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Prognostic value of admission high-sensitivity troponin in patients with ST-elevation myocardial infarction.

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Abstract:	<p>Background and aim: Although the diagnostic usefulness of high-sensitivity cardiac troponin T (hs-cTnT) is well established in ST-segment elevation myocardial infarction (STEMI), its prognostic relevance in risk stratification of STEMI patients remains obscure. This study sought to determine the prognostic value of pre-reperfusion (admission) and post-reperfusion (12h) hs-cTnT in STEMI patients treated with primary percutaneous coronary intervention (PPCI).</p> <p>Methods: Retrospective observational longitudinal study including consecutive STEMI patients treated with PPCI at a university hospital in the northeast of England. Hs-cTnT was measured at admission to the catheterization laboratory and 12h after PPCI. Clinical, procedural, and laboratory data were prospectively collected during patient hospitalisation (Jun/2010 – Dec/2014). Mortality data were obtained from the UK Office of National Statistics. The study endpoints were in-hospital and overall mortality.</p> <p>Results: A total of 3,113 patients were included. Median follow-up was 53 months. Admission hs-cTnT>515ng/L (4th quartile) was</p>

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	<p>independently associated with in-hospital mortality (HR=2.53 per highest to lower quartiles; 95%CI: 1.32-4.85; p=0.005) after multivariable adjustment for a clinical model of mortality prediction. Likewise, admission hs-cTnT>515ng/L independently predicted overall mortality (HR=1.27 per highest to lower quartiles; 95%CI: 1.02-1.59; p=0.029). Admission hs-cTnT correctly reclassified risk for in-hospital death [net reclassification index (NRI)=0.588%, p<0.001) and overall mortality (NRI=0.178%, p=0.001). Conversely, 12h hs-cTnT was not independently associated with mortality.</p> <p>Conclusion: Admission, but not 12h post-reperfusion, hs-cTnT predicts mortality and improves risk stratification in the PPCI era. These results support a prognostic role for admission hs-cTnT whilst challenge the cost-effectiveness of routine 12h hs-cTnT measurements in STEMI patients.</p>

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Prognostic value of admission high-sensitivity troponin in patients with ST-elevation myocardial infarction

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Abstract

Background and aim: Although the diagnostic usefulness of high-sensitivity cardiac troponin T (hs-cTnT) is well established in ST-segment elevation myocardial infarction (STEMI), its prognostic relevance in risk stratification of STEMI patients remains obscure. This study sought to determine the prognostic value of pre-reperfusion (admission) and post-reperfusion (12h) hs-cTnT in STEMI patients treated with primary percutaneous coronary intervention (PPCI).

Methods: Retrospective observational longitudinal study including consecutive STEMI patients treated with PPCI at a university hospital in the northeast of England. Hs-cTnT was measured at admission to the catheterization laboratory and 12h after PPCI. Clinical, procedural, and laboratory data were prospectively collected during patient hospitalisation (Jun/2010 – Dec/2014). Mortality data were obtained from the UK Office of National Statistics. The study endpoints were in-hospital and overall mortality.

Results: A total of 3,113 patients were included. Median follow-up was 53 months. Admission hs-cTnT>515ng/L (4th quartile) was independently associated with in-hospital mortality (HR=2.53 per highest to lower quartiles; 95%CI: 1.32-4.85; p=0.005) after multivariable adjustment for a clinical model of mortality prediction. Likewise, admission hs-cTnT>515ng/L independently predicted overall mortality (HR=1.27 per highest to lower quartiles; 95%CI: 1.02-1.59; p=0.029). Admission hs-cTnT correctly reclassified risk for in-hospital death [net reclassification index (NRI)=0.588%, p<0.001] and overall mortality (NRI=0.178%, p=0.001). Conversely, 12h hs-cTnT was not independently associated with mortality.

Conclusion: Admission, but not 12h post-reperfusion, hs-cTnT predicts mortality and improves risk stratification in the PPCI era. These results support a prognostic role for admission hs-cTnT whilst challenge the cost-effectiveness of routine 12h hs-cTnT measurements in STEMI patients.

Keywords: STEMI; primary PCI; risk stratification; mortality; cardiac troponin

Key Messages

What is already known about this subject?

Troponin levels are routinely used in clinical practice for the diagnosis of myocardial infarction but the prognostic value of hs-cTnT assays in the era of PPCI is controversial.

What does this study add?

This study shows that hs-cTnT levels at admission to the catheterisation laboratory, but not hs-cTnT routinely measured 12h post-PPCI, predict mortality and improve risk stratification in patients with STEMI.

How might this impact on clinical practice?

These findings support a prognostic role for admission hs-cTnT but not for routine 12h hs-cTnT measurements in STEMI patients.

Patient and public involvement: patients were not involved at any stage of this study.

1. Introduction

Despite implementation of evidence-based therapy for ST-segment elevation myocardial infarction (STEMI), including primary percutaneous coronary intervention (PPCI), global short and long-term mortality rates (in-hospital: 7% - 11%; 1 to 5-year: 11% - 23%) remain elevated in this condition (1-3). These figures highlight the current need for risk algorithms that enable clinicians to precisely distinguish between STEMI patients at extreme high versus lower risk, which is crucial to guide secondary prevention strategies post-STEMI (4). In this context, circulating biomarkers that reflect the severity of pathological mechanisms associated with STEMI may act as integrating factors that, combined with traditional outcome predictors, could have a significant additive prognostic value in optimizing risk stratification with a view to improving long-term treatment strategies for STEMI patients.

High-sensitivity cardiac troponin (hs-cTn) assays are the gold-standard biomarkers to assess acute myocardial injury (5, 6). When coupled with clinical evidence of myocardial ischaemia, acute rise and/or fall of hs-cTn levels compose the criteria for the diagnosis of myocardial infarction (5, 6). Despite its ancillary diagnostic role, there is scarce and contradictory evidence examining the prognostic value of current hs-cTn assays in STEMI patients undergoing PPCI (7-11). Few studies with small cohorts suggest differential prognostic roles for pre- and post-reperfusion hs-cTn levels (7-11). Nonetheless direct comparisons between these two measurement time points have never been performed in large cohorts. We hypothesized that pre- and post-reperfusion hs-cTn levels may reflect distinct processes associated with myocardial injury and reperfusion and hence may provide different prognostic information. This study aimed to compare the prognostic relevance of admission and 12h post-reperfusion hs-cTnT levels for mortality prediction and risk stratification in a large cohort of STEMI patients treated with PPCI.

2. Methods

Patient population

Data from consecutive STEMI patients treated with PPCI at the Freeman Hospital (Newcastle upon Tyne, UK) between June 2010 and December 2014 were collected prospectively. Diagnosis of STEMI was based on the presence of chest pain suggestive of myocardial ischaemia lasting longer than 30 minutes accompanied by ST-segment elevation or new left bundle branch block on the ECG (6). Patients were considered for PPCI if they presented within 12h of symptom onset. STEMI patients were given 300 mg of aspirin and were transferred directly to the cardiac catheterization laboratory. On arrival, a loading dose of a second antiplatelet along with standard doses of heparin or bivalirudin were administered according to international guidelines (12). Glycoprotein (GP) IIb/IIIa inhibitors were administered by discretion of the operator during PPCI. When patients were admitted several times for PPCI, only data from their first presentation was included for analysis.

