

## The Clinical Importance of Troponin Elevation in Ischaemic Cerebrovascular Events: A Clinical Review

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### INTRODUCTION

Stroke is the second leading cause of death worldwide, and one of the leading causes of disability in both developed and developing countries<sup>[1]</sup>. Stroke is a clinical syndrome with 3 main pathologic types [ischaemic stroke, intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (SAH)]. Each has several subtypes with distinct underlying vascular pathologies<sup>[2]</sup>.

Ischaemic stroke is far the most common type of acute cerebrovascular events and the TOAST classification denotes five subtypes of ischemic stroke: (1) large-artery atherosclerosis; (2) cardioembolism; (3) small-vessel occlusion; (4) stroke of other determined etiology; and (5) stroke of undetermined etiology<sup>[3]</sup>.

Cardioembolic stroke accounts for approximately 1/3-1/4 of ischaemic strokes; the most common disorders associated with a high risk of cardioembolism are atrial fibrillation, recent myocardial infarction, mechanical prosthetic valve, dilated cardiomyopathy and mitral rheumatic stenosis<sup>[1,3-5]</sup>.

Cardiac troponins have been accepted as the gold standard in the diagnosis and risk stratification of acute coronary syndromes<sup>[4]</sup>. Cardiac troponin is composed of three subunits T, I, and C, which are the products of different genes. The total mass of the troponin complex is minuscule when compared with the protein mass of other myofibrillar proteins like actin and myosin<sup>[5]</sup>. However both troponin T and I are ideally suited for the detection of myocardial damage as they are expressed as cardio-specific isoforms. There is a distinct release kinetics following myocardial infarction (MI) show a first peak resulting from the loosely bound troponin pool and a second prolonged elevation due to degradation of the contractile apparatus<sup>[5]</sup>.

### ABSTRACT

Cardiac troponin I (cTnI) and troponin T are recognized as sensitive and specific markers of cardiac injury and their elevation can occur after ischaemic stroke in the absence of primary cardiac causes. The background and clinical importance of stroke-related myocardial injury is not well understood. We made a systematic review to collect articles focusing on troponin elevation in ischaemic cerebrovascular diseases. Based on systematic research raised troponins were associated with unfavourable outcome and increased mortality rates. Despite of extensive literature it is still a matter of debate whether raised troponins are caused by a preceding myocardial event with subsequent cardioembolic stroke or they represent cardiac injury due to elevated levels of circulating catecholamines. The majority of available evidence supports the hypothesis that elevated catecholamine levels result from a nonspecific physiologic stress response, though the mechanism has not been definitively established. On the other hand, there are two ongoing trials to clarify the background of myocardial injury in ischaemic stroke.

On the other hand, nonischemic causes of troponin elevation should be kept in mind since troponin elevation indicates the presence, not the mechanism, of myocardial injury<sup>[4]</sup>. In the clinical work it is really difficult to interpret dynamic changes of troponin especially in the absence of chest pain in conditions such as renal failure, ischaemic stroke, haemorrhagic stroke, seizures, subarachnoid haemorrhage, acute brain injury, pulmonary embolism, sepsis, acute perimyocarditis, Takotsubo cardiomyopathy, acute heart failure, and tachycardia<sup>[4,5]</sup>.

Now there is extensive literature on troponins in ischaemic stroke, which suggest that abnormal concentrations of cardiac troponins are frequently detectable, cardiac troponins might be released by other mechanisms than acute coronary syndromes (ACS), such as reversible myocardial ischaemia as a consequence of vegetative overload and associated with worse functional outcomes and increased mortality rates, but results are controversial<sup>[4-6]</sup>. However, it is not fully elucidated whether raised troponin concentrations are related to a previous myocardial event with subsequent cardioembolic stroke or an uncontrolled stress test as the consequence of insular damage with catecholamine overload.

The aim of our review was to collect articles based on the etiology and clinical importance of troponin elevation in acute ischaemic stroke. We searched PubMed, MEDLINE, and the Cochrane Library restricted to English language publications to December, 2012. We used these search items in the following combinations: troponin I, troponin T, stroke, ischaemic stroke, outcome, mortality, death, cardiac death, echocardiography, follow-up. After reviewing the abstracts, we obtained and reviewed the full text and reference lists of relevant articles.

## TROPONIN ELEVATION IN ISCHAEMIC STROKE

Ischaemic stroke is a major public health problem. It is the third leading cause of death worldwide and results in hospital admissions, morbidity, and long-term disability<sup>[1]</sup>. Accurate definition of the mechanism of stroke is crucial as this will guide the most effective care and therapy<sup>[6]</sup>. Cardioembolic cerebral infarction accounts approximately for one quarter of all cerebral infarcts<sup>[6]</sup>.

