%)	48 (16%)	14 (18%)	0.81
Diabetes mellitus	32 (9%)	20 (7%)	12 (15%)	0.021
Current smoker	193 (52%)	160 (55%)	33 (41%)	0.034
Body mass index (kg/m^2)	27 ± 4	27 ± 4	26 ± 5	0.39
Heart rate (beats per minute)	77 ± 24	76 ± 24	80 ± 25	0.24
Systolic blood pressure (mm Hg)	136 ± 26	134 ± 25	142 ± 29	0.03
Diastolic blood pressure, (mm Hg)	82 ± 17	81 ± 16	85 ± 20	0.06
Symptom-to-balloon time (minutes)	190 [126;306]	180 [120;300]	200 [142;366]	0.11
Estimated glomerular filtration rate (mL/min/1.73m^2)	74 ± 22	76 ± 21	69 ± 24	0.009
Troponin I (μg/L)	110 [29;232]	94 [26;217]	161 [42;295]	0.017
C-reactive peptide (mg/L)	3 [1;8]	3 [1;7]	4 [2;17]	0.007
Culprit coronary narrowing				
-Left anterior descending artery	178 (48%)	132 (45%)	46 (58%)	0.048
-Right coronary artery	152 (41%)	125 (43%)	27 (34%)	0.15
-Circumflex artery	42 (11%)	36 (12%)	6 (8%)	0.23
Multivessel coronary disease	103 (28%)	80 (27%)	23 (29%)	0.80
Thrombolysis in myocardial infarction flow grade*				0.042
-0	13 (4%)	12 (4%)	1 (1%)	
-1	17 (5%)	9 (3%)	8 (10%)	
-2	31 (8%)	25 (9%)	6 (8%)	
-3	307 (83%)	243 (84%)	64 (81%)	
Echocardiography				
Left ventricular interal diameter (cm)	4.9 ± 0.7	4.8 ± 0.6	5.1 ± 0.7	<0.001
Left ventricular mass index (g/m^2)	91 [75;111]	89 [74;106]	101 [82;121]	<0.001
Left atrial volume index (mL/m^2)	25 ± 7	25 ± 7	25 ± 7	0.50
E/A	1.1 ± 0.4	1.1 ± 0.4	1.1 ± 0.4	0.67
Deceleration time (ms)	199 ± 55	200 ± 52	196 ± 66	0.66
e'(cm/s)	7.4 ± 2.2	7.6 ± 2.2	6.7 ± 2.0	0.001
E/e'	10 [8;13]	10 [8;12]	11 [9;15]	0.005
Diastolic dysfunction				0.002
-Normal	104 (28%)	90 (31%)	14 (18%)	
-Grade 1	83 (23%)	66 (23%)	17 (21%)	
-Grade 2	156 (42%)	119 (41%)	37 (46%)	
-Grade 3	25 (7%)	13 (5%)	12 (15%)	
Left ventricular ejection fraction (%)	46 ± 9	47 ± 8	41 ± 10	<0.001
Wall motion score index	1.6 [1.3;1.9]	1.5 [1.3;1.8]	1.8 [1.4;2.2]	<0.001
Speckle tracking				
Frame rate (frames/second)	85 ± 23	87 ± 22	81± 24	0.05
Global longitudinal strain (%)	−12 ± 4	−13 ± 4	−11 ± 4	<0.001
Systolic strain rate (s^{-1})	−0.72 ± 0.21	−0.75 ± 0.20	−0.62 ± 0.19	<0.001
Diastolic strain rate (s^{-1})	0.79 ± 0.30	0.83 ± 0.29	0.67 ± 0.27	<0.001
E/diastolic strain rate	1.10 ± 0.58	1.04 ± 0.47	1.35 ± 0.82	<0.001
Tissue Doppler Imaging				
Isovolumic relaxation time (ms)	103 ± 23	103 ± 21	103 ± 27	0.87
Isovolumic contraction time (ms)	31 ± 14	30 ± 13	37±15	<0.001
Ejection time (ms)	256 ± 32	259 ± 30	247 ± 37	0.005
Myocardial performance index (%)	53 ± 14	52 ± 13	58 ± 17	0.001
Global s' (cm/s)	5.2 ± 1.1	5.4 ± 1.1	4.8 ± 1.2	<0.001
Global e' (cm/s)	−5.6 ± 1.8	−5.7±1.8	−5.0 ± 1.7	0.002
Global a' (cm/s)	−6.4 ± 1.6	−6.5±1.5	−6.1 ± 1.6	0.05
Global longitudinal displacement (mm)	8.4 ± 2.2	8.7 ± 2.1	7.3 ± 2.3	<0.001

Continuous variables exhibiting Gaussian distribution are expressed as means ± standard deviation. Those not showing Gaussian distribution are expressed as medians with interquartile ranges.

a' = late diastolic myocardial tissue velocity; e' = early diastolic myocardial tissue velocity; E/A = ratio of early to late transmitral inflow velocities; E/e' = ratio of early transmitral inflow velocity to early diastolic myocardial tissue velocity; s' = systolic myocardial tissue velocity.