Study design

This was a retrospective longitudinal cohort study. The primary data source was the local coronary artery disease (CAD) database (Dendrite Clinical Systems, Ltd., Oxford, England, UK). The data are annually submitted to the National Institute for Cardiovascular Outcomes Research (NICOR) audit registry and are regularly validated. Baseline demographics and clinical parameters were prospectively collected at the end of each procedure by the attending physician. Post-procedural clinical data were updated on discharge by Freeman Hospital database managers.

Mortality data were provided by the Office of National Statistics, which records all deaths in the UK. The National Health Service (NHS) patient unique identification number (NHS number) available in the Office of National Statistics dataset was used to link mortality information to our database. The cut-off date for mortality assessment in every patient was the 20th of June 2017. The

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prognostic endpoints were (i) in-hospital mortality, defined by all-cause deaths during hospitalisation and (ii) overall all-cause mortality, which included in-hospital and post-hospital discharge deaths. This study complied with the Declaration of Helsinki.

Cardiac troponin measurement

Serum samples were obtained from arterial blood collected from the radial or femoral sheath on admission to the catheterization laboratory (immediately prior to PPCI) as well as from venous blood samples collected 12 hours post-PPCI. Cardiac troponin T was quantified with the Roche Elecsys hs-cTnT assay on the Cobas e601 module (Roche Diagnostics, United Kingdom). According to manufacturer information, the hs-cTnT assay has a limit of detection reported at 2.05 ng/L and coefficient of variation <10% at the 99th percentile (14 ng/L).

Statistical analysis

Differences in distribution of baseline characteristics between survivors and non-survivors were assessed by t-test or Mann-Whitney U test for continuous variables and chi-square test for categorical variables. Patients were assigned to quartiles according to admission or 12h hs-cTnT levels. Comparisons in distributions of baseline variables between hs-cTnT quartile groups were performed with the Kruskal-Wallis test with Dunn’s correction for multiple comparisons for continuous variables or with the Chi-square test for categorical variables. Survival distributions between distinct admission and 12h hs-cTnT quartile groups were estimated by Kaplan-Meier survival analysis (log-rank test).

A core clinical model for prediction of overall mortality was determined by stepwise backwards multivariable Cox regression analysis. Clinical, biochemical, and peri-procedural variables were used to derive such model, many of which compose previously published or established risk prediction tools, such as the GRACE score (13)(1, 3) (**Supplemental table 1**). Variables that

showed significant ($p < 0.05$) association with mortality by multivariable Cox regression were selected to compose the prediction model (**Supplemental table 1**). Independent association between admission and 12h hs-cTnT and the study endpoints was assessed by stepwise backwards multivariable Cox regression over the core prediction model. The percentage of missing values for the confounders included in the multivariable Cox regression analysis were all below 6% (**Supplemental table 2**). Only cases with complete data for all variables were included in the Cox regression analysis.

Proportional-hazards regression models with 3-knots restricted cubic splines (i.e. natural splines) (RCSs) of either admission hs-cTnT or 12h hs-cTnT were implemented to model the association between hs-cTnT and the study endpoints without linearity assumptions (14). This approach sought to circumvent limitations associated with the categorization of a continuous variable whilst exploring non-linear relationships between hs-cTnT and the outcomes. Finally, the additive predictive value of hs-cTnT over core predictors of in-hospital and overall mortality was estimated by i) likelihood ratio tests for nested multivariable models and b) continuous net reclassification index (NRI). We used bootstrapping with 1,000 replicates to construct bias-corrected 95% confidence intervals around the NRI estimate (15). All tests were two-tailed. Statistical analyses were performed by SPSS software v22.0 (IBM, New York, USA) or Stata package, version 16.0 (StataCorp, College Station, Texas, USA). Statistical significance was deemed at $p < 0.05$ unless stated otherwise. Detailed information about the proportional-hazards regression and dose-response curves can be found in the **Supplemental Methods**.

3. Results

Admission and 12h hs-cTnT reflect distinct clinical risk profiles

From the 3,408 consecutive patients, those who did not have admission hs-cTnT (n = 195, 5.7%), 12h hs-cTnT (n = 57, 1.6%), or both (n = 43, 1.2%) quantified were excluded, resulting in a final cohort of 3,113 patients. Clinical and peri-procedural baseline characteristics of the study population are summarized in **table 1**. The distribution of parameters traditionally related to worse risk profile differed between admission and 12h hs-cTnT quartile groups. Increasing admission hs-cTnT levels were associated with more frequent inter-hospital transfer than direct admission to the catheterization laboratory from ambulance (p < 0.001) (**Supplemental table 3**). This was reflected by longer symptom-onset-to-reperfusion time (p < 0.001) and door-to-balloon time (p = 0.008), notably in the highest admission hs-cTnT quartile group (hs-cTnT > 515ng/L; **Supplemental table 3**). In addition, these patients presented with higher heart rate (p< 0.001), increased incidence of cardiogenic shock (p < 0.001), and lower haemoglobin levels (p < 0.001) (**Supplemental table 3**). Finally, in terms of peri-procedural parameters, greater use of femoral access (p < 0.001) and incidence of coronary slow flow phenomenon (p = 0.005) were observed with increasing admission hs-cTnT (**Supplemental table 3**). Consequently, the incidence of in-hospital and overall mortality was significantly greater in the highest admission hs-cTnT quartile group (**Supplemental table 3**). In contrast, no difference in the distribution of these variables was observed among 12h hs-cTnT quartiles, except for cardiogenic shock (**Supplemental table 4**).

Prognostic value of admission and 12h hs-cTnT

In-hospital mortality rate was 3% (n = 94 deaths) and overall mortality was 16.4% (n = 509 deaths) at a median follow-up period of 53 months (interquartile range 37 – 68 months) (**Supplemental table 3**). Kaplan-Meier survival analysis revealed a significant association

between increasing admission hs-cTnT quartiles and higher probability of in-hospital and overall mortality (**Figures 1A and 1B**). For 12h hs-cTnT quartiles, there was no association with in-hospital mortality but a significant correlation with overall mortality (**Figures 1C and 1D**). In addition, univariable Cox regression analysis showed that admission hs-cTnT levels $> 515\text{ng/L}$ (4th quartile) were associated with higher risk of in-hospital and overall mortality (**Table 2**). In contrast, 12h hs-cTnT levels $> 5,221\text{ng/L}$ (4th quartile) were not associated with higher risk of in-hospital mortality but conferred significantly higher risk of overall mortality (**Table 2**).

