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

Jose Coelho-Lima, Georgios Georgiopoulos, Javed Ahmed, Syeda E R Adil, David Gaskin, Constantinos Bakogiannis, Kateryna Sopova, Fareen Ahmed, Haaris Ahmed, Luke Spray, Gavin Richardson, Alan J Bagnall, Konstantinos Stellos, Kimon Stamatakis, Ioakim Spyridopoulos

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 patients with STEMI remains obscure. This study sought to determine the prognostic value of pre-reperfusion (admission) and post-reperfusion (12-hour) hs-cTnT in patients with STEMI treated with primary percutaneous coronary intervention (PPCI).

Methods Retrospective observational longitudinal study including consecutive patients with STEMI treated with PPCI at a university hospital in the northeast of England. hs-cTnT was measured at admission to the catheterisation laboratory and 12 hours after PPCI. Clinical, procedural and laboratory data were prospectively collected during patient hospitalisation (June 2010–December 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 3113 patients were included. Median follow-up was 53 months. Admission hs-cTnT >515 ng/L (fourth quartile) was independently associated with in-hospital mortality (HR=2.53 per highest to lower quartiles; 95% CI: 1.82 to 3.52; p<0.005) after multivariable adjustment for a clinical model of mortality prediction. Likewise, admission hs-cTnT >515 ng/L independently predicted overall mortality (HR=1.27 per highest to lower quartiles; 95% CI: 1.02 to 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, 12-hour hs-cTnT was not independently associated with mortality.

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

INTRODUCTION

Despite implementation of evidence-based therapy for ST-segment elevation myocardial infarction (STEMI), including primary percutaneous coronary intervention (PPCI), global short-term and long-term mortality rates (in-hospital: 7%–11%; 1–5 years: 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 patients with STEMI at extreme high versus lower risk, which is crucial to guide secondary prevention strategies post-PPCI.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 optimising risk stratification with a view to improving long-term treatment strategies for patients with STEMI.

High-sensitivity cardiac troponin T (hs-cTnT) 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-cTnT 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-cTnT assays in patients with STEMI undergoing PPCI.7–11 Few studies with small cohorts suggest differential prognostic roles for pre-reperfusion and post-reperfusion hs-cTnT levels.7–11 Nonetheless, direct comparisons between these two measurement time points have never been performed in large cohorts. We hypothesised that pre-reperfusion and post-reperfusion hs-cTnT 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 12-hour post-reperfusion hs-cTnT levels for mortality prediction and risk stratification in a large cohort of patients with STEMI treated with PPCI.

METHODS

Patient population

Data from consecutive patients with STEMI 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...
Coronary artery disease

suggestive of myocardial ischaemia lasting longer than 30 min accompanied by ST-segment elevation or new left bundle branch block on the ECG. Patients were considered for PPCI if they presented within 12 hours of symptom onset. Patients with STEMI were given 300 mg of aspirin and were transferred directly to the cardiac catheterisation laboratory. On arrival, a loading dose of a second antiplatelet along with standard doses of heparin or bivalirudin were administered according to international guidelines. 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 were included for analysis.

Study design
This was a retrospective longitudinal cohort study. The primary data source was the local coronary artery disease database (Dendrite Clinical Systems, Oxford, England, UK). The data are annually submitted to the National Institute for Cardiovascular Outcomes Research 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 20 June 2017. The prognostic endpoints were (1) in-hospital mortality, defined by all-cause deaths during hospitalisation and (2) 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 catheterisation 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, UK). 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 X² test for categorical variables. Patients were assigned to quartiles according to admission or 12-hour 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 X² test for categorical variables. Survival distributions between distinct admission and 12-hour 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 periprocedural variables were used to derive such model, many of which compose previously published or established risk prediction tools, such as the GRACE score

RESULTS
Admission and 12-hour hs-cTnT reflect distinct clinical risk profiles
From the 3408 consecutive patients, those who did not have admission hs-cTnT (n=195, 5.7%), 12-hour hs-cTnT (n=57, 1.6%) or both (n=43, 1.2%) quantified were excluded, resulting in a final cohort of 3113 patients. Clinical and periprocedural baseline characteristics of the study population are summarised in table 1. The distribution of parameters traditionally related to worse risk profile differed between admission and 12-hour hs-cTnT quartile groups. Increasing admission hs-cTnT levels were associated with more frequent interhospital transfer than direct admission to the catheterisation laboratory from ambulance (p<0.001) (online 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 >515 ng/L; online 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) (online supplemental table 3). Finally, in terms of periprocedural 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 (online supplemental table 3). Consequently, the incidence of in-hospital and overall mortality was significantly greater in the highest admission hs-cTnT quartile group (online supplemental table 3). In contrast, no difference in the distribution of these variables was observed among 12-hour hs-cTnT quartiles, except for cardiogenic shock (online supplemental table 4).

