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ACUTE CORONARY SYNDROMES

The significance of circulating levels of both cardiac troponin I and high-sensitivity C reactive protein for the prediction of intravenous thrombolysis outcome in patients with ST-segment elevation myocardial infarction

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Objectives: To evaluate, using continuous 12-lead ECG ST-segment monitoring, the role of circulating levels of both cardiac troponin I (cTnI) and high-sensitivity C reactive protein (hs-CRP), on presentation, in the prediction of intravenous thrombolysis outcome in patients with ST-segment elevation myocardial infarction (STEMI).

Design and setting: Prospective observational study in a tertiary referral centre.

Patients: 786 consecutive patients with STEMI, who received intravenous thrombolysis in the first 6 h from index pain.

Main outcome measures: The incidence of failed thrombolysis and of cardiac death by 30 days. Failed thrombolysis was defined as the absence of abrupt and sustained ⩾50% ST-segment recovery in the first 90 min after the initiation of intravenous thrombolysis.

Results: The incidence of failed thrombolysis and 30-day cardiac death was 57.4% and 11.8%, respectively. By multivariate logistic regression analysis according to tertiles of both cTnI (RR, 1.5; 95% CI 1.1 to 1.8, p = 0.004 for highest vs middle third; 2.2, 1.9 to 3.5, p<0.001 for highest vs lowest third; 1.5, 1.2 to 1.8, p = 0.001 for middle vs lowest third) and hs-CRP (RR, 2.0, 95% CI, 1.6 to 2.2; p<0.001 for highest vs middle third; 2.6, 2.1 to 3.5, p<0.001 for highest vs lowest third; 1.3, 1.2 to 1.7, p = 0.02 for middle vs lowest third), were independently associated with failed thrombolysis. Moreover, by multivariate Cox regression analysis according to tertiles of both cTnI (HR 1.2, 95% CI 1.1 to 1.8, p = 0.03 for highest vs middle third; 1.5, 1.2 to 2.2, p = 0.004 for highest vs lowest third; 1.1, 0.6 to 1.4, p = 0.6 for middle vs lowest third) and hs-CRP (HR1.2, 95% CI 1.1 to 1.6, p = 0.04 for highest vs middle third; 1.7, 1.3 to 2.6, p = 0.001 for highest vs lowest third; 1.1, 0.9 to 2.1, p = 0.1 for middle vs lowest third), were independently related with an increased risk of 30-day cardiac death.

Conclusions: High circulating levels of both cTnI and hs-CRP are related with an independent increased risk of intravenous thrombolysis failure and 30-day cardiac death in patients who received intravenous thrombolysis in the first 6 h of STEMI.

Although primary percutaneous coronary angioplasty represents the preferable reperfusion strategy in patients with ST-segment elevation myocardial infarction (STEMI), intravenous thrombolysis remains the more frequently used therapy in this setting.[1] Although the benefits of intravenous thrombolysis are unequivocal, reperfusion fails in a significant proportion of patients, portending an adverse short- and long-term prognosis.[2] The identification of the predictors of intravenous thrombolysis failure is essential in everyday clinical practice but remains a challenge. In an attempt to identify these predictors, several clinical and angiographic characteristics, as well as biochemical markers have been suggested.[3] In particular, in coronary angiography or serial snapshot ECGs, elevated circulating levels of either cardiac troponin (cTn)[4–6] or C reactive protein (CRP)[7 8] have been related to intravenous thrombolysis failure and prognosis. However, the significance of simultaneously assessed cTn and CRP in this setting has not previously been evaluated in a prospective study.

For many years, coronary angiography and serial snapshot ECGs were used as the methods of choice in the evaluation of intravenous thrombolysis failure. Recently, it has been suggested that ST-segment monitoring by continuous 12-lead ECG provides a more accurate and dynamic depiction of the course of tissue-level myocardial reperfusion during intravenous thrombolysis for STEMI than either coronary angiography or serial snapshot ECGs.[9]

The aim of the present study was to prospectively investigate the possible association of elevated circulating levels of both cTnI and high-sensitivity C reactive protein (hs-CRP) on presentation with intravenous thrombolysis outcome, using the relatively novel method of ST-segment monitoring by continuous 12-lead ECG, in patients with STEMI. In particular, the possible association of both cTnI and hs-CRP on presentation with the incidence of intravenous thrombolysis failure and cardiac death at 30 days was evaluated.