After adjustment for the core mortality prediction model including age, current smoking, diabetes mellitus, previous myocardial infarction, admission haemoglobin, admission creatinine, heart rate on admission, anterior myocardial infarction, administration of glycoprotein IIb/IIIa inhibitors, TIMI score 3 post-PPCI, and door-to-balloon time by multivariable Cox regression, admission hs-cTnT was an independent predictor of in-hospital mortality (HR = 2.53 per highest to lower quartiles, 95% CI = 1.32 – 4.85, $p = 0.005$) (**Table 2**). Admission hs-cTnT was also independently associated with overall mortality (HR = 1.27 per highest to lower quartiles, 95% CI = 1.02 – 1.59, $p = 0.029$) after adjusting for the core mortality prediction model (**Table 2**). Conversely, 12h hs-cTnT was not an independent predictor of overall mortality (**Table 2**).

Dose-response relationship between levels of continuous hs-cTnT and study endpoints

A non-linear association of circulating levels of admission and 12h hs-cTnT with both in-hospital and overall mortality was observed (**Figure 2**). Interestingly, dose-response curve analysis, revealed distinct patterns of associations with mortality between admission and 12h hs-cTnT (**Figure 2**). In specific, admission hs-cTnT was consistently positively associated with in-hospital mortality (adjusted HR= 3.42 for 80th vs. 20th percentiles, 95% CI 1.83-6.39, $p < 0.001$; **Figure 2A**) after adjustment for the variables in the core model whereas 12h hs-cTnT was not (adjusted HR=0.96 for 80th vs. 20th percentiles, 95%CI 0.51-1.80, $p=0.663$; **Figure 2B**). With regards to

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overall mortality, admission hs-cTnT (adjusted HR=1.32 for 80th vs. 20th percentiles, 95%CI 1.05-1.65, p=0.015; **Figure 2C**) but not 12h hs-cTnT (adjusted HR=0.87 for 80th vs. 20th percentiles, 95%CI 0.69-1.10, p=0.256; **Figure 2D**) was significantly associated with increased risk after adjusting for the core clinical model of overall mortality prediction. Interestingly, 12h hs-cTnT was inversely associated with overall mortality at low and medium concentrations [adjusted HR=0.72 for 60th (nadir) vs. 1st percentile, 95% CI 0.57-0.91, p=0.006; **Figure 2D**].

Admission hs-cTnT confers incremental calibration and reclassification value over core predictive models of in-hospital and overall mortality

Admission hs-cTnT conferred additive calibration (likelihood ratio test p<0.001) and reclassification value (overall continuous NRI=0.588, 95% CI 0.278-0.903, p<0.001) over the core in-hospital mortality prediction model (**Table 2**). The reclassification value of admission hs-cTnT was driven by correctly reclassifying into lower risk patients who did not die across hospitalization (70.5%) whereas 11.8% of patients who experienced the adverse outcome (i.e., in hospital mortality) were inappropriately reclassified into lower risk (Table 2). Similarly, admission hs-cTnT improved the goodness of fit of the core model (likelihood ratio test p=0.001) for overall mortality and correctly reclassified patients without the events into lower risk (57.6%) while a smaller fraction of patients who died were incorrectly classified (39.8%, overall NRI=0.178, 95% CI 0.037-0.311, p=0.001, **Table 3**).

3. Discussion

This study main findings are that: (i) admission hs-cTnT was independently associated with both in-hospital and long-term mortality whilst 12h hs-cTnT was not; (ii) admission hs-cTnT displayed a consistently positive dose-response association with mortality whereas 12h hs-cTnT presented an inverse correlation with long-term mortality in low to medium concentrations; (iii) most importantly, addition of admission hs-cTnT to baseline clinical predictors of in-hospital and overall mortality improved the calibration of the best prognostic core model and correctly reclassified patients who did not die into lower risk, especially for in-hospital mortality.

The occurrence of STEMI confers a greater risk of subsequent major adverse cardiovascular events (MACE) and death. Accumulating evidence suggests that a more aggressive secondary prevention strategy post-acute coronary syndrome (ACS) is beneficial in terms of survival and reduction of ischaemic events (16-20). Risk stratification is fundamental to tailor secondary prevention strategies. To this end, several short and long-term mortality risk prediction models have been assessed in STEMI cohorts (21-23) but have not yet been incorporated into clinical guidelines (24). Given the significant unmet need for optimizing risk stratification in STEMI patients, the identification of markers that can provide incremental prognostic value over traditional outcome predictors is warranted.

In this study, we directly compared the prognostic value of admission versus 12h hs-cTnT in a large cohort of 3,113 consecutive STEMI patients of one tertiary NHS hospital covering 1.6 million individuals in the northeast of England. Admission hs-cTnT was an independent predictor of short and long-term mortality while 12h hs-cTnT was not. In support of this observation, increased admission hs-cTnT was linked with a higher risk profile in these patients compared to 12h hs-cTnT. Specifically, admission hs-cTnT, but not 12h hs-cTnT, was associated with (i) worse physiological status at presentation, including lower haemoglobin levels, higher heart rate, and increased incidence of cardiogenic shock; as well as (ii) parameters affecting the timing of

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revascularization, including more frequent inter-hospital transfer, longer door-to-balloon and symptom-onset-to-reperfusion time. This unfavourable profile at presentation, reflected by higher admission hs-cTnT levels, might explain the association of admission hs-cTnT with adverse procedural parameters, such as increased need for femoral access and higher incidence of coronary slow flow phenomenon.

The clinical prognostic utility of admission hs-cTnT was further confirmed by a substantial incremental predictive value over the best prognostic multivariable model for mortality in terms of calibration and reclassification. Importantly, our model incorporated confounders previously shown to be independently associated with mortality in patients with ACS and STEMI in large studies, such as age, diabetes mellitus, smoking, heart rate at presentation, creatinine levels, and TIMI flow post-reperfusion (1, 3, 13). Taken together, these findings suggest that admission hs-cTnT is a marker that may cumulatively inform about the duration of ischaemia, risk profile at presentation until the time of PPCI, adverse PPCI-related parameters, and the risk of mortality thereafter. In accordance with these results, three previous small studies suggested that admission cTn could predict 30-day, 9-month, and 1-year post-PPCI mortality in STEMI patients (11, 25)(26). Future studies should compare the prognostic performance between admission hs-cTnT and emerging biomarkers of cardiac ischaemia and reperfusion injury, such as microRNAs, in large cohorts (27).

In addition, our findings show that 12h hs-cTnT may not provide clinically useful prognostic information in the era of PPCI. Currently, there is conflicting evidence regarding the short-term prognostic utility of post-procedural hs-cTn derived from relatively small STEMI populations lacking long-term follow-up (7-10). For example, in a recent study by Cediél et al. (7) peak levels of both contemporary cTnI and hs-cTnT assays did not predict MACE in 1,260 consecutive STEMI patients at 30 days and 1 year post-PPCI (7). In contrast, in a post-hoc analysis from a multicenter, phase II, randomized placebo-controlled trial (PROTECTION AMI trial) (10) post-

PCI levels of cTnI were predictors of outcome in 1,066 patients. Accordingly, Ndrepepa G et al. showed that post-PPCI hs-cTnT was an independent predictor of 3-year all-cause mortality (26).

Although not explicitly recommended by current international guidelines, post-PPCI hs-cTnT measurements are a common practice in some centres. Our findings suggest that post-PPCI hs-cTnT quantification is questionable, given that 12h hs-cTnT does not seem to provide relevant prognostic information while it may bring additional economic burden to health systems.

