

## PAPER

# Prognostic significance of admission levels of troponin I in patients with acute ischaemic stroke

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**Objectives:** Successful prediction of cardiac complications early in the course of acute ischaemic stroke could have an impact on the clinical management. Markers of myocardial injury on admission deserve investigation as potential predictors of poor outcome from stroke.

**Methods:** We prospectively investigated 330 consecutive patients with acute ischaemic stroke admitted to our emergency department based stroke unit. We analysed the association of baseline levels of cardiac troponin I (cTnI) with (a) all-cause mortality over a six month follow up, and (b) in-hospital death or major non-fatal cardiac event (angina, myocardial infarction, or heart failure).

**Results:** cTnI levels on admission were normal (lower than 0.10 ng/ml) in 277 patients (83.9%), low positive (0.10–0.39 ng/ml) in 35 (10.6%), and high positive (0.40 ng/ml or higher) in 18 (5.5%). Six month survival decreased significantly across the three groups ( $p < 0.0001$ , log rank test for trend). On multivariate analysis, cTnI level was an independent predictor of mortality (low positive cTnI, hazard ratio (HR) 2.14; 95% CI 1.13 to 4.05;  $p = 0.01$ ; and high positive cTnI, HR 2.47; 95% CI 1.22 to 5.02;  $p = 0.01$ ), together with age and stroke severity. cTnI also predicted a higher risk of the combined endpoint "in-hospital death or non-fatal cardiac event". Neither the adjustment for other potential confounders nor the adjustment for ECG changes and levels of CK-MB and myoglobin on admission altered these results.

**Conclusions:** cTnI positivity on admission is an independent prognostic predictor in acute ischaemic stroke. Whether further evaluation and treatment of cTnI positive patients can reduce cardiac morbidity and mortality should be the focus of future research.

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Cardiac comorbidities account for almost 20% of deaths after ischaemic stroke,<sup>1,2</sup> and can contribute to poor outcome in the remaining patients.<sup>3</sup> If patients with acute stroke at risk of myocardial injury could be identified on hospital admission, those suitable for specific preventive or therapeutic measures could be targeted. Currently, the cardiac troponins are considered the most accurate biomarkers of myocardial necrosis available in the clinical setting.<sup>4,5</sup> Previous research has shown that high levels of cardiac troponin T (cTnT) or I (cTnI) are found in a substantial proportion of patients with stroke and are associated with poorer in-hospital prognosis.<sup>6,7</sup> However, in published studies, the assays were performed after an unspecified delay from onset of stroke or there were small numbers of patients. Causes of death were also not investigated.

To test the hypothesis that if determined early in the course of ischaemic stroke, troponin levels can help predict cardiac complications and death, we studied the frequency and the prognostic correlates of elevated cTnI levels on admission in a cohort of consecutive patients referred to an emergency department based stroke unit (SU). We also evaluated other biomarkers of myocardial necrosis (creatin kinase-MB (CK-MB) and myoglobin) and electrocardiogram (ECG) findings, obtained on admission to the SU, to verify whether they added to the prognostic information provided by the troponin levels.

## SUBJECTS AND METHODS

### Study cohort

From February 2001 through January 2002, all patients with an acute ischaemic stroke admitted to the emergency department based SU of the teaching hospital of the University of Rome "La Sapienza" were included in the

study. Patients are admitted to this six bed unit from the emergency room at the discretion of the neurologist on duty, after computed tomography (CT) or magnetic resonance imaging (MRI) has confirmed the diagnosis of acute stroke. There are no selection criteria for referral to the SU. However, in the event that more patients with stroke present simultaneously to the emergency department than are beds available in the SU, priority is given to patients with more recent onset.

The study protocol was approved by the institutional review board. The requirement for informed consent was waived because screening for myocardial injury is usual practice in patients with acute cardiovascular conditions.

### Baseline data collection

On admission to the SU, a venous blood sample was obtained for cardiac markers; the levels of cTnI were measured by immunoassay using a Dimension Rxl system (Dade Behring; Deerfield, IL) in the hospital central laboratory on receipt of the sample. According to the manufacturer this system can detect a minimum cTnI level of 0.04 ng/ml, while the 99th percentile of the normal reference range is 0.07 ng/ml. The system allows CK-MB mass and myoglobin levels to be assayed simultaneously on the same sample. This was done in most cases.

