Editorial

The diagnostic role of cardiac troponin I beyond acute myocardial infarction

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The discovery of troponins in the 1960s, followed by the three troponin subunits—C, I and T, and identification of specific cardiac isoforms of troponin I (cTnI) and troponin T (cTnT) have led to our current understanding of these specific cardiac injury markers and their clinical applications (1-3). Since the first clinical-pathological recordings of acute myocardial infarction (AMI) in the late nineteenth century (4,5), its diagnostic criteria have evolved continuously since the earlier 1960s World Health Organisation myocardial infarction register (6).

Publication of the universal definition of myocardial infarction (MI) in 2007 provided a better understanding for clinicians of the five main types of AMI (7). Not so for type 2 MI. Although there is a unified concept of oxygen demand supply imbalance precipitating a type 2 MI, the diverse circumstances leading to this acute imbalance, varying severity of coronary and other non-coronary condition(s) precipitating the event, and other variable factors are making up a very heterogenous and ill-defined group of patients. As such, three major subgroups have been recently presented—type 2 MI due to coronary mechanisms, systemic illnesses, and tachyarrhythmias. Each of these subgroups had a different clinical course and outcome, and a better prognosis was observed in those with tachyarrhythmias (8).

The American Heart Association and National Institute for Health and Care Excellence (NICE) have defined AMI with the presence of a sudden complete or incomplete coronary artery blockage resulting in heart muscle damage or death (9,10). One major shift of focus in the latest 4th definition of myocardial infarction is a revised attempt to differentiate between AMI and non-ischaemic causes of myocardial injury (11).

Instead of adding a secondary diagnosis of type 2 AMI to a primary diagnosis of a tachyarrhythmia, it may be more informative to diagnose myocardial injury secondary to a tachyarrhythmia with/without obstructive coronary artery disease, and with/without ventricular dysfunction (12). In the clinical setting of an acute presentation atrio-ventricular nodal re-entrant tachycardia with no evidence of obstructive coronary artery disease and normal left ventricular function, the patient can be cured with electrophysiological ablation and have a normal life expectancy. Instead of the clinician making a diagnosis of type 2 AMI, adopting the term myocardial injury can promote a better psychological health, a more acceptable societal option for the patient, and without compromising epidemiological coding.

Extending our understanding beyond the diagnostic and prognostic role of cardiac troponin biomarkers in AMI, elevated cardiac troponin levels can occur in a variety of non-ischaemic myocardial injury, e.g., myocarditis, pulmonary embolism, hypotension, exacerbation of chronic

obstructive pulmonary disease, sepsis or septicaemia, etc. (13). Patients with non-ischaemic myocardial injury have variable clinical symptoms that are similar or indistinguishable from MI, including a rise and fall pattern of cardiac troponins, and electrocardiographic changes which are indistinguishable from ischaemic myocardial injury. Both ischaemic and non-ischaemic myocardial injury can co-exist in the above clinical situations. Hence, clinicians face a subjective dilemma in diagnosing some and not all these cases with type 2 MI, adding complexity and uncertainty to diagnoses and clinical management. There are yet other situations outside the context of AMI or non-ischaemic myocardial injury which elevated cardiac troponin levels above the 99th percentile were found in apparently healthy adults (14,15).

The paper presented by Oh *et al.* (16) examines the prognostic role of measuring cardiac troponin I on admission amongst patients who underwent a scheduled, non-emergency hospital admission under the care of non-cardiac physicians or surgeons. This was a large, retrospective, single centre cohort of patients with established comorbidities, who underwent a planned hospital admission and was a stable group clinically. The high exclusion rate of 239,645/289,764 (82.7%) without documentation of comorbidities can be an important confounding bias. Propensity score matched pairs with adjustments for departments of admission and caliper widths were used to reduce statistical bias.

The higher prevalence of pre-existing cardiovascular comorbidities (myocardial infarction, heart failure, peripheral vascular disease, cerebrovascular disease) among patients with cTnI measurement could have resulted in a higher baseline usage rate of cardiovascular drugs.

Not knowing the precise reasoning for requesting cTnI test on admission was an important missing piece of information. It was likely that the admission clinician had reacted to the cardiac history, any cardiac symptoms on admission, and other comorbidities which triggered the measurement of cTnI. A reduced 1-year mortality was seen in the group with cTnI testing on admission, compared with the other standard care group [3.8% *vs.* 5.9%, hazard ratio (HR) 0.78, 95% confidence interval (CI): 0.68–0.89, P<0.001). The Kaplan-Meier survival curves in the two groups started to separate at about 2 months after their scheduled admission.

The mechanisms which brought out this survival advantage can be further explored. The finding of an elevated cTnI on admission had led to more cardiac investigations, drug treatments, intensive care, and cardiologist evaluation during in-hospital stay, and these continued into the post discharge period of care. Only small proportions in the cTnI testing group received non-invasive coronary testing or coronary angiogram (5.3% in total), and percutaneous coronary intervention or coronary artery bypass grafting (0.9% in total) during in-hospital care, rising to 15.6% and 3.2% respectively in the post discharge period. The survival benefit from cTnI testing upon admission was not likely to come through coronary revascularisation in this cohort, although these treatment modalities should be explored further in future studies.

Within the cTnI testing group, an elevated cTnI level on admission was found to be a prognostic marker for the in-hospital, 30-day and 1-year mortality among patients who underwent a scheduled hospital admission. Despite the patients (n=512) with elevated cTnI receiving more cardiac investigations, drug treatments, intensive care, cardiologist evaluation, and coronary revascularisation during their in-hospital and post discharge period, they experienced a higher in-hospital, 30-day and 1-year mortality. One should not conclude that these investigations and treatments were not effective, as they could have prevented more deaths, and were beneficial in the entire cohort who received cTnI testing (n=6,145). Patient factors, timing of various investigations and treatments, and low rates for coronary revascularisation are reasons to be explored further for a better outcome.

Benefits of measuring cTnI among comorbid patients from the outpatient clinic who are scheduled to have a hospital admission under non-cardiac physicians can be explored further, as potential treatments can be offered to those who have coronary artery disease, ventricular dysfunction, or valve disease. The usefulness of measuring cardiac Troponins can extend beyond the diagnosis of AMI or non-ischaemic myocardial injury, and into other non-emergency clinical situations such as those comorbid patients from the outpatient medical clinic who are scheduled to have a hospital admission under non-cardiac physicians.

Nonetheless, we must also not forget that biomarkers (whether blood, urine or imaging based) for cardiovascular risk prediction have their limitations. They can be non-specific for outcomes, reflecting a sick patient or a sick heart (17). Furthermore, some biomarkers have a diurnal variation and assay variability, not to mention expense and

time delay in obtaining an actionable result. The holy grail may well be to find the perfect biomarker with 'perfect' sensitivity and specificity that offers the balance between simple measurements, low costs, and rapid diagnosis.

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