In our study, while admission hs-cTnT showed consistently increasing hazard ratios with increasing concentrations, we observed a negative association between long-term mortality and low-medium concentrations of 12h hs-cTnT. Considering that successful coronary reperfusion leads to a rapid washout of troponin within the initial 12h (28), it may be hypothesized that this “protective” attribute of low to medium 12h hs-cTnT concentrations could be a reflection of successful reperfusion whereas higher hs-cTnT levels at 12h might reflect a slower release of troponin due to impaired reperfusion (29). Nano technology could be used in future trials to track troponin release in real time, thereby monitoring the reperfusion process as well as performing risk assessment right from hospital admission (30).

The present study has some limitations. Firstly, this was a retrospective, observational study. Therefore, there may have been relevant parameters that were not controlled for. For instance, echocardiographic data was only available for a minority of patients and hence not included in the prediction model. Secondly, 12h hs-cTnT measurements were performed as part of routine clinical care, as per departmental standard operating protocol. Therefore, slight inter-patient variation in terms of blood collection timing at 12h post-reperfusion could have occurred. Consequently, this study cannot entirely exclude the possibility that 12h hs-cTnT could be a significant predictor of mortality with larger cohorts or strict sampling, in the context of a clinical trial. Thirdly, there was a small percentage of missing data for each variable included in the model. However, complete case analysis was the method used to deal with missing data and should not produce bias as the

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data was missing at random. Finally, generalisability of our findings should be taken with caution. In specific, hs-cTnT quartile thresholds were derived within-sample which poses a risk of model overfitting and requires validation in other cohorts.

In conclusion, this study provides evidence of an important and distinct role of admission hs-cTnT levels in predicting prognosis in STEMI patients undergoing PPCI as compared to 12h hs-cTnT. Our results strongly support the hypothesis that admission hs-cTnT levels combined with traditional outcome predictors could efficiently stratify patients with respect to their risk for mortality. Early and exact identification of STEMI patients at extreme mortality risk, facilitated by admission hs-cTnT measurements, may allow clinicians to properly diversify the escalation of medical care and precisely apply an intensified secondary prevention strategy. Finally, we demonstrate that 12h hs-cTnT levels do not seem to be useful for prognostic stratification of STEMI patients.

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stratification of patients with ST-segment elevation myocardial infarction” at the European Society of Cardiology (ESC) Congress 2019.

Contributorship statement: JCL and GG performed data analyses and interpretation and drafted the manuscript; JA, SERA, DG, FA, and AB performed data collection; CB, KS, LS, GR, and AB critically revised the manuscript for important intellectual content; K Stellos, K Stamatelopoulos, and IS provided substantial contributions to the conception and design of the work and critically revised the manuscript; KS and IS are responsible for the overall content of the work as guarantors.

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Table 1. Baseline characteristics of the study cohort.

Variable	Entire cohort	Survivors	Non-survivors	<i>p</i> value
Sample size, n (%)	3,113 (100)	2604 (83.6)	509 (16.4)	
Gender (female), n (%)	2,211 (71)	706 (27.1)	196 (38.5)	<0.001*
Age [years, mean (SD)]	62.9 (12.7)	60.7 (11.9)	73.9 (11.1)	<0.001#
Risk factors, n (%)				
Smoking status				
Never smoked	781 (26.7)	669 (26.8)	112 (25.8)	0.661*
Ex-smoker	813 (27.8)	638 (25.6)	175 (40.3)	<0.001*
Current smoker	1,335 (45.6)	1,188 (47.6)	147 (33.9)	<0.001*
Family history of CAD	1,361 (46.1)	1,232 (49)	129 (29.5)	<0.001*
Hypertension	1,434 (46.1)	1,132 (43.5)	302 (59.3)	<0.001*
Diabetes Mellitus	393 (12.8)	291 (11.3)	102 (20.6)	<0.001*
Hypercholesterolemia	1,216 (39.1)	1,017 (39.1)	199 (39.1)	0.986*
Obesity	807 (28.2)	723 (29.5)	84 (20.1)	<0.001*
Medical history of CAD, n (%)				
Previous angina	529 (17.1)	403 (15.5)	126 (25.6)	<0.001*
Previous MI	321 (10.4)	218 (8.4)	103 (21.1)	<0.001*
Previous PCI	201 (6.5)	157 (6)	44 (8.7)	0.025*
Previous CABG	56 (1.8)	41 (1.6)	15 (3)	0.033§
Clinical characteristics on admission				
Heart rate, bpm [median (IQR)]	75 (63 – 88)	74 (62 – 87)	80 (65 – 95)	<0.001§
Systolic BP, mmHg [median (IQR)]	127 (109 – 147)	127 (110 – 147)	123 (100 – 145)	0.001§
Cardiogenic shock, n (%)	128 (4.1)	69 (2.7)	59 (11.7)	<0.001*
Admission route, n (%)				
Emergency services	2,264 (72.3)	1,898 (72.9)	366 (71.9)	0.649*
Inter-hospital transfer	849 (27.3)	706 (27.1)	143 (28.1)	0.649*
Door to balloon, min [median (IQR)]	23 (18 – 33)	23 (17 – 32)	26 (19 – 38)	<0.001§
Onset to reperfusion, min [median (IQR)]	132 (104 – 187)	164 (115 – 261)	193 (131 – 313)	<0.001§
Infarct location, n (%)				
Anterior	1,207 (39.3)	979 (37.9)	228 (46.2)	0.001*
Biochemical tests [median (IQR)]				
Admission haemoglobin, g/dL	13.8 (12.6 – 14.9)	14 (12.8 – 15)	12.7 (11.3 – 14)	< 0.001§
Admission creatinine, µmol/L	81 (69 – 96)	79 (68 – 93)	91 (75 – 119)	<0.001§
Admission hs-cTnT, ng/L	121 (39 – 515)	104 (35 – 429)	229 (68 – 974)	< 0.001§
12h hs-cTnT, ng/L	2,200 (775 – 5,223)	2,170 (767 – 5,063)	2,319 (815 – 6,543)	0.053§
Arterial access, n (%)				