Abbreviations: CRP, C reactive protein; cTn (I or T), cardiac troponin (I or T); hs-CRP, high-sensitivity C reactive protein; STEMI, ST-segment elevation myocardial infraction

Table 1 Baseline characteristics according to tertiles of cardiac troponin I concentration (n = 786)

	Lowest third (n = 262) (0–0.3 ng/ml)	Middle third (n = 263) (0.4–1.2 ng/ml)	Highest third (n = 261) (1.3–54.9 ng/ml)	p Value
Age (years)	59.8 (8.7)	60.8 (8.8)	61.5 (8.8)	0.09
Male	221 (84.4%)	213 (81%)	185 (70.9%)	<0.001
Hypertension	118 (45%)	133 (50.6%)	128 (49%)	0.4
Current cigarette smoking	165 (63%)	151 (57.4%)	152 (54.4%)	0.2
Diabetes mellitus	67 (25.6%)	87 (33.1%)	97 (37.2%)	0.02
Hypercholesterolaemia	176 (67.2%)	155 (58.9%)	169 (64.8%)	0.2
Past myocardial infarction*	43 (16.4%)	55 (20.9%)	32 (12.3%)	0.02
Past coronary angioplasty*	34 (13%)	38 (14.4%)	29 (11.1%)	0.5
Past bypass surgery*	19 (7.3%)	28 (10.6%)	20 (7.7%)	0.4
Time from onset of symptoms to initiation of thrombolysis (h)	2.6 (1.2)	3.6 (1.5)	4.4 (1.2)	<0.001
Anterior myocardial infarction†	146 (55.7%)	139 (52.9%)	135 (51.7%)	0.6
Fibrin-specific fibrinolytic agent‡	237 (90.5%)	235 (89.4%)	224 (85.8%)	0.3
Leads with ST-segment elevation	4.4 (1.5)	4.4 (1.6)	4.3 (1.5)	0.9
Magnitude of maximal ST-segment (mm)	5.1 (1.5)	4.3 (1.5)	4.1 (1.5)	<0.001
Killip class II–IV	36 (13.7%)	36 (13.7%)	34 (13%)	0.4
Systolic blood pressure <100 mm Hg	8 (3.1%)	10 (3.8%)	7 (2.7%)	0.6
Heart rate >100 beats per min	25 (9.5%)	35 (13.3%)	32 (12.3%)	0.4
hs-C reactive protein (mg/l) median (range)	7.4 (0.1–74.5)	7.5 (0.4–65.3)	7.3 (0.1–33.9)	0.4

hs, high sensitivity.
Data are presented as mean (SD), or number (%), or as specified.
*History of occurrence ⩾1 month before study.
†Current event.
‡Alteplase, reteplase or tenekteplase.

METHODS

Study patients

From August 1998 to December 2003, consecutive eligible patients with STEMI, who were admitted at Tzanio Hospital, Piraeus, Greece, were included in the study. Eligible patients were required to have continuous pain that was refractory to nitrates on presentation, lasting ⩾30 min; ST-segment elevation of ⩾2 mm in ⩾2 contiguous precordial leads, or ⩾1 mm in ⩾2 contiguous limb leads; and intravenous thrombolysis starting in the first 6 h after the index pain. Patients with left bundle branch block; conditions known to affect circulating levels of the study biomarkers (eg, renal or hepatic dysfunction, inflammatory diseases, history of myocardial infarction or coronary revascularisation in the last month); premature discontinuation of intravenous thrombolysis owing to complications; or technical problems in the interpretation of the continuous 12-lead ECG ST-segment monitoring data were excluded. Moreover, because treatment with rescue angioplasty was not the standard of care in our department, when the study was started, patients who received this treatment were not included.