* Thrombolysis in myocardial infarction flow grade was assessed postreperfusion.

Table 2
Derivation cohort: Characteristics stratified by risk groups

	Low-risk group (n = 167) WMSI < 2.22 and GLSRe ≥ 0.82s^{-1} *or* WMSI < 2.22, GLSRe < 0.82s^{-1} and E/e' < 7.6	Intermediate risk group (n = 166) WMSI < 2.22, GLSRe < 0.82s^{-1} E/e' ≥ 7.6	High-risk group (n = 21) WMSI ≥ 2.22	p value
Incidence rate (per 100 patient/year)	1.73 (1.04-2.87)	6.88 (5.17-9.16)	34.07 (20.87-55.61)	
Age (years)	59 ± 10	66 ± 12	60 ± 12	<0.001
Men	127 (76%)	124 (75%)	16 (76%)	0.86
Prior myocardial infarction	6 (4%)	6 (4%)	2 (10%)	0.42
Hypertension	41 (25%)	66 (40%)	7 (33%)	0.014
Hypercholesterolemia	23 (14%)	33 (20%)	4 (19%)	0.18
Diabetes mellitus	4 (2%)	21 (13%)	4 (19%)	<0.001
Current smoker	97 (58%)	74 (45%)	12 (57%)	0.09
Body mass index (kg/m^2)	26 ± 4	27 ± 4	26 ± 5	0.40
Estimated glomerular filtration rate (mL/min/m^2)	77 ± 20	72 ± 22	75 ± 28	0.40
Troponin I (μg/L)	78 [26;186]	153 [35;252]	203 [56;546]	<0.001
C-reactive peptide (mg/L)	3 [1;5]	4 [2;12]	9 [3;19]	<0.001
Culprit coronary narrowing				
-Left anterior descending artery	62 (37%)	90 (54%)	14 (67%)	<0.001
-Right coronary artery	82 (49%)	59 (36%)	5 (24%)	0.002
-Circumflex artery	23 (14%)	16 (10%)	2 (10%)	0.26
Multivessel coronary disease	42 (25%)	47 (28%)	7 (33%)	0.36
Thrombolysis in myocardial infarction flow grade*				0.023
-0	3 (2%)	9 (6%)	1 (5%)	
-1	3 (2%)	10 (6%)	3 (14%)	
-2	15 (9%)	12 (7%)	2 (10%)	
-3	143 (87%)	133 (81%)	15 (71%)	
Echocardiography				
Left ventricular internal diameter (cm)	4.8 ± 0.6	4.9 ± 0.7	5.5 ± 0.9	<0.001
Left ventricular mass index (g/m^2)	86 [70;99]	95 [78;118]	109 [93;134]	<0.001
Left atrial volume index (mL/m^2)	24 ± 7	25 ± 7	27 ± 7	0.17
E/A	1.2 ± 0.3	1.0 ± 0.4	1.1 ± 0.5	<0.001
Deceleration time (ms)	196 ± 50	204 ± 59	181 ± 73	0.86
e' (cm/s)	8.9 ± 2.0	6.3 ± 1.5	5.4 ± 1.4	<0.001
Diastolic dysfunction				<0.001
-Normal	92 (55%)	10 (6%)	0 (0%)	
-Grade 1	19 (11%)	56 (34%)	5 (25%)	
-Grade 2	51 (31%)	85 (52%)	8 (40%)	
-Grade 3	4 (2%)	13 (8%)	7 (35%)	
Left ventricular ejection fraction (%)	49 ± 8	44 ± 8	32 ± 8	<0.001
Speckle tracking				
Global longitudinal strain (%)	−15 ± 3	−11 ± 2	−7 ± 2	<0.001
Systtolic strain rate (s^{-1})	−0.84 ± 0.19	−0.65 ± 0.15	−0.44 ± 0.18	<0.001
E/GLSRe	0.81 ± 0.22	1.30 ± 0.51	1.71 ± 1.25	<0.001
Tissue Doppler Imaging				
Isovolumic relaxation time (ms)	96 ± 18	109 ± 25	103 ± 25	<0.001
Isovolumic contraction time (ms)	27 ± 10	33 ± 12	50 ± 30	<0.001
Ejection time (ms)	265 ± 26	251 ± 31	219 ± 31	<0.001
Myocardial performance index (%)	47 ± 9	58 ± 15	70 ± 16	<0.001
Global s' (cm/s)	5.7 ± 1.1	5.0 ± 0.9	3.9 ± 1.0	<0.001
Global e' (cm/s)	−6.7 ± 1.6	-4.7 ± 1.4	−3.9 ± 1.0	<0.001
Global a' (cm/s)	−6.5 ± 1.5	−6.5±1.5	−5.5 ± 1.5	0.22
Global longitudinal displacement (mm)	9.5 ± 2.1	7.8 ± 1.8	5.1 ± 1.7	<0.001

