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# Global left ventricular myocardial work index and medium-term adverse cardiovascular events after ST-elevation myocardial infarction

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ABSTRACT

*Background:* Left ventricular global longitudinal strain (GLS) has incremental prognostic value over ejection fraction (EF) in patients with ST-segment-elevation myocardial infarction (STEMI), but it is also load dependent. It has been recently demonstrated that Myocardial work (MW), integrating blood pressure with GLS, predicts long-term all-cause mortality. We aimed to further explore the prognostic value of MW for cardiovascular endpoints in patients with STEMI.

*Methods and results:* Retrospective study of 200 consecutive patients admitted with a STEMI, mean age of 62 (SD 12) years, 79.5% males, that survived to discharge. Transthoracic echocardiography was performed before discharge (5 ± 3 days after admission). Mean follow-up was 790 days. The primary outcome was a composite of cardiovascular death, non-fatal myocardial infarction, and unplanned cardiovascular admission (ACE). During follow-up, 26 patients had a ACE. In univariable Cox regression analysis, male gender, body mass index, GRACE risk score and Global Work Index (GWI) were selected to the multivariable analysis, in which, only GWI (per 100 mmHg% decrease: hazard ratio estimate 1.19, 95% confidence interval 1.07–1.34, $p$-value = 0.002) remained independently associated with ACE, with effective reclassification of non-events. The best GWI cut-off to predict ACE was ≤1165 mmHg% (Log-rank, $p$ = 0.034).

*Conclusions:* LV GWI is independently associated with medium-term ACE. Nevertheless, prospective studies in a larger sample of patients are warranted to confirm this finding.

## 1. Introduction

Until recently, left ventricular (LV) systolic function assessment relied solely on Ejection Fraction (EF) and Global Longitudinal Strain (GLS), the latter having the advantage of being a more sensitive parameter for early detection of mild systolic dysfunction. Nevertheless, despite being more accurate, strain is also load dependent [1,2]. LV strain can be reduced in response to increased afterload, leading to misinterpretations of the true contractile function [1,2].

Myocardial work (MW) has been introduced in recent years as a non-invasive measurement of LV function, by deriving pressure-strain loops, incorporating afterload information, and quantifying LV energy waste [3]. The combination of LV strain data and non-invasively estimated pressure curves, allows estimation of MW by the pressure-strain loop [3,4]. Therefore, it includes information from both load and deformation. It has the advantage of being less load dependent and it can be an additional tool to evaluate LV function.

The clinical utility of MW has already been demonstrated in different cardiovascular conditions, such as for the identification of resynchronization therapy responders and coronary occlusion in patients with acute coronary syndrome [5–10]. Furthermore, it has also been shown that these parameters have excellent repeatability and reproducibility [3,5–8,11]. Previous studies demonstrated the usefulness of MW to predict all-cause mortality in patients with myocardial infarction [11]. However, this endpoint reflects an heterogenous group of situations, including non-cardiovascular deaths. For specific major cardiovascular events this information is scarce. Therefore, the objective of our study was to assess if MW can be used clinically to assess the risk of medium-

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term adverse cardiovascular events after a ST-elevation acute myocardial infarction (STEMI).

## 2. Methods

This is a single-centre, retrospective, cohort study, including all consecutive patients admitted with a STEMI in our Cardiac Intensive Care Unit during the year 2018, treated with successful primary percutaneous coronary intervention, that survived to discharge, and had a complete transthoracic echocardiogram performed before discharge. STEMI was defined by an acute chest pain (or equivalent symptoms of ischemia) with <12 h duration, together with a 12-lead ECG with persistent ST-segment elevation (new or presumably new ST elevation at the J-point in at least two contiguous leads). All patients had confirmed increase in cardiac troponins and coronary angiography confirmed the presence of a coronary artery occlusion or critical stenosis (culprit lesion). Furthermore, all patients underwent a successful percutaneous coronary angioplasty of the culprit lesion (final TIMI flow grade 2–3), and additionally, complete percutaneous revascularization of additional coronary lesions (whenever present) was performed before discharge. Patients with suboptimal image quality for strain and myocardial work analysis were excluded, as well as patients with moderate to severe valvular heart disease (including aortic stenosis) and atrial fibrillation. Patients with left bundle branch block were also excluded because this conduction disturbance interferes with MW assessment. Baseline clinical characteristics were collected by review of the electronic medical record and GRACE risk score 2.0 was calculated for each patient [12]. All patients included in the study were followed-up for at least two years after admission, either by a telephone contact performed by a dedicated nursing team, according to the Department's protocol, or by a regular Cardiology consultation, and data was also retrieved by review of the electronic medical record. The outcomes evaluated were all-cause mortality, cardiovascular death, non-fatal myocardial infarction, stroke, unplanned cardiovascular admission (hospitalisation for unplanned coronary revascularization - due to stable or unstable angina - or heart failure decompensation). For the purpose of the present analysis, the primary outcome was a composite of cardiovascular mortality, myocardial infarction and unplanned cardiovascular admission – adverse cardiovascular events (ACE).

