Editorial

How does a high sensitivity cardiac troponin I assay help us when patients with chronic renal failure present to the emergency department?

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The frequency of chronic kidney disease (CKD) increases with age and CKD is present in 45% of the USA population at the age of seventy (1). Cardiovascular disease is more common in those with CKD and death from cardiovascular disease as well as events and hospitalisation are increased in this population (2,3). Therefore, there is a significant interest in patients who present with acute myocardial infarction (AMI) in the setting of CKD. Previous data have shown worse outcomes in patients with AMI who have coexistent renal dysfunction (4).

Over the last 20 years' troponin has been the main marker for AMI because of its exquisite specificity for cardiac tissue and superior sensitivity for myocardial damage. Several generations of assays for troponin have improved the assay to a point where we now can measure troponin concentrations in the majority of healthy normal subjects (with so called high sensitivity troponin assays). Routinely we use the 99th percentile of healthy subjects as the upper limit of normal. Values above the 99th percentile are one of the main criteria used in the current definition of AMI (5). However, troponin values can be elevated in a variety of clinical situations that are not AMI. One of those situations is chronic renal impairment. Troponin values are increased in a significant proportion of patients with severe renal failure who do not have an AMI. While not necessarily associated with immediate AMI, a number of studies have shown that troponin values are an independent marker of future risk of cardiovascular outcomes in patients without cardiovascular symptoms but with chronic renal failure or on haemodialysis (6-9).

In an important study Ian Gunsolus and colleagues investigate in a prospective manner the accuracy of a high sensitivity troponin I (hsTnI) assay in a group of patients presenting to the emergency department of Hennepin County medical centre in Minneapolis, USA (10). The strengths of the study are its prospective nature, the fact that it included all patients, where serial troponin values were requested by clinicians for the evaluation of possible AMI, the careful clinical evaluation and the follow up with all-cause mortality for 2 years.

The investigators studied 1,555 patients presenting to the Emergency department who had serial troponin levels measured as well as an eGFR available. In a previous publication using the same cohort (11), the authors found that MI was diagnosed in 12.9% of the cohort using the contemporary cardiac troponin I assay and 10.4% using the hsTnI assay. These data confirm the experience from Australia and New Zealand that the frequency of a diagnosis of AMI's was not markedly increased after the introduction of a hsTnI assay (12). Gunsolus and colleagues extend the scope of their previous studies to look particularly at the effect of renal function in the present study (10). In their cohort of 1,555 patients presenting to the emergency department only about half had normal renal function, 25% had mildly impaired renal function (eGFR >60 and <90 mL/min/1.73 m^2), 15% had moderately impaired renal function (eGFR >30 to 60) and the remainder had an eGFR <30 or were on dialysis. Patients with impaired renal

function were on average older, had a higher prevalence of hypertension and diabetes and more commonly a previous history of coronary artery disease. Heart failure was also more frequently seen in the group with renal failure as was AF and a history of vascular disease.

The authors find that the frequency of AMI in this population presenting to the ED increases as renal function worsens. AMI was diagnosed in 7% in patients with normal renal function, in 11% with mild, 18 with moderate and 21% with severe renal failure. Independently of renal function the hscTnI assay was picking up AMI in over 90% within three hours. There seems to be a small further benefit between three and six hours mainly in the dialysis group, but the small number of patients with AMI makes this more difficult to assess. Therefore, sensitivity for AMI is maintained with the hsTnI assay. As expected the specificity for AMI of an elevated hsTnI decreases with worsening renal function (from 92.1% specificity in patients with normal renal function decreasing stepwise to 41% in patients on dialysis). With decreasing specificity, the positive predictive value of elevated troponin levels decreases. The negative predictive value of a normal troponin remains high. The authors have further investigated all-cause mortality over 2 years and showed that patients with measurable hsTnI values within the normal range (below the 99th percentile) have worse survival than patients with undetectable troponin values. Finally, the authors have shown that independent of the hscTnI level, mortality rates increase with worsening renal impairment. These American data provide a welcome addition to the literature. In 2015 Twerenbold and co-authors investigated 7 sensitive and highly sensitive assays for cTn in over 2,000 patients with suspected AMI (AMI rate 36% in patients with CKD) and claimed that the optimal cut off for cTn in patients with CKD is significantly higher than in patients without renal failure (13). This is not supported in this study that had a larger number of patients with CKD and included patients on dialysis. Two studies from Europe have recently been published in *Circulation* (14,15). In the first of these the APACE (Advantageous Predictors of Acute Coronary Syndrome Evaluation) investigators studied 3,254 adult patients presenting to 12 emergency departments in 5 countries in Europe with symptoms suggestive of AMI (e.g., acute chest discomfort and angina pectoris) with an onset or peak within the last 12 hours (14). This is a further study from the cohort described in reference 13. The investigators evaluated a 0 and 1 hour pathway described by the European Society of Cardiology (ESC) in the 487 patients (15%) with CKD compared to those with normal renal function. Similar to the findings of Gunsolus (10) using either hsTnT or hsTnI the investigators found reduced specificity for rule in AMI. They similarly find a higher incidence of AMI in patients with CKD presenting with chest pain to the ED. The incidence of NSTEMI in patients with renal failure (median eGFR 48) was 31% compared with 13% in patients with normal renal function (median eGFR 93). Overall the rapid rule out pathway was less effective in patients with in renal failure mainly because there were few patients with hsTnI values <5 ng/L.

In a second large study from the UK Miller-Hodges, Anand and co-workers investigate 4,726 patients presenting to the ED of 3 Scottish hospitals with suspected acute coronary syndromes (15). Just over 900 of these patients had renal impairment defined as an eGFR of <60 by the MDRD formula. Similar to the Swiss and the American studies a low hsTnI concentration (<5 ng/L) at presentation was present less frequently than in patients with normal renal function, but still conferred a low risk for the primary outcome (negative predictive value, 98.4%). In agreement with the findings in Minnesota (10) the positive predictive value and specificity at the 99th centile was lower in patients with renal impairment. Again the 1-year rate of patients who suffered a subsequent type 1 AMI or cardiac death was higher in patients with measurable hsTnI within the normal range compared to those with values below the measurement range.

What do these studies tell us about the management of our patients with renal disease in regards to the investigation of chest pain and possible acute coronary syndromes? Firstly, we should remember that an elevated hsTnI in a patient with renal failure does confer an increased risk of cardiac death even in the absence of symptoms. Secondly, we now know that patients with CKD presenting to ED with chest pain have a higher frequency of AMI than those with normal renal function. Thirdly we have 3 independent studies showing us that the new hsTn assays have a high sensitivity to detect AMI and a high specificity to rule out AMI, if the values are low. However, in the population with renal failure there is a substantial fraction of patients that will require repeated testing and further investigations before the final diagnosis can be made and optimal management can be determined for them.

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Footnote

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