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EDITORIAL

Troponin Elevation After Ischemic Stroke and Future Cardiovascular Risk: Is the Heart in the Right Place?

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Our understanding of the intricate relationship between the heart and the brain has evolved beyond the prevailing paradigm where cardiac mechanisms cause brain injury, to now include a bidirectional interaction, where an acute derangement of one organ system adversely affects the other. Acute brain injury in the form of an ischemic or hemorrhagic stroke is a trigger for myocardial injury, often referred to as neurocardiogenic syndromes, which can range from asymptomatic troponin elevations to symptomatic myocardial ischemic injury, and even symptomatic heart failure such as Takotsubo cardiomyopathy.[1] Large case series evaluating factors associated with neurocardiogenic syndromes have implicated stroke severity and location of the infarct as key factors.[2] Additionally, myocardial injury portends poor outcomes, and is independently associated with severe disability and death after stroke.[3] Given that neurocardiogenic syndromes encompass a wide range of cardiac abnormalities, it is unclear if each subtype adversely affects stroke outcomes. Emerging evidence suggests that one neurocardiogenic syndrome, Takotsubo cardiomyopathy, results in both, a short- and long-term risk of major adverse cardiovascular events, ischemic stroke, and death, regardless of the inciting trigger.[4] However, whether troponin elevation also results in a similarly higher risk of future cardiovascular events is poorly studied.

See Article by Scheitz et al.

In this context, the study by Scheitz and colleagues in this issue of the *Journal of the American Heart Association* (*JAHA*) assumes significance.[5] The authors performed a prospective, observational study of 562 patients with a first-ever stroke, with longitudinal follow up. The exposure was the level of high sensitivity-cardiac troponin T, obtained within 7 days of stroke symptom onset, and dichotomized based on a cut-off of 14 ng/L (the upper reference limit). The primary outcome was a major vascular event, defined as a composite of any stroke (ischemic or hemorrhagic), myocardial infarction, and all-cause mortality, while the secondary outcome was ischemic stroke alone. Cox regression analyses showed that an elevated high sensitivity troponin was associated with a 2-fold heightened risk of a major vascular event, compared with patients without. Surprisingly, there was no relationship with recurrent ischemic stroke. The authors should be congratulated on this important study which has several strengths

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Table 1. Characteristics of Studies Evaluating the Relationship Between Troponin Elevation After Stroke and Subsequent Cardiovascular Risk

Study (Year)	Design	Sample Size	Exposure	Outcomes	Effect Size HR/OR (95% CI)
Stahrenberg[8] (2012)	Prospective	197	Hs-troponin	MACCE*+revascularization+CHF hospitalization	3.2 (N/A)
Raza (2014)[7]	Retrospective	200	Cardiac troponin I	MACE† (included coronary revascularization; no stroke events)	9.8 (2.4–39.4)
Ahn (2019)[6]	Prospective	1092		MACCE*	2.8 (1.8–4.3)
Scheitz (2021)[5]	Prospective	562	Hs-troponin	MACCE*	2.0 (1.3–3.3)

CHF indicates congestive heart failure; CI, confidence interval; HR, hazard ratio; Hs, high sensitivity; MACE, major adverse cardiovascular events; MACCE, major adverse cerebrovascular and cardiovascular events; N/A, not available; and OR, odds ratio.

*MACCE included any stroke, myocardial infarction, and cardiovascular death.

†MACE included myocardial infarction and cardiovascular death.

including the prospective design, fairly large sample size, and robust longitudinal follow up. These findings build on the results from a cohort study from Korea with over 1000 stroke patients, which reported the clinical significance of troponin elevation in regards to subsequent major vascular events (Table).[6] Smaller studies from other parts of the world have also yielded similar findings.[7,8] The present study stands apart for assessing recurrent ischemic stroke as a stand-alone secondary outcome. Given that a prior stroke is a significant risk factor for recurrent stroke, it is important to delineate if myocardial injury independently increases this risk after an incident stroke.[9] Although no such association was observed, this result was likely due to lack of study power for the secondary outcome.