Other data collected on admission included age, sex, history of the disease, presence of vascular risk factors, and findings at general physical examination, including the Killip class. Killip class I was defined as the absence of rales over the lung fields and the absence of S3 gallop. Class II included

**Abbreviations:** cTnI, cardiac troponin I; cTnT, cardiac troponin T; MI, myocardial infarction; NIHSS, National Institutes of Health Stroke Scale; SU, stroke unit

**Table 1** Baseline characteristics and medical history of the patients by troponin levels

Characteristics	cTnI (ng/ml)			p linear	p value
	<0.1	0.1–0.39	≥0.4		
No. of patients*	277/330 (83.9)	35/330 (10.6)	18/330 (5.5)		
Demographics					
Age in years†	68.5 (12.4)	72.9 (13.0)	69.7 (14.2)	0.688	0.148
Men*	140/277 (50.5)	19/35 (54.3)	11/18 (61.1)	0.356	0.645
Women*	137/277 (49.5)	16/35 (45.7)	7/18 (38.9)	0.356	0.645
Medical history*					
Hypertension	173/275 (62.9)	24/35 (68.6)	12/18 (66.7)	0.549	0.778
Diabetes mellitus	55/275 (20.0)	4/35 (11.4)	5/18 (27.8)	0.969	0.320
Atrial fibrillation	60/276 (21.7)	14/35 (40.0)	3/18 (16.7)	0.405	0.044
Prior myocardial infarction	36/275 (13.1)	6/35 (17.1)	4/18 (22.2)	0.225	0.476
Stable angina	9/275 (3.3)	–	–	0.214	0.410
Prior stroke	47/277 (17.0)	13/35 (37.1)	4/18 (22.2)	0.113	0.017
Prior transient ischaemic attack	33/277 (11.9)	3/35 (8.6)	–	0.057	0.261
Current smoker	68/273 (24.9)	3/34 (8.8)	6/17 (35.3)	0.771	0.060
Hypercholesterolaemia	45/273 (16.5)	5/33 (15.2)	1/18 (5.6)	0.265	0.465
Physical exam					
Heart rate, bpm†	77 (15)	84 (18)	85 (23)	0.033	0.006
Systolic blood pressure, mm Hg†	154 (27)	160 (43)	160 (32)	0.500	0.532
Diastolic blood pressure, mm Hg†	90 (16)	93 (23)	90 (15)	0.914	0.705
Killip class ≥II*	25/277 (9.0)	8/35 (22.9)	8/18 (44.4)	<0.001	<0.001
Interval between stroke onset and cTnI assay <6 hours*	137/277 (49.5)	15/35 (42.9)	8/18 (44.4)	0.475	0.717
NIHSS score†	6.9 (6.5)	12.4 (9.8)	13.8 (7.9)	<0.001	<0.001

\*Values are number (%).  
 †Values are mean (SD).  
 cTnI, cardiac troponin I; NIHSS, National Institutes of Health Stroke Scale.

patients who had rales across ≤50% of the lung fields or the presence of an S3 gallop. Class III was defined as rales across >50% of the lung fields and class IV as pulmonary oedema with hypoperfusion (cardiogenic shock). The neurological deficit was graded using the National Institutes of Health Stroke Scale (NIHSS).<sup>8</sup> The aetiology of the stroke was classified according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria.<sup>9</sup>

All patients had a standard 12 lead ECG on admission recorded at 25 mm/s and calibrated at 1 cm/mV. For the purposes of this study, ECG tracings were coded and interpreted by two investigators blinded to the rest of the patients’ data, who analysed heart rate and rhythm, duration of PR, QT and rate-corrected QT (QTc by Bazett’s formula), duration, axis, and morphology of the QRS complex, degree and pattern of ST segment displacement, T wave configuration, and the Sokolow–Lyon voltage. Interobserver differences were resolved by consensus. P wave morphology and atrioventricular conduction were not evaluated in patients with atrial fibrillation, atrial flutter, and in those with pacemakers.