Radial	2,640 (85.1)	2270 (87.2)	370 (72.8)	< 0.001*
Femoral	464 (14.9)	329 (12.6)	135 (26.6)	< 0.001*
Brachial	6 (0.2)	3 (50)	3 (50)	0.093*
GPIIb/IIIa medication, n (%)	2,016 (65.2)	1750 (67.7)	266 (52.6)	< 0.001*
Contrast volume, mL [median (IQR)]	140 (110 – 180)	140 (110 – 175)	150 (110 – 180)	0.590§
TIMI flow pre-PCI, n (%)				
1	136 (4.5)	108 (4.3)	28 (5.7)	0.178*
2	275 (9.2)	227 (9)	48 (9.7)	0.622*
3	384 (12.8)	316 (12.6)	68 (13.8)	0.461*
Thrombectomy	1,866 (60.2)	1592 (61.4)	274 (53.9)	0.002*
Number of stents				
0	174 (5.6)	107 (4.1)	67 (13.2)	< 0.001*
1	1,707 (54.8)	1454 (55.8)	253 (49.7)	0.011*
2	870 (27.9)	738 (28.3)	132 (25.9)	0.268*
3	266 (8.5)	219 (8.4)	47 (9.2)	0.543*
Intra-procedural complications				
Coronary slow flow	59 (1.9)	35 (1.3)	24 (4.7)	< 0.001*
Coronary dissection	37 (1.2)	32 (1.2)	5 (1)	0.639*
Direct current cardioversion	26 (0.8)	15 (0.6)	11 (2.2)	< 0.001*
TIMI flow post-PCI, n (%)				
0	72 (2.4)	42 (1.7)	30 (6.2)	< 0.001*
1	30 (1)	19 (0.8)	11 (2.3)	0.002*
2	123 (4.1)	82 (3.3)	41 (8.4)	< 0.001*
3	2,776 (92.5)	2372 (94.3)	404 (83.1)	< 0.001*

Comparisons in the distribution of variables between survivors and non-survivors were performed using t-test (#) or Mann-Whitney U (§) and chi-square test (*) for continuous and categorical variables, respectively.

Abbreviations: BP, blood pressure; CABG, coronary artery bypass graft; CAD, coronary artery disease; cTnT, cardiac troponin T; GP IIb/IIIa, glycoprotein IIb/IIIa; hs-cTnT, high sensitivity cardiac troponin T; IQR, interquartile range; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction angiographic score.

Table 2. Association of admission and 12h hs-cTnT with the study endpoints by univariable and multivariable Cox regression

	Study endpoints			
	In-hospital mortality		Overall mortality	
	HR* (95% CI)	p-value	HR* (95% CI)	p value
Admission hs-cTnT (unadjusted)	4.26 (2.80 – 6.47)	< 0.001	1.83 (1.53 – 2.19)	< 0.001
Admission hs-cTnT (Core model)	2.53 (1.32 – 4.85)	0.005	1.27 (1.02 – 1.59)	0.029
	HR† (95% CI)	p-value	HR† (95% CI)	p value
12h hs-cTnT (unadjusted)	1.10 (0.69 – 1.73)	0.679	1.40 (1.16 – 1.69)	< 0.001
12h hs-cTnT (Core model)	1.35 (0.69 – 2.65)	0.373	1.15 (0.92 – 1.44)	0.214

*HR corresponds to admission hs-cTnT levels > 515ng/L (4th quartile versus the lower quartiles).

†HR corresponds to 12h hs-cTnT levels > 5,221ng/L (4th quartile versus the lower quartiles).

Core model for mortality prediction: age (per decade), current smoking, diabetes mellitus, previous myocardial infarction, pre-PPCI haemoglobin, pre-PPCI creatinine (per 100mmol/L), heart rate on admission, anterior myocardial infarction, administration of glycoprotein IIb/IIIa inhibitors, TIMI score 3 post-PPCI, door-to-balloon time.

Abbreviations: CI, confidence interval; GPIIb/IIIa, glycoprotein IIb/IIIa; HR, hazard ratio; hs-cTnT, high sensitivity cardiac troponin T; SE, standard error; PPCI, primary percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction score.

Table 3. Additive predictive value of admission hs-cTnT over the core model for in-hospital and overall all-cause mortality

	Calibration		Reclassification			
	LR test chi-squared	P-value	Events	Non events	Overall NRI (95% CI)**	P-value
*In-hospital death	15.47	<0.001	-11.8%	+70.5%	+0.588 (0.278, 0.903)	<0.001
*Overall all-cause mortality	11.73	0.001	-39.8%	+57.6%	+0.178 (0.037, 0.311)	0.001

*High-sensitivity cTnT was added on the core model including age, pre-PCI haemoglobin, pre-PCI creatinine, heart rate on admission, cardiogenic shock on admission, femoral access, anterior myocardial infarction, TIMI flow 3 post-PPCI

** 95% bias-corrected CIs were derived from bootstrapping with 1,000 replicates

LR depicts goodness of fit of predicted against observed values (calibration)

Events and non-events depict percentage of patients reclassified to higher or lower risk in patients with or without the event, respectively

(-) depicts incorrect reclassification and (+) depicts correct reclassification of risk within the events or non-events groups

Overall NRI depicts a unitless measure of reclassification (range 0-2)

Abbreviations: LR: likelihood ratio, NRI: net reclassification index, PPCI: percutaneous coronary intervention, TIMI: Thrombolysis in Myocardial Infarction

Figure legends

Figure 1. Admission and 12h post-PPCI hs-cTn levels, and mortality in STEMI patients.

Kaplan-Meier survival curves depicting the association of admission hs-cTnT quartiles with probability of in-hospital (A) and overall (B) mortality in STEMI patients. Kaplan-Meier survival curves displaying the association between 12h post-PCI hs-cTnT quartiles and in-hospital (C) as well as overall mortality (D).

Figure 2. Dose-response relationship between continuous hs-cTnT and mortality.

Smoothed restricted cubic spline (RCS) plots of the log hazard ratio (HR) for in-hospital (A, B) and overall mortality (C, D) versus levels of admission hs-cTnT (A, C) and post-PCI hs-cTnT (B, D). Three knots were fixed at the 10th (16 and 257.1ng/L for admission and 12h cTnT, respectively), 50th (121 and 2,200ng/L for admission and 12h cTnT, respectively) and 90th (1,557 and 9,547ng/L for admission and 12h cTnT, respectively) percentile of cTnT distribution. The upper- and lower-most dotted curves represent the 95% CI about the predicted HRs (middle solid line). Vertical dashed lines indicate the location of the 20th and 80th percentile of continuous hs-cTnT distribution which are further compared (difference in log hazard ratio for the 80th percentile of hs-cTnT versus the 20th percentile as the reference value) after controlling for age, current smoking, diabetes mellitus, previous myocardial infarction, pre-PPCI haemoglobin, pre-PPCI creatinine, heart rate on admission, anterior myocardial infarction, administration of glycoprotein IIb/IIIa inhibitors, TIMI score 3 post-PPCI, door-to-balloon time. $P_{\text{for non-linearity}}$ is derived from the Wald test for the non-linear term of the RCS; P_{overall} stems from the joint Wald test for the linear and non-linear term of RCS. To enhance clarity of graphics, values exceeding the 90th percentile of hs-cTnT distribution were censored in corresponding plots. A horizontal dotted line (grey color) has been placed at 0 value of Y axis to indicate absence of association with the outcome. CI, confidence intervals; hs-cTnT, high-sensitivity cardiac troponin T; PPCI, primary percutaneous coronary intervention.

