Whose heart will get broken? Troponin testing and future heart failure

Roland R.J. van Kimmenade1,2 and James L. Januzzi Jr2*

1Department of Cardiology, University Hospital Maastricht, The Netherlands; and 2Division of Cardiology, Massachusetts General Hospital, Boston, MA 02114, USA

Online publish-ahead-of-print 4 March 2009

This editorial refers to ‘Cardiac troponin-I and risk of heart failure: a community-based cohort study†, by J. Sundström et al., on page 773

After the introduction of troponin T (cTnT) and later troponin I (cTnI) as useful markers of myocardial necrosis, their testing has quickly redefined clinical cardiology. Indeed, the importance of troponin (cTn) for the diagnosis of myocardial injury has recently been reaffirmed in the ‘Universal Definition of Myocardial Infarction’: ‘If biomarkers have been measured... and are normal, the determinations of these take precedence over... imaging criteria’.2 This well illustrates that despite all technological developments in imaging techniques over the last two decades, cTn testing remains the gold standard for the identification of acute myocardial injury.

There is, however, a potential weakness in cTn testing that is widely acknowledged: notwithstanding the superior accuracy of detecting myocardial injury, an elevated cTn concentration does not provide any insight into the mechanism of heart injury, and a broad differential diagnosis to explain cTn release in the absence of regional myocardial infarction (including cardiomyopathies, pulmonary embolism, renal failure, and even acute cerebral pathologies) should be routinely considered when using these valuable tests.2

While the foregoing differential diagnosis is well understood in the application of cTn in those with acute symptoms, what remains less well understood is the significance of cTn elevation—even at low levels—among ‘apparently well’ subjects.

Providing some answer to this question, in a previous study, Wallace and colleagues demonstrated, in a population cohort, that measurable concentrations of cTnT were extremely uncommon, but, when present, such cTnT levels were typically associated with structural heart disease or risk factors for it.3 However, the assay used in this analysis lacked sufficient analytical precision at very low cTnT values, so it remained unclear whether any detectable troponin release was necessarily associated with structural heart disease, and no data were provided regarding cTnT and risk for adverse outcome.

Recently, newer and more sensitive assays for cTn measurement have been developed, and in some cases have already been introduced into clinical use.4 These ‘highly sensitive’ assays may detect even the slightest degree of myocardial injury, with a precision that exceeds prior iterations of methods for cTn detection. Thus, while these highly refined sensitive assays may provide earlier and more sensitive detection of myocardial injury, it is likely that they will also trade-off extraordinary sensitivity with reduced specificity for classic ‘myocardial infarction’, something clinicians will have to grapple with. Moreover, as even more highly sensitivity methods for cTn measurement are developed, we may indeed find that release of an extraordinarily low concentration of cTn is in fact a common phenomenon, even in the absence of obvious structural heart disease.

In light of this discussion, it begs the question: what exactly is a physiological cTnT or cTnI anyway, and what does it mean if they are elevated in someone who appears normal? Should we worry? What should we do? The recent interesting study by Sundström and co-workers offers some insight into the significance of cTn release in ostensibly normal patients.5 In a community-based study of 1089 asymptomatic elderly men without prevalent left ventricular hypertrophy, valvular disease, or heart failure at enrolment, a cTnI $\geq 0.03 \mu g/L$—a value conventionally viewed as being inconsequentially low—was associated with a hazard ratio of 5.25 for heart failure, compared with persons with cTnI <0.01 $\mu g/L$, even when adjusted for relevant covariates, such as N-terminal pro-B type natriuretic peptide (NT-proBNP) or incident and prevalent myocardial infarction. Further, the authors found that each 0.01 $\mu g/L$ increase in the cTnI serum concentrations was associated with a hazard ratio of 1.26 for subsequent heart failure, remaining robust even when NT-proBNP concentrations were added to the model. The authors conclude that low level (but nonetheless detectable) cTnI concentrations reflect subclinical cardiomyocyte damage, and are independently associated in a
graded fashion with the development of heart failure in an elderly community population.

As is always the case with provocative and potentially ground-breaking discoveries, this study raises several questions that it cannot answer, most importantly why or how do these subjects develop heart failure? It would have been difficult to provide detailed cardiac structure and functional phenotyping such as with echocardiography, cardiac magnetic resonance imaging, or coronary angiography, but such data at present are needed, particularly as the association between cTn and heart failure in this study appeared to remain even when adjusting for conventional heart failure risk factors.

Where is the field of cardiac biomarkers presently, and where is it heading? Across a wide range of patient types, including in apparently well subjects, we now have an ample amount of studies that demonstrate the value of cardiac biomarkers such as cTn and natriuretic peptides for predicting hazard, even in the general population. A common theme—even in apparently normal patients—is that it is clearly not ‘normal’ to have elevated biomarker concentrations, irrespective of how ‘well’ the individual appears.

Interesting findings, but hollow ones if we cannot do something about that risk. Since the lifetime risk for heart failure is 1 in 5, this may clearly be a ripe target for a biologically guided interventional approach. We would suggest that the burning imperative now is not only to identify the ideal strategy to screen patients for risk for cardiovascular complications, but also to prevent the predicted development of these impending complications before they occur. Does cTn, for instance, identify the asymptomatic elderly person who might benefit from aggressive β-adrenergic blockade or angiotensin-converting enzyme (ACE) inhibition? At present it remains unclear. Further, it remains unclear if specific markers will partition with benefits of specific drugs, e.g. cTn with β-adrenergic blockade and natriuretic peptides with ACE inhibitor use.

This is the real heart of the matter for those interested in taking biomarker studies to the next level: now that we are well aware that tests such as cTn or natriuretic peptides predict risk for adverse cardiac outcomes in a robust fashion, we greatly need large interventional cardiac biomarker studies to illuminate the path forwards for clinicians. These much needed studies must show us if biomarkers can be used to reduce risk inexpensively and reliably via their ability to identify an actionable therapeutic imperative. We are firmly headed in this direction—highly sensitive cTn testing has arrived, highly sensitive methods for natriuretic peptide testing are here to stay, and a wide array of other useful markers that identify inflammation, oxidative stress fibrosis, and remodelling are on the near horizon for clinical application. The relevant challenge for clinical cardiology in the 21st century will be confidently (but carefully) to enter into the era of biologically tailored care using these tools to improve the healthcare of our patients. The fine study by Sundström and co-workers is a proper and necessary step in this direction.

Acknowledgements
R.R.J.v.K. has been supported by an ICIN (Interuniversity Cardiovascular Institute of the Netherlands) fellowship grant.

Conflict of interest: none declared.

References
8. Clerico A, Fortunato A, Ripoli A, Prontera C, Zuccheli GC, Emdin M. Distri-