**Follow up and endpoints**

Incident in-hospital events were ascertained and characterised by structured data abstraction from medical records. Patients who survived the acute phase and were discharged home or to an inpatient rehabilitation, or a nursing home were further followed up at minimum six months after the index stroke by telephone calls. The patient themselves, or alternatively a family member or a caregiver, were interviewed by a trained assessor using an ad hoc questionnaire that included the occurrence and date of death after hospital discharge as a specific item.

Mortality was the main endpoint of the study. The detailed information available regarding the period of hospitalisation was used to classify in-hospital death as due to neurological or cardiac causes following slightly modified published criteria.<sup>10</sup> In-hospital deaths from other causes were not observed in this cohort. Death was “neurological” if due to the incident stroke or recurrent stroke and it was considered as related to the incident stroke in the following cases: (a) death due to

stroke induced brain herniation (progressive stroke, brain oedema, intra-infarct haematoma) or respiratory arrest (brain stem infarct); (b) death from aspiration or aspiration pneumonia due to dysphagia in the acute stroke phase; and (c) death by incident stroke related immobilisation (for example, pneumonia or pulmonary embolism). “Cardiac” deaths were due to acute myocardial infarction (MI), heart failure, or arrhythmia (including sudden death). We also examined the combined endpoints of in-hospital death or non-fatal MI, and in-hospital death or one of the acute non-fatal cardiac events: MI or heart failure. MI was defined according to the guidelines of the European Society of Cardiology.<sup>11</sup>

When a patient had more than one of these events, only the first was considered in the analysis. All clinical and instrumental cardiac variables were defined according to recently published guidelines.<sup>12</sup>

**Data analysis**

Patients were categorised into one of three groups according to the level of cTnI on admission: normal (lower than 0.10 ng/ml), low positive (0.10–0.39 ng/ml), and high positive (0.40 ng/ml or higher). These cut points were chosen on the basis of the most recent relevant literature.<sup>13 14</sup> The groups were compared with regard to the admission variables and follow up events using  $\chi^2$  test for trend, and one way analysis of variance (ANOVA) for linear trend. Pearson’s  $\chi^2$ , conventional one way ANOVA, and Wilcoxon’s signed rank test were also performed as ancillary statistics. Unadjusted Kaplan–Meier survival plots were compared using the log rank test for linear trend.

Cox proportional hazards models were used to compute hazard ratios of all-cause mortality according to cTnI levels after adjustment for potential confounders. Patients with normal cTnI served as the reference group. Initial analyses involved adjustments for age, sex, and NIHSS score. Further procedures were conducted to account for the possible influence of any baseline variable associated with cTnI in the univariate analysis at a probability threshold of 0.1 or lower. We also investigated whether the relationship between cTnI level and risk of death was modified when ECG findings

**Table 2** Blood tests on admission by troponin levels

Characteristics	cTnI (ng/ml)			p linear	p value
	<0.1	0.1–0.39	≥0.4		
No. of patients*	277 (83.9)	35 (10.6)	18 (5.5)		
Haemoglobin, g/dl†	14.0 (1.7)	13.9 (2.0)	12.4 (2.2)	<0.001	0.001
Haematocrit, %†	42.5 (4.8)	42.2 (6.1)	37.8 (6.5)	<0.001	0.001
White blood cells, 1000/mm <sup>3</sup> †	8.96 (3.52)	9.76 (3.23)	12.01 (6.59)	0.001	0.003
Platelets, 1000 cells/mm <sup>3</sup> †	231 (84)	256 (135)	228 (80)	0.899	0.293
Fibrinogen, mg/dl†	387 (115)	443 (153)	449 (167)	0.055	0.013
Glucose, mg/dl†	128 (54)	122 (37)	139 (48)	0.364	0.534
Blood urea nitrogen, mg/dl†	20 (9)	25 (15)	28 (10)	0.003	0.001
Creatinine, mg/dl†	1.29 (1.37)	1.23 (0.41)	1.64 (1.13)	0.288	0.535

\*Values are number (%).

†Values are mean (SD).

cTnI, cardiac troponin I

and levels of CK-MB and myoglobin were included in the model. We repeated adjusted analyses within strata of covariates to explore possible effect modification. SPSS statistical software was used for all analyses. A probability value of <0.05 was considered statistically significant.

