Since the first reports of an independent association between microalbuminuria or proteinuria and an increased risk for vascular events and death in the 1980s (1,2), there has been an explosion of research into the biological implications of urinary albumin excretion. A simple Medline search combining the terms “albuminuria” or “proteinuria” with “cardiovascular disease,” for example, reveals more than 10,000 citations on this topic since the first descriptions in 1984. By and large, these studies have confirmed that the presence of albuminuria is independently associated with the risk for death, myocardial infarction, stroke, and other cardiovascular (CV) events (3–5).

Progress in this field has been paralleled by a coincident recognition during the same period of a strong, independent association between the presence of reduced GFR and the risks for CV morbidity and mortality (6,7). Although low GFR and albuminuria do occur in isolation from one another, the two conditions frequently coexist and in many cases may result from similar pathologic changes within the glomerulus.

This shared underlying pathology raises the important question of whether the individual associations of low GFR and albuminuria with CV risk signify unique pathophysiologic pathways or are simply different markers of the identical underlying biological processes. Although epidemiologic studies cannot answer this question definitively, recent studies have attempted to provide insight by analyzing the extent to which the risks associated with albuminuria and low GFR are independent of each other. Studies examining this question have generally confirmed that the associations between albuminuria or low GFR and CV outcomes are independent of each other, although not all studies have found that there is effect modification when both GFR and albuminuria are present (statistical interaction) (8–10).

A related and equally important issue is whether measuring both albuminuria and GFR simultaneously provides additional clinical utility compared with measuring one of these factors. Even if GFR and albumin excretion reflect distinct biological processes and are independently associated with CV outcomes, adding both factors to a predictive model will not necessarily improve the ability to identify individuals at high risk in a clinically or statistically significant manner. This difference arises because statistical association and discrimination—the ability of a predictive model to discriminate between individuals with and without an event—can diverge. If a baseline predictive model performs relatively well, then the addition of new risk factors to the model is unlikely to improve risk prediction in a statistically significant manner unless the new risk factor has not only a statistically significant association with the outcome in question but also a very strong association with the outcome (11). In short, given the utility of existing models in predicting CV risk, such as the Framingham Risk Score, the bar for entry into future risk scores has been set high. Furthermore, it must be kept in mind that small, statistically significant improvements in risk prediction are not clinically relevant if they fail to move the risk estimate enough in one direction or another to change the recommended treatment approach for that individual.

To date, relatively few analyses have directly addressed the question of whether simultaneous measurements of GFR and albumin excretion improves the prediction of CV events. However, a handful of studies have suggested that measuring both factors does offer advantages over measuring only one (12,13). In this issue of the CJASN, Bello et al. (14) address these issues by examining the associations between estimated GFR and albuminuria (or proteinuria) and four CV outcomes: Hospitalization for stroke, heart failure, peripheral vascular disease, or coronary revascularization.

Although the analysis is limited only to individuals who had a clinical rationale for checking both serum creatinine and either albumin or protein excretion—thereby precluding extrapolation of the results to the general population—the final data set nevertheless included more than 1.5 million representatives of a population commonly seen by internists and nephrologists. The results convincingly demonstrate that among patients who have protein excretion and creatinine checked during the course of routine clinical care, the risk for these four events increases at any given level of estimated GFR in individuals with higher degrees of protein or albumin excretion.

A number of unique features in this analysis add new information beyond what has been previously established. Using a large provincial database, the
authors were able to estimate albumin excretion on the basis of multiple measurements (for at least some individuals) rather than on the basis of a single measurement as in most previous studies. Given the large variation that can occur from day to day in albumin excretion, this represents a significant strength of the current analysis. Second, because of the nature of the database, the sample size of the study is much larger and presumably more broadly inclusive than the populations included in many previous studies. Last, the authors provide evidence that albuminuria (and proteinuria) is independently associated with stroke, congestive heart failure, peripheral vascular disease, and coronary revascularization—outcomes that have not been widely studied as individual events as opposed to as components of a combined CV end point.

Are these findings clinically useful? Here the answer is less clear. Although hospitalization for stroke and heart failure is a relatively good surrogate for the underlying clinical events of interest, it is less clear that predicting hospitalization for the other events studied—peripheral vascular disease and coronary revascularization—is useful. In contrast to stroke and heart failure—clinical events that tend to have dramatic presentations uniformly mandating hospitalization—the latter events represent more complex entities. The decision to revascularize a peripheral or coronary lesion is complex and may vary widely on the basis of a patient's previous vascular history, symptom tolerance, and risk aversion, as well as the physician's practice style and available resources. In many cases, this decision may also be specifically influenced by knowledge of an individual's underlying renal function (15). Although tools to predict stroke, heart failure, or peripheral and CV events such amputations and myocardial infarction have an obvious use, it may simply not make much sense to try to predict the clinical decision to hospitalize a patient for a revascularization procedure.

A more fundamental issue concerns the authors' suggestion that their data "suggest that proteinuria and eGFR should be used for risk stratification of people with CKD."

The magnitudes of the increase in risk in this study were large and suggest that changes in urinary protein excretion are associated with clinically meaningful differences in the level of risk, and they are consistent with the idea that inclusion of proteinuria in risk prediction scores is likely to result in statistically significant improvements in risk prediction. However, as noted above the demonstration of statistically significant associations for both GFR and albuminuria/proteinuria is not equivalent to proving that use of both factors improves risk stratification. There is room for doubt on this point, and, unfortunately, while providing convincing evidence that albumin excretion is associated with CV events, Bello et al. (14) miss a unique opportunity to prove definitively their hypothesis that measuring both albumin excretion and creatinine improves risk stratification for CV events.

This is a critical point because emerging evidence increasingly suggests that the reduction of albuminuria—at least in individuals without markedly reduced GFR—does not improve clinical outcomes (5,16,17). Clearly, more work needs to be done in this area, and the available trials should not be considered the last word. However, as a community, we need to at least consider the possibility that albuminuria is an imperfect surrogate and poor therapeutic target for CV risk reduction. In this case, continued interest into the association would be warranted only on the basis of evidence proving that measurement of albuminuria provides measurable improvements in CV risk stratification.

Clinical trials that definitively test whether reducing albuminuria simultaneously reduces CV mortality and epidemiologic analyses designed to demonstrate definitively whether the measurement of albuminuria permits better identification of individuals at increased risk compared with measurement of GFR alone are urgently needed. The case that albuminuria is associated with CV risk has been well demonstrated in the article by Bello et al. (14) and its predecessors dating back to the 1980s. It is now time to move forward and definitively determine whether measuring albumin excretion is clinically useful.

Disclosures
None.


See related article, “Associations Among Estimated Glomerular Filtration Rate, Proteinuria, and Adverse Cardiovascular Outcomes,” on pages 1418–1426.