Continuous variables exhibiting Gaussian distribution are expressed as means ± standard deviation. Those not showing Gaussian distribution are expressed as medians with interquartile ranges.

a' = late diastolic myocardial tissue velocity; e' = early diastolic myocardial tissue velocity; E/A = ratio of early to late transmitral inflow velocities; E/e' = ratio of early transmitral inflow velocity to early diastolic myocardial tissue velocity; GLSRe = diastolic strain rate; s' = systolic myocardial tissue velocity; WMSI = wall motion score index.

* Thrombolysis in myocardial infarction flow grade was assessed postreperfusion.

Table 3
Derivation cohort: Cox regression analysis with risk groups

	Univariable model			Multivariable model[§]	
	HR (95% CI)	p value	c-stat	HR (95% CI)	p value
GLS, per % decrease	1.20 (1.13-1.28)	<0.001	0.659	1.02 (0.90-1.15)	0.78
WMSI, per 1 increase	5.61 (3.31-9.49)	<0.001	0.680	1.65 (0.63-4.37)	0.31
LVEF, per % decrease	1.07 (1.04-1.09)	<0.001	0.664	1.03 (0.99-1.06)	0.13
E/e', per 1 increase	1.06 (1.02-1.10)	0.006	0.582	1.00 (0.96-1.05)	0.85
E/GLSRe, per 1 increase	1.63 (1.32-2.02)	<0.001	0.623	1.11 (0.68-1.79)	0.68
Age, per year increase	1.02 (1.00-1.04)	0.057	0.558	1.00 (0.97-1.02)	0.77
Male gender	1.24 (0.73-2.12)	0.427	0.518		
Diabetes mellitus	2.06 (1.12-3.81)	0.021	0.532	1.48 (0.73-3.01)	0.28
Current smoker	0.62 (0.40-0.96)	0.034	0.567	0.62 (0.38-1.03)	0.06
Systolic blood pressure, per mm Hg increase	1.01 (1.00-1.02)	0.036	0.554	1.01 (1.00-1.02)	0.20
Estimated glomerular filtration rate, per 1 mL/min increase	1.01 (1.00-1.02)	0.014	0.571	1.00 (0.98-1.01)	0.53
Culprit coronary lesion: left anterior descending artery	1.54 (0.99-2.39)	0.058	0.552		
Troponin quartiles					
Troponin I < 28.7 μg/L	Reference group		0.591	Reference group	
Troponin I: 28.7-110.0 μg/L	1.47 (0.74-2.92)	0.27		1.34 (0.64-2.79)	0.44
Troponin I: 110.0-238 μg/L	1.18 (0.58-2.42)	0.65		0.93 (0.42-2.07)	0.86
Troponin I > 238 μg/L	2.48 (1.31-4.67)	0.005		1.36 (0.63-2.91)	0.43
C-reactive peptide >3mg/L	1.38 (0.88-2.16)	0.16	0.540		
Thrombolysis in myocardial infarction flow grade	0.92 (0.69-1.23)	0.58	0.515		
Low-risk group*	Reference group		0.697		
Intermediate risk group[†]	3.67 (2.05-6.56)	<0.001		2.52 (1.24-5.11)	0.011
High risk group[‡]	14.28 (7.03-29.04)	<0.001		4.37 (1.40-13.66)	0.011

GLS = global longitudinal strain; GLSRe = global longitudinal early diastolic strain rate; HR = hazard ratio; WMSI = wall motion score index.
* WMSI < 2.22 and GLSRe $\geq 0.82s^{-1}$ *or* WMSI < 2.22 and GLSRe $< 0.82s^{-1}$ and E/e' < 7.6.
† WMSI < 2.22, GLSRe $< 0.82s^{-1}$ and E/e' $\geq$ 7.6.
‡ WMSI $\geq$ 2.22.
§ Adjusted for significant clinical predictors, age and the established echocardiographic predictors.

