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Measurement of left ventricular end-diastolic pressure improves the prognostic utility of the Global Registry of Acute Coronary Events score in patients with ST-segment elevation myocardial infarction

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KEYWORDS

- depressed left ventricular function
- risk stratification
- STEMI

Abstract

Aims: This study aimed to evaluate the clinical significance of measuring left ventricular end-diastolic pressure (LVEDP) in patients with ST-segment elevation myocardial infarction (STEMI).

Methods and results: We retrospectively analysed clinical data from 277 patients with STEMI between October 2006 and June 2014. LVEDP and left ventricular ejection fraction (LVEF) were perioperatively measured during percutaneous coronary intervention (PCI). The primary endpoint was a major adverse cardiac event (MACE) such as cardiac death, non-fatal myocardial infarction, or hospitalisation due to heart failure during the observation period. The independent predictors were identified by Cox proportional hazards regression analysis. Continuous net reclassification improvement (cNRI) and integrated discrimination improvement (IDI) were conducted to assess the incremental prognostic value of adding cardiovascular parameters, including LVEDP, to the Global Registry of Acute Coronary Events (GRACE) score. The mean follow-up period was 44±31 months. A MACE occurred in 33 patients (12.0%). In the Cox proportional hazards regression model, after adjusting for confounding factors, LVEDP was an independent predictor of a MACE (hazard ratio [HR] 1.11, 95% confidence interval [CI]: 1.06-1.17, p<0.001). In addition, the predictive value of the GRACE score for a MACE was significantly improved by LVEDP (NRI 0.66, 95% CI: 0.32-1.01, p<0.001; IDI 0.06, 95% CI: 0.02-0.11, p=0.001), but not by LVEF (NRI 0.14, 95% CI: -0.22-0.50, p=0.44; IDI 0.01, 95% CI: 0.00-0.03, p=0.11).

Conclusions: The results of this study demonstrated that evaluating LVEDP provides an additive prognostic value over conventional risks estimated by the GRACE score among STEMI patients.

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Abbreviations

GRACE	Global Registry of Acute Coronary Events
IABP	intra-aortic balloon pump
IDI	integrated discrimination improvement
LVEDP	left ventricular end-diastolic pressure
LVEDV	left ventricular end-diastolic volume
LVEF	left ventricular ejection fraction
MACE	major adverse cardiac event
NRI	net reclassification improvement
PCI	percutaneous coronary intervention
STEMI	ST-segment elevation myocardial infarction
TIMI	Thrombolysis In Myocardial Infarction

Introduction

The incidence of ST-segment elevation myocardial infarction (STEMI) remains a leading cause of morbidity and mortality in patients with atherosclerotic risk factors. Myocardial ischaemia (MI) after STEMI initiates both systolic and diastolic myocardial dysfunction with subsequent advanced left ventricular (LV) remodelling[1,2]. Therefore, the development of more physiologically integrative methods for predicting global LV function during the acute phase of STEMI may be required for a better prognosis. LV end-diastolic pressure (LVEDP) is easily obtained from catheterisation during the follow-up of patients with STEMI. Currently, there are accumulating data on LVEDP in predicting outcomes in patients with MI[3-5].

Risk stratification using clinical markers or parameters such as the Global Registry of Acute Coronary Events (GRACE) score has been widely used to predict clinical outcomes after STEMI[6,7]. However, the GRACE score lacks haemodynamic information defining LV systolic and diastolic function. Therefore, this study investigated the additive prognostic value of LVEDP over the GRACE score in patients with STEMI undergoing successful percutaneous coronary intervention (PCI).

Methods

STUDY POPULATION

This retrospective study analysed data from 277 consecutive patients who underwent PCI for STEMI at Toho University Omori Medical Center (Tokyo, Japan) between October 2006 and June 2014. Patients were included if they had STEMI with characteristic chest pain within 12 hours before hospital admission. All patients underwent successful PCI with subsequent left ventriculography (LVG) to measure LVEDP and LV ejection fraction (LVEF). STEMI was diagnosed by electrocardiography as (i) an ST elevation of ≥2 mm either in two contiguous anterior-lateral leads or in inferior leads, or (ii) a new left bundle branch block with concordant ST elevation of 1 mm[8]. Patients who lacked LVG data and had a Thrombolysis In Myocardial Infarction (TIMI) flow grade of <3 after PCI were excluded. This study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the relevant ethics committee at Toho University Faculty of Medicine (No. M16259). Baseline clinical information was obtained from medical records. Cardiovascular risk factors including diabetes, dyslipidaemia, hypertension, and current smoking were defined in accordance with the accepted criteria[9-11]. Baseline laboratory data and information on blood pressure and heart rate were collected at admission. Troponin I and creatinine kinase myocardial band (CK-MB) were measured at least twice a day, until peak values were recorded. For each patient, the GRACE risk score was calculated using eight specific variables collected upon admission as reported (http://www.gracescore.org/website/webversion.aspx).