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee (INV 329–1228/2022). For retrospective analysis of clinically acquired data, the institutional review board waived the need for patient written informed consent. This research did not receive any specific grant from funding agencies in the public, commercial, or not for profit sectors.

### 2.1. Echocardiographic study

We performed a complete transthoracic study with Vivid E95™ or Vivid 9™ ultrasound equipment (GE Healthcare) and a 3.5 MHz transducer. All recordings and measurements were made according to the European Association of Cardiovascular Imaging guidelines [13–16]. Valvular event timing was measured by pulsed-wave Doppler. Mitral valve opening and closure were measured from transmitral inflow Doppler profiles in the apical four-chamber view with the sample placed at the mitral valve leaflets. Aortic valve opening and closure were measured from a Doppler profile in the apical five chamber view with the sample placed in the LV outflow tract. For strain analysis, images were acquired in apical four, two and three-chamber views, and the transducer settings of the B-mode image were adjusted to a frame rate of at least 55 frames per second (ideally at 60–80). The grey scale definition was optimized to improve endocardial and myocardial definition to adequately assess GLS by 2D speckle tracking. Images were stored in digital cine-loops with three sequential beats for offline analysis. Strain was analysed with a semiautomated process and peak systolic longitudinal strain was synchronized with the QRS complex of the electrocardiogram. Blood pressure was measured with the patient on a left lateral decubitus position (brachial blood pressure) with an automatic sphygmomanometer, and peak systolic LV pressure was assumed to be equal to the peak arterial pressure. MW was calculated according to published recommendations, using a commercially available software package (EchoPAC™ workstation, version 203, GE) that derived non-invasive pressure-strain loops (Supplemental Fig. 1) [17]. MW was used to evaluate global constructive work (GCW - the positive work performed during shortening in isovolumetric contraction and systole, and the negative work during lengthening in isovolumetric relaxation), global wasted work (GWW -the negative work made during lengthening in isovolumetric contraction and systole and the positive work performed during shortening in isovolumetric relaxation, global work efficiency [GWE = GCW/(GCW + GWW) 100%] and global work index (GWI – total work within the area of the LV pressure-strain loop calculated from mitral valve closure to mitral valve opening). MW measurements were made by a single operator.

### 2.2. Statistical analysis

Quantitative variables were tested for normality with the Kolmogorov-Smirnov test. Normal quantitative variables are reported as mean and standard deviation (SD). Non-normal variables are reported as median and interquartile range (25th percentile – 75th percentile). Categorical variables are reported as percentages. Differences between groups were tested with the Chi-square test or Fisher's exact test, as appropriate. For categorical variables. Student's *t*-test or Mann-Whitney test were used to compare quantitative variables.

A time-dependent area under the Receiver Operating Characteristics (ROC) curve was used to study its discriminative ability regarding future occurrence of ACE along the follow-up time. The inverse probability of censoring weight method was applied to estimate these time-dependent area under the ROC curve.

Univariable and multivariable Cox proportional hazards regression analysis (Method: Enter) were performed. Proportional Hazards assumption was confirmed by visual assessment of Kaplan-Meier curves, log(−log) plots and by a test based on scaled Schoenfeld residuals. Variables that attained a *p*-value <0.25 in the univariable analysis were candidates to the multivariable model, as well as variables with known impact on prognosis after acute myocardial infarction. GRACE risk score was utilized to incorporate the most important confounding variables into the multivariable analysis, avoiding model overfitting. Crude and adjusted hazard ratios were estimated with corresponding 95% confidence intervals.

Cut-off values of GWI for identifying patients at high risk for ACE were assessed using the partial function plots obtained by the additive Cox regression model, to assess the functional form of covariates in the Cox proportional hazards model [18]. ACE event-free survival rates were obtained using the Kaplan-Meier estimator and compared using the Log-rank test.

Overall measures of model performance were obtained with the likelihood ratio (LR) test statistic. This test was also used to assess the added value of EF, GLS and GWI to the model with GRACE risk score alone. Model choice also considered Akaike Information Criterion (AIC) (lower values correspond to better model performances). In order to quantify the improvement resulting from adding GWI to model with GRACE risk score, continuous Net Reclassification Index (NRI) and Integrated Discrimination Index (IDI) for censored data were also calculated. The NRI quantifies the correctness of upward and downward movement of predicted probabilities as a result of adding a new marker to an existing baseline model. The IDI quantifies the magnitude of change in those probabilities.

A level of significance $\alpha = 0.05$ was considered. IBM SPSS Statistical software, version 26 (IBM SPSS Inc., Chicago, IL) and R software (R Core Team 2021. R: A language and environment for statistical computing - R

Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.) were used for statistical analysis.