There is an extensive literature based on troponin elevation in ischaemic stroke, however the aetiology of increased cTn in the setting of stroke has not been entirely elucidated<sup>[5]</sup>. In some patients, raised troponin could reflect a preceding acute coronary syndrome with subsequent embolisation. Based on previous studies, the risk of thrombotic stroke can be as high as 3.7%<sup>[7]</sup>. However, patchy myocyte damage (myocytolysis) has also been suggested as the consequence of the activation of the sympathoadrenal system (that can be linked to insular damage)<sup>[8]</sup>.

In the first study conducted by James *et al* troponin elevation was associated with increased mortality (relative risk 3.2) and taking 17 possible predictors of death into account only a raised troponin T concentration age and an altered level of consciousness at presentation independently predicted an adverse outcome. The cases of death were not reported (cardiac vs non-cardiac), However, their cohort included 57/181 patients with known ischaemic heart disease and no previous cardiac events had been identified (Table 1 and 2, ref 25).

In a recent literature based review and meta-analysis, Kerr *et al* identified 15 studies including 2,901 patients. Overall 18.1% had a positive troponin level. These patients were more likely to have electrocardiogram (ECG) changes suggestive of myocardial ischaemia, and there was an independent association with death (OR 2.9; 95% CI 1.7-4.8). However, there was residual heterogeneity between studies and there was no sufficient evidence from the existing literature to establish the cause or causes of elevated troponin after acute stroke. Finally, the causes of death were not reported<sup>[9]</sup>.

We identified 20 articles based on this topic<sup>[10-29]</sup> (Table 1 in the manuscript and table 2 is a supplementary table). A variety of different troponin assays and other biomarkers were used, with different cut-off values and methodology. Only a few studies focused on cardiac assessment (transthoracic echocardiogram and cardiac death) (Table 1).

Hjalmarsson *et al*<sup>[11]</sup> analysed the importance of electrocardiographic (ECG) abnormalities and elevated serum cardiac troponin (cTnT) as potential predictors for acute and long-term mortalities after stroke in a follow-up of 478 patients. Cox regression confirmed the predictive value of QTc, cTnT, age, and stroke severity, as markers of acute mortality in relation to stroke. The most

**Table 1** Baseline characteristics

Author	Study	Population	Troponin	Cut-off	Other biomarker
Santamarina <sup>[10]</sup>	Prospective	294	not reported	0.05 ng/mL	brain natriuretic peptide (BNP), D-dimer, CK-MB, myoglobin
Hjalmarsson <sup>[11]</sup>	Prospective	478	cTnT	0.03 ng/mL	not reported
Wira <sup>[12]</sup>	Retrospective	200	cTnI	not reported	not reported
Song <sup>[13]</sup>	Prospective	455	cTnT	0.01 ng/mL	not reported
Etgen <sup>[14]</sup>	Prospective	171	cTnT cTnI	0.01 ng/mL 0.03 ng/mL	N-terminal pro-brain natriuretic peptide (NT-proBNP)
Darki <sup>[15]</sup>	Retrospective	137	cTnI	0.10 ng/dL	brain natriuretic peptide (BNP)
Ay <sup>[16]</sup>	Prospective	32	cTnT	0.1 ng/mL	Serum CK-MB, myoglobin, and total CK
Fure <sup>[17]</sup>	Prospective	279	cTnT	0.04 mcg/L	not reported
Iltumur <sup>[18]</sup>	Prospective	57	cTnI	1 ng/mL	creatin kinase-MB (CK-MB), troponin I (TnI) and NT-proBNP
Jensen <sup>[19]</sup>	Prospective	244	cTnT	0.03 mcg/L	creatin kinase-MB (CK-MB)
Scheitz <sup>[20]</sup>	Retrospective	715	cTnT	0.03 mcg/L	not reported
Chalela <sup>[21]</sup>	Retrospective (ischemic + haemorrhagic stroke)	160	cTnI	0.02 ng/mL	not reported
Ay <sup>[22]</sup>	Prospective	730	cTnT	0.1 ng/mL	not reported
Di Angelantonio <sup>[23]</sup>	Prospective	330	cTnI	0.1 ng/mL	not reported
Hajdinjak <sup>[24]</sup>	Prospective	106	cTnT	0.04 mcg/L	NT-proBNP
James <sup>[25]</sup>	Prospective	181	cTnT	0.1 mcg/L	not reported
Sandhu <sup>[26]</sup>	Prospective	351 (ischaemic stroke, intracerebral haemorrhage and subarachnoid haemorrhage)	cTnI	0.4 ng/mL	not reported
Apak <sup>[27]</sup>	Prospective	62 (ischaemic + haemorrhagic stroke)	cTnT	0.1 ng/mL	creatin kinase (CK), CK-MB, lactate dehydrogenate (LDH)
Beaulieu-Boire <sup>[28]</sup>	Prospective	408	cTnI	0.03 mcg/L	not reported
Bugnicourt <sup>[29]</sup>	Retrospective	402	cTnI	0.03 mcg/L	not reported

Table 2 Methodology and results.