The primary endpoint was a major adverse cardiac event (MACE), including cardiac death, non-fatal myocardial infarction, and heart failure requiring hospitalisation, during the observation period.

INVASIVE CORONARY ANGIOGRAPHY PROTOCOL

Primary PCI was performed according to standard methods[8]. Patients who received a diagnosis of STEMI were treated with 100 mg aspirin and either 150 mg clopidogrel or 200 mg ticlopidine before catheterisation. There was no case of thrombolysis during PCI. Procedural success was defined as a successful guidewire and balloon crossing with residual stenosis >50% and TIMI flow grade ≥3 after coronary stenting. Measurements of LVEDP and LVEF during LVG were performed as described[12].

STATISTICAL ANALYSIS

Data were analysed with the Statistical Package for EZR for Windows, Version 1.35 (Saitama Medical Center, Japan)[13]. Continuous variables are expressed as the mean±standard deviation. The Kolmogorov-Smirnov test was applied to test for normal distribution. Continuous variables were compared using the Student's t-test. Demographics, traditional risk factors, and clinical outcomes were compared using Pearson's chi-square test or Fisher's exact test, as appropriate, for categorical data, and were expressed as percentages. A Kaplan-Meier analysis was performed to calculate the unadjusted MACE rate according to the median value of LVEDP. Cox proportional hazards regression analysis was used to identify independent predictors of MACE during the observation period. The multivariate model was built by backward stepwise variable selection, with entry and exit criteria set at $p<0.05$. We used the area under the curve (AUC) by receiver operating characteristic for the prediction of MACE to assess the added value of LVEDP or LVEF over assessment of the GRACE score. Continuous net reclassification improvement (cNRI) and integrated discrimination improvement (IDI) were also used to investigate whether LVEDP or LVEF reclassified patients with respect to MACE risk relative to their GRACE score.

Results

PATIENT CHARACTERISTICS AND INCIDENCE OF MACE

We evaluated 277 patients hospitalised due to confirmed STEMI. During the mean follow-up period of 44±31 months, 33 patients (12.0%) developed a MACE **(Table 1)**. Patients with a MACE were older than those without a MACE. The GRACE score was

Table 1. Baseline characteristics of patients with and without a MACE.

		With a MACE (n=33)	Without a MACE (n=244)	*p*-value
Demographics				
Age, years		70.6±12.1	63.5±12.0	0.001
Male (%)		24 (72.7)	198 (81.1)	0.07
Body mass index		23.8±6.5	23.6±5.3	0.86
Diabetes (%)		12 (36.4)	74 (30.3)	0.54
Hypertension (%)		20 (60.6)	140 (57.4)	0.85
Dyslipidaemia (%)		10/33 (30.3)	97/244 (39.8)	0.34
Current smoking habit (%)		20 (60.6)	151 (62.1)	0.86
Previous MI (%)		3 (9.1)	10 (4.1)	0.19
Previous PCI (%)		4 (12.1)	11 (4.1)	0.08
Previous CABG (%)		0 (0)	1 (0.4)	0.99
Onset-to-balloon time, hours		4.4±2.5	4.2±2.7	0.71
Heart rate, bpm		74.3±27.3	74.7±19.7	0.90
Systolic blood pressure, mmHg		133.9±36.6	139.5±31.5	0.34
Killip class	I (%)	28 (84.9)	217 (88.9)	0.19
	II (%)	0 (0.0)	11 (4.5)	
	III (%)	4 (12.1)	9 (3.7)	
	IV (%)	1 (3.0)	7 (2.9)	
Laboratory data				
Peak troponin I, U/L		118.7±124.3	90.5±95.5	0.12
Peak CK-MB, U/L		323.2±299.1	259.5±242.5	0.17
Haemoglobin level, g/L		14.1±1.8	14.0±2.0	0.75
Creatinine, mg/dl		0.8±0.2	0.8±0.2	0.78
BNP, pg/mL		133.0±236.0	94.0±123.9	0.14
GRACE score		161.3±35.3	144.7±32.4	<0.001
Use of IABP		4 (12.1)	7 (2.9)	0.03
Medications before PCI				
Aspirin (%)		2 (6.1)	24 (9.8)	0.75
ARB (%)		3 (9.1)	32 (13.1)	0.78
ACE inhibitors (%)		1 (3)	6 (2.5)	0.59
Beta-blockers (%)		0 (0)	6 (2.5)	0.99
Statins (%)		1 (3)	19 (7.8)	0.48
Medications after PCI				
Aspirin (%)		33 (100)	244 (100)	0.99
ARB (%)		13 (39.4)	79 (32.4)	0.50
ACE inhibitors (%)		17 (51.5)	137 (56.1)	0.71
Beta-blockers (%)		26 (78.8)	177 (72.5)	0.53
Statins (%)		23 (69.7)	175 (72.0)	0.83