The hospital ethics committee approved the study and informed consent was obtained from all participants.

Analysis of study biomarkers

On admission, venous blood samples were obtained before administration of drugs. Coded plasma samples were stored at –80°C for analysis of cTnI and hs-CRP at the end of the study. Plasma cTnI levels were measured by an enzyme-based immunoassay (AxSYM cTnI, Abbott Diagnostics, Abbott Park, Illinois, USA) with analytical sensitivity at 0.02 ng/ml (at a 95% level of confidence), coefficient of variation range at 0.16–0.27 and threshold level for the diagnosis of myocardial infarction being ⩾0.4 ng/ml. Plasma hs-CRP levels were measured by a highly sensitive nephelometric method (BNII; Dade Behring, Liederbach, Germany) with a lower limit of detection at 0.1 mg/l and intra-assay and interassay coefficients of variation being 3.3% and 3. 2%, respectively.

Treatment

Either streptokinase or a fibrin-specific fibrinolytic agent (alteplase, reteplase or tenekteplase) was used. Chewable aspirin was administered at a dose of 160–325 mg on presentation and was continued indefinitely. Unfractioned heparin was given, as appropriate, in a bolus of 5000 units on presentation, followed by intravenous infusion titrated to a therapeutic, activated partial thromboplastin time. Heparin was continued in uncomplicated cases for 48 h. Further drug therapy including, nitrates, β blockers, angiotensin-converting enzyme inhibitors and statins were prescribed at the discretion of the attending doctor.

Continuous 12-lead ST-segment monitoring

The Eagle 4000 monitor (GE Marquette Medical Systems, Milwaukee, Wisconsin, USA) was connected to each patient immediately after admission to the coronary care unit. ST-segment recording was started with the first-acquired ECG (reference ECG) and continued for at least 24 h using the ST Guard system (GE Marquette Medical Systems). The operation of this system has been described previously.[10 11] In summary, it collects ECG waveforms and produces the median QRS-T complexes for the last 10 s of every 1 min period for each of the 12 leads. From these averaged QRS-T complexes, an ST-segment trend curve is constructed for each lead and displayed on a computerised workstation and stored after eliminating periods of inadequate technical quality. The ST-segment trend of the lead with the highest ST-segment elevation is selected for the analysis of ST-segment recovery. During a peak period of ongoing or worsening ST-segment elevation, the reference ECG is continuously updated to the ECG with the most severe ST-segment elevation. In the present study, the absence of abrupt and sustained ⩾50% ST-segment recovery from the last updated reference ECG in the first 90 min after the start of intravenous thrombolysis was used to define failed reperfusion.[12] All ST-segment trends were analysed off-line by one well-trained investigator blinded to the patients' clinical and biochemical data.

Table 2 Baseline characteristics according to tertiles of high-sensitivity C reactive protein concentration (n = 786)

