immune mechanisms mediating tubular injury. Tubulitis, invasion of the tubular epithelium by infiltrating T cells and macrophages, is a diagnostic feature of acute cellular rejection of renal allografts.\textsuperscript{10} This raises the question of whether tubulitis in IgAN progressors recapitulates the same process. The answer is negative. As van Es \textit{et al.}\textsuperscript{3} document, there is a paucity of macrophages and CD4\textsuperscript{+} T lymphocytes infiltrating tubules of early IgAN progressors. In contrast, the tubulitis pattern of renal allografts is full of macrophages and mostly of CD4\textsuperscript{+} and CD8\textsuperscript{+} T cells that contain cytotoxic granules (perforin and granzyme A/B) or the cytotoxic effector ligand FasL.\textsuperscript{10} The absence of both perforin and granzyme A/B from NKG7\textsuperscript{+}/CD8\textsuperscript{+} IELs in IgAN progressors is another important feature that contrasts with the allograft-infiltrating CD8\textsuperscript{+} cytotoxic T lymphocytes. Consequently, what are the immune mechanisms engaged by NKG7\textsuperscript{+}/CD8\textsuperscript{+} IELs that inflict tubular injury? The answer is unknown. However, on the basis of the localization of NKG7\textsuperscript{+}/CD8\textsuperscript{+} IELs in intact and atrophic tubules, we postulate two complementary mechanisms of adaptive and innate CD8\textsuperscript{+} T cell-mediated tubular injury. The first mechanism (schematized in Figure 1a) proposes that the T-cell receptors on NKG7\textsuperscript{+}/CD8\textsuperscript{+} cells mediate the cytotoxic response to either cross-presented exogenous antigen or an endogenous antigen produced by the tubules. Also, the antiapoptotic action of transforming growth factor-β and interleukin-15, along with the expression of CD103 that binds to E-cadherin on tubular cells, allows NKG7\textsuperscript{+}/CD8\textsuperscript{+} IELs to persist and cause disruption of the tubular structure and function. The second mechanism (schematized in Figure 1b) proposes the innate immune response of the NKG7\textsuperscript{+}/CD8\textsuperscript{+} IELs as a mediator of tubulitis. The primary function of sentinel CD8\textsuperscript{+} IELs is to sustain epithelial integrity by eliminating stressed cells. The CD8\textsuperscript{+} IELs express a variety of NK cell–lineage receptors, among which is the NKG2D activating receptor. Under stress conditions, epithelial cells express major histocompatibility complex class I chain-related proteins (MICA or MICB) that serve as ligands of NKG2D, hence targeting the cells for cytolyis and elimination. These are minimal models inspired by the study of van Es \textit{et al.}\textsuperscript{5} Their clinical relevance needs to be ascertained in future investigations.

The seminal report by van Es \textit{et al.}\textsuperscript{5} will enhance the clinical utility of renal biopsy early in IgAN to predict progression. Importantly, the novel discovery of NKG7\textsuperscript{+}/CD8\textsuperscript{+} IELs\textsuperscript{’} association with tubulitis implicates this specialized T-cell subset as a mediator of nephron injury. Finally, we envisage that targeted inhibition of NKG7\textsuperscript{+}/CD8\textsuperscript{+} cells could be of therapeutic value, especially as an adjunct supplement to other therapeutic strategies aimed at IgAN.

**DISCLOSURE**

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**The challenge of discovering patient-level cardiovascular risk factors in chronic kidney disease**

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The goal of developing a CKD-specific cardiovascular risk score remains elusive and difficult. One approach to develop such a score is to evaluate conventional cardiovascular risk factors in an outcomes model. Nontraditional risk factors such as albuminuria can then be tested to evaluate the predictive value of these markers over and above traditional risk factors for patient-level decision making.