ACE inhibitor: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; BNP: brain natriuretic peptide; CABG: coronary artery bypass grafting; CK-MB: creatinine kinase-myocardial band; GRACE: Global Registry of Acute Coronary Events; IABP: intra-aortic balloon pump; MACE: major adverse cardiac event; MI: myocardial infarction; PCI: percutaneous coronary intervention

significantly higher and the use of an intra-aortic balloon pump (IABP) was more frequent in patients with a MACE relative to those who did not experience such an event. There was a tendency towards statistical significance in gender and prior PCI rates between the two groups. There was no significant difference in prescribed medications including angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, beta-blockers, and statins after STEMI between the two groups. **Table 2** shows the angiographic and haemodynamic data during catheterisation. There was no significant difference in the number of diseased vessels and the location of culprit lesions found with coronary angiography between the two groups. In contrast, LVEDP was significantly higher and LVEF was significantly lower in patients with a MACE. Among the MACE components, there were 13 cardiac deaths (5.0%), 10 incidents of non-fatal myocardial infarction (3.6%), and 10 hospitalisations due to heart failure (3.6%).

Table 2. Catheterisation analysis of patients with and without a MACE.

		With a MACE	Without a MACE	*p*-value
Angiographic data				
Number of diseased vessels	1 (%)	20 (60.6)	147 (60.2)	0.99
	2 (%)	12 (36.4)	71 (29.1)	
	3 (%)	1 (3.0)	26 (10.7)	
Culprit lesions	RCA (%)	10 (30.3)	90 (36.9)	0.42
	LAD (%)	21 (63.6)	125 (51.2)	
	LCX (%)	2 (6.1)	29 (11.9)	
TIMI flow=0 or 1 before PCI (%)		23 (69.7)	178 (73.0)	0.81
Haemodynamic data				
LVEDP, mmHg		26.6±6.9	21.2±6.9	<0.001
LVEF, %		51.4±14.7	55.6±11.2	<0.05

LAD: left anterior descending artery; LCX: left circumflex artery; LVEDP: left ventricular end-diastolic pressure; LVEF: left ventricular ejection fraction; MACE: major adverse cardiac event; PCI: percutaneous coronary intervention; RCA: right coronary artery; TIMI: Thrombolysis In Myocardial Infarction

ASSOCIATION BETWEEN HIGHER LVEDP AND THE INCIDENCE OF MACE

Patients were divided into two groups according to the median value of LVEDP (21 mmHg). As shown in **Table 3**, patients with LVEDP ≥21 mmHg had higher incidences of cardiac death, non-fatal myocardial infarction and MACE, as compared with patients with LVEDP <21 mmHg. Also, on Kaplan-Meier analysis, patients with LVEDP ≥21 mmHg showed higher rates of MACE incidence **(Figure 1)**.

INDEPENDENT PREDICTORS OF MACE

Age, use of IABP, LVEDP, LVEF, and GRACE score were applied to the Cox proportional hazards regression model to identify independent predictors of a MACE. In **Table 4**, after adjustment by

Table 3. Incidence of MACE components according to the median value of LVEDP (21 mmHg).