Figure 1

338x190mm (300 x 300 DPI)

Figure 2

253x190mm (300 x 300 DPI)

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Supplements

Supplemental methods

Proportional-hazards regression and dose-response curves

The proportional hazards assumption in Cox regression analyses was evaluated graphically and statistically by using the Schoenfeld residuals. Selection of optimal number of knots for restricted cubic splines (RCS) was based on log likelihood ratio tests. Knots for RCS were fixed at the 10th, 50th and 90th percentile of the hs-cTnT distribution. The smoothed plots of log hazard ratio (HR) for each outcome versus the continuous hs-cTnT (dose-response curves) were controlled for the covariates that comprised the corresponding core model. Non-linear and the overall associations of the transformed hs-cTnT (i.e., RCS) with logHR were assessed by examining the statistical significance (Wald test) of the non-linear or both (linear and non-linear) terms (1). We also compared the 80th against the 20th percentile of the hs-cTnT values distribution to derive statistical inference on the association between circulating levels of this biomarker and the outcomes of the study after controlling for the core model.

Supplemental tables

Supplemental table 1. Establishing a core model of mortality prediction in STEMI.

Variable	Multivariable Cox-regression	
	HR (95% CI)	p value
Age (per decade)	2.41 (2.12 – 2.74)	<0.001
Gender (female)	0.77 (0.61 – 1.00)	0.052
Current smoking	1.85 (1.42 – 2.42)	<0.001
Family history of CAD	0.81 (0.63 – 1.04)	0.111
Hypertension	1.21 (0.94 – 1.54)	0.130
Diabetes Mellitus	1.48 (1.11 – 1.98)	0.007
Obesity	0.92 (0.67 – 1.25)	0.692
Hypercholesterolaemia	0.91 (0.73 – 1.18)	0.505
Previous angina	0.97 (0.71 – 1.33)	0.875
Previous MI	1.62 (1.22 – 2.16)	0.001
Previous PCI	0.97 (0.59 – 1.61)	0.928
Previous CABG	0.74 (0.37 – 1.48)	0.402
Admission haemoglobin	0.89 (0.83 – 0.95)	0.001
Admission creatinine (per 100mmol)	1.26 (1.09 – 1.45)	0.001
Heart rate (per 10 beats)	1.07 (1.02 – 1.13)	0.004
Cardiogenic shock	1.22 (0.67 – 2.21)	0.505
Inter-hospital transfer	0.83 (0.63 – 1.10)	0.203
Onset to reperfusion (min)	1.00 (1.00 – 1.00)	0.848
Door to balloon (min)	1.00 (1.00 – 1.00)	<0.001
Anterior MI	1.38 (1.10 – 1.74)	0.005
Femoral access	1.23 (0.91 – 1.66)	0.160
GPIIb/IIIa inhibitors	0.78 (0.61 – 0.98)	0.036
Contrast volume (ml)	1.00 (1.00 – 1.00)	0.109
TIMI 3 flow pre-PCI	0.86 (0.59 – 1.24)	0.428
Thrombectomy	1.17 (0.92 – 1.49)	0.178
Coronary slow flow	1.32 (0.70 – 2.51)	0.384
TIMI 3 flow post-PCI	0.48 (0.35 – 0.65)	<0.001

Abbreviations: CAD, coronary artery disease; CI, confidence interval; GPIIb/IIIa, glycoprotein IIb/IIIa; HR, hazard ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction angiographic score.

Supplemental table 2. Percentage of missing data for variables included in the core prediction models of in-hospital and longer-term mortality

Variable	Missing cases	
	n	%
Age	0	0
Current smoking	184	5.9
Diabetes	31	1
Previous MI	27	0.9
Pre-PCI haemoglobin	38	1.22
Pre-PCI creatinin	35	1.12
Heart rate at admission	63	2.02
Cardiogenic shock	18	0.6
Anterior MI	39	1.3
Femoral access	3	0.1
Contrast volume	54	1.73
GPIIb/IIIa medication	21	0.7
TIMI flow 3 post-PCI	112	3.6

Abbreviations: GPIIb/IIIa, glycoprotein IIb/IIIa; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction angiographic score.

Supplemental table 3. Baseline clinical characteristics of the study population according to admission hs-cTnT quartiles

Variable	Entire cohort	1 st quartile of admission hs-cTnT (< 39 ng/L)	2 nd quartile of admission hs-cTnT (39 – 121ng/L)	3 rd quartile of admission hs-cTnT (122 – 515 ng/L)	4 th quartile of admission hs-cTnT (> 515 ng/L)	p value
Sample size, n (%)	3,113 (100)	794 (25.5)	765 (24.6)	777 (25)	777 (25)	
Gender (male), n (%)	2,211 (71)	575 (72.4)	551 (72)	536 (69)	549 (70.7)	0.432
Age [years, mean (SD)]	62.9 (12.7)	59.9 (11.5)	62.8 (12.7)	64.9 (12.7)	64.1(13.3)	<0.001
Risk factors, n (%)						
Smoking status						
Never smoked	781 (26.7)	179 (23.5)	193 (26.7)	214 (29.3)	195 (27.3)	0.088
Ex-smoker	813 (27.8)	186 (24.4)	230 (31.8)	195 (26.7)	202 (28.3)	0.014
Current smoker	1,335 (45.6)	396 (52)	300 (41.5)	322 (44)	317 (44.4)	<0.001
Family history of CAD	1,361 (46.1)	386 (50.2)	337 (46.2)	345 (46.4)	293 (41.2)	0.007
Hypertension	1,434 (46.1)	360 (45.3)	355 (46.4)	374 (48.1)	345 (44.4)	0.492
Diabetes Mellitus	393 (12.8)	98 (12.5)	98 (13)	89 (11.5)	108 (14.1)	0.514
Hypercholesterolemia	1,216 (39.1)	329 (41.4)	303 (39.6)	290 (37.3)	294 (37.8)	0.327
Obesity	807 (28.2)	235 (31.2)	209 (29.1)	169 (23.9)	194 (28.3)	0.019
Medical history of CAD, n (%)						
Previous angina	529 (17.1)	144 (18.2)	148 (19.4)	122 (15.8)	115 (15)	0.073
Previous MI	321 (10.4)	84 (10.6)	87 (11.4)	80 (10.4)	70 (9.2)	0.538
Previous PCI	201 (6.5)	65 (8.2)	52 (6.8)	42 (5.4)	42 (5.4)	0.077
Previous CABG	56 (1.8)	16 (2)	13 (1.7)	15 (1.9)	12 (1.5)	0.895
Clinical characteristics on admission						

