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

E Di Angelantonio, M Fiorelli, D Toni, M L Sacchetti, S Lorenzano, A Falcou, M V Ciarla, M Suppa, L Bonanni, G Bertazzoni, F Aguglia, C Argentino

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) inhospital 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 "inhospital 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.

Cardiac comorbidities account for almost 20% of deaths after ischaemic stroke, and can contribute to poor outcome in the remaining patients. 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. 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 inhospital prognosis.

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 (creatine 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...
The presence of an S3 gallop. Class III was defined as rales across all four lung fields. Class II was defined as rales in two or more lung fields or the presence of an S4 gallop. Class I was defined as rales in one lung field or the absence of rales.

The aetiology of the stroke was divided into three categories: (a) embolic (e.g., due to atrial fibrillation, valvular heart disease, cardiac myxoma, or left atrial thrombus); (b) non-embolic (e.g., due to dissection of the intracranial vessels, subarachnoid haemorrhage); (c) stroke due to hypoperfusion (cardiogenic shock). The neurological discharge was graded using the National Institutes of Health Stroke Scale (NIHSS). The aetiology of the stroke was classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.

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 were further followed up at minimum six months after discharge. The patient themselves, or alternatively a representative member of their family, 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 procedures were conducted to account for the possible influence of any baseline variable associated with Ctni in the univariate analysis. The results were compared with regard to the admission variables and follow-up events using Cox proportional hazards models. The groups were compared with regard to the admission variables and follow-up events using the log rank test for trend and first order ANOVA, and Wilcoxon's signed rank test for non-parametric one way ANOVA. Pearson's χ² test was performed as ancillary statistics. Unadjusted Kaplan–Meier survival plots were compared using the log rank test after adjustment for potential confounders. Patients with normal cTnI served as the reference group. Initial analyses were performed as exploratory analysis. All clinical and instrumental cardiac variables were defined according to recently published guidelines.

The patients had either a critical (cTnI >0.40 ng/ml) or normal (<0.40 ng/ml) troponin I level. The influence of any baseline variable associated with cTnI in the univariate analysis at a probability threshold of 0.1 or the basis of the most recent relevant literature. The groups were compared with regard to the admission variables and follow-up events using the log rank test for trend and first order ANOVA. Pearson's χ² test was performed as ancillary statistics. Unadjusted Kaplan–Meier survival plots were compared using the log rank test after adjustment for potential confounders. Patients with normal cTnI served as the reference group. Initial analyses were performed as exploratory analysis. All clinical and instrumental cardiac variables were defined according to recently published guidelines.

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. The groups were compared with regard to the admission variables and follow-up events using the log rank test for trend and first order ANOVA. Pearson's χ² test was performed as ancillary statistics. Unadjusted Kaplan–Meier survival plots were compared using the log rank test after adjustment for potential confounders. Patients with normal cTnI served as the reference group. Initial analyses were performed as exploratory analysis. All clinical and instrumental cardiac variables were defined according to recently published guidelines.

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>cTnI (ng/ml)</th>
<th>Value</th>
<th>Mean (SD)</th>
<th>t value</th>
<th>P value</th>
<th>P linear</th>
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<tbody>
<tr>
<td>Age (years)</td>
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<td></td>
<td>62.9 (13.9)</td>
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<td></td>
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<tr>
<td>Gender</td>
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<td></td>
<td></td>
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<tr>
<td>Race</td>
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<td></td>
<td>0.445</td>
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<tr>
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<td>0.445</td>
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<tr>
<td>Prior stroke</td>
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<tr>
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<tr>
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<tr>
<td>Ctni, cardiac troponin I</td>
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<td>0.445</td>
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<tr>
<td>NIHSS score</td>
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<td></td>
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<tr>
<td>Interval between stroke onset and cTnI assay</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>cTnI, cardiac troponin I</td>
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<td></td>
<td>0.445</td>
<td></td>
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<td></td>
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<tr>
<td>NIHSS score</td>
<td></td>
<td></td>
<td>0.445</td>
<td></td>
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</tr>
</tbody>
</table>

*Values are number (%).

Values are mean (SD).

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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 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.

**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 82/330 (24.8%), stroke of undetermined aetiology 17/330 (5.2%). There were no signifi-
cant 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
to 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 II (p<0.001). Several routine
blood tests were significantly associated with the cTnI levels
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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 abnor-
mal 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 323 (98%) patients were available for diagnostic
coding (table 3). Of these, 14 (4%) had a cardiac pacemaker,
1 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

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

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>cTnI (ng/ml)</th>
<th>p linear</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;0.1</td>
<td>0.1–0.39</td>
<td>&gt;0.4</td>
</tr>
<tr>
<td>No. of patients*</td>
<td>277 (82)</td>
<td>34 (10.5)</td>
<td>18 (5.5)</td>
</tr>
<tr>
<td>Haemoglobin, g/dl†</td>
<td>14.0 (1.7)</td>
<td>13.9 (2.0)</td>
<td>12.4 (2.2)</td>
</tr>
<tr>
<td>Haematocrit, %</td>
<td>42.5 (4.8)</td>
<td>42.2 (6.1)</td>
<td>37.8 (6.5)</td>
</tr>
<tr>
<td>White blood cells, 1000/mm³†</td>
<td>8.96 (3.52)</td>
<td>9.76 (3.23)</td>
<td>12.01 (6.59)</td>
</tr>
<tr>
<td>Platelets, 1000 cells/mm³†</td>
<td>231 (84)</td>
<td>256 (135)</td>
<td>228 (80)</td>
</tr>
<tr>
<td>Fibrinogen, mg/dl†</td>
<td>387 (115)</td>
<td>443 (153)</td>
<td>449 (167)</td>
</tr>
<tr>
<td>Glucose, mg/dl†</td>
<td>128 (54)</td>
<td>122 (37)</td>
<td>139 (48)</td>
</tr>
<tr>
<td>Blood urea nitrogen, mg/dl†</td>
<td>20 (9)</td>
<td>25 (15)</td>
<td>28 (10)</td>
</tr>
<tr>
<td>Creatinine, mg/dl†</td>
<td>1.29 (1.37)</td>
<td>1.23 (0.41)</td>
<td>1.64 (1.13)</td>
</tr>
</tbody>
</table>

*Values are number (%).
†Values are mean (SD).
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, cTnT 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 β-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. 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. 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, the criterion for abnormally high troponin was a concentration of cTnT higher than 0.1 µg/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. 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 findings² and reiterate the possibility of insufficient sensitivity of ECG in detecting acute myocardial damage.

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**Table 4** Inhospital events by troponin levels

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

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

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>cTnI 0.1–0.39 ng/ml</td>
<td>2.14</td>
<td>1.13 to 4.05</td>
<td>0.01</td>
</tr>
<tr>
<td>cTnI ≥0.4 ng/ml</td>
<td>2.47</td>
<td>1.22 to 5.02</td>
<td>0.01</td>
</tr>
<tr>
<td>Age, years</td>
<td>1.05</td>
<td>1.02 to 1.08</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NIHSS score</td>
<td>1.14</td>
<td>1.10 to 1.18</td>
<td>0.01</td>
</tr>
</tbody>
</table>

NIHSS, National Institutes of Health Stroke Scale.
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, fibrinogen, and white blood cell count.

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. 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 inhospital 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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