## RESULTS

A total of 330 consecutive patients with acute ischaemic stroke (48.5% women, mean age 69 years, 48.5% admitted within six hours of onset) were included in the study. cTnI levels were normal in 277 (83.9%) patients, low abnormal in 35 (10.6%), and high abnormal in 18 (5.5%). Among the latter, the maximum observed value was 23 ng/ml and the median was 0.65 ng/ml.

The distribution of ischaemic stroke subtypes was as follows: large vessel disease 79/330 (24%), small vessel disease 27/330 (8.2%), cardioembolic 82/330 (24.8%), stroke of undetermined aetiology 125/330 (37.8%), and other determined aetiology 17/330 (5.2%). There were no significant differences in the distribution of abnormal cTnI levels between the different stroke subtypes.

### Physical examination, neurological status, blood tests, and vascular risk factors

Table 1 gives the findings at clinical examination and from the medical history on admission by cTnI levels. There were no significant differences between the three cTnI groups with regard to age, sex, and delay between stroke onset and assay of markers of myocardial necrosis. Increasing levels of cTnI were associated with an increasingly severe neurological

deficit, as measured by the NIHSS score ( $p < 0.001$ ). A significant, positive dose–response relationship was also observed between cTnI and heart rate ( $p = 0.033$ ), and between cTnI and Killip class  $\geq$ II ( $p < 0.001$ ). Several routine blood tests were significantly associated with the cTnI levels (table 2). In the trend analysis, haemoglobin and haematocrit appeared to decrease ( $p < 0.001$  for both), whereas blood urea nitrogen, white blood cell count and, marginally, fibrinogen, increased ( $p = 0.003$ ,  $p = 0.001$ , and  $p = 0.055$ , respectively) across the three cTnI groups.

### CK-MB and myoglobin

CK-MB levels were available for 300 patients (91%), and myoglobin levels for 313 (95%). The upper limits of the reference intervals for CK-MB and myoglobin were 5 ng/ml and 90 ng/ml, respectively. Among patients with normal, low positive, and high positive cTnI, prevalence rates of abnormally high CK-MB ( $>5$  ng/ml) were 3.2% ( $n = 8$ ), 9.4% ( $n = 3$ ), and 43.8% ( $n = 7$ ), respectively ( $p = 0.001$ ) and of abnormally high myoglobin ( $>90$  ng/ml) were 28.1% ( $n = 74$ ), 52.9% ( $n = 18$ ), and 56.3% ( $n = 9$ ), respectively ( $p = 0.001$ ).

### ECG findings

ECGs of 325 (98%) patients were available for diagnostic coding (table 3). Of these, 14 (4%) had a cardiac pacemaker, 11 in the group with normal cTnI and 3 in the group with high positive cTnI ( $p = 0.016$ ). These patients were excluded from subsequent analyses. Compared with patients with normal cTnI, patients with low positive, but not those with

**Table 3** ECG findings on admission by troponin levels

Characteristics	cTnI (ng/ml)			p linear	p
	<0.1	0.1–0.39	≥0.4		
No. of patients*	273/325 (84.0)	34/325 (10.5)	18/325 (5.5)		
Pacemaker*	11/273 (4.0)	–	3/18 (16.7)	0.124	0.016
Atrial fibrillation or flutter*	49/273 (17.9)	13/34 (38.2)	2/18 (11.1)	0.397	0.013
PR, ms†‡	168 (28)	177 (33)	166 (29)	0.789	0.350
QRS duration, ms†§	102 (18)	102 (18)	104 (56)	0.915	0.993
QTc, ms†§	394 (46)	396 (56)	415 (59)	0.102	0.260
ST–T depression*§	11/261 (4.2)	3/34 (8.3)	3/15 (20.0)	0.007	0.022
ST–T elevation*§	2/261 (0.8)	1/34 (2.9)	–	0.520	0.439
T wave inversion*§	49/261 (18.8)	11/34 (32.4)	6/15 (40.0)	0.011	0.037
Q waves*§	34/261 (13.0)	4/34 (12.1)	4/15 (26.7)	0.259	0.311
Right bundle branch block*§	32/262 (12.2)	5/34 (14.7)	3/15 (20.0)	0.358	0.643
Left bundle branch block*§	3/262 (1.1)	1/34 (2.9)	1/15 (6.7)	0.082	0.206
Sokolow–Lyon index $>35$ mm*§	28/262 (9.9)	5/34 (14.7)	4/15 (26.7)	0.042	0.109

\*Values are number (%).