## 3. Results

### 3.1. Baseline characteristics

We reviewed all patients that fulfil inclusion criteria and underwent a complete echocardiographic study before discharge, between January and December 2018. From a total of 221 patients, 18 were excluded due to poor acoustic window for strain and myocardial work analysis and three did not have information on blood pressure. A total of 200 patients were included in the analysis, with a mean age of 62 (SD = 12) years, 79.5% males. The echocardiographic study was performed at a mean of 5 (SD = 3) days (median 5 days) after admission. Mean frame rate was 69 (SD = 5) frames per second. Table 1 summarizes patient's baseline and main echocardiographic characteristics. Mean follow-up was 790 (SD = 145) days (median 767 days). During follow-up, 10 patients died (four classified as cardiovascular deaths), 12 patients had a myocardial infarction, and 25 patients had an unplanned cardiovascular admission (nine due to heart failure decompensation). Overall, 26 patients (13%) had an adverse cardiovascular event during follow-up. Because non-cardiovascular mortality can be a competing event, we have checked the events in every patient that died of a non-cardiovascular cause. All of them had a cardiovascular event before dying and were therefore included in the ACE group. Therefore, it was not deemed necessary to perform a competing risk analysis.

**Table 1**
Baseline characteristics in the overall population and according to events (ACE).

| Variables | Total $n = 200$ | No ACE $n = 174$ | ACE $n = 26$ | p-value |
|---|---|---|---|---|
| Age (years) | 62 (12) | 61 (12) | 66 (13) | 0.032 |
| Males (%) | 79.5 | 81.0 | 69.2 | 0.258 |
| BMI (Kg/m2) | 26.1 (24.5–29.4) | 25.8 (24.4–29.0) | 26.9 (24.7–30.1) | 0.161 |
| Hypertension (%) | 56.0 | 54.6 | 65.4 | 0.411 |
| Diabetes (%) | 23.0 | 21.8 | 30.8 | 0.448 |
| Smoking (%) | 49.5 | 48.3 | 57.7 | 0.493 |
| Dyslipidaemia (%) | 47.5 | 46.0 | 57.7 | 0.365 |
| Previous Myocardial Infarction (%) | 10.5 | 9.2 | 19.2 | 0.225 |
| Previous stroke (%) | 5.5 | 4.6 | 11.5 | 0.158 |
| Anterior STEMI (%) | 42.5 | 41.4 | 50.0 | 0.537 |
| SBP on admission (mmHg) | 134 (120–158) | 131 (120–158) | 135 (120–152) | 0.184 |
| DBP on admission (mmHg) | 79 (70–91) | 76 (69–90) | 80 (70–93) | 0.713 |
| Heart rate on admission (bpm) | 75 (67–88) | 72 (60–82) | 80 (69–95) | 0.022 |
| Killip class >1 on admission (%) | 15.0 | 12.1 | 34.6 | 0.007 |
| GRACE risk score | 115 (32) | 113 (32) | 125 (31) | 0.078 |
| Discharge medication (%) | | | | |
| DAPT | 98.5 | 98.3 | 100.0 | 1.000 |
| RAAS inhibitors | 96.0 | 96.6 | 92.3 | 0.279 |
| Betablockers | 91.0 | 90.8 | 92.3 | 1.000 |
| Statins | 97.5 | 97.1 | 100.0 | 1.000 |
| Echocardiographic data: | | | | |
| LVEDV/BSA (ml/m2) | 52.1 (44.8–59.2) | 50.6 (44.1–56.4) | 53.6 (46.7–63.0) | 0.009 |
| LVESD/BSA (ml/m2) | 24.4 (18.8–29.4) | 21.4 (16.7–26.8) | 27.3 (22.5–33.9) | 0.001 |
| E/e' | 10.8 (4.6) | 10.4 (4.1) | 13.6 (6.5) | 0.023 |
| LVEF (%) | 52.7 (9.3) | 53.6 (9.0) | 46.6 (9.4) | <0.001 |
| GLS (%) | - 14.1 (4.0) | −14.5 (3.8) | −11.7 (4.1) | 0.001 |
| GWI (mmHg%) | 1161 (378) | 1196 (371) | 939 (351) | 0.001 |
| GCW (mmHg%) | 1468 (427) | 1502 (421) | 1243 (406) | 0.004 |
| GWW (mmHg%) | 167 (118–228) | 154 (101−223) | 178 (132–238) | 0.853 |
| GWE (%) | 87 (83–92) | 90 (86–93) | 84 (79–87) | 0.074 |

BMI – body mass index; STEMI – ST-elevation myocardial infarction; SBP – systolic blood pressure; DBP – diastolic blood pressure; DAPT – double antiplatelet treatment; RAAS – renin angiotensin aldosterone system; LVEDV – left ventricular end-diastolic volume; BSA – body surface area; LVESV – left ventricular end-systolic volume; LVEF – left ventricular ejection fraction; GLS – global longitudinal strain; GWI – global work index; GCW – global constructive work; GWW – global wasted work; GWE – global work efficiency; ACE – adverse cardiovascular events.