Author	Troponin elevation	ECG changes	Cardiac assessment	Cardiac outcome	Anatomic correlation	Outcome	Follow up	Other
Santamarina <sup>[6]</sup>	Not reported	Not reported	24 h ECG monitoring, TTE	Not reported	Not reported	High-level CK-MB and BNP during the acute phase of ischemic stroke are associated with an embolic source.	No	No
Hjalmarsson <sup>[7]</sup>	17.3%	73.6% of the patients had one or more pathological findings on the ECG (most frequently Q wave, left ventricular hypertrophy, ST depression, T wave inversion, QTc)	ECG	The most common cause of death was neurological/stroke-related (11.3%), followed by cardiac (3.3%).	Not reported	Elevated initial cTnT is strongly related to poor outcome, both during the acute phase and one year after stroke	1 year	Prolonged repolarization time independently predicts poor prognosis during the acute phase, but not one year after stroke
Wirat <sup>[9]</sup>	13 %	20.4% patients had ischemic changes on ECG defined as T-wave inversions or ST-segment depressions	ECG, TTE	28.5% had evidence of systolic dysfunction, 18% patients had evidence of diastolic dysfunction on echocardiograms	Not reported	Higher in-hospital mortality rates among patients with troponin I elevation	no	Higher in-hospital mortality rates among patients with systolic dysfunction, atrial fibrillation and ischemic changes on initial ECG
Song <sup>[10]</sup>	10.8%	Abnormalities on including ECG, were more frequent in the elevated serum cTnT group	ECG, TTE	Abnormalities on echocardiogram were more frequent in the elevated serum cTnT group	Elevated was associated with damages to the insular lobe.	The outcome of acute ischemic stroke was worse for patients with elevated cTnI than for those with normal cTnI.	30 days	Insular-lobe involvement, cardioembolic stroke and unfavorable outcome were independently related to elevated serum cTnI
Etgen <sup>[11]</sup>	Raised cTnI in 7.8% and cTnT in 4.6 %	No patient had changes during electrocardiography suggesting cardiac ischemia	ECG, TTE	81 patients (53%) had signs of left ventricular hypertrophy, and in 6 (4%) patients, cardiac thrombi were detected.	Not reported	Neither NT-proBNP nor cardiac troponins influence clinical outcome if other risk factors are considered.	90 days	Significant impact on the outcome was detected for lesion size, insular involvement, sex, age, and stroke severity.
Dark <sup>[12]</sup>	17.5% had a positive troponin level	Not reported apart from AF (18.2 %)	ECG, TTE	67% patients with a positive troponin level had a new wall motion abnormality on echocardiogram	Not reported	Elevated troponin, BNP, 100, and ejection fraction, 45% were found to be predictors of wall motion abnormalities	no	The log odds of an abnormal echocardiogram with an elevated troponin or BNP value were 4.38 and 2.26.
Ay <sup>[13]</sup>	Troponin T did not exceed the reference range in any patients	No reported	Not reported	Na	Na	Normal troponin T along with elevated CK-MB signifies that CK-MB is not the biological marker for myocytolysis	no	CK-MB elevations in stroke patients are likely to be noncardiac in origin.
Fure <sup>[14]</sup>	TnT was elevated in 9,6 %	QTc (36.0%), ST depression (24.5%), atrial fibrillation (19.9%) and T wave inversion (17.8%)	No	Not reported	Not reported	TnT rise was significantly associated with a poor short-term outcome (modified Rankin scale >3) at discharge	no	Patients with acknowledged coronary heart disease had a significantly higher prevalence of pathological findings
Ilumur <sup>[15]</sup>	16% had a positive troponin level.	At baseline, 33% had atrial fibrillation, and 75% had ST depression or ischemic T waves. However, only 23 patients (40%) had dynamic ST-T changes	ECG, TTE	Echocardiography was abnormal in 26% patients (either an LVEF ≤50% or wall motion abnormality)	Insular involvement	13 patients (23%) with AIS died; of these, 8 were cardiac-related, but 5 were not.	10 days	Insular involvement had significantly higher NT-proBNP, TnI, and CK-MB (levels, and significantly lower LVEF