	Lowest third (n = 261; 0.1–6.4 mg/l)	Middle third (n = 263; 6.5–10.4 mg/l)	Highest third (n = 262; 10.5–74.5 mg/l)	p Value
Age (years)	60.3 (8.9)	61 (8.9)	60.8 (8.5)	0.6
Male	206 (78.9%)	208 (79.1%)	205 (78.2%)	0.9
Hypertension	124 (47.5%)	127 (48.3%)	128 (48.9%)	0.9
Current cigarette smoking	167 (64%)	147 (55.9%)	144 (55%)	0.07
Diabetes mellitus	79 (30.3%)	69 (33.8%)	83 (31.7%)	0.7
Hypercholesterolaemia	161 (61.7%)	163 (62%)	176 (67.2%)	0.3
Past myocardial infarction*	45 (17.2%)	40 (15.2%)	45 (17.2%)	0.8
Past coronary angioplasty*	32 (12.3%)	31 (11.8%)	38 (14.5%)	0.6
Past bypass surgery*	27 (10.3%)	19 (7.2%)	21 (8%)	0.4
Time from onset of symptoms to initiation of thrombolysis (h)	3.5 (1.5)	3.4 (1.5)	3.5 (1.4)	0.8
Anterior myocardial infarction†	156 (59.8%)	133 (50.6%)	131 (50%)	0.04
Fibrin-specific fibrinolytic agent‡	237 (90.8%)	232 (88.2%)	227 (86.6%)	0.3
No of leads with ST-segment elevation	4.5 (1.5)	4.4 (1.5)	4.3 (1.5)	0.4
Magnitude of maximal ST-segment (mm)	4.5 (1.5)	4.5 (1.5)	4.5 (1.6)	1
Killip class II–IV	37 (14.2%)	40 (15.2%)	29 (11.1%)	0.4
Systolic blood pressure <100 mm Hg	9 (3.4%)	3 (1.1%)	13 (5%)	0.04
Heart rate >100 beats per min	27 (10.3%)	24 (9.1%)	41 (15.6%)	0.05
Cardiac troponin I (ng/ml) (median (range))	0.4 (0–54.5)	0.4 (0–47.2)	0.4 (0–54.9)	0.6

Data are presented as mean (SD), or number (%), or as specified.
*History of occurrence ⩾1 month before study.
†Current event.
‡Alteplase, reteplase or tenekteplase.

Clinical follow-up

In-hospital and postdischarge follow-up data were prospectively collected on predesigned case report forms. After discharge, patients were followed up at 30 days on an outpatient basis or by telephone interview. Cardiac death by 30 days was the prespecified end point of the study. Cardiac death was defined as any incidence of sudden unexplained death, death due to fatal myocardial infarction and death after re-hospitalisation because of heart failure or possible acute myocardial ischaemia. The diagnosis of cardiac death was verified by a review of death certificates, discharge medical reports, hospitals records or contact with the attending doctors.

Statistical analysis

Values are expressed as mean (SD) for normally distributed variables and as median (range) for non-normally distributed study biomarkers. The study patients were classified according to the tertiles of circulating levels of cTnI and hs-CRP. Comparisons of continuous variables according to tertiles of the study biomarkers were made using analysis of variance or the Kruskal–Wallis test, as appropriate. The Bonferroni test in analysis of variance or Mann–Whitney U test was used, as appropriate, for pairwise comparisons of continuous variables between tertiles. Associations between categorical variables were tested by χ^2 or Fisher's test, as appropriate. Correlations between continuous variables were evaluated using Spearman's r. Multivariate logistic regression and multivariate Cox proportional hazard regression analysis were constructed for the determination of multivariate predictors of thrombolysis failure and cardiac death by day 30, respectively. All baseline characteristics and the tertiles of circulating levels of cTnI and hs-CRP were evaluated as possible predictors, and those with a $p<0.1$ were included in the multivariate models. Event-free survival was analysed by the Kaplan–Meier method, and the log-rank test was used for comparisons of the curves. All tests were two-tailed, and $p<0.05$ was considered significant. Statistical analysis was performed with SPSS statistical software V.11.0.

RESULTS

Baseline characteristics

A total of 840 consecutive eligible patients with STEMI were initially included but 54 patients were excluded because of technical problems in the interpretation of the continuous 12-lead ECG ST-segment monitoring data. Thus, 786 patients were included into the final analysis.

The time from the onset of symptoms to patients' presentation was positively correlated with the baseline cTnI levels (Spearman's $r = 0.5$; $p<0.001$), was inversely related to the magnitude of the maximal ST-segment elevation (Spearman's $r = -0.4$; $p<0.001$) but was not associated with the baseline levels of hs-CRP (Spearman's $r = 0.2$; $p = 0.2$). Circulating levels of cTnI and hs-CRP were not significantly interrelated (Spearman's $r = 0.04$; $p = 0.1$). Tables 1 and 2 give the differences in baseline characteristics according to tertiles of circulating levels of cTnI and hs-CRP, respectively.