### 3.2. Characterization of patients with ACE

Patients with ACE were older, had higher heart rate and worst Killip class on admission (Table 1). Discharge medication was not significantly different between groups. Regarding echocardiographic data, patients in the ACE group had worst left ventricular function, both systolic and diastolic. GWI and GCW were significantly impaired in patients with ACE, compared to patients without ACE. There was a marginal impairment of GWE and GWW was similar between groups.

### 3.3. MW implications in the outcome

By univariable analysis, variables associated with ACE were age, admission heart rate and Killip class, GRACE risk score, left ventricular function (EF and GLS) and GWI (Table 2). In a multivariable model, GWI remained independently associated with ACE (per 100 mmHg% decrease: HR 1.19, 95% CI 1.07–1.34, $p$-value = 0.002), after adjustment for the potential clinical predictors of outcome. GLS and GWI are highly correlated ($r = -0.792$, $p < 0.001$), Therefore, GLS was not included in the multivariable model to avoid collinearity problems. The time dependent discriminative ability of GWI to distinguish between patients who had ACE from those who did not, was characterized by the

**Table 2**
Cox regression analysis to assess risk of major adverse cardiovascular events during follow-up.

| Variables | Univariable (Hazard ratio estimate, 95% CI) | p-value | Multivariable (Hazard ratio estimate, 95% CI) | p-value |
|---|---|---|---|---|
| Age (per 10-year increase) | 1.45 (1.05–2.01) | 0.025 | – | |
| Male gender | 0.55 (0.24–1.26) | 0.155 | 0.54 (0.23–1.26) | 0.155 |
| BMI (per unit increase) | 1.07 (0.98–1.16) | 0.138 | – | |
| Smoking | 1.39 (0.64–3.034) | 0.405 | – | |
| Hypertension | 1.56 (0.69–3.49) | 0.283 | – | |
| Dyslipidaemia | 1.53 (0.70–3.32) | 0.287 | – | |
| Diabetes | 1.53 (0.67–3.52) | 0.315 | – | |
| Admission HR (per 10 bpm increase) | 1.03 (1.01–1.05) | 0.002 | – | |
| Admission SBP (per unit increase) | 1.01 (0.99–1.02) | 0.177 | – | |
| Killip class >1 | 3.68 (1.64–8.26) | 0.002 | – | |
| GRACE score (per unit increase) | 1.01 (1.00–1.02) | 0.055 | 1.01 (1.00–1.02) | 0.198 |
| Anterior MI | 1.43 (0.66–3.08) | 0.363 | – | |
| RAASi on discharge | 0.50 (0.12–2.11) | 0.344 | – | |
| Betablocker on discharge | 1.18 (0.28–5.00) | 0.820 | – | |
| Ejection fraction | 0.93 (0.89–0.97) | <0.001 | – | |
| GLS (per unit increase) | 1.21 (1.08–1.35) | 0.001 | – | |
| GWI (per 100 units decrease) | 1.21 (1.08–1.35) | 0.001 | 1.19 (1.07–1.34) | 0.002 |

BMI – body mass index; HR – heart rate, SBP – systolic blood pressure, STEMI – ST-elevation myocardial infarction; RAASi – renin angiotensin aldosterone system inhibitors; GLS – global longitudinal strain; GWI – global work index; CI – confidence interval.
Variables included in the multivariable model: Gender, GRACE risk score and GWI.

following time-dependent area under the ROC curve to t (time in months): $t = 6$, 67.4%; $t = 12$, 65.5%; $t = 24$, 69.5%. Overall, the value obtained for the global model was 0.68, showing a modest discriminative ability. Moreover, GRACE risk score also showed a modest discriminative ability in this sample of patients, with a c-statistic of 0.63.

To further explore the variables associated with ACE, several multivariable Cox regression models were fitted to the data. The LR$\chi^2$ test for nested models demonstrated that GWI added statistically significant prognostic value to multivariable models including GRACE risk score, while GLS and LVEF did not add incremental value to models including GRACE and GWI (Fig. 1). Furthermore, all the models incorporating LVEF, GLS and GWI demonstrated a lower AIC compared to models with GRACE score alone.