†Values are mean (SD).

‡Patients with atrial fibrillation or flutter, or pacemaker excluded.

§Patients with pacemaker excluded.

cTnI, cardiac troponin I.

**Table 4** Inhospital events by troponin levels

Characteristics	cTnI (ng/ml)			p linear	p
	<0.1	0.1–0.39	≥0.4		
No. of patients*	277/330 (83.9)	35/330 (10.6)	18/330 (5.5)		
Inhospital events (%)					
Death	20/277 (7.2)	13/35 (37.1)	8/18 (44.4)	<0.001	<0.001
Death or non-fatal myocardial infarction	23/273 (8.4)	14/34 (41.2)	9/17 (52.9)	<0.001	<0.001
Death or any non-fatal cardiac event	38/273 (13.9)	15/34 (44.1)	9/17 (52.9)	<0.001	<0.001

high positive cTnI, more frequently had atrial fibrillation or flutter. Among the whole cohort, prevalence of ECG findings related to myocardial ischaemia or necrosis was 1% (3/310) for ST segment elevations, 5.4% (17/310) for ST segment depressions, 21.3% (66/310) for T wave inversions, and 13.5% (42/310) for Q waves. ST segment depression and T wave inversion were significantly more likely with increasing cTnI levels ( $p = 0.007$  and  $p = 0.011$ , respectively). However, prevalence of the latter ECG abnormalities in the presence of abnormal troponin levels was modest, as in the group with high positive cTnI only 40% of patients had a T wave inversion, and only 20% had ST segment depression. In the same group, cTnI levels did not differ between patients with at least one abnormal ECG finding compatible with ischaemia or necrosis as opposed to those with an unremarkable tracing ( $p = 0.25$ ). Finally, ventricular hypertrophy (Sokolow–Lyon index) was significantly more likely with increasing cTnI levels.

**Outcome**

All patients had a complete inhospital follow up; two patients (0.6% of the initial cohort) could not be reached for post discharge telephone interviews. The remainder had a follow up of at least six months (mean 152 days, median 144, range 2–489), during which 65 (19.7%) patients died, 41 in hospital and 24 after discharge. There were 14 cardiac deaths (eight MI, five heart failure, one sudden death), which in the three cTnI groups accounted for 25.0%, 30.8%, and 62.5%, respectively, of the inhospital deaths ( $p = 0.1$ ). During hospital stay five (1.5%) patients had a non-fatal MI, and 12 (3.6%) another major non-fatal cardiopulmonary event. Rates of death, death or non-fatal MI, and death or major non-fatal cardiopulmonary event during hospital stay are summarised in table 4. All these endpoints were more common in patients with low or high abnormal cTnI, showing a graded trend. In particular, the inhospital case-fatality ratio was 7.2% (20/277) in patients with cTnI <0.10 ng/ml, 37.1% (31/35) in patients with cTnI 0.10–0.39 ng/ml, and 44.4% (8/18) in those with cTnI ≥0.40 ng/ml ( $p < 0.001$ ). Patients with elevated cTnI were mostly treated with nitrates, in some cases with the addition of  $\beta$ -blockers. They were all also on aspirin, or low molecular weight heparin, or both. No invasive diagnostic or therapeutic interventions (coronary angiography, angioplasty, thrombolysis) were performed.

The Kaplan–Meier curves in the fig 1 show that there was a distinctive prognostic gradient across the three cTnI groups over the entire follow up ( $p < 0.0001$ ), with mortality increasing with cTnI levels. Table 5 gives the hazard ratios for all-cause mortality in patients with abnormal troponin levels. cTnI was still an independent predictor of mortality after adjustment of age and baseline NIHSS score. Neither the additional control for ECG abnormalities, CK-MB, and myoglobin, nor that for possible confounders (any other clinical or instrumental baseline variable associated with cTnI at univariate analysis at a probability threshold of 0.1) materially altered these results.