Predictors of failed thrombolysis

The ECG criterion of abrupt and sustained ⩾50% ST-segment recovery was not attained (failed thrombolysis) by 451 (57.4%) patients.

There was a significant gradual increased risk of failed thrombolysis with increasing tertiles of circulating levels of either cTnI (32.7%, 60.2% and 82.3% for the highest, middle and lowest thirds, respectively; $p<0.001$) or hs-CRP (33.2%, 53.1% and 86.5% for the highest, middle and lowest thirds, respectively; $p<0.001$). Table 3 presents univariate and multivariate relative risks of failed thrombolysis according to tertiles for circulating levels of cTnI and hs-CRP. By multivariate logistic regression analysis, smoking, diabetes, time from onset of symptoms to initiation of intravenous thrombolysis and tertiles for circulating levels of both cTnI and hs-CRP were independently associated with thrombolysis failure.

Study biomarkers and cardiac death by day 30

By day 30, 93 (11.8%) patients had died for cardiac reasons. During this period, 99.1%, 94.7%, 92.3% and 74.6% of patients received aspirin, β blockers, angiotensin-converting enzyme inhibitors and statins, respectively, with no differences between groups defined by tertiles for cTnI or hs-CRP. Kaplan–Meier univariate estimates of cardiac death between tertiles of cTnI and hs-CRP are presented in fig 1. There was a significant gradual increased risk of 30-day cardiac death with increasing baseline circulating levels of either cTnI (7.3%, 10.3% and 18% for lowest, middle and highest thirds, respectively; $p<0.001$) or hs-CRP (6%, 11.5% and 18.1%, respectively; $p<0.001$). Table 4

Table 3 Predictors of failed thrombolysis

Predictors	Univariate logistic regression		Multivariate logistic regression	
	RR (95% CI)	p Value	RR (95% CI)	p Value
Age (per decade)	1.2 (1.1 to 1.4)	0.01	1 (0.8 to 1.3)	0.8
Current cigarette smoking	0.6 (0.4 to 0.8)	<0.001	0.6 (0.4 to 0.9)	0.006
Diabetes mellitus	1.8 (1.3 to 2.4)	<0.001	1.5 (1.1 to 2.2)	0.02
Magnitude of maximal ST segment (mm)	0.7 (0.6 to 0.8)	<0.001	0.9 (0.8 to 1.1)	0.3
Time from onset of symptoms to initiation of thrombolysis (h)	1.9 (1.7 to 2.2)	<0.001	1.7 (1.5 to 2)	<0.001
Cardiac troponin by tertiles				
Highest vs middle third	1.7 (1.4 to 2)	<0.001	1.5 (1.1 to 1.8)	0.004
Highest vs lowest third	2.5 (2.1 to 3)	<0.001	2.2 (1.9 to 3.5)	<0.001
Middle vs lowest third	1.5 (1.3 to 1.8)	<0.001	1.5 (1.2 to 1.8)	0.001
High-sensitivity C reactive protein by tertiles				
Highest vs middle third	2 (1.7 to 2.4)	<0.001	2 (1.6 to 2.2)	<0.001
Highest vs lowest third	3 (2.5 to 3.6)	<0.001	2.6 (2.1 to 3.5)	<0.001
Middle vs lowest third	1.3 (1.1 to 1.7)	0.01	1.3 (1.2 to 1.7)	0.02