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Heart rate, bpm [median (IQR)]	75 (63 – 88)	70 (60 – 82)	75 (63 – 88)	76 (64 – 88)	80 (68 – 95)	<0.001
Systolic BP, mmHg [median (IQR)]	127 (109 – 147)	126 (110 – 147)	126 (110 – 144)	128 (110 – 149)	126 (107 – 147)	0.848
Cardiogenic shock, n (%)	128 (4.1)	14 (1.8)	24 (3.2)	34 (4.4)	56 (7.3)	<0.001
Admission route, n (%)						
Emergency services	2,264 (72.3)	670 (84.4)	563 (73.6)	524 (67.4)	507 (65.3)	<0.001
Inter-hospital transfer	849 (27.3)	124 (15.6)	202 (26.4)	253 (32.6)	270 (34.7)	<0.001
Door to balloon, min [median (IQR)]	23 (18 – 33)	23 (18 – 31)	23 (17 – 34)	23 (18 – 32)	24 (18 – 36)	0.008
Onset to reperfusion, min [median (IQR)]	132 (104 – 187)	132 (104 – 187)	164 (117 – 241)	190 (127 – 289)	219 (134 – 445)	<0.001
Infarct location, n (%)						
Anterior	1,207 (39.3)	223 (28.4)	292 (38.5)	315 (41)	377 (49.3)	<0.001
Biochemical tests [median (IQR)]						
Admission haemoglobin, g/dL	13.8 (12.6 – 14.9)	14.2 (13 – 15.2)	13.9 (12.7 – 15)	13.6 (12.3 – 14.7)	13.5 (12.3 – 14.7)	< 0.001
Admission creatinine, µmol/L	81 (69 – 96)	80 (69 – 93)	82 (70 – 96)	80 (67 – 95)	81 (69 – 99)	0.019
Admission hs-cTnT, ng/L	121 (39 – 515)	19 (12 – 28)	69 (54 – 89)	227 (160 – 340)	1,239 (740 – 2,373)	< 0.001
12h hs-cTnT, ng/L	2,200 (775 – 5,223)	1,615 (570 – 3,939)	1,543 (534 – 4,138)	2,182 (619 – 4,867)	3,798 (1,699 – 7,279)	< 0.001
Arterial access, n (%)						
Radial	2,640 (85.1)	702 (88.6)	663 (86.7)	647 (83.3)	628 (80.9)	< 0.001
Femoral	464 (14.9)	89 (11.2)	102 (13.3)	128 (16.5)	145 (18.7)	< 0.001
Brachial	6 (0.2)	1 (0.1)	0 (0)	2 (0.2)	3 (0.4)	0.342
GPIIb/IIIa medication, n (%)	2,016 (65.2)	506 (64.1)	483 (63.5)	487 (63.2)	540 (69.9)	0.016
Contrast volume, mL	140 (110 – 180)	140 (100 – 170)	140 (100 – 170)	140 (100 – 170)	150 (120 – 200)	< 0.001
TIMI flow pre-PCI, n (%)						

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1						
2						
3	1	136 (4.5)	35 (4.6)	28 (3.8)	44 (5.8)	0.195
4	2	275 (9.2)	68 (8.9)	72 (9.8)	82 (10.9)	0.066
5	3	384 (12.8)	71 (9.3)	120 (16.3)	118 (15.7)	< 0.001
6						
7	Thrombectomy	1,866 (60.2)	513 (64.8)	462 (60.6)	441 (57)	0.009
8	Number of stents					
9						
10	0	174 (5.6)	25 (3.1)	43 (5.6)	48 (6.2)	0.002
11	1	1,707 (54.8)	476 (59.9)	441 (57.6)	420 (54.1)	< 0.001
12	2	870 (27.9)	207 (26.1)	202 (26.4)	223 (28.7)	0.152
13	3	266 (8.5)	67 (8.4)	56 (7.3)	64 (8.2)	0.242
14	> 3	95 (3.1)	19 (2.4)	23 (3)	22 (2.8)	0.307
15						
16	Intra-procedural complications					
17						
18	Coronary slow flow	59 (1.9)	7 (0.9)	16 (2.1)	11 (1.4)	0.005
19	Coronary dissection	37 (1.2)	14 (1.8)	7 (0.9)	11 (1.4)	0.170
20	Direct current cardioversion	26 (0.8)	7 (0.9)	6 (0.8)	7 (0.9)	0.989
21						
22	TIMI flow post-PCI, n (%)					
23						
24	0	72 (2.4)	16 (2.1)	18 (2.4)	16 (2.1)	0.642
25	1	30 (1)	5 (0.6)	3 (0.4)	8 (1.1)	0.022
26	2	123 (4.1)	9 (1.2)	22 (3)	30 (4)	< 0.001
27	3	2,776 (92.5)	743 (96.1)	693 (94.2)	700 (92.8)	< 0.001
28						
29	Outcome					
30						
31	In-hospital mortality, n (%)	94 (3)	4 (0.5)	14 (1.8)	18 (2.3)	<0.001
32	Overall mortality, n (%)	509 (16.4)	69 (8.7)	113 (14.8)	141 (18.1)	<0.001
33						
34						
35						

Abbreviations: BP, blood pressure; CABG, coronary artery bypass graft; CAD, coronary artery disease; cTnT, cardiac troponin T; GP IIb/IIIa, glycoprotein IIb/IIIa; hs-cTnT, high sensitivity cardiac troponin T; IQR, interquartile range; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction angiographic score.

Supplemental table 4. Baseline clinical characteristics of the study population according to 12h post-reperfusion hs-cTnT quartiles.

Variable	Entire cohort	Lowest 12h hs-cTnT quartile (< 776 ng/L)	2 nd 12h hs-cTnT quartile (776 – 2,200ng/L)	3 rd 12h hs-cTnT quartile (2,201 – 5,221 ng/L)	4 th 12h hs-cTnT quartile (> 5,221 ng/L)	p value
Sample size, n (%)	3,110	778	779	776	777	
Gender (male), n (%)	2,211 (71)	536 (68.9)	533 (68.4)	552 (71.1)	589 (75.8)	0.005
Age [years, mean (SD)]	62.9 (12.7)	61.6 (12.1)	62.4 (12.9)	62.6 (12.8)	64.9 (12.8)	< 0.001
Risk factors, n (%)						
Smoking status						
Never smoked	781 (26.7)	181 (24.8)	190 (25.8)	207 (28.2)	203 (28)	0.368
Ex-smoker	813 (27.8)	203 (27.8)	183 (24.8)	203 (27.7)	224 (30.9)	0.085
Current smoker	1,335 (45.6)	347 (47.5)	364 (49.4)	324 (44.1)	299 (41.2)	0.009
Family history of CAD	1,361 (46.1)	347 (47.1)	351 (47)	354 (48.2)	309 (42)	0.075
Hypertension	1,434 (46.1)	365 (46.9)	365 (46.9)	343 (44.2)	361 (46.5)	0.670
Diabetes Mellitus	393 (12.8)	102 (13.3)	96 (12.4)	91 (11.8)	104 (13.5)	0.724
Hypercholesterolemia	1,216 (39.1)	321 (41.3)	317 (40.7)	300 (38.7)	278 (35.8)	0.111
Obesity	807 (28.2)	211 (29.4)	188 (26.1)	223 (31.1)	185 (26)	0.074
Medical history of CAD, n (%)						
Previous angina	529 (17.1)	147 (19.2)	132 (17.1)	128 (16.6)	122 (15.7)	0.311
Previous MI	321 (10.4)	98 (12.8)	76 (9.9)	69 (8.9)	78 (10.1)	0.075
Previous PCI	201 (6.5)	57 (7.4)	50 (6.4)	46 (6)	48 (6.2)	0.690
Previous CABG	56 (1.8)	25 (3.2)	13 (1.7)	14 (1.8)	4 (0.5)	0.001
Clinical characteristics on admission						
Heart rate, bpm [median (IQR)]	75 (63 – 88)	73 (61 – 87)	75 (63 – 88)	74 (63 – 90)	77 (65 – 90)	0.098
Systolic BP, mmHg [median (IQR)]	127 (109 – 147)	127 (110 – 145)	128 (110 – 148)	127 (110 – 150)	125 (105 – 143)	0.019