Our proposed risk model suggested WMSI, E/e', and GLSRe to be target variables, and all have previously shown predictive value.[14–17] Although LVEF remains the cornerstone post-MI, it does not account for regional dysfunction, and in the case of acute MI, a compensatory hyperkinetic response from outside the culprit lesion area may serve to uphold the LVEF.[18] An assessment by WMSI may detect these regional disparities and therefore be more useful in the post-MI setting. However, whether WMSI is preferable to GLS is unclear with conflicting evidence on the field that is insufficient to favor one measure over the other.[17,19,20] The choice of method should rely on practical considerations. GLS is favored by the automated software theoretically subject to less variability than WMSI, which is more dependent on experience. Our findings with regards to WMSI are in line with the study of Munk et al[17], but at odds with other studies. This may be explained by the fact that echocardiographic analyses, including WMSI, were performed by an experienced clinician with unlimited time for analyses. In a clinical setting, considering the time spared by using speckle tracking, particularly in clinics with limited expertise and experience in assessing WMSI, GLS seems favorable. Indeed, although our model did not select GLS in the algorithm, it was nevertheless a strong predictor of outcome. With regard to the other measures in the algorithm, E/e' has shown prognostic value in several cohorts as it reflects filling pressure, and GLSRe may serve as a more global assessment of LV stiffness and combined they, therefore, give a robust evaluation of diastolic dysfunction. Another important finding from our model was that the risk categorization provided a higher predictive value as shown from the C-statistics than the individual echocardiographic measures, suggesting that a combined approach yields more information than by considering individual measures.

Recently, Prastaro et al comprehensively outlined the evidence of different measures in an expert review, and even though Prastaro et al recognized the studies to be heterogeneous in terms of population selection, outcomes, and time periods, they still proposed an algorithm to guide risk stratification.[8] This algorithm encompasses an assessment of LVEF, mitral regurgitation grade, diastolic dysfunction, GLS, pulmonary artery pressure and RV strain to assess prognosis after acute MI. However, the proposed algorithm relies on the authors' expert opinion as a synthesis from the available evidence, and the algorithm in itself is not evidence-based. Furthermore, it offers no explanation of how the variables in the model were selected. Until this model has been tested or validated, a cautious approach should be made in recommending this model.

Other algorithms, not based on echocardiography, such as the GRACE score have also been investigated and are in use clinically for prognostic assessment.[21] However, this score focuses strictly on the risk of all-cause mortality and on a short-term basis. We did not have the clinical information to investigate if the echocardiographic variables would add prognostic information in addition to this clinical risk score. However, it should be noted that although the high-risk group by our model had more extensive MI and less

successful reperfusion, the risk of outcome was not driven by established cardiovascular risk factors such as age, gender, hypertension, etc., suggesting that our model detects patients at high risk who may be designated low risk based on the clinical features. Furthermore, the GRACE score divides patients in low, intermediate and high risk based on cut-offs for ST-elevation MI of 4.4% and 11% for 6 months outcome. Our model used wider ranges of risk, with a different end point and longer follow-up, and the model should, therefore, be interpreted in the context of this framework.

We excluded patients with atrial fibrillation rhythm during the echocardiogram since this arrhythmia often distorts the echocardiographic measures due to the highly variable pre- and afterload conditions. However, atrial fibrillation patients are often excluded in related studies, thus the potential predictors that we sought to investigate may not apply to these patients anyway. We used 2 different versions of EchoPac for analyses in the 2 cohorts because the validation cohort was analyzed at a time when we only had BT 113 available.

Our study did not include Killip class, which is an established clinical way of predicting mortality post-MI. However, this classification pertains to 30-day mortality and we investigated long-term outcomes. Finally, we do not have data on medication, which could represent residual confounders.

By extension, since the validation cohort was extracted from a clinical registry we did not have information symptom-to-balloon time, prior MI nor biochemical data.

In conclusion, in patients with STEMI treated with pPCI, we devised an echocardiographic risk model. The model suggests that by only considering 3 measures (WMSI, GLSRe and E/e') clinicians can risk-stratify patients in a simple and efficient manner without having to consider a large variety of other proposed predictors of outcome. This may ease and streamline the risk assessment in the clinic.

Disclosures

None.

Author Contributions

FJO: Conceptualization, methodology, formal analysis, writing – original draft and editing.

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KGS: Methodology, investigation, review, editing and final approval of manuscript.

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Supplementary materials

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