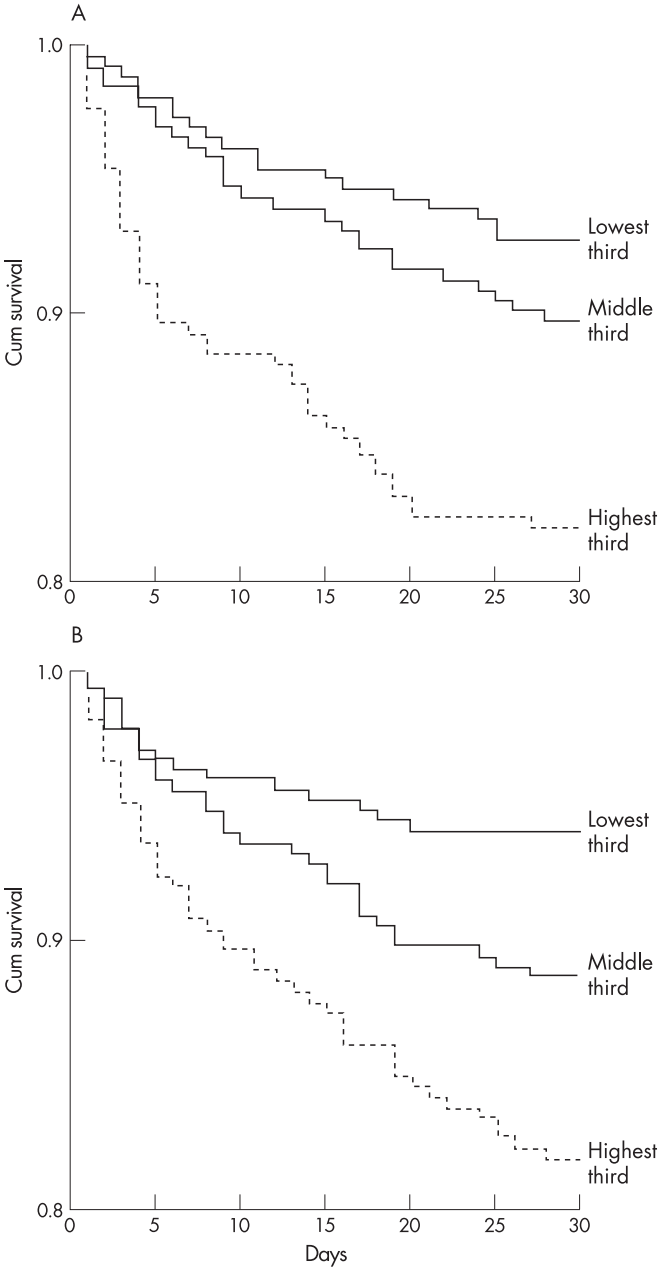

Figure 1 Kaplan–Meier univariate estimates for cardiac death by day 30 according to tertiles of circulating levels of (A) cardiac troponin I and (B) high-sensitivity C reactive protein on presentation. Cum, cumulative.

presents univariate and multivariate hazard ratios of 30-day cardiac death. By multivariate Cox regression analysis according to tertile, circulating levels of both cTnI and hs-CRP were independently associated with an increased risk of 30-day cardiac death.

DISCUSSION

The present study has shown that elevated circulating levels of both cTnI and hs-CRP on presentation are significantly and independently associated with the incidence of both failed intravenous thrombolysis and 30-day cardiac death, in patients who received intravenous thrombolysis in the first 6 h of STEMI. Although previous studies, using serial snapshot ECGs or coronary angiography, have found an association of elevated circulating levels of cTn[4–6] or CRP[7 8] on presentation with failed intravenous thrombolysis and prognosis in patients with STEMI, no previous study has evaluated the significance of simultaneously assessed cTnI and hs-CRP in this setting. Tanasijevic *et al*[4] and Stewart *et al*[5] have shown that an elevated cTn (I or T) circulating level on presentation was inversely related to the rate of thrombolysis in myocardial infarction (TIMI) 3 flow in the coronary angiography at 60 and 90 min, respectively. Stubbs *et al*[6] have shown that an elevated circulating level of cTnT on presentation was a negative predictor of the presence of non-invasive signs of reperfusion. Our earlier study[7] and one by Dibra *et al*[8] have previously found that elevated circulating levels of CRP on admission were associated with failed intravenous thrombolysis estimated by serial snapshot ECGs and technetium sestamibi scintigraphy, respectively. Oltrona *et al*[13] have recently reported an independent predictive value of both cTnI and CRP regarding 30-day mortality in patients who presented in the first 12 h after an acute coronary syndrome.