This study in question has some noteworthy limitations including lack of data on antithrombotic medication initiation or resumption after stroke, a treatment strategy proven to decrease cardiovascular risk.[10] Moreover, the study examined baseline comorbidities, and did not account for changes in risk factors or new diagnoses over time. Furthermore, the study did have information on stroke subtype, which may be relevant to the degree of myocardial injury. It would also be interesting to note the differences in troponin elevation in patients with and without occult sources of cardiac embolism such as atrial fibrillation, cardiac thrombus, and severe heart failure.

Nevertheless, the results of this study raise some intriguing points. First, isolated transient myocardial injury after stroke is not a benign finding despite the normalization of troponin values, similar to Takotsubo cardiomyopathy. Second, the question that arises is whether myocardial injury after stroke is a chicken or egg phenomenon? Our current state of literature does not allow this temporal distinction. Transient troponin elevation, a manifestation of neurocardiogenic injury can occur in up to half of all stroke patients and is believed to be mediated by a catecholamine surge and microvascular coronary endothelial dysfunction, among other mechanisms, which ultimately leads to myocardial remodeling weeks to months after the initial injury.[1] On the other hand, myocardial injury in some cases, may be a consequence of an underlying cardiac embolic source and may provide clues to the stroke mechanisms particularly in the absence of occult causes. For instance, in a prospective cohort study of 1234 patients with ischemic stroke, early positive troponin was associated with a cardioembolic source, and did not correlate with stroke severity.[11] Since nearly a third of strokes have no identifiable cause, a subset generally referred to cryptogenic stroke or embolic stroke of undetermined source (ESUS), an improved understanding of myocardial injury may help guide interpretation of cardiac biomarker derangements in the clinical setting.[12] Clinicians have increasingly recognized the role of non-traditional cardiac sources of emboli under the ESUS construct, with emphasis on atrial cardiopathy and silent myocardial infarction.[12] This has spurred a new line of investigation evaluating parameters on cardiac evaluations, otherwise neglected in prior years, including atrial chamber dilation on echocardiography and p-wave terminal force or Q wave on electrocardiography. Along similar lines, re-exploration of serum biomarkers of cardiac injury, which is relatively inexpensive and perhaps more feasible, are warranted.

Third, the severity of myocardial injury after stroke may help in stratifying the risk of recurrent cardiovascular events, and tailoring therapies. Future studies should therefore aim to incorporate objective measure of cardiac dysfunction in ascertaining the cardiovascular risk akin to the CHA_2DS_2-VASC score for atrial fibrillation. Finally, with the emergence of direct oral anticoagulants, the role of anticoagulation is being explored in non-traditional embolic strokes, such as ESUS. Current American Heart Association guidelines recommend antiplatelet therapy for secondary stroke and cardiovascular risk prevention, in the absence of occult indications for anticoagulation.[13] Whether antiplatelet therapy alone is adequate in the presence of myocardial injury is, however, unclear. In a secondary

analysis of the COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial, among patients with stable cardiovascular disease, low-dose rivaroxaban plus aspirin was associated with fewer cardiovascular events,[14] including large, significant reductions in cardioembolic strokes and ESUS.[15]

Ongoing clinical trials such as ARCADIA (Atrial Cardiopathy and Antithrombotic Drugs in Prevention After Cryptogenic Stroke) are examining the ideal antithrombotic strategy in patients with ESUS and atrial cardiopathy.[16] Expanding these indications to other forms of myocardial injury may help shed light on the optimal strategies to mitigate the risk of subsequent cardiovascular events. Regardless, the present study brings to focus the complex interplay between the heart and the brain, and highlights the need for more such clinical studies to better delineate the clinical implications of the myocardial injury after stroke.

ARTICLE INFORMATION

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