	LVEDP ≥21 mmHg	LVEDP <21 mmHg	*p*-value
MACE, n (%)	27 (18.5)	6 (4.6)	<0.001
Cardiac death, n (%)	11 (7.5)	2 (1.5)	0.02
Non-fatal MI, n (%)	9 (6.2)	1 (0.8)	0.02
Hospitalisation due to heart failure, n (%)	7 (4.8)	3 (2.3)	0.34

LVEDP: left ventricular end-diastolic pressure; MACE: major adverse cardiac event; MI: myocardial infarction

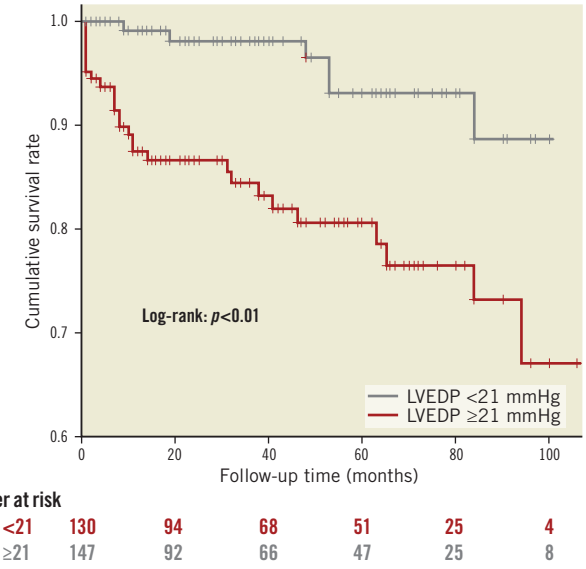

Figure 1. *Kaplan-Meier curves for MACE according to the median value of LVEDP (21 mmHg).*

these variables without LVEDP, age, use of IABP and LVEDP were associated with the incidence of a MACE (model 1). In the full adjusted model, LVEDP, age, and the use of IABP were found to be associated with the incidence of a MACE.

INCREMENTAL PROGNOSTIC VALUE OF LVEDP OVER THE GRACE SCORE

For the incidence of MACE, the incremental predictive value of LVEDP and LVEF over the GRACE score was evaluated. As shown in **Figure 2A** and **Figure 2B**, including the LVEF data with the GRACE score did not improve the area under the curve (AUC) for the GRACE score alone (p=0.54), but there was a tendency towards statistical significance for the LVEDP to increase the AUC over the GRACE score alone (p=0.06). In addition, we assessed the additive predictive value of the LVEDP or LVEF in combination with the GRACE score by cNRI and IDI. As shown in **Table 5**, the addition of LVEDP successfully recategorised patients based on the GRACE score alone, but the addition of LVEF did not.

Discussion

We evaluated the possibility of using LVEDP for the early risk stratification of patients with STEMI who were successfully treated by PCI. LVEDP was significantly higher in patients who developed a MACE. In addition, LVEDP provided an incremental prognostic value over the GRACE risk score according to reclassification analyses, but LVEF did not.

This study demonstrated that the LVEDP was superior to other common clinical factors such as infarct size and LVEF in predicting long-term outcomes after STEMI. Our negative impact of LVEF at admission was consistent with the data by Dutcher et al[7]. Of note, as was shown in the previous study, we also found that LVEF is an independent predictor of a MACE in multivariate

