Cardiac Biomarkers in Renal Disease: The Fog Is Slowly Lifting

It has long been known that among patients with end-stage renal disease (ESRD), cardiac disease is the single greatest cause of mortality, accounting for nearly one half of all deaths (1). Among community-based populations, renal insufficiency is an independent predictor of the risk of subsequent ischemic heart disease, conferring a risk equivalent to that of diabetes (2). Furthermore, the presence of even moderate renal impairment in a patient presenting with an acute coronary syndrome (ACS) is a strong short-term prognostic indicator, significantly increasing the 30-day risk of myocardial infarction, heart failure, and cardiac death (3). Thus, a strong and pervasive link clearly exists between kidney failure and cardiac disease. The common challenge to the nephrologist, cardiologist, and emergency physician therefore lies in successfully recognizing those patients within their scope of practice who are most at risk, thereby allowing targeted application of interventions designed to circumvent adverse outcomes. Accordingly, there is an exigent need for the clinical laboratory to identify and make available reliable assays for biomarkers that can predict adverse events across a range of clinical settings and among patients with various degrees of kidney dysfunction, as well as to elucidate the performance characteristics and limitations of each of these markers.

A variety of individual biomarkers have previously been evaluated for this purpose, and several have been found to successfully predict outcome in patients with kidney disease. These include markers of myocardial necrosis, such as cardiac troponin T (cTnT) and I (cTnI) (4); markers of heart failure, such as B-type natriuretic peptide (BNP) and its associated inactive N-terminal fragment (NT-proBNP) (5); and the marker of systemic inflammation, high-sensitivity C-reactive protein (hsCRP) (6). However, fulfillment of the obvious potential of these biomarkers to have a positive impact on the care of renal failure patients has been elusive because of unresolved clinical concerns that have caused application of these markers in this critical patient subgroup to lag behind their otherwise rapid integration in a broad spectrum of practice settings. In fact, it is fair to say that the short history of cardiac biomarker use among renal failure patients to date has been mostly characterized by controversy among scientists and confusion among clinicians.

In this issue of Clinical Chemistry, Apple et al. (7) bring us a small step closer to lifting the fog of controversy and confusion by reporting on the potential clinical use of a multimarker panel approach for risk stratification (prediction of 2-year all-cause mortality) among a cohort of 399 patients with ESRD. By measuring plasma concentrations of four biomarkers (cTnT, cTnI, NT-proBNP, and hsCRP) and linking the results to an existing clinical database, this investigation provides an opportunity to make direct comparisons of biomarker performance while eliminating the confounding effects of variations in study population and methodology common to previous cross-study comparisons. In addition, because the markers included in this study are of three distinct physiologic classes, the data allow exploration of the potential for more sophisticated approaches to risk stratification than are allowed by single-marker testing alone.

An important consideration in the use of any biomarker is its propensity to provide falsely positive results, and this point is particularly important for the troponins. Among patients with intact renal function, the cardiac troponins have nearly perfect sensitivity and specificity for detecting myocardial necrosis and are widely accepted for short- and long-term risk assessment. Although numerous reports have clearly demonstrated that both cTnT and cTnI also have prognostic significance among patients with ESRD, sizeable barriers remain to clinicians’ acceptance of the troponins as valuable risk stratification tools among this patient group. More specifically, continuous debate over the past decade concerning the etiology of increased cTnT among renal failure patients with no other signs of myocardial damage has led to lingering skepticism among many clinicians. The initial hypothesis of fetal expression of cTnT in skeletal muscle of ESRD patients was later discredited and replaced by the theory that cross-reactivity of the antibodies in the first-generation assays caused false-positive tests (8); however, unexplained increases have since also been reported with second- and third-generation assays. Adding fuel to the fire, Diris et al. (9) recently demonstrated that cTnT increases in proportion to the length of time on dialysis. Linking these findings to the growing evidence of the presence of cTnT fragments in serum, these investigators postulated that in vivo fragmentation of cTnT occurs, leading to the accumulation over time of small (<25 kDa) immunoreactive cTnT fragments (as well as the intact molecule) in patients on hemodialysis. The inventor and patent holder of the cTnT assay, Hugo Katus, has since disputed this latest theory and continues to offer a convincing argument that these “false” positive tests do in fact represent clinically significant, if asymptomatic, myocardial damage (10). Thus, the only clear findings to date concerning these unexplained “false positives” are that the controversy has clearly driven innovation and discovery in the laboratory and that the ultimate acceptance of troponins by community physicians as a useful test for risk stratification of renal failure patients will not occur until further research definitively resolves this debate.