**DISCUSSION**

The release of cardiac enzymes in the acute phase of ischaemic stroke began to be documented in the late 1970s.<sup>15</sup> On the basis of further research, myocardial injury after stroke or other acute cerebral lesions was attributed to abnormally high levels of plasma catecholamines secondary to rapidly increasing intracranial pressure.<sup>16</sup> Currently, cardiac troponins are considered the most accurate biomarker of myocardial injury available in the clinical setting. In the first report of an association between troponin levels and poor outcome in a cohort of consecutive ischaemic stroke patients,<sup>6</sup> the criterion for abnormally high troponin was a concentration of cTnT higher than 0.1  $\mu$ g/l. Assays were performed 12–72 hours after admission and after an unspecified delay from the onset of stroke. Troponin levels were elevated in 17% of the patients, and troponin positivity was found to be associated with a threefold increase in risk of inhospital death. Further evidence of a link between high troponin levels and poor prognosis came from a cohort of patients hospitalised for an acute disease of the central nervous system. In the whole series, patients with cTnI of 0.4 ng/ml or higher had an odds ratio of 6.4 for 30 day mortality.<sup>7</sup> However, the cohort included only six patients with ischaemic stroke.

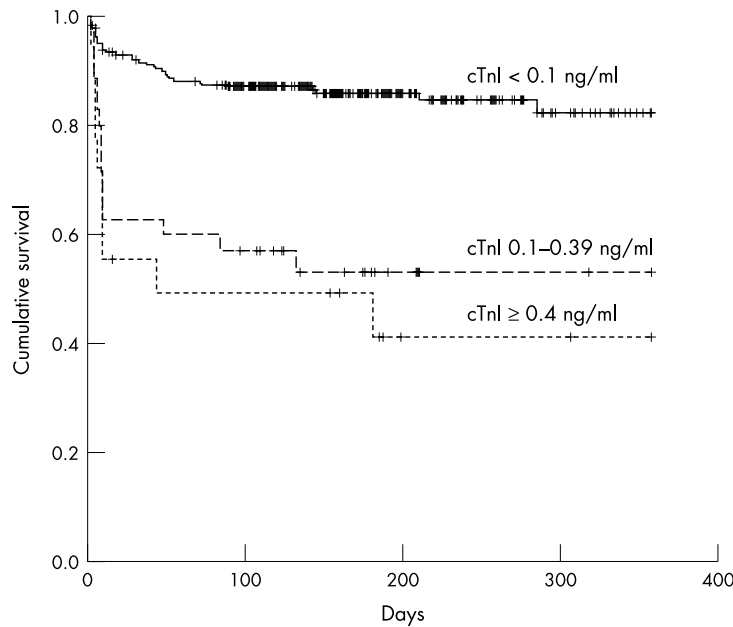
Overall, at the threshold of cTnI ≥0.1 ng/ml, 16.6% of our patients tested positive for abnormal troponin on admission. Using the more conservative cut point of cTnI ≥0.4 ng/ml, 5.5% tested positive. CK-MB and myoglobin showed a consistent association with troponin levels but, compared with the latter, confirmed to be less accurate indicators of myocardial damage. Taking a cTnI concentration ≥0.4 ng/ml as the reference standard, CK-MB appeared to have low sensitivity (43.8%), but good specificity (96.8%), whereas myoglobin had slightly higher sensitivity (56.0%) and worse specificity (71.9%). These findings indicate, on average, myocardial injury was slight in our cohort, and it would have escaped detection in approximately half of the cases if the admission work up had been limited to CK-MB and myoglobin. ECG was not more informative. The tracings on admission were unremarkable in more than 50% of patients with cTnI levels of 0.4 ng/ml or higher, and in nearly 80% of those with cTnI levels between 0.1 ng/ml and 0.4 ng/ml. These results parallel previous findings<sup>7</sup> and reiterate the possibility of insufficient sensitivity of ECG in detecting acute myocardial damage.

**Table 5** Hazard ratios for all-cause mortality, adjusted for age and NIHSS score on admission

Characteristics	Hazard ratio	95% CI	p value
cTnI 0.1–0.39 ng/ml	2.14	1.13 to 4.05	0.01
cTnI ≥0.4 ng/ml	2.47	1.22 to 5.02	0.01
Age, years	1.05	1.02 to 1.08	<0.001
NIHSS score	1.14	1.10 to 1.18	0.01

NIHSS, National Institutes of Health Stroke Scale.