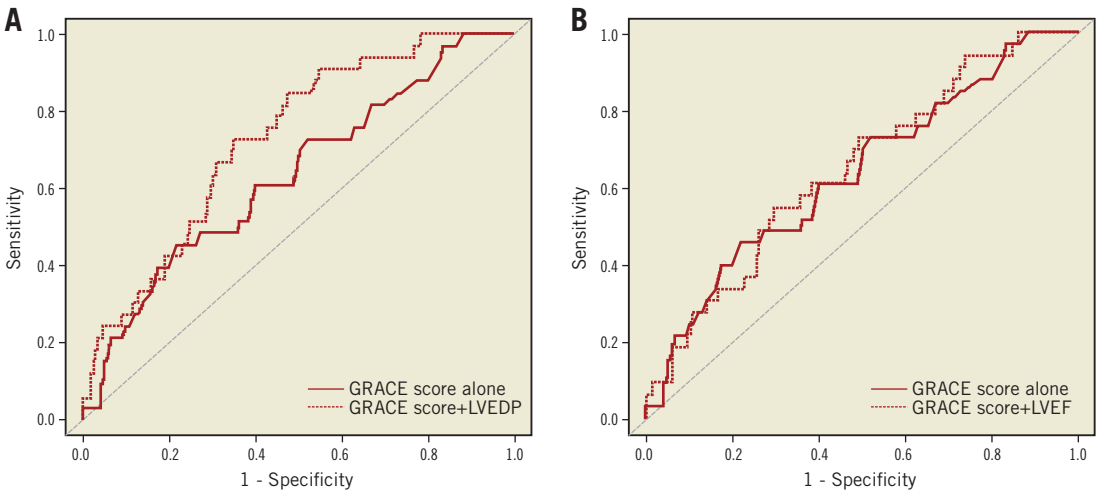

Figure 2. *The predictive value of LVEDP and LVEF by ROC curve analysis for MACE incidence. A) Comparison of the AUC to predict MACE between GRACE score and GRACE score + LVEDP. B) Comparison of the AUC to predict MACE between GRACE score and GRACE score + LVEF.*

Table 4. Cox proportional hazards regression model to predict a MACE.

	Univariate analysis		Multivariate analysis model 1		Multivariate analysis model 2	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age	1.05 (1.02-1.08)	<0.001	1.05 (1.02-1.09)	<0.001	1.07 (1.02-1.11)	<0.001
Male	0.71 (0.31-1.58)	0.4	–	–	–	–
Diabetes	1.28 (0.63-2.62)	0.48	–	–	–	–
Current smoking habits	0.91 (0.46-1.73)	0.79	–	–	–	–
Previous PCI	2.41 (0.84-6.88)	0.1	–	–	–	–
Killip class II or more	1.40 (0.92-2.13)	0.1	–	–	–	–
Baseline TIMI flow 0 or 1	1.08 (0.75-1.57)	0.65	–	–	–	–
Creatinine level	1.05 (0.20-5.32)	0.94	–	–	–	–
Haemoglobin level	1.00 (0.84-1.20)	0.93	–	–	–	–
BNP level	1.00 (0.00-1.00)	0.13	–	–	–	–
Peak CK-MB level	1.00 (0.99-1.00)	0.19	–	–	–	–
Use of IABP	4.33 (1.50-12.4)	<0.01	7.90 (2.60-24.0)	<0.001	4.28 (1.35-13.57)	0.01
Onset-to-balloon time	1.02 (0.90-1.15)	0.72	–	–	–	–
LAD culprit	1.79 (0.88-3.66)	0.1	–	–	–	–
LVEDP	1.11 (1.06-1.17)	<0.001	–	–	1.13 (1.06-1.20)	<0.001
LVEF	0.96 (0.93-0.99)	0.02	0.96 (0.94-0.99)	0.02	0.99 (0.96-1.02)	0.74
GRACE score	1.01 (1.00-1.02)	0.003	1.00 (0.99-1.01)	0.64	1.00 (0.98-1.01)	0.79

BNP: brain natriuretic peptide; CI: confidence interval; CK-MB: creatinine kinase-myocardial band; GRACE: Global Registry of Acute Coronary Events; HR: hazard ratio; IABP: intra-aortic balloon pump; LAD: left anterior descending artery; LVEDP: left ventricular end-diastolic pressure; LVEF: left ventricular ejection fraction; MACE: major adverse cardiac event; PCI: percutaneous coronary intervention; TIMI: Thrombolysis In Myocardial Infarction

Table 5. Reclassification analysis of patients based on the GRACE score alone and the GRACE score with the LVEDP or LVEF.

	AUC	*p*-value	cNRI	*p*-value	IDI	*p*-value
GRACE	0.63	–	–	–	–	–
LVEDP	0.71	–	–	–	–	–
LVEF	0.57	–	–	–	–	–
GRACE + LVEDP	0.72	0.06	0.66 (0.32-1.01)	<0.001	0.06 (0.02-0.11)	0.001
GRACE + LVEF	0.65	0.54	0.14 (–0.22-0.50)	0.44	0.01 (0.00-0.03)	0.11