Author	Troponin elevation	ECG changes	Cardiac assessment	Cardiac outcome	Anatomic correlation	Outcome	Follow up	Other
Jensen <sup>[6]</sup>	10% had raised TnI concentrations	Atrial fibrillation (18%), left ventricular hypertrophy (9%), ST-T changes (25%).	ECC, myocardial perfusion scintigraphy	Only 7 patients (3%) had elevations of TnI or creatine kinase-MB and electrocardiographic changes suggesting acute myocardial infarctions	Not reported	Overall, 36 patients (15%) died during follow-up. Patients without TnI elevations had a significantly improved survival	19 months	Perfusion abnormalities on myocardial perfusion scintigraphy at rest were not more frequent in patients with TnI levels
Scheitz <sup>[7]</sup>	Frequency of cTnI elevation was 14%	Not reported, but stroke was more often considered cardioembolic in the troponin group	Not reported	Not reported	Insular cortex involvement was independently associated with raised troponin	Increased cTnI on admission was an independent predictor of unfavorable outcome and in-hospital mortality	Not reported	Factors independently associated with increased cTnI were higher stroke severity, renal insufficiency, pre-existing coronary artery disease, hypercholesterolemia and insular cortex involvement
Chalela <sup>[8]</sup>	Elevated TI occurred in 10 (6%)	ECG changes suggestive of cardiac ischemia occurred in 2 of the 10 patients with high TI who had a stroke.	ECC, TTE	Ventricular arrhythmias, congestive heart failure, post-infarct pericarditis, and sudden death did not occur.	Not reported	TI elevation was associated with stroke severity as determined by NIHSS	Not reported	Cardiac injury in acute stroke can occur in the absence of chest pain, ischemic ECG changes, or focal akinesis on TTE.
Ay <sup>[9]</sup>	10%, but 6.8% of all eligible patients there was no clear explanation for cTnI elevation	Not reported	Not reported	Not reported	Right insula is associated with elevated serum cardiac troponin T level	Not reported	Not reported	Brain regions that were a priori associated with cTnI elevation included the right posterior, superior, and medial insula and the right inferior parietal lobule
Di Angelantonio <sup>[20]</sup>	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%).	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	ECC	cTnI independently predicted a higher risk of the combined endpoint "in-hospital death or non-fatal cardiac event"	Not reported	cTnI level was an independent predictor of mortality together with age and stroke severity	6 months	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.
Hajdinjak <sup>[21]</sup>	cTnI levels were elevated in 16/106 (15.1%) patients	28% had atrial fibrillation and 24% had ST-T changes	ECC	The different causes of mortality were equally distributed between patients with or without elevated troponin T values.	Not reported	Increased troponin T levels were associated with death	Not reported	Combined measurement of troponin T plus NT-proBNP was most predictive of survival in stroke patients
James <sup>[22]</sup>	Troponin T concentration was raised (> 0.1 ig/l) in 17% (30) of patients admitted with an acute ischaemic stroke.	Not reported	Not reported	Not reported	Not reported	Serum troponin T concentration at hospital admission is a powerful predictor of mortality	60 days	Troponin T concentration, age, and an altered level of consciousness at presentation predicted an adverse outcome.
Sandhu <sup>[23]</sup>	Patients with ischaemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage with elevated troponin I levels had increased in-hospital mortality	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported

Table 2 Methodology and results.

Author	Troponin elevation	ECG changes	Cardiac assessment	Cardiac outcome	Anatomic correlation	Outcome	Follow up	Other
Apak <sup>[24]</sup>	32% demonstrated elevations in cTnT	42 % demonstrated ST-T changes	EKG, TTE	Serum levels of cTnT were inversely correlated with LVEF	Serum levels of cTnT were positively correlated with stroke volume	Measurement of the serum levels of cTnT is of clinical importance in evaluating myocardial injury and provides a useful aid in estimating the volume of stroke lesions	Not reported	Not reported
Beaulieu-Boire <sup>[25]</sup>	11.3% had elevated cTnI levels	Not reported	EKG, TTE	Patients with elevated cTnI levels were more likely to have a new or recurrent MI within 3 months	Not reported	cTnI elevation predicts newonset AF on 24-hour Holter measurement in patients may indicate a poorer prognosis and a higher risk of stroke, MI, and death at 3 months.	90 days	No
Bugnicourt <sup>[26]</sup>	Not reported	27 (6.7%) patients had NAF	EKG	Not reported	Not reported	Moderately elevated troponin levels in acute ischaemic stroke are independently associated with NAF	Not reported	Stepwise logistic regression identified elevated cTnI levels and active smoking as independent factors for NAF.

common cause of death was neurological/stroke-related (11.3%), followed by cardiac (3.3%). Among the patients with elevated cTnT, 17.0% received the diagnosis of acute myocardial infarction, and about 34% of all patients with elevated cTnT had elevated serum creatinine. In the whole group of patients with abnormal cTnT - but without myocardial infarction or renal insufficiency - 30-day mortality was 24.5%, compared with 4.4% in the group with normal cTnT ( $p<0.001$ ).