In 1948, the United States Public Health Service initiated a community-based epidemiological study in Framingham, Massachusetts, to uncover environmental and personal factors associated with the subsequent appearance and progression of cardiovascular diseases.\textsuperscript{1} At first examination of this cohort, 898 men and 1,107 women aged 45–62 who appeared clinically well underwent a thorough history, physical examination, and laboratory evaluation.\textsuperscript{2} In 1957, a report of a 4-year follow-up revealed 52 cases of coronary heart disease in men and 32 cases in women. Blood pressure, relative body weight, and the serum cholesterol
concentration were found to be elevated in those who developed the disease. From this experiment, the term ‘risk factor’ was born, so named because it helps in the assessment of future cardiovascular events. Age, sex, smoking, hypertension, and serum cholesterol levels remain the most enduring risk factors because these ‘traditional’ risk factors appear to contain most of the information deemed necessary to predict cardiovascular events. More recently, the presence of additional — nontraditional — risk factors has been linked to the risk of future cardiovascular events (Figure 1). Although nontraditional risk factors may increase the relative risk of future clinical cardiovascular events, such an increase in relative risk may not reach a magnitude that is sufficient to improve individual-level decision making.

An evaluation of a recent study from the Framingham Offspring Cohort offers insights into the relative importance of nontraditional risk factors as predictors of population risk vis-à-vis prediction of patient-level risk. Between 1995 and 1998, Wang et al. examined participants in the Framingham Heart Study and followed them for up to 10 years for cardiovascular events or death. A panel of biomarkers of inflammation (C-reactive protein), endothelial function (homocysteine, urinary albumin-to-creatinine ratio), thrombosis–fibrinolysis pathway (fibrinogen, D-dimer, plasminogen-activator inhibitor type 1), and neurohormones (B-type natriuretic peptide, N-terminal pro-ANP, serum aldosterone, plasma renin) was used to predict risk over and above conventional risk factors (age, sex, body mass index, serum creatinine, smoking, blood pressure, total cholesterol, high-density lipoprotein cholesterol, diabetes mellitus). Only two biomarkers — urinary albumin-to-creatinine ratio and B-type natriuretic peptide — emerged as statistically significant epidemiological risk factors over and above conventional risk factors for future cardiovascular events. But for individual decision making, the incremental value of even these statistically significant population-level risk factors was small. The area under receiver operating characteristic (ROC) curve that took age, sex, and conventional risk factors into account to predict cardiovascular events was 0.76, whereas the comparable area under ROC curve that took age, sex, and multi-marker strategy into account was 0.70. A combination of the conventional and newer risk factors yielded only a small increment in area under ROC curve to 0.77.

In contrast to the two markers that were predictive of cardiovascular events, there were five markers that were of statistical importance in the Cox model over and above conventional risk factors to predict death. These were B-type natriuretic peptide, homocysteine, renin, C-reactive protein, and urinary albumin-to-creatinine ratio. The area under ROC curve that took age, sex, and conventional risk factors into account to predict death was 0.80, whereas the comparable area under ROC curve that took age, sex, and multi-marker strategy into account was 0.79. A combination of the conventional and newer risk factors yielded only a small increase in area under ROC curve to 0.82. Thus, even an extensive panel of biomarkers was unable to meaningfully alter the predictive utility of nontraditional risk factors.

More recently, chronic kidney disease (CKD) itself has been recognized to confer increased cardiovascular risk. In patients with CKD, it is well recognized that the Framingham risk score underestimates cardiovascular risk, and thus an alternative strategy for cardiovascular risk profiling equally as robust as the Framingham risk score in patients with CKD is not available.

To provide more reliable risk stratification and explore the provenance of heightened risk for cardiovascular events, several investigators have explored nontraditional risk factors. The hunt for nontraditional risk factors that may be etiologically significant is exemplified by the humbling story of hyperhomocysteinemia. Although elevated homocysteine concentration is also associated with higher blood pressure, diabetes mellitus, and CKD, epidemiological observations demonstrated that hyperhomocysteinemia was associated with increased atherothrombotic risk after multivariate adjustment. Thus drugs that lower homocysteine, such as folic acid and pyridoxine, seemed attractive choices to reduce this cardiovascular risk factor. Disappointingly, randomized trials have not provided any support for this hypothesis. Thus, homocysteine appears to be a marker, not a mediator, of increased atherothrombotic risk in patients with or without CKD.