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Cardiogenic shock, n (%)	128 (4.1)	27 (3.5)	21 (2.7)	34 (4.4)	43 (5.6)	0.030
Admission route, n (%)						
Emergency services	2,264 (72.7)	549 (70.6)	578 (74.2)	556 (71.6)	579 (74.5)	0.222
Inter-hospital transfer	849 (27.3)	229 (29.4)	201 (25.8)	220 (28.4)	198 (25.5)	0.222
Door to balloon, min [median (IQR)]	23 (18 – 33)	24 (18 – 34)	23 (17 – 33)	23 (17 – 33)	23 (18 – 33)	0.266
Onset to reperfusion, min [median (IQR)]	168 (117 – 267)	160 (113 – 263)	169 (118 – 269)	174 (118 – 277)	172 (119 – 255)	0.185
Infarct location, n (%)						
Anterior	1,207 (39.3)	258 (33.7)	269 (35.1)	272 (35.4)	406 (52.5)	<0.001
Biochemical tests [median (IQR)]						
Admission haemoglobin, g/dL	13.8 (12.6 – 14.9)	13.8 (12.4 – 14.9)	13.8 (12.6 – 14.8)	13.8 (12.6 – 14.9)	13.9 (12.6 – 15.1)	0.194
Admission creatinine, µmol/L	81 (69 – 96)	79 (67 – 94)	77 (67 – 93)	82 (69 – 94)	85 (72 – 100)	<0.001
Admission hs-cTnT, ng/L	121 (39 – 515)	71 (28 – 176)	102 (34 – 472)	160 (44 – 600)	256 (56 – 1,037)	<0.001
12h hs-cTnT, ng/L	2,200 (775 – 5,223)	331 (154 – 551)	1,344 (1,041 – 1,740)	3,377 (2,744 – 4,143)	8,433 (6,480 – 10,000)	<0.001
Arterial access, n (%)						
Radial	2,640 (85.1)	648 (83.4)	666 (85.6)	661 (85.3)	664 (85.5)	0.583
Femoral	464 (14.9)	126 (16.2)	112 (14.4)	112 (14.5)	112 (14.4)	0.686
Brachial	6 (0.2)	3 (0.4)	0 (0)	2 (0.3)	1 (0.1)	0.342
GPIIb/IIIa medication, n (%)	2,016 (65.2)	487 (63.2)	492 (63.6)	514 (66.4)	521 (67.6)	0.200
Contrast volume, mL	140 (110 – 180)	130 (100 – 160)	140 (110 – 170)	150 (110 – 180)	150 (120 – 190)	<0.001
TIMI flow pre-PCI, n (%)						
0	136 (4.5)	402 (53.7)	514 (69)	609 (81.6)	683 (89.5)	<0.001
1	275 (9.2)	52 (7)	40 (5.4)	27 (3.6)	17 (2.2)	<0.001

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2	384 (12.8)	107 (14.3)	87 (11.7)	48 (6.4)	33 (4.3)	<0.001
3	1,866 (60.2)	187 (25)	104 (14)	62 (8.3)	30 (3.9)	<0.001
Thrombectomy		392 (50.6)	452 (58.3)	487 (62.8)	534 (69)	<0.001
Number of stents	174 (5.6)					
0	1,707 (54.8)	45 (5.8)	39 (5)	61 (7.9)	28 (3.6)	0.003
1	870 (27.9)	452 (58.1)	424 (54.4)	412 (53.1)	419 (53.9)	0.203
2	266 (8.5)	206 (26.5)	222 (28.5)	219 (28.2)	222 (28.6)	0.770
3	95 (3.1)	59 (7.6)	72 (9.2)	57 (7.3)	78 (10)	0.168
> 3		16 (2.1)	22 (2.8)	26 (3.4)	30 (3.9)	0.193
Intra-procedural complications	59 (1.9)					
Coronary slow flow	37 (1.2)	11 (1.4)	16 (2.1)	18 (2.3)	14 (1.8)	0.602
Coronary dissection	26 (0.8)	9 (1.2)	9 (1.2)	10 (1.3)	9 (1.2)	0.993
Direct current cardioversion		8 (1)	4 (0.5)	6 (0.8)	8 (1)	0.634
TIMI flow post-PCI, n (%)	72 (2.4)					
0	30 (1)	16 (2.1)	18 (2.4)	23 (3.1)	15 (2)	0.528
1	123 (4.1)	9 (1.2)	5 (0.7)	12 (1.6)	4 (0.5)	0.138
2	2,776 (92.5)	14 (1.9)	26 (3.5)	33 (4.4)	48 (6.4)	<0.001
3	13.8 (12.6 – 14.9)	717 (94.8)	699 (93.4)	679 (90.9)	680 (91)	0.007
Outcome						
In-hospital mortality, n (%)	94 (3)	24 (3.1)	18 (2.3)	23 (3)	26 (3.3)	0.661
Overall mortality, n (%)	509 (16.4)	123 (15.8)	119 (15.3)	110 (14.2)	154 (19.8)	0.016

Abbreviations: BP, blood pressure; CABG, coronary artery bypass graft; CAD, coronary artery disease; cTnT, cardiac troponin T; GP IIb/IIIa, glycoprotein IIb/IIIa; hs-cTnT, high sensitivity cardiac troponin T; IQR, interquartile range; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction angiographic score.

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1. Stamatelopoulos K, Mueller-Hennessen M, Georgiopoulou G, Sachse M, Boeddinghaus J, Sopova K, et al. Amyloid-beta (1-40) and Mortality in Patients With Non-ST-Segment Elevation Acute Coronary Syndrome: A Cohort Study. *Ann Intern Med.* 2018;168(12):855-65.

2. Fox KA, Fitzgerald G, Puymirat E, Huang W, Carruthers K, Simon T, et al. Should patients with acute coronary disease be stratified for management according to their risk? Derivation, external validation and outcomes using the updated GRACE risk score. *BMJ Open.* 2014;4(2):e004425.

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	3
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5 / 6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5 / 6
		(b) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5 / 6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	5/10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7 / 8
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7 / 8
		(b) Describe any methods used to examine subgroups and interactions	7 / 8
		(c) Explain how missing data were addressed	8
		(d) If applicable, explain how loss to follow-up was addressed	N/A
		(e) Describe any sensitivity analyses	-
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	10
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10/24
		(b) Indicate number of participants with missing data for each variable of interest	4 (Appendix)
		(c) Summarise follow-up time (eg, average and total amount)	11
Outcome data	15*	Report numbers of outcome events or summary measures over time	Figure 2

1	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11/12
2			(b) Report category boundaries when continuous variables were categorized	11/12
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
4	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12/13
5	Discussion			
6	Key results	18	Summarise key results with reference to study objectives	14
7	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
8	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15/16
9	Generalisability	21	Discuss the generalisability (external validity) of the study results	17
10	Other information			
11	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	9

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.