In the study of Wira *et al* two hundred acute ischaemic stroke (AIS) patients were identified with an overall in-hospital mortality rate of 8%. In their cohort 28.5% had an ejection fraction less than 50%, 20.4% had ischemic changes on ECG, 18% presented in active atrial fibrillation<sup>[12]</sup>. Subgroup analysis revealed higher in-hospital mortality rates among those with systolic dysfunction (15.8% vs 4.9%;  $P=0.0180$ ), troponin elevation (38.1% vs 3.4%;  $P<0.0001$ ), atrial fibrillation on ECG (33.3% vs 3.8%;  $P=0.0003$ ), and ischemic changes on ECG (17.1% vs 6.1%;  $P=0.0398$ ) compared with those without. On the other hand, it was not reported whether ischaemic ECG or left ventricular dysfunction are due to stress-related cardiomyopathy or to an ongoing acute coronary syndrome, furthermore the causes of death were also unknown.

Song *et al*<sup>[13]</sup> identified the relationships between elevated cTnT and stroke severity, location, and prognosis in the cohort of 416 patients. Abnormalities on cardiologic evaluations including ECG, serum CK-MB, and echocardiogram (focal wall hypokinesia, lobal hypokinesia and decreased ejection fraction) were more frequent in the elevated serum cTnT group than in the normal serum cTnT group. However, patients in the elevated serum cTnT group did not satisfy the current clinical, ECG or echocardiographic criteria for AMI and the ST segment elevations and depressions were not prominent enough to meet the existing criteria of an acute coronary syndrome<sup>[13]</sup>. Elevated cTnT was associated with severe neurological deficits at stroke onset and damages to the insular lobe and unfavourable short-term outcome. Death rates were not reported.

Darki and his workgroup evaluated 137 consecutive with acute ischaemic stroke. All patients had laboratory markers drawn on admission, including troponin and brain natriuretic peptide, along with transthoracic echocardiogram with Doppler<sup>[15]</sup>. Twenty-four of 137 patients (17.5%) had a positive troponin level. Sixteen of 24 (67%) patients with a positive troponin level had a new wall motion abnormality on echocardiogram that was suggestive of unstable atherosclerotic disease. The inferior and septal walls were the most common locations for abnormality. On the other hand, abnormal ST-T wave changes on a resting ECG were not predictive of abnormal echocardiogram in their population, however, on statistical analysis significant association could be detected between troponin and brain natriuretic peptide elevation with positive segmental wall motion abnormality on echocardiogram.

In another study including 279 patients the rate of TnT was elevated was 9.6%<sup>[17]</sup>. There was a significantly higher prevalence of elevated TnT amongst stroke patients with recognized coronary disease compared with patients without such disease ( $P<0.05$ ). In the subgroup without known coronary disease, elevated TnT was detected in only nine patients. The most frequent ECG changes were prolonged QTc (36.0%), ST depression (24.5%), atrial fibrillation (19.9%) and T wave inversion (17.8%). Patients with acknowledged coronary heart disease had a significantly higher prevalence of pathological findings regarding Q waves, R waves, ST depression and T waves compared with patients without such disease ( $P<0.05$  in all mentioned ECG items)<sup>[17]</sup>.

In the study of Jensen *et al* 244 patients with acute ischemic stroke

but without overt ischemic heart disease were enrolled. Troponin T (TnT) and creatine kinase-MB (CK-MB) concentrations were measured and 12-lead electrocardiograms obtained daily during the first 5 days of admission<sup>[19]</sup>. Myocardial perfusion scintigraphy was performed in patients with TnT levels of 0.10 mcg/L and in comparable controls without elevation of TnT. Perfusion abnormalities on myocardial perfusion scintigraphy at rest were not more frequent or pronounced in patients than in the control group. Patients with elevated TnT had higher frequencies of heart and/or renal failure and had significantly increased mortality compared with patients without TnT elevations (adjusted hazard ratio 3.39, 95% confidence interval 1.34 to 8.60,  $p=0.01$ ). Interestingly, in only 3%, a pattern of increase and decrease of TnT and/or CK-MB combined with electrocardiographic signs of myocardial ischemia was noted, an observation suggesting that the underlying mechanism of an increase in TnT is only rarely an acute myocardial infarction<sup>[19]</sup>.

Scheitz *et al.*<sup>[20]</sup> performed a retrospective analysis including all consecutive ischemic stroke patients admitted to a stroke unit within 72 h after symptom onset in a one-year period. Frequency of cTnT elevation was 14%. Factors independently associated with increased cTnT were higher stroke severity ( $p=0.04$ ), renal insufficiency ( $p<0.001$ ), pre-existing coronary artery disease ( $p=0.03$ ), hypercholesterolemia ( $p=0.02$ ) and insular cortex involvement ( $p<0.001$ ). After exclusion of patients with renal insufficiency and coronary artery disease frequency of cTnT elevation was 10% and only insular cortex involvement remained significantly associated. Increased cTnT on admission was an independent predictor of unfavorable outcome [adjusted odds ratio 2.65 (95% confidence interval 1.29-5.46)] and in-hospital mortality [4.51 (1.93-10.57)] although the causes of death were not reported<sup>[20]</sup>.