Another non-conventional risk factor of great interest is the presence of inflammation, which is frequently activated in patients with CKD and may contribute to accelerated atherosclerosis. Low-grade

Figure 1 | Impact of traditional and nontraditional risk factors and CKD on cardiovascular events. Traditional risk factors are causally linked to cardiovascular events. Chronic kidney disease (CKD) also elevates the risk of cardiovascular events. The independent role of nontraditional risk factors in patient-level cardiovascular risk is less clear. CKD-specific, cardiovascular risk factors for patient-level decision making remain to be defined.
inflammation can be measured by high-sensitivity C-reactive protein (CRP). Elevated levels of CRP are associated with elevated cardiovascular risk. Weiner et al. 3 (this issue) explore the impact of CKD, inflammation, and the interaction of CKD and inflammation on cardiovascular events in two well-characterized cohorts from the Cardiovascular Health Study and the Atherosclerosis in Communities Study. The three criteria defining inflammation were the highest quartile of fibrinogen, the lowest quartile of albumin, and the highest quartile of race-specific white blood cell count; the diagnosis of inflammation required that two of the three criteria be present. Inflammation was associated with increased hazards for stroke, cardiac events, or death after adjustment for conventional risk factors that ranged between 35% and 50%. In patients with CKD, the hazard ratio was similarly elevated between 15% and 25%. These data confirm previous results from the Cardiovascular Health Study cohort of an association of cardiovascular mortality with markers of inflammation such as CRP and interleukin-6. 10 When compared with a reference group of patients without inflammation and without CKD, those with CKD alone had an increase in hazards of hard cardiovascular end points of 20%–60%, those with inflammation alone had an increase of 40%–60%, and those with both inflammation and CKD had an increase in hazards of 40%–100%. The interaction of inflammation and CKD was not statistically significant. Thus, the central message of this report is that inflammation is associated with increased cardiovascular risk in those with CKD that is similar to the risk in those without CKD; there is no special predilection for cardiovascular events in inflamed patients with CKD. As an aside, the investigators demonstrated that the combination of high white blood cell count and low serum albumin concentration was similar to elevated CRP in predicting outcomes.

Although the authors do not report the predictive performance for cardiovascular events of these inflammation biomarkers as area under ROC curves, given the low hazard ratios it is very unlikely that incorporation of these inflammation biomarkers in the Framingham risk score will improve our ability to predict cardiovascular events or death in patients with CKD. In fact, the area under ROC curves was not improved in the Cardiovascular Health Study when markers of inflammation were added to traditional risk factors. 10 Similar results have emerged from general-population surveys. For example, the Dallas Heart Study investigators measured CRP in 3,373 randomly selected, community-dwelling subjects and performed electron-beam computed tomography scans to detect coronary calcification and magnetic resonance imaging to measure aortic plaque. 11 They found a modest association of inflammation with the prevalence of subclinical atherosclerosis. But this association was not independent of traditional cardiovascular risk factors. Taken together, these results do not support the routine use of CRP in the general population or in patients with CKD for patient-level cardiovascular risk assessment.

The goal of developing a CKD-specific cardiovascular risk score remains elusive and difficult. An approach provided by Framingham Heart Study investigators where cardiovascular risk is systematically evaluated for each risk factor over and above the traditional risk may be a valuable lesson for future research to define cardiovascular risk in patients with CKD for patient-level decision making. 4 Nontraditional risk factors such as albuminuria, cystatin C, B-type natriuretic peptide, and CRP can then be tested to evaluate the predictive value of these markers over and above traditional risk factors. Subsequently, measures to lower the level of these risk factors with dietary, lifestyle, or pharmacological maneuvers can be tested to ascertain whether any of these risk factors are causally associated with cardiovascular risk. Perhaps this strategy can help unravel the mystery of elevated cardiovascular risk in CKD patients and assist decision making at the level of the individual patient.

DISCLOSURE
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