Adding GWI to a model with GRACE score, resulted in an overall improvement of NRI of 41.8%, 95% CI 0.6 to 83% ($p = 0.047$), being more significant for non-events (NRI 26.4%, 95% CI 12 to 41%), and less for events (NRI 15.4%, 95% CI -23 to 54%). IDI was also significant (0.064, 95% CI 0.021 to 0.106, $p = 0.034$). Adding GWI to a model with GRACE score + GLS, resulted in a slight improvement in overall NRI (35.7%, 95% CI -5 to 77%, $p = 0.089$), albeit not achieving statistical significance, particularly regarding non-events (NRI 12.6%, 95% CI -2 to 27%), and less for events (23.1%, 95% CI -15 to 61%). IDI was not significant (0.008, 95% CI -0.003 to 0.019, $p = 0.140$).

The best GWI cut-off to predict ACE was 1165 mmHg% (Supplemental Fig. 2). This cut-off showed a sensitivity of 69% and a specificity of 54% to predict ACE. Patients with lower GWI had higher admission heart rate and worst Killip class, more often anterior STEMI, higher LV volumes, worst LV function and impaired MW parameters, apart from GWW that only showed a trend to be higher (Table 3). Regarding outcomes, they had higher all-cause mortality and more cardiovascular admissions, particularly heart failure hospitalisation. Overall, they had more ACE during the 2-year follow-up (Log-rank, $p = 0.023$) (Fig. 1). A GWI $\leq$ 1165 mmHg% showed a HR of 2.53, 95% CI of 1.10–5.83 ($p$-value = 0.029) for ACE (unadjusted). After adjustment for GRACE risk score, it remained an independent predictor of outcome (HR 2.43, 95% CI of 1.05–5.59, $p = 0.037$).

## 4. Discussion

The present study provides evidence of the prognostic value of GWI in patients with STEMI that survived to discharge, showing that patients with impaired GWI have worst medium-term prognosis. In addition, this finding is independent of clinical parameters with implications in the outcome.

MW is characterized by four distinct components, and each of these components provides different information that contribute to the understanding of LV mechanics. GWI quantifies the indexed total work performed by the LV throughout the entire mechanical systole including isovolumetric contraction and relaxation and corresponds to the myocardial energy translated into mechanical energy between mitral valve closure and opening [19]. GCW quantifies the energy consumed by the myocardium that effectively contributes to cardiac output [19]. GWW quantifies the energy consumed by the myocardium that is wasted and does not contribute to cardiac output [19]. GWE reflects the net percentage of MW performed that is actually translated into cardiac output [19]. Of the MW indices, GWI, representing the area within the LV pressure-strain loop, provides the most comprehensive estimate of LV function, accounting for LV contractility, desynchrony, isovolumetric relaxation, and afterload [19].

MW was validated by comparing it with invasive LV pressure-strain loops, as well as by correlating it with oxygen consumption and regional myocardial glucose uptake and metabolism obtained through positron emission tomography [3]. By taking into account the loading conditions during myocardial deformation, MW have enhanced accuracy, making it theoretically an appealing approach for comprehensive assessment of myocardial function, enabling the detection of subclinical myocardial dysfunction [19]. It facilitates the quantification of both the global and regional contractile capacity of the myocardium, in a thorough understanding, and provides insights into its energetics and O2 consumption [19].

In previous studies, in the context of heart failure with reduced EF, GWI was shown to be a predictor of all-cause mortality and HF hospitalisation, and it correlated with peak oxygen consumption and N-terminal pro-B-type natriuretic peptide levels particularly in patients with ischemic dilated cardiomyopathy [19]. Furthermore, in patients with coronary artery disease and normal MV function but wall motion abnormalities, GWI and GCW are usually significantly depressed [19]. Although the presence of coronary artery disease does not directly affect the loading conditions of the LV, the impaired oxygen metabolism in ischemic myocardium can have an impact on MW[19]. Therefore, assessment of regional instead of global MW may be helpful for diagnosing ischemia. After STEMI, ischemia induces changes in myocardial metabolism, reducing ATP formation, leading to LV contractile dysfunction and abnormal MW[19].

The role of myocardial work indices in the context of acute myocardial infarction was first reported by Lustosa et al. [11] In a sample of 507 patients with STEMI, submitted to primary percutaneous coronary intervention, a reduced LV GWE < 86%, measured within 48 h of admission, was associated with all-cause mortality and this effect was independent of other variables. In addition, the same group subsequently showed that in patients with reduced LVEF after STEMI, higher baseline LV GWI was independently associated with LVEF recovery at 6 months follow-up [20]. Therefore, it better identified patients that are less likely to improve LV function. A LV GWI < 750 mmHg% was independently associated with all-cause mortality, and it also showed incremental prognostic value over LVEF and minor incremental value over LV GLS [20]. Moreover, in patients with STEMI there are changes in MW from baseline to 3 months that may reflect myocardial stunning. In fact, at 3-months, they also showed that patients with LV remodelling had significantly impaired global myocardial work indices compared to patients without remodelling [21,22]. Another group studied microvascular perfusion with contrast echocardiography within 48 h after percutaneous coronary intervention in STEMI patients and found that microvascular perfusion abnormalities are very prevalent, in 60% of the patients, and this was associated with a significant impairment of GWI, GCW, GWE and GLS[23]. Additionally, GWI was independently associated with microvascular dysfunction [23].