Coelho-Lima J, et al. Heart 2021;0:1–8. doi:10.1136/heartjnl-2021-319225
## Table 1  Baseline characteristics of the study cohort

| Variable                          | Entire cohort | Survivors | Non-survivors | P value |
|-----------------------------------|---------------|-----------|---------------|---------|
| Sample size, n (%)                | 3113 (100)    | 2604 (83.6) | 509 (16.4) |         |
| Gender (female), n (%)            | 2211 (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†|
| 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                    | 1335 (45.6)   | 1188 (47.6)  | 147 (33.9)  | <0.001* |
| Family history of CAD             | 1361 (46.1)   | 1232 (49)    | 129 (29.5)  | <0.001* |
| Hypertension                      | 1434 (46.1)   | 1132 (43.5)  | 302 (59.3)  | <0.001* |
| Diabetes mellitus                 | 393 (12.8)    | 291 (11.3)   | 102 (20.6)  | <0.001* |
| Hypercholesterolaemia             | 1216 (39.1)   | 1017 (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, mm Hg (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                | 2264 (72.7)   | 1898 (72.9)  | 366 (71.9)  | 0.649*  |
| Interhospital 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                          | 1207 (39.3)   | 979 (37.9)   | 228 (46.2)  | 0.001*  |
| Biochemical tests (median (IQR))  |               |            |               |         |
| Admission haemoglobin, g/L        | 138 (126–149) | 140 (128–150) | 127 (113–140) | <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†|
| 12-hour hs-CtNT, ng/L             | 2200 (775–5223) | 2170 (767–5063) | 2319 (815–6543) | 0.053†|
| Arterial access, n (%)            |               |            |               |         |
| Radial                            | 2640 (84.9)   | 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 (0.1)      | 3 (0.6)     | 0.093*  |
| GP IIb/IIIa medication, n (%)     | 2016 (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                      | 1866 (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                                 | 1707 (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 (8.2)    | 0.543*  |
| Intraprocedural 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* |

*Continued*
Coronary artery disease

Table 1  Continued

| Variable | Entire cohort | Survivors | Non-survivors | P value |
|----------|---------------|-----------|---------------|---------|
| 1        | 30 (1)        | 19 (0.8)  | 11 (2.3)      | 0.002*  |
| 2        | 123 (4.1)     | 82 (3.3)  | 41 (8.4)      | <0.001* |
| 3        | 2776 (92.5)   | 2372 (94.3)| 404 (83.1)    | <0.001* |

Bold values indicate statistical significance.
*Comparisons in the distribution of variables between survivors and non-survivors were performed using $\chi^2$ for continuous and categorical variables.
†Comparisons in the distribution of variables between survivors and non-survivors were performed using Mann-Whitney U test for continuous and categorical variables.
‡Comparisons in the distribution of variables between survivors and non-survivors were performed using t-test for continuous and categorical variables.
BP, blood pressure; bpm, beats per minute; CABG, coronary artery bypass graft; CAD, coronary artery disease; hs-cTnT, high-sensitivity cardiac troponin T; GP IIb/IIIa, glycoprotein IIb/IIIa; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction.

Prognostic value of admission and 12-hour 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 (IQR 37–68 months) (online 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 (figure 1A,B). For 12-hour hs-cTnT quartiles, there was no association with in-hospital mortality but a significant correlation with overall mortality (figure 1C,D). In addition, univariable Cox regression analysis showed that admission hs-cTnT levels >515 ng/L (fourth quartile) were associated with higher risk of in-hospital and overall mortality (table 2). In contrast, 12-hour hs-cTnT levels >5221 ng/L (fourth 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 GP IIb/IIIa inhibitors, thrombolysis in myocardial infarction (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.