In their well-designed study Di Angelantonio *et al.*<sup>[23]</sup> prospectively investigated 330 consecutive patients with acute ischaemic stroke admitted to the emergency department based stroke unit. 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”<sup>[23]</sup>. In their unique study they reported causes of death by troponin levels, which had 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<sup>[23]</sup>.

## DISCUSSION

Based on the collected articles we were not able to clarify the etiology of troponin elevation in ischaemic stroke. There was no clear definition of troponin elevation, different workgroups used different troponin assays and cut-off values, however, the

prevalence of elevated troponin was reasonably consistent across most of the different types of troponin assay and choice of threshold. On the other hand, relatively few studies used the current ESC recommendations<sup>[30]</sup>.

It has been consistent in the majority of these studies that elevated troponin were more likely to have ECG changes suggestive of myocardial ischemia, but usually did not fulfill the current criteria of myocardial infarction. Atrial fibrillation (AF) (especially new onset or previously not known) has been associated with troponin elevation. The presence of atrial fibrillation has been associated with higher in-hospital mortality, not just in ischemic stroke patients population as a whole, but also in cardioembolic stroke subtype patients based on previous findings<sup>[31]</sup>. It can be the consequence of an acute myocardial event or it may be due to mechanisms such as increased ventricular rate causing oxygen demand/mismatch and myocardial ischaemia, volume and pressure overload, changes in microvascular blood flow, atrial calcium overload, oxidative stress, or alterations in tissue structure<sup>[32]</sup>. Based on recent trials using novel oral anticoagulants in atrial fibrillation detectable troponin levels were common in AF patients and were associated with had an increased risk of stroke, other ischaemic events, and a higher mortality regardless of their risk stratification<sup>[32]</sup>.

Relatively few studies have examined wall motion abnormalitis (using echocardiography or myocardial perfusion scintigraphy). Based on these studies the inferior and septal walls, if any, were the most common locations for abnormality. However, patients in the elevated serum troponin group did not satisfy the current clinical, ECG or echocardiographic criteria for AMI<sup>[30]</sup>.

Lesions in the insular cortex have been associated with raised troponin and unfavourable outcome in several studies suggesting acute catecholamine release and stress-related cardiac changes. There seems to be a direct association of insular damage and troponin raise. The insula is the site for the integration of sensory, autonomic, and limbic functions through its reciprocal connections and is involved in cardiac autonomic control based on both experimental and human studies<sup>[22,33]</sup>. It appears to be there is a right-sided dominance for sympathetic and left-sided dominance for parasympathetic effects on the heart<sup>[22,33]</sup>. The resulting augmentation of intracardiac sympathetic nerve activity can provoke myocytolysis with arrhythmogenic potential, even in the absence of symptomatic coronary artery disease<sup>[30]</sup>. There was a strong association of the activation of the sympathoadrenal system and myocardial damage (measured by troponin assays), which was related to stroke severity and short-term prognosis<sup>[34-36]</sup>.

Vast majority of these studies showed that troponin elevation has been associated with unfavourable outcome and mortality but is not entirely clear whether causes of death are cardiac of origin or not.

In summary, raised troponins are associated with ECG changes and wall motion abnormalities do not seem to be fulfilling the current AMI criteria suggesting an extracardiac origin. They are also associated with insular damage, unfavourable outcome and increased mortality rates raising the possibility neurocardiogenic injury as the consequence of insular damage and subsequent catecholamine overload. On the other hand, the etiology of troponin elevation cannot be clarified based on the above mentioned studies and warrants further examination in high-quality studies.

## CURRENT CONCEPTS

The current concept about raised troponins in ischaemic stroke is that the observed cardiac abnormalities are secondary to increased/

disturbed sympathetic activity provoked by acute stroke<sup>[4,5]</sup>. An exaggerated catecholamine release may lead to excessive release of intracellular calcium ions and subsequent reversible myocyte dysfunction. An alternate explanation is that the catecholamine surge acts as an uncontrolled severe myocardial stress test, which essentially reveals stable coronary plaques or induces a Takotsubo disease<sup>[4,5]</sup>.