The value of MW early after STEMI in assessing the risk of major adverse cardiovascular events has not been reported previously. A recent study, by Coisne et al., showed that by assessing MW one-month after the index event, GWE is independently associated with higher major adverse events (cardiovascular death, heart failure and unplanned coronary revascularization) and a GWE < 91% improves post-MI patient risk stratification [24]. However, the study from Coisne also included patients with non-STEMI, which is a heterogeneous group, and the echocardiographic assessment was performed one-month after admission. But in real-life, it is essential to perform risk stratification as early as possible to adjust secondary prevention strategies according to patient needs. Therefore, it is important to predict events at an earlier stage and that is the main reason why we decided to analyse the impact of MW at discharge.

Our study showed that, as expected, patients with ACE during the follow-up were older and clinical presentation was substantially worse. They also had worse left ventricular function, as assessed by LVEF and GLS. Importantly, most MW parameters were more impaired, compared to patients that did not have any event. Only GWW was not statistically different but there was a clear trend towards a worst performance, suggesting that in a larger sample, these differences in wasted work might me more significant.

GWI was the MW parameter that showed the strongest association for the primary outcome and indeed, in univariable Cox regression it was clearly associated with the outcome. This was further confirmed by

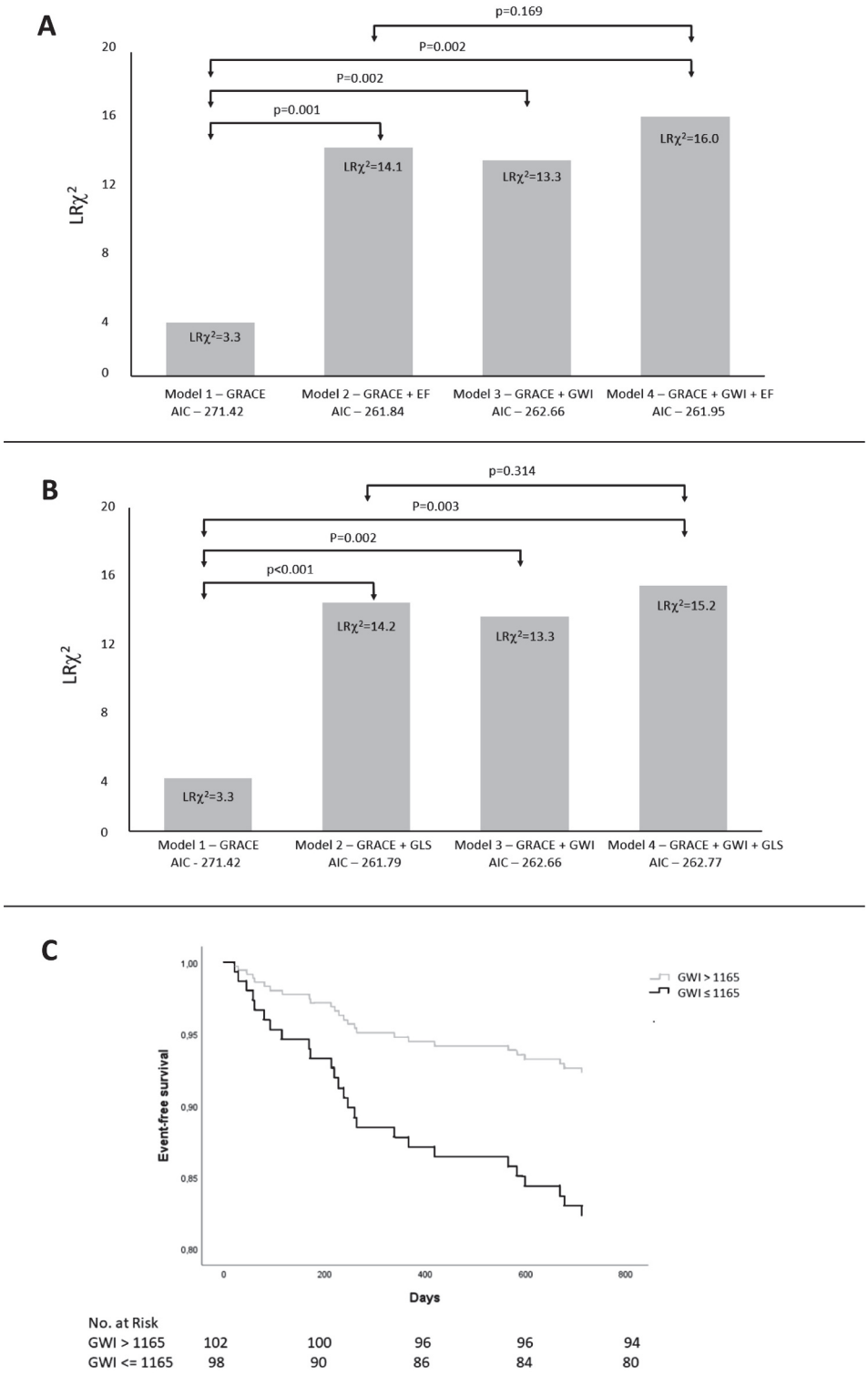


**Fig. 1.** A: Incremental prognostic value of LV GWI for ACE. The LR$\chi$2 test demonstrated that LV GWI adds significant prognostic value to a model including GRACE risk score, while GLS do not add incremental value to models including GRACE risk score and GWI; B: Incremental prognostic value of LV GWI for ACE. The LR$\chi$2 test demonstrated that LV GWI adds significant prognostic value to a model including GRACE risk score, while LVEF do not add incremental value to models including GRACE risk score and GWI; C: Estimated Kaplan-Meier survival curves for the GWI cut-off point (1165 mmHg%) adjusted for GRACE risk score. EF – ejection fraction, GLS – global longitudinal strain, GWI – global work index, LV – left ventricular; LR – likelihood ratio.

**Table 3**
Characteristics and outcomes according to Global Work Index cut-off.