![Figure 1](https://via.placeholder.com/150)

Figure 1  Admission and 12-hour post-PPCI hs-cTnT levels and mortality in patients with STEMI. Kaplan-Meier survival curves depicting the association of admission hs-cTnT quartiles with probability of in-hospital (A) and overall (B) mortality in patients with STEMI. Kaplan-Meier survival curves displaying the association between 12-hour post-PCI hs-cTnT quartiles and in-hospital (C) as well as overall mortality (D). hs-cTnT, high-sensitivity cardiac troponin T; PPCI, primary percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.
per highest to lower quartiles, 95% CI=1.32 to 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 to 1.59, p=0.029) after adjusting for the core mortality prediction model (table 2). Conversely, 12-hour 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 12-hour 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 12-hour 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 to 6.39, p<0.001; figure 2A) after adjustment for the variables in the core model, whereas 12-hour hs-cTnT was not (adjusted HR=0.96 for 80th vs 20th percentiles, 95% CI 0.51 to 1.80, p=0.663; figure 2B). With regard to overall mortality, admission hs-cTnT was associated with increased risk after adjusting for the core clinical model of overall mortality prediction. Interestingly, 12-hour 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 to 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 to 0.903, p<0.001) over the core in-hospital mortality prediction model (table 3). The reclassification value of admission hs-cTnT was driven by correctly reclassifying into lower risk patients who did not die across hospitalisation (70.5%), whereas 11.8% of patients who died were incorrectly classified (39.8%, overall NRI=0.178, 95% CI 0.037 to 0.311, p=0.001, table 3).

**DISCUSSION**

This study’s main findings are that: (1) admission hs-cTnT was independently associated with both in-hospital and long-term mortality while 12-hour hs-cTnT was not; (2) admission hs-cTnT displayed a consistently positive dose–response association with mortality, whereas 12-hour hs-cTnT presented an inverse correlation with long-term mortality in low-to-medium concentrations; (3) 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 (MACEs) 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. Risk stratification is fundamental to tailor secondary prevention strategies. To this end, several short-term and long-term mortality risk prediction models have been assessed in STEMI cohorts but have not yet been incorporated into clinical guidelines. Given the significant unmet need for optimising risk stratification in patients with STEMI, 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 12-hour hs-cTnT in a large cohort of 3113 consecutive patients with STEMI of one tertiary NHS hospital covering 1.6 million individuals in the northeast of England. Admission hs-cTnT was an independent predictor of short-term and long-term mortality while 12-hour hs-cTnT was not. In support of this observation, increased admission hs-cTnT was linked with a higher risk profile in these patients compared with 12-hour hs-cTnT. Specifically, admission hs-cTnT, but not 12-hour hs-cTnT, was associated with (1) worse physiological status at presentation, including lower haemoglobin levels, higher heart rate and increased incidence of cardiogenic shock; as well as (2) parameters affecting the timing of revascularisation, including more frequent interhospital 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 levels, might explain the association of admission hs-cTnT with both in-hospital and overall mortality.
**Figure 2** Dose–response relationship between continuous hs-cTnT and mortality. Smoothed restricted cubic spline (RCS) plots of the log HR for in-hospital (A, B) and overall mortality (C, D) versus levels of admission hs-cTnT (A and C) and post-PCI hs-cTnT (B and D). Three knots were fixed at the 10th (16 and 257.1 ng/L for admission and 12-hour cTnT, respectively), 50th (121 and 2200 ng/L for admission and 12-hour cTnT, respectively) and 90th (1557 and 9547 ng/L for admission and 12-hour cTnT, respectively) percentile of cTnT distribution. The uppermost and lowermost 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 HR for the 80th percentile of hs-cTnT vs 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 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 colour) has been placed at 0 value of Y axis to indicate absence of association with the outcome. hs-cTnT, high-sensitivity cardiac troponin T; PPCI, primary percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction.

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

|                | Calibration | Redefinition |
|----------------|-------------|--------------|
|                | LR test X²  | 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 to 0.903) | <0.001 |
| Overall all-cause mortality† | 11.73       | 0.001        | −39.8% | +57.6%     | 0.178 (0.037 to 0.311) | 0.001  |

*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).

Bold values indicate statistical significance.