The occupation of the cardio-adrenoreceptors induces catecholamine toxicity in the cardiomyocytes and can result as a Takotsubo cardiomyopathy, which is characterized by the onset of an acute coronary syndrome associated with a specific and reversible apical and wall motion abnormality despite the lack of coronary artery disease<sup>[37]</sup>. Typically, echocardiography showed apical and midventricular wall motion abnormalities and hyperkinesis of the basal myocardial segments<sup>[37]</sup>. These wall motion abnormalities did not correspond to a single epicardial coronary distribution. Apical and midventricular wall motion abnormalities can induce a dynamic obstruction in the LV outflow associated with a systolic anterior motion of the mitral leaflet<sup>[37]</sup>. It has been recently shown that Takotsubo cardiomyopathy is not a rare complication of acute ischemic stroke. It most often occurred soon after stroke onset and was commonly asymptomatic. Female sex and insular damage were predominant features of the stroke patients who experienced development of this cardiomyopathy<sup>[38]</sup>. However, it is worth to mention, that increased cardiac troponins after acute stroke also occurs in many patients without Takotsubo cardiomyopathy.

On the other hand, our literature search could not confirm the presence of a stress related cardiomyopathy in the background of raised troponin and impaired left ventricular function. The problem with the neuromediated theory is that the patients will not be evaluated by a cardiologist if elevation of troponin is detected<sup>[39]</sup>. In this context, it is important to remember that following AMI the incidence of ischemic stroke is markedly increased, particularly during the first 30 days after the cardiac index event and troponin levels can be elevated for 2 or 3 weeks, so ECG and cardiac biomarker changes can be related to a preceding myocardial event (and do not forget about silent AMIs, which are responsible for approximately 25% of all events)<sup>[39]</sup>. This problem may even be worse in patients with stroke due to cognitive and language impairments<sup>[39]</sup>. Furthermore, based on several studies, elevated troponin levels were independently associated with new-onset atrial fibrillation, which could be the consequence of an acute coronary syndrome<sup>[9,29]</sup>.

## HOW TO MANAGE IT?

Since the coexistence of coronary artery disease has strong impact on the long-term prognosis of ischemic stroke patients, those with concomitant elevated troponin values should routinely undergo evaluation by a cardiologist to prevent more fatalities linked to their potential cardiac comorbidity<sup>[40,41]</sup>.

Based on the recent ESC guidelines the definition of acute coronary syndrome with persistent ST-segment elevation (STEMI) contains the detection of cardiac biomarker values (preferably troponin) with at least one value above the 99<sup>th</sup> percentile of the upper reference limit and with at least one symptom (including symptoms of ischaemia; new or presumably new significant ST-T changes or new LBBB; development of pathological Q waves in the ECG; or imaging evidence of new loss of viable myocardium, or new regional wall motion abnormality)<sup>[24]</sup>. The initial diagnosis is usually made in the emergency room based on the history of nitrate resistant chest

pain lasting for more than twenty minutes which can be radiated to the left arm or to the neck and typically ST segment elevations. Atypical signs contain left bundle branch block, ventricular paced rhythm, patients without ST elevation but with persistent ischaemic symptoms, isolated posterior myocardial infarction or ST-segment elevation in lead aVR<sup>[24]</sup>. If the diagnosis is unclear or doubtful emergency imaging (as opposed to waiting for the biomarkers to become elevated) allows the provision of timely reperfusion therapy to these patients. Two-dimensional echocardiography can help to identify pericardial effusion or signs of pulmonary embolism or dissection. Wall-motion abnormalities can be due to other causes than myocardial ischaemia, but absence of these excludes major myocardial infarction<sup>[24]</sup>. Usually urgent coronarography (if available) and revascularisation (if necessary) are recommended.

Based on our literature search only the minority of ischaemic stroke patients with raised troponin fulfilled the current criteria of STEMI. The other possibility in the background of raised troponin is acute coronary syndrome without persistent ST-segment elevation with subsequent cardioembolic stroke. Atypical complaints are more often observed in older (>75 years) patients, in women, and in patients with diabetes, chronic renal failure, or dementia<sup>[42]</sup>. Absence of chest pain leads to under-recognition and under-treatment of the disease. The diagnostic and therapeutic challenges arise especially when the ECG is normal or nearly normal, or conversely when the ECG is abnormal at baseline due to underlying conditions such as intraventricular conduction defects or left ventricular (LV) hypertrophy<sup>[42]</sup>.

So to exclude an acute myocardial event (STEMI or non-STEMI) diagnosis should be based on a combination of clinical history, symptoms, physical findings, repeated or continuous ECG monitoring (ST changes), and biomarkers<sup>[24,42]</sup>. Blood has to be drawn promptly for troponin (cardiac troponin T or I) measurement. The test should be repeated 6-9 h after initial assessment if the first measurement is not conclusive. Repeat testing after 12-24 h is advised if the clinical condition is still suggestive of ACS. An echocardiogram is usually recommended for all patients to evaluate regional and global LV function and to rule in or rule out differential diagnoses<sup>[24,42]</sup>. Some patients may require urgent coronary angiography (with or without revascularisation), or coronary CT angiography can be an alternative if results are inconclusive and the likelihood of an ACS is low<sup>[24,42]</sup>. In patients without recurrence of pain, normal ECG findings, negative troponin tests, and a low risk score, a noninvasive stress test for inducible ischaemia is recommended before deciding on an invasive strategy<sup>[24,42]</sup>.