It must also be recognized that although “standardization” of cardiac biomarker threshold determinations based on a percentile value for a reference population and/or an acceptable CV has been a clear step forward for most clinical and research applications, cutoffs derived in this manner do not necessarily optimize prognostic utility. They also do not allow a “level playing field” for making direct marker comparisons when applied to renal failure patients because the degree to which marker
kinetics vary with renal function may differ greatly among markers of the same physiologic class (i.e., between cTnT and cTnI or BNP and NT-proBNP). Although the report by Apple et al. (7) in this issue does not explicitly acknowledge this problem, to the authors’ credit, they have included tertile analyses and areas under the ROC curve for each assay in addition to comparing the predictive values of each marker based on reference interval-generated cutoffs. As their comparisons incidentally illustrate, logical but markedly different conclusions were reached, depending on which of these methods are included and/or emphasized during data analysis. Similarly, in another investigation, Aviles et al. (11) elegantly demonstrated that when a better risk stratification cutoff of 0.1 μg/L was used rather than the lower 99th percentile reference value of 0.01 μg/L, cTnT successfully predicted adverse events in patients with ACS independent of and across the full range of patients’ creatinine clearance. We therefore believe that the ongoing efforts aimed at standardization of biomarker reporting should also include more specific guidelines for studies of renal failure patients that address the most appropriate threshold determination and marker comparison methods (12).

The natriuretic peptides have recently gained a great deal of attention, not only for their clear diagnostic value in patients with heart failure but also as tools for risk stratification in patients with suspected ACS. Patients receiving hemodialysis are usually exposed to increased peripheral vascular resistance and volume abnormalities and, thus, chronically increased ventricular afterload; significant increases in both BNP and NT-proBNP are therefore generally expected, and the information they provide should be interpreted accordingly in these patients. NT-proBNP is predominantly excreted by the kidneys, in contrast to clearance of BNP by receptor internalization and neutral endopeptidase degradation in plasma; this has led to concerns that NT-proBNP may be inferior to BNP in patients with kidney disease because of frequent “false positive” results. Indeed, in the report by Apple et al. (7), application of the threshold derived from the 99th percentile of the reference interval led to 99% of ESRD patients testing “positive” for NT-proBNP, leading the authors to correctly state that this marker has “poor prognostic ability . . . to discriminate all-cause mortality between normal and increased concentrations”. However, drawing conclusions concerning the clinical utility of NT-proBNP from these data alone would be highly misleading. Tertile analysis of the same data demonstrated prognostic ability similar to the other three markers tested, and none of the five other assays had a greater area under the curve for the prediction of mortality, thus suggesting considerable potential for clinical use of NT-proBNP in this population if a higher threshold were applied (7). In another study, ROC curve analysis determined that for BNP, a cutoff concentration of 390 ng/L, which would otherwise be considered inappropriately high (reference interval, <100 ng/L), was optimal for predicting adverse cardiac events in hemodialysis patients (5).

Inflammatory disorders are also commonplace in patients with kidney disease, and vascular inflammation has been increasingly implicated in the pathogenesis of ACS. hsCRP, although not cardiac specific, has been shown to predict adverse cardiac events in a variety of clinical settings and seems to be the most robust noninvasive measure of inflammatory state currently available, making exploration of its prognostic ability among renal failure patients a logical next step. The data presented by Apple et al. (7) confirm previous reports that although hsCRP concentrations are above normal (99th percentile of the reference interval) in one half or more of ESRD patients, increased concentrations are independently associated with higher subsequent mortality. These findings are consistent with other investigations of renal failure patients demonstrating correlations between serum hsCRP concentrations and creatinine clearance, neutrophil count (6), and carotid atheromatous plaque formation (13). Together, the body of evidence strongly suggests that increased hsCRP remains a strong indicator of both systemic vascular inflammation and prognosis among this patient subgroup.

The vast preponderance of past biomarker investigations have focused on either a single marker or comparison of markers of the same group (i.e., markers of myocardial necrosis). However, an increasing number of studies have demonstrated the potential benefits of using a panel of cardiac markers, an approach that has been particularly successful for short-term risk stratification of ACS patients (14). Apple et al. (7) have now demonstrated similar advantages for a multimarker strategy for long-term risk stratification of ESRD patients. Although further work is needed to identify the most appropriate threshold values for clinical use of each marker in this population and to determine the optimum algorithm for combining multiple marker results with clinical variables, the potential clearly exists to stratify ESRD patients into layered groups with quantifiable risk and perhaps in the future to target specific therapies to each patient subgroup according to their risk and cardiovascular physiologic profile.

References


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