*95% bias-corrected CIs were derived from bootstrapping with 1000 replicates.

†hs-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.

hs-cTnT, high-sensitivity cardiac troponin T; LR, likelihood ratio; NRI, net reclassification index; PPCI, primary percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction.
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. 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 patients with STEMI. 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.

In addition, our findings show that 12-hour 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-cTnT derived from relatively small STEMI populations lacking long-term follow-up. For example, in a recent study by Cediel et al., peak levels of both contemporary cTnI and hs-cTnT assays did not predict MACE in 1260 consecutive patients with STEMI at 30 days and 1 year post-PPCI. In contrast, in a post-hoc analysis from a multicentre, phase II, randomised placebo-controlled trial (PROTECTION AMI trial), post-PCI levels of cTnI were predictors of outcome in 1066 patients. Accordingly, Ndrepepa et al showed that post-PPCI hs-cTnT was an independent predictor of 3-year all-cause mortality. 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 12-hour 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 HRs with increasing concentrations, we observed a negative association between long-term mortality and low-medium concentrations of 12-hour hs-cTnT. Considering that successful coronary reperfusion leads to a rapid washout of troponin within the initial 12 hours, it may be hypothesised that this ‘protective’ attribute of low-to-medium 12-hour hs-cTnT concentrations could be a reflection of successful reperfusion, whereas higher hs-cTnT levels at 12 hours might reflect a slower release of troponin due to impaired reperfusion. 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.

The present study has some limitations. First, this was a retrospective, observational study. Therefore, there may have been relevant parameters that were not controlled for. For instance, echocardiographic data were only available for a minority of patients and hence not included in the prediction model. Second, 12-hour hs-cTnT measurements were performed as part of routine clinical care, as per departmental standard operating protocol. Therefore, slight interpatient variation in terms of blood collection timing at 12-hour post-reperfusion could have occurred. Consequently, this study cannot entirely exclude the possibility that 12-hour hs-cTnT could be a significant predictor of mortality with larger cohorts or strict sampling, in the context of a clinical trial. Third, 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 data were 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 patients with STEMI undergoing PPCI as compared with 12-hour 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 patients with STEMI 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 12-hour hs-cTnT levels do not seem to be useful for prognostic stratification of patients with STEMI.

Author affiliations
1Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UK
2School of Biomedical Engineering and Imaging Sciences, King’s College, London, UK
3Department of Clinical Therapeutics, School of Medicine, National and Kapodistrian University of Athens School of Health Sciences, Athens, Greece
4Department of Cardiology, Freeman Hospital, Newcastle Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK
5Respiratory Unit, Royal Stoke University Hospital, Stoke-on-Trent, UK
6Biosciences Institute, Newcastle University, Newcastle upon Tyne, UK

Presented at
Part of the research data shown in this manuscript was presented as a poster entitled ‘The additive value of pre- and post-reperfusion cardiac troponin T levels in risk stratification of patients with ST-segment elevation myocardial infarction’ at the European Society of Cardiology (ESC) Congress 2019.

Contributors JC-L and GG performed data analyses and interpretation and drafted the manuscript. JA, SERA, DG, FA and AJB performed data collection. CB, KS, LS, GR and AJB critically revised the manuscript for important intellectual content. KStellos,
KStamatelopoulos 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.

Funding JC-L is supported by a PhD scholarship (Ministry of Education of Brazil) and an academic development scholarship from Newcastle University. G.Georgiopoulous was supported by Onassis Foundation under the special grant & support program for scholar’s association members (Grant No. 82P 001/2019-2020). K.Stellos is supported by the European Research Council MODVASC grant. K.ropova is supported by a scholarship from the German Heart Foundation (Deutsche Herzstiftung). IS is supported by the British Heart Foundation and Newcastle upon Tyne Hospitals NHS Charity.