| Variables | GWI > 1165 mmHg% $n = 102$ | GWI ≤ 1165 mmHg% $n = 98$ | p-value |
|---|---|---|---|
| Age (years) | 61.7 (11.4) | 61.3 (12.8) | 0.821 |
| Male gender (%) | 82.4 | 76.5 | 0.398 |
| BMI (Kg/m2) | 25.8 (24.4–29.0) | 26.9 (24.7–30.1) | 0.245 |
| Hypertension (%) | 58.8 | 53.1 | 0.498 |
| Diabetes (%) | 26.5 | 19.4 | 0.307 |
| Smoking (%) | 46.1 | 53.1 | 0.398 |
| Dyslipidaemia (%) | 42.2 | 53.1 | 0.161 |
| Previous Myocardial Infarction (%) | 13.7 | 7.1 | 0.198 |
| Previous stroke (%) | 5.9 | 5.1 | 1.000 |
| Anterior STEMI (%) | 28.4 | 57.1 | <0.001 |
| SBP on admission (mmHg) | 132 (120–158) | 135 (120–152) | 0.637 |
| DBP on admission (mmHg) | 76 (69–90) | 80 (70–93) | 0.342 |
| Heart rate on admission (bpm) | 72 (60–82) | 80 (69–96) | 0.001 |
| Killip Class >1 (%) | 5.9 | 24.5 | <0.001 |
| GRACE risk score | 111 (30) | 119 (33) | 0.097 |
| Discharge medication (%) | | | |
| DAPT | 97.1 | 100.0 | 0.247 |
| RAAS inhibitors | 94.1 | 98.0 | 0.280 |
| Betablockers | 88.2 | 93.9 | 0.252 |
| Statins | 96.1 | 99.0 | 0.369 |
| Echocardiographic data: | | | |
| LVEDV/BSA (ml/m2) | 50.6 (44.1–56.4) | 53.6 (46.7–63.0) | 0.019 |
| LVESD/BSA (ml/m2) | 21.4 (16.7–26.8) | 27.3 (22.5–33.9) | <0.001 |
| E/e' | 10.2 (3.5) | 11.4 (5.4) | 0.069 |
| LVEF (%) | 56.9 (7.8) | 48.3 (8.8) | <0.001 |
| GLS (%) | −16.7 (3.2) | −11.5 (2.8) | <0.001 |
| GWI (mmHg%) | 1426 (1269–1596) | 867 (718–1011) | <0.001 |
| GCW (mmHg%) | 1718 (1585–1919) | 1121 (970–1341) | <0.001 |
| GWW (mmHg%) | 153 (101–223) | 177 (132–238) | 0.057 |
| GWE (%) | 90 (86–93) | 84 (79–87) | <0.001 |
| Outcomes (%) | | | |
| All-cause mortality | 1.0 | 9.2 | 0.009 |
| Cardiovascular mortality | 1.0 | 3.1 | 0.361 |
| Myocardial infarction | 5.9 | 6.1 | 1.000 |
| Stroke | 1.0 | 2.0 | 0.972 |
| Cardiovascular admission | 7.8 | 17.3 | 0.069 |
| Heart failure admission | 0 | 9.2 | 0.001 |
| ACE | 7.8 | 18.4 | 0.045 |

BMI – body mass index; STEMI – ST-elevation myocardial infarction; SBP – systolic blood pressure; DBP – diastolic blood pressure; DAPT – double antiplatelet treatment; RAAS – renin angiotensin aldosterone system; LVEDV – left ventricular end-diastolic volume; BSA – body surface area; LVESV – left ventricular end-systolic volume; LVEF – left ventricular ejection fraction; GLS – global longitudinal strain; GWI – global work index; GCW – global constructive work; GWW – global wasted work; GWE – global work efficiency; ACE – adverse cardiovascular events.

