Editorial

Cardiac Troponins and Renal Failure

The Evolution of a Clinical Test

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In this issue of *Circulation*, Khan and colleagues present the results of an elegantly performed meta-analysis of the prognostic implications of elevated levels of troponin T and I among asymptomatic patients with end-stage renal disease. After systematically collating the results of 28 cohort studies involving 3931 patients, they noted that an elevated troponin T level identified a group of end-stage renal disease patients with high mortality risk. Although elevated troponin I was also associated with increased risk, the exact effect size was difficult to assess because of a lack of standardization of current assays. The authors noted that despite the consistent association between elevated troponin T and mortality, the effect might be overestimated because of publication bias and study heterogeneity. Nonetheless, this meta-analysis, along with the specific reports of the largest published cohort studies, provides robust evidence that troponin T elevation in the setting of end-stage renal disease is ominous.

The development of troponin measurement in the absence of end-stage renal disease is an excellent paradigm for the modern evolution of clinical tests. Troponin T and troponin I are both integral parts of the cardiac muscle infrastructure and play critical roles in excitation-contraction coupling. The diagnostic importance of troponin elevation stems from its release into the bloodstream when there is some type of damage to cardiac myocyte cell-wall integrity. The high sensitivity of troponin for detecting even small myocardial infarctions has led to widespread recommendations for its routine measurement for the diagnosis of myocardial infarction. It could be argued, though, that elevated troponin to diagnose myocardial infarctions that were of little prognostic importance in patients with mild-to-moderate degrees of renal impairment. Another important finding from the analysis of the GUSTO IV (Global Use of Streptokinase and Tissue-plasminogen activator for Occluded arteries) acute coronary syndrome cohort indicated that this was not so. In fact, if anything, troponin elevation was of slightly greater prognostic importance in patients with mild-to-moderate degrees of renal impairment. Another important finding from the analysis of the GUSTO IV cohort was confirmation of the extraordinarily high risk associated with even minor degrees of renal dysfunction. However, important limitations of the GUSTO IV analysis were the very small number of patients with severe or end-stage renal disease and its confinement to symptomatic patients.

End-stage renal disease brings with it a whole new set of clinical challenges for cardiovascular physicians. Cardiovascular events are the most common cause of death in end-stage renal disease. Although troponin elevations in a setting of suspected acute coronary syndromes among these patients is clearly of substantial prognostic importance, the fact that troponin elevations are common in asymptomatic end-stage renal disease is ominous.

The measurement of troponin in acute coronary syndromes has completed the evolution of a modern clinical test. The test has diagnostic value in that it identifies clinical settings in which cardiac myocyte necrosis has occurred. More importantly, the test has prognostic value in that it identifies acute coronary syndrome patients who are at substantially increased risk for death or recurrent myocardial infarction. But of greatest importance, the test has therapeutic value in that it identifies those patients for whom aggressive drug and interventional therapy improves outcome. 

Troponin has been known to be elevated in the setting of even mild degrees of renal failure. At one time, it was considered that an elevation of troponin in a setting of decreased creatinine clearance was not of substantial diagnostic or prognostic importance. A careful analysis of the GUSTO IV (Global Use of Streptokinase and Tissue-plasminogen activator for Occluded arteries) acute coronary syndrome cohort indicated that this was not so. In fact, if anything, troponin elevation was of slightly greater prognostic importance in patients with mild-to-moderate degrees of renal impairment. Another important finding from the analysis of the GUSTO IV cohort was confirmation of the extraordinarily high risk associated with even minor degrees of renal dysfunction. However, important limitations of the GUSTO IV analysis were the very small number of patients with severe or end-stage renal disease and its confinement to symptomatic patients.

Still, one might argue that no matter how prognostically powerful a clinical test might be, the real acid test is whether or not the knowledge generated by that test leads to a change in therapy that improves outcome. In the case of troponin and acute coronary syndrome, this has recently been shown to be the case in well-done, randomized clinical trials. It is quite clear that modern interventions for acute coronary syndromes, including the administration of IIb/IIIa antiplatelet inhibitors and a routine invasive strategy, are effective primarily in patients with troponin elevations. In the TACTICS (Treat angina with Aggrastat and determine Cost of Therapy with Invasive or Conservative Strategy)-TIMI (Thrombolysis In Myocardial Infarction) 18 trial, even seemingly minor increases in troponin correctly identified those patients who benefited from a routine invasive strategy. Those patients who did not have a troponin elevation gained no benefit from an invasive strategy and may even have been harmed.

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renal disease patients has brought with it the promise of a powerful means of risk stratification in these already high-risk patients. The current meta-analysis by Khan and colleagues provides the clinical community with a reasonable degree of certainty that routine measurement of troponin T is prognostically valuable. It is important to keep in mind that this measurement should be obtained just before dialysis, because there is evidence that dialysis can affect troponin levels. Where in the clinical evolution of clinical tests are we with troponin measurement in the setting of end-stage renal disease? Although troponin measurement may have developed originally as a diagnostic test for myocardial infarction, in end-stage renal disease, it is not at all clear what we are diagnosing. The mechanism of troponin elevation in asymptomatic dialysis patients is not known. Perhaps troponin elevations reflect microinfarctions or left ventricular hypertrophy. One large study found that dialysis patients with elevated troponin were more likely to have severe angiographic coronary disease. Still, even if we don’t know what we are diagnosing when we find an elevated troponin level in a dialysis patient, we know that we have hit on an important prognostic measure that identifies an increased risk of death. We may want to know exactly what it is we are diagnosing so that this knowledge can help us develop the test to its next level, namely, as a guide to definitive therapy. In the dialysis setting, troponin has not evolved to that point. We do not know whether or not a dialysis patient with elevated troponin should receive more aggressive medical therapy for atherosclerotic disease or whether these patients should be considered for aggressive coronary revascularization even in the absence of symptoms. Future large-scale randomized trials are now essential to answer these critically important questions.

The measurement of blood troponin levels represents a great example of complete and incomplete evolution of clinical tests. This evolution parallels the hierarchy of standard epidemiological investigations. Testing for diagnosis is at the level of the cross-sectional study, which is inherently limited by lack of time-related directionality. Just knowing whether or not a diagnosis of disease is present is no longer of great interest if prognostic import does not accompany this. Assessing the association between a clinical test and prognosis raises the level of clinical investigation to that of cohort studies, in which there is a forward time-related directionality. The ability of a clinical test to help physicians ensure the best outcomes for their patients requires the highest level of clinical investigation, namely, the randomized trial. In the setting of acute coronary syndromes, the evolution for troponin is complete. Randomized trials have shown that routine measurement of troponin identifies those patients who should receive certain types of care. In the setting of renal disease, the evolution of troponin as a clinical test is well on its way but is still incomplete. Now that we know that elevated troponin has prognostic value, we eagerly await large-scale clinical trials to identify its therapeutic value and bring its evolutionary path to the highest, most relevant clinical level.

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