AUC: area under the curve; cNRI: continuous net reclassification improvement; GRACE: Global Registry of Acute Coronary Events; IDI: integrated discrimination improvement; LVEDP: left ventricular end-diastolic pressure; LVEF: left ventricular ejection fraction

analysis[14]. However, this impact was eliminated when adjusted by LVEDP. These interesting findings may be due to the relationship between an increase in LVEDP and subsequent LV remodelling. As described in the Frank-Starling law, compensatory increases in LV end-diastolic volume (LVEDV) and LVEDP maintain stroke volume during severe LV dysfunction after STEMI[15]. In those cases, the renin-angiotensin system and sympathetic nervous system are highly activated with inducible monotype hypertrophy and compensatory LV dilation in the long term[16-18]. According to a study by Garber et al[19], LVEDV at baseline is an independent predictor of LV remodelling after STEMI. The ventricular dilation and wall thinning that result from infarct zone expansion reportedly increase LVEDV during the early phase of MI. Interestingly, we previously reported that increasing LVEDP is associated with LV dilation during the acute phase after STEMI, showing that both LV end-systolic volume index (LVESVI) and LV end-diastolic volume index are significantly higher in patients with higher LVEDP[5]. In addition, we also found that there is a relationship between higher LVEDP and subsequent progression of LV remodelling after STEMI, showing that LVESVI after PCI remains higher during long-term follow-up in patients with higher LVEDP, irrespective of baseline LVEF. Through these processes, the higher LVEDP may influence LV function and long-term clinical outcomes after STEMI. Therefore, this invasive but simple method to assess global LV function and systemic haemodynamics may affect current early risk stratification after STEMI. We found that the GRACE score was not a significant factor in our multivariate analysis, suggesting that it is basically more suitable for assessing the short-term outcome after STEMI, whereas limited studies have demonstrated that it is also a preferred scoring system for risk stratification in the long term[20,21]. Of importance, the GRACE score does not provide haemodynamic information (i.e., LVEDP or LVEF); very little has been investigated about the additive impact of LVEDP to risk stratification using prognostic factors over clinical risk scores including the GRACE score. This study demonstrated that its inclusion resulted in a tendency to increase

the AUC relative to that with the GRACE score alone to predict MACE incidence. In addition, by adding the LVEDP information to the GRACE score, 66% of patients were successfully recategorised. Interestingly, these effects were not observed by inclusion of LVEF. Our results are similar to those in a study by Abu-Assi et al, which showed that the addition of LVEF did not provide incremental prognostic information to the GRACE score in patients with acute coronary syndrome[22]. The authors found that there was high collinearity between the GRACE score and LVEF, suggesting that the GRACE score predicts prognosis effectively irrespective of LVEF. These results were consistent with a previous study in which a higher LVEDP was found to have comparable prognos-tic value with risk scores including the GRACE risk score[23]. In the light of these data, it is worth emphasising the periprocedural assessment of LVEDP during PCI in patients with STEMI.

Limitations

This study had the following limitations. This was a single-centre, observational cohort study of a relatively small population. In this retrospective setting, a variability of follow-up duration according to the different enrolment timing might have affected the results. In fact, most of the patients during 2011 and 2014 were followed for less than the mean follow-up period of 44 months (97 out of 110). In addition, because we possibly excluded those with very low LVEF due to intolerability to undergo LVG, the subsequent prognostic impact of LVEF might be underestimated. Thus, a pro-spective large-scale multicentre clinical setting is needed for further confirmation. Of importance, as was shown in our previous reports[5], the combined assessment of LVEDP and LVEF at admission was a useful prognostic parameter after STEMI. Therefore, the patho-physiological mechanism of LV remodelling after STEMI may be clarified by serial haemodynamic assessment including LVEDP and LVEF in the larger sample size. In addition, lower LVEF and larger infarct size were not associated with worse outcome in the current study, because patients with cardiac shock and higher peak troponin I levels were excluded from this study due to the lack of data on LVG. In addition, the optimal timing of LVEDP measurements remains unclear. LVEDP measurements at different time points may be more informative for treatment strategy and predicting prognosis. Finally, the relationship between increasing LVEDP and LV remod-elling needs further assessment. For example, imaging modalities such as cardiac magnetic resonance may be less invasive and more useful for assessing the progression of LV remodelling.

Conclusions

Including LVEDP measurements provides additional information to the GRACE risk score for assessing the risk of

Impact on daily practice

The assessment of LVEDP guides care after STEMI.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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