The main problem is that there are no straight guidelines for patients with concomitant ACS and ischaemic stroke. The current AHA guidelines recommend routine baseline ECG and troponin measurement for all ischemic stroke patients but based on this the initiation of intravenous tPA should not be delayed<sup>[43]</sup>. It is not entirely clear based on recent ESC and AHA guidelines how to manage these patients (for example, admission to a stroke unit or coronary care unit, how to manage ischaemic stroke, how to carry out PTCA if necessary etc)<sup>[24,42,43]</sup>.

The current concept of troponin elevation in ischemic stroke is the nervous system's capacity to injure the heart. Stress-related cardiomyopathies can be observed in the four following situations: Takotsubo cardiomyopathy or apical ballooning syndrome; acute left ventricular dysfunction associated with subarachnoid hemorrhage; acute left ventricular dysfunction associated with pheochromocytoma and exogenous catecholamine administration; acute left ventricular dysfunction in the critically ill<sup>[37]</sup>. There is a significant overlap among

these entities and it is a challenge to manage them. In general, patients with suspected and/or proved Takotsubo or other stress-related cardiomyopathy must be monitored in intensive care. Because massive catecholamine release was observed in stress-induced stunned myocardium, beta agonists and vasopressors might be avoided whenever possible even in acute circulatory failure and mechanical circulatory support preferred if necessary. Sympathetic activation suggested the use of beta blocker therapy as soon as LV failure was corrected<sup>[37]</sup>. The presence of a dynamic obstruction in the LV outflow precluded the initiation of an angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, or diuretic treatment because of a possible potentiation. Anticoagulation with heparin was required to prevent left ventricle thrombus formation. Echocardiographic examination will be regularly performed after hospital discharge to evaluate the resolution of LV dysfunction, which is complete in the majority of the patients after 1 to 3 months<sup>[37]</sup>.

## FUTURE CONCEPTS

The background of troponin elevation in ischaemic stroke is not entirely clear. The most important thing is to exclude an ongoing myocardial event with atypical presentations especially in the elderly or patients with dementia.

The current concept is a neurocardiac injury triggered by damages in the insular cortex leading to a vegetative overload resulting in myocardial damage or stress related cardiomyopathy but results are controversial and are not supported by high-quality evidence.

There are two ongoing trials to clarify whether there is a co-existing coronary disease or myocardial damage is related to neurogenic injury.

The primary objective of the prospective observational trial TRELAS (TROponin Elevation in Acute ischemic Stroke) is to investigate the frequency and underlying pathomechanism of cTnT elevation in acute ischemic stroke patients in order to give guidance for clinical practice<sup>[44]</sup>. All consecutive patients with acute ischemic stroke admitted within 72 hours after symptom onset to the Department of Neurology at the Campus Benjamin Franklin of the University Hospital Charité will be screened for cTnT elevations (i.e.  $\geq 0.05$   $\mu\text{g/L}$ ) on admission and again on the following day. Patients with increased cTnT will undergo coronary angiography within 72 hours. Diagnostic findings of coronary angiograms will be compared with age- and gender-matched patients presenting with Non-ST-Elevation myocardial infarction to the Department of Cardiology. The primary endpoint of the study will be the occurrence of culprit lesions in the coronary angiogram indicating underlying co-morbid obstructive coronary artery disease. Secondary endpoints will be the localization of stroke in the cerebral imaging and left ventriculographic findings of wall motion abnormalities suggestive of stroke-induced global cardiac dysfunction<sup>[44]</sup>.

In another prospective trial 500 consecutive ischemic stroke patients admitted at the Comprehensive Stroke Center will be enrolled within 12 h from stroke onset<sup>[45]</sup>. The set of examinations will consist of: (1) Acute brain computed tomography or magnetic resonance imaging (2) Laboratory tests: (A) within 12 h from stroke onset: NT pro B-type of natriuretic peptide, pro-atrial natriuretic peptide, creatinekinase MB, troponin T (cTnT), interleukin 6, procalcitonin, high sensitive C-reactive protein and D-dimers. (B) control level of cTnT after 4 h from admission (C) nonacute laboratory samples within 60 h from stroke onset: glycated haemoglobin, serum lipids; (3) Electrocardiogram (ECG) on admission and 4 h from stroke onset; (4) Transesophageal or transthoracic echocardiography and 24-h

ECG Holter within 15 days from stroke onset; (5) Neurosonological examination within 60 h from stroke onset; (6) Thirty patients with a positive finding of acute myocardial ischemia (ECG, cTnT) will be examined by coronary angiography (CAG).

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## CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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