The present study confirms and further expands all these previous observations. This is the first study that prospectively evaluated the predictive value of simultaneously assessed circulating levels of cTnI and hs-CRP, using the novel and accurate modality of continuous 12-lead ECG ST-segment monitoring,[9] in a relatively large cohort of patients who received intravenous thrombolysis in the first 6 h of STEMI.

Although the exact pathophysiological mechanisms for the present results are not completely known, it has been speculated that elevated circulating levels of cTnI or hs-CRP may reflect the presence of an infarct-related thrombus more resistant to either fibrinolytics or primary coronary angioplasty,[14] and greater microvascular dysfunction or damage,[4–8] which, as observed in the present study, may account for intravenous thrombolysis failure and increased 30-day mortality.

Table 4 Univariate and multivariate predictors of 30-day cardiac death

	Univariate Cox regression		Multivariate Cox regression	
Predictors	**HR (95% CI)**	**p Value**	**HR (95% CI)**	**p Value**
Age (per decade)	2.9 (2.2 to 3.9)	<0.001	2.1 (1.5 to 2.7)	<0.001
Female sex	2.1 (1.3 to 3.1)	0.001	1 (0.6 to 1.7)	0.9
Hypertension	2.5 (1.6 to 3.8)	<0.001	1.1 (0.7 to 1.8)	0.8
Current cigarette smoking	0.4 (0.3 to 0.6)	<0.001	0.8 (0.5 to 1.2)	0.3
Diabetes mellitus	4.5 (2.9 to 6.9)	<0.001	2.6 (1.6 to 4.1)	<0.001
Past myocardial infarction*	1.8 (1.2 to 2.9)	0.01	1.1 (0.9 to 3.2)	0.1
Time from onset of symptoms to initiation of thrombolysis (h)	1.5 (1.1 to 2.2)	<0.001	0.9 (0.8 to 1.1)	0.5
Anterior myocardial infarction†	1.8 (1.2 to 2.8)	0.008	2 (1.3 to 3.2)	0.002
Magnitude of maximal ST-segment (mm)	0.7 (0.6 to 0.8)	<0.001	0.9 (0.8 to 1.1)	0.5
Killip class II–IV	3.4 (2.2 to 5.3)	<0.001	2.1 (1.3 to 3.3)	0.002
Systolic blood pressure <100 mm Hg	4.7 (2.5 to 8.8)	<0.001	4 (2.1 to 7.7)	<0.001
Heart rate >100 beats per min	2.2 (1.3 to 3.6)	0.002	1.6 (0.9 to 2.7)	0.08
Failed thrombolysis	4.5 (2.5 to 7.9)	<0.001	1.9 (1.1 to 3.7)	<0.001
Cardiac troponin I by tertiles				
Highest vs middle third	1.4 (1.1 to 2.4)	0.01	1.2 (1.1 to 1.8)	0.03
Highest vs lowest third	1.6 (1.3 to 2.1)	<0.001	1.5 (1.2 to 2.2)	0.004
Middle vs lowest third	1.2 (0.8 to 2.6)	0.2	1.1 (0.6 to 1.4)	0.6
High-sensitivity C-reactive protein by tertiles				
Highest vs middle third	1.6 (1.1 to 2.6)	0.03	1.2 (1.1 to 1.6)	0.04
Highest vs lowest third	1.8 (1.3 to 2.4)	<0.001	1.7 (1.3 to 2.6)	0.001
Middle vs lowest third	1.4 (1 to 2.2)	0.05	1.1 (0.9 to 2.1)	0.1

*History of occurrence ⩾1 month before study
†Current event.

CONCLUSIONS

The results of the present study indicate that high circulating levels of both cTnI and hs-CRP on presentation are associated with an increased risk of intravenous thrombolysis failure and 30-day cardiac death. The present results suggest that the combined use of markers of myocardial necrosis and inflammation may provide enhanced early risk stratification in patients who receive intravenous thrombolysis in the first 6 h of STEMI.

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