**Figure 1** Kaplan–Meier survival curves by baseline troponin cut points. The number of patients at risk at baseline, 100 days, 200 days, and 300 days for each cut point is shown at the bottom of the graph.

No. of patients remaining at risk

cTnI < 0.1 ng/ml	227	210	75	27
cTnI 0.1–0.39 ng/ml	35	19	6	3
cTnI ≥ 0.4 ng/ml	18	8	2	1
Total	330	237	83	31

In our study, patients with acute ischaemic stroke with low or high abnormal cTnI levels on admission to an emergency department had an increased risk of death of 2.1 and 2.5, respectively, compared with patients with normal cTnI, an excess risk apparent across demographic and clinical subgroups. The fact that patients were accrued consecutively and prospectively and our choice of mortality as the main endpoint for the analysis reduced the possible bias which could have arisen from the partly retrospective retrieval of outcome data. Our results confirm the association between elevated troponin and poor outcome in patients with stroke, and extend previous findings, by also demonstrating higher mortality in patients with low troponin positivity. In addition, we have reported causes of death by troponin levels, which have not been previously reported in acute ischaemic stroke. Of the patients whose cTnI levels on admission to an emergency department were 0.4 ng/ml or higher, nearly half died in hospital. In that subgroup, roughly two thirds of patients died of cardiac causes, as opposed to one third cardiac deaths among patients with normal or low abnormal troponin. This difference did not reach statistical significance, but it seems reasonable to speculate that in a sizable proportion of patients with high positive troponin, myocardial damage either directly caused death or contributed significantly to an unfavourable outcome.

The excess mortality associated with low troponin positivity is more difficult to explain. Patients whose cTnI levels on admission were comprised (between 0.1 ng/ml and 0.39 ng/ml) did not die from a cardiac cause more often than patients with normal troponin. On the other hand, adjustment of stroke severity reduced but did not eliminate the significant association between low positive cTnI and an increased risk of death. Troponin levels on admission may therefore represent a surrogate marker for the systemic severity of acute ischaemic stroke, apparently able to exert a negative influence on the neurological evolution of the disease.

Another possible explanation is that troponin elevation may be a marker of unstable plaques in the coronary circulation, thereby indicating higher probability of an adverse prognosis due to recurrent myocardial ischaemia. In any case, it is worthwhile pointing out that in our cohort both low and high abnormal troponin levels retained their significant association with an increased risk of death even after adjustment of other well known systemic predictors of poor stroke outcome, such as glycaemia,<sup>17</sup> fibrinogen,<sup>18</sup> and white blood cell count.<sup>19</sup>

Our investigation has several limitations. First, in most cases we relied on a single baseline blood sample and thus we could not account for variations in troponin levels that occur over time. Repeat assays could provide additional information on the development and evolution of myocardial injury in patients with acute stroke and on its prognostic implications. Secondly, we did not investigate drug treatment as a possible confounder. Thirdly, we lacked data on the possible influence of the location of the brain lesion on the occurrence of the myocardial damage. In particular, involvement of the insular cortex is known to be associated with more frequent occurrence of cardiac complications after acute stroke, probably via an increased sympathetic tone mediated by the cerebral autonomic centres.<sup>20</sup> The possibility that troponin elevations may be related to stroke involving the insula deserves further investigation.

Notwithstanding these limitations, these data extend current understanding of the implications of troponin positivity in acute ischaemic stroke. Clinicians should consider adding a cTnI test to the admission work up, as high troponin levels seem to impart a significantly higher risk of in-hospital cardiac complications and death. CK-MB or myoglobin levels and ECG changes are much less accurate predictors. Rather than an indiscriminate strategy of systematic screening, it may be more cost efficient to limit the cTnI assay to patients having higher probability of a

positive test—that is, those with a recent history of angina or MI, or those presenting with chest pain, ECG signs of cardiac ischaemia, or severe stroke. Whether further evaluation and treatment of cTnI positive patients can reduce cardiac morbidity and mortality should be the focus of future research.

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