multivariable analysis, with an increase in risk for ACE of 19% per 100 mmHg% decrease in GWI. Moreover, compared to a model with GRACE risk score alone, the inclusion of GWI improved model performance with effective reclassification, particularly for non-events. A trend for effective reclassification was also apparent for non-events by adding GWI to a model with GRACE risk score and GLS. Therefore, adding GWI to a model with GRACE risk score (and to a lesser extent with GLS), can improve classification of patients, particularly patients at low probability for ACE in the follow-up. By better identifying patients with lower risk of events, it can enable a tailored post-discharge patient management plan, ultimately avoiding potential adverse effect associated with the high intensity prescribed medication. In addition, GRACE risk score showed a modest discriminative ability in our sample of patients, with a c-statistic of 0.63. This was not an unexpected finding, because we only included patients that survived to discharge, and therefore, patients with higher short-term (in-hospital) events were not included in our sample. For that reason, our results only apply to patients that survived to discharge and not to all patients with STEMI, where the incremental value of GWI might not be significant when associated with GRACE risk score. Additionally, we identified the best cut-off for this outcome, and patients with a GWI ≤ 1165 mmHg% had an increased risk of 2.4-fold for ACE.

The mechanisms by which GWI is associated with MACE can be explained by what has been previously described. Indeed, GWI corresponds to the myocardial energy translated into mechanical energy between mitral valve closure and opening and is a maker of regional metabolic disturbances related to ischemia [19]. Moreover, it is independently associated with microvascular dysfunction, as well as with adverse remodelling at 6 months follow-up[21–24]. All these mechanisms can contribute to the occurrence of adverse cardiac events after STEMI, from death to coronary and heart failure events, and GWI is a non-invasive surrogate marker that can be helpful in the risk assessment of those patients before discharge.

### 4.1. Limitations

As in previous studies of MW in STEMI patients, this is a retrospective, cohort, and single-centre study. The retrospective nature of the study can cause some uncorrected and residual confounding; therefore, validation in a prospective and multicentre cohort in still needed. Furthermore, the commercial software used for the measurement of MW is only available from a single vendor and we do not know if our results can be applicable in the future with different software from other vendors. Indeed, we can expect some differences between vendors, as it is currently observed for strain analysis.

We chose to evaluate patients at discharge. In fact, current guidelines recommend routine echocardiography before discharge in all STEMI patients to assess LV function, as well as other parameters that may influence outcomes. However, our choice can create an issue of survival bias. Nevertheless, patients that died before discharge were in a very ominous clinical condition, and the benefits brought by this assessment could have also been biased. Our decision to apply this tool clinically in those patients that survived to discharge was associated with the possibility that they will probably benefit the most from this detailed risk stratification process. Another arguing fact associated with this timing is that the effect of optimal medical treatment might not be established at such an earlier stage. In fact, we can expect a reversal of myocardial stunning in the first few months, with possible impact in prognosis. However, risk stratification should be performed as early as possible, and therefore it was important to analyse if this tool can be helpful to assess earlier the risk of events, to adjust patient's treatment accordingly.

In addition, the study population is relatively small, which limits the number of parameters that can be adjusted for, to avoid overfitting. It should also be noted the relatively few events in the study, that might have limited the reclassification analysis. We obtained effective reclassification in the non-event group in the model with GRACE + GWI compared to GRACE alone, but only a trend when comparing GRACE+GLS and adding GWI to this model. Therefore, the generated hypothesis require validation in future studies with larger sample size. Finally, it is important to acknowledge that in some patients (8.1% of our initial sample), it was not possible to assess MW due to poor-acoustic window and some patients were excluded.

## 5. Conclusions

Myocardial work parameters, specifically left ventricular Global Work Index, can be a useful tool to apply in clinical practice to assess medium-term risk of major adverse cardiovascular events in patients that survived to discharge after a hospital admission for ST-elevation acute myocardial infarction. With that additional information, we can better decide which patient might benefit more from a more aggressive anti-ischemic therapy, as well as titration and implementation of heart failure-specific medical therapies. Additional prospective studies in

larger samples are necessary to confirm our findings.

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## CRediT authorship contribution statement

**Ana Teresa Timóteo:** Validation, Investigation, Data curation. **Ana Galrinho:** Validation, Investigation, Data curation. **Pedro Rio:** Validation, Investigation, Data curation. **Ana Luísa Papoila:** Validation, Investigation, Formal analysis. **Marta Alves:** Validation, Investigation, Formal analysis. **Rui Cruz Ferreira:** Validation, Investigation.

## Declaration of competing interest

None to declare.

## Data availability

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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