Disclaimer The sponsors had no role in the study design, data collection and analysis, writing of the manuscript or in the decision to submit the manuscript for publication.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

Data availability statement Data are available upon reasonable request.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMI Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

ORCID IDs Jose Coelho-Lima http://orcid.org/0000-0003-2212-1922
Kimon Stamatelopoulos http://orcid.org/0000-0002-7752-7949
Ioakim Spyridopoulos http://orcid.org/0000-0002-2750-2444

REFERENCES
1 Chung S-C, Gedeon R, Nicholas O, et al. Acute myocardial infarction: a comparison of short-term survival in national outcome registries in Sweden and the UK. Lancet 2014;383:1305–12.
2 Chung S-C, Sundstorm L, Gale CP, et al. Comparison of hospital variation in acute myocardial infarction care and outcome between Sweden and United Kingdom: population based cohort study using nationwide clinical registries. BMJ 2015;351:h3913.
3 Pedersen F, Butymovich V, Kelbaek H, et al. Short- and long-term cause of death in patients treated with primary PCI for STEMI. J Am Coll Cardiol 2014;64:2101–8.
4 Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J 2016;37:2315–61.
5 Thygesen K, Mair J, Giannitsis E, et al. How to use high-sensitivity cardiac troponin in acute cardiac care. Eur Heart J 2012;33:2251–7.
6 Thygesen K. What’s new in the fourth universal definition of myocardial infarction? Eur Heart J 2018;39:3757–8.
7 Cediel G, Rueda F, Garcia C, et al. Prognostic value of new-generation troponins in ST-segment-elevation myocardial infarction in the modern era: the RUTI-STEMI study. J Am Heart Assoc 2017;6. doi:10.1161/JAHA.117.007252. [Epub ahead of print: 23 12 2017].
8 Boden H, Ahmed TAN, Valders MA, et al. Peak and fixed-time high-sensitive troponin for prediction of infarct size, impaired left ventricular function, and adverse outcomes in patients with first ST-segment elevation myocardial infarction receiving percutaneous coronary intervention. Am J Cardiol 2013;111:1387–93.
9 Bubar J, Laish-Farkash A, Koren-Morag N, et al. Cardiac troponin elevation pattern in patients undergoing a primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: characterization and relationship with cardiovascular events during hospitalization. Coron Artery Dis 2015;26:503–9.
10 Hall TS, Hallen J, Krucoff MW, et al. Cardiac troponin I for prediction of clinical outcomes and cardiac function through 3-month follow-up after primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. Am J Heart 2015;169:257–65.
11 Wang TKM, Snow TAC, Chen Y, et al. High-sensitivity troponin level pre-catheterization predicts adverse cardiovascular outcomes after primary angioplasty for ST-elevation myocardial infarction. Eur Heart J Acute Cardiovasc Care 2014;3:118–25.
12 Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC), Steg PG, James SK, et al. ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2012;33:2569–619.
13 Fox KAA, Fitzgerald G, Puyrimer E, et al. Should patients with acute coronary disease be stratified for management according to their risk? Derivation, external validation and outcomes with the updated GRACE risk score. BMJ Open 2014;4:e004425.
14 Stamatelopoulos K, Mueller-Hennissen M, Georgiopoulous G, et al. Amyloid B (1–40) and Mortality in Patients With Non-ST-Segment Elevation Acute Coronary Syndrome: A Cohort Study. Ann Intern Med 2018;168:855–63.
15 Pennica M, D’Agostino RB, Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. Stat Med 2011;30:11–21.
16 Reffelmann T, Kloner RA. The “no-reflow” phenomenon: basic science and clinical implications. Circulation 2002;87:162–8.
17 Ndrepepa G, Kufner S, Hoyos M, et al. Intracellular compartmentation of cardiac troponin T and its release kinetics in patients with reperfused and nonreperfused acute myocardial infarction. Clin Chem 2014;60:2003–9.
18 Zelinski TA, Wiviott SD, Riz I, et al. Sirtuin9 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet 2019;393:31–9.
19 Schwartz GG, Steg PG, Sarek M, et al. Allocumbus and cardiovascular outcomes after acute coronary syndrome. N Engl J Med 2018;379:2097–107.
20 Sabatine MS, Giugliano RP, Kech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017;376:1713–22.
21 Buber J, Laish-Farkash A, Koren-Morag N, et al. The “no reoass” phenomenon: basic science and clinical implications. Circulation 2002;87:162–8.
22 Hallen J, Hallén J, Krucoff MW, et al. Cardiac troponin for prediction of infarct size, impaired left ventricular function, and adverse outcomes in patients with first ST-segment elevation myocardial infarction receiving percutaneous coronary intervention. Am J Cardiol 2013;111:1387–93.