EDITORIAL COMMENT

Why Is Chronic Kidney Disease the “Spoiler” for Cardiovascular Outcomes?*

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The modern-day, first-world epidemics of obesity and hypertension are central drivers of an epidemic of combined chronic kidney disease (CKD) and cardiovascular disease (CVD) (1). Among those with diabetes for 25 years or more, the prevalence of diabetic nephropathy in type 1 and type 2 diabetes is 57% and 48%, respectively (2). Approximately half of all cases of end-stage renal disease (ESRD) are due to diabetic nephropathy, with most of these cases driven by obesity-related type 2 diabetes and hypertension. With the graying of America, and cardiovascular care shifting towards the elderly, there is an imperative to understand why decreasing levels of renal dysfunction act as a major adverse prognostic factor after cardiovascular events.

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CKD AND RISK

Chronic kidney disease is defined through a range of estimated glomerular filtration rate (eGFR) values by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative, as depicted in Figure 1 (3). Most studies of cardiovascular outcomes have found that a breakpoint for increased risk of restenosis, recurrent myocardial infarction (MI), congestive heart failure, and cardiovascular death occurs below an eGFR of 60 ml/min/1.73 m², which roughly corresponds to a serum creatinine (Cr) of $>1.5$ mg/dl in the general population (4–7). Because Cr is a crude indicator of renal function, and often underestimates renal dysfunction in women and the elderly, calculated measures of eGFR by the Cockcroft-Gault equation or by the Modification of Diet in Renal Disease equations, now available on personal digital assistants, are the preferred methods of estimating and reporting renal dysfunction (3). In addition, microalbuminuria at any level of eGFR is considered to represent CKD, and has been thought to occur as the result of hyperfiltration in the kidneys due to diabetes and hypertension-related changes in the glomeruli (8). There have been several definitions developed for microalbuminuria (8). A simple definition for microalbuminuria is 30 to 300 mg/l on a single voided casual specimen; $>300$ mg/l is usually considered gross proteinuria. In this issue of the Journal, Freeman et al. (9) describe the influence of baseline renal dysfunction on the outcomes of 889 patients with acute coronary syndromes (ACS). This article highlights several of the leading explanations for why CKD is such a potent risk factor for adverse outcomes after cardiovascular events: 1) excess comorbidities in patients with CKD; 2) lesser use of beneficial therapies in patients with CKD, or therapeutic nihilism; 3) excess toxicities from conventional therapies used; and 4) the unique pathobiology of the CKD state, which leads to accelerated and more severe cardiovascular disease.

EXCESS COMORBIDITIES

Population-based studies have demonstrated that there are higher rates of diabetes, poorly controlled hypertension, elevated triglycerides, lower high-density lipoprotein cholesterol, and elevated lipoprotein(a) levels in patients with CKD and ESRD (10). However, there are lower rates of smoking in the same groups compared to the general population. There are insufficient data regarding CVD family history or exercise to make conclusions regarding these contributory CVD risks to the CKD and ESRD populations. It is clear that age is a contributing factor to the elevated risk of CKD. In the study by Freeman et al. (9), there was a 14-year difference between those above and below the cutpoint of 60 m/min/1.73 m². However, for those with ESRD, where the mean age is 56 years in U.S. dialysis patients, age alone cannot be an explanatory factor for adverse outcomes. Multivariate analyses used in almost every retrospective study reported, when controlling for all known confounders including age, have demonstrated an independent association between CKD and cardiovascular outcomes. The paper by Freeman et al. (9) is no exception. Of particular interest is the observation that when diabetes and renal function are taken into consideration together, CKD is the dominant risk factor. In the study by Freeman et al. (9), the adjusted odds ratio for in-hospital mortality for diabetes was 2.17, whereas the calculated odds ratio for those with eGFR $<30$ ml/min would be 5.27 when using eGFR $>90$ ml/min as the referent. In the Bypass Angioplasty Revascularization Investigation Trial, again CKD (defined as baseline Cr $>1.5$ mg/dl) was found to be a more important factor related to survival than diabetes, with relative risks of 2.31 and 1.80, respectively (Fig. 2) (7). These data taken together suggest a considerable amount of the risk conveyed by the diabetic state is really driven by the degree of renal dysfunction present.

UNDERUSE OF CARDIOPROTECTIVE THERAPIES

Given the excess comorbidities in patients with CKD and ESRD, it is not unexpected that reduced rates of proven
therapies may explain, in part, the outcomes observed. Although data to support this hypothesis are limited, Beattie et al. (5) have recently reported that in the setting of ST-segment myocardial infarction, there are graded decreases in the use of routine therapies as renal function declines. The paper by Freeman et al. (9) also demonstrated reduced rates of catheterization, angioplasty, and glycoprotein (GP) IIb/IIIa inhibitor usage in patients with more advanced CKD. Of interest is the observation that with lower rates of catheterization, the relative rates of bypass surgery increased, suggesting that the burden of severe coronary disease is far greater in those with CKD. It is certainly conceivable that quality programs may target these opportunities for improvement, especially with respect to the use of aspirin, beta-blockers, agents that block the renin angiotensin system (RAS), reperfusion therapy, and revascularization where possible. In a recent analysis, aspirin and beta-blockers, although underused in CKD patients with acute MI, demonstrated a consistent and large mortality benefit across all strata of renal dysfunction (11).

EXCESS TOXICITIES OF THERAPIES

It is clear that patients with CKD and ESRD have worsened outcomes after angioplasty and bypass surgery, and this in part can be considered a "toxicity" of the therapy offered. However, data on the drug toxicities and drug interactions that result in poor outcomes in CKD and ESRD patients are difficult to find. One of the reasons for this is that CKD and ESRD are routinely excluded from randomized trials. The study by Freeman et al. (9) demonstrated both risks and benefits with the use of GP IIb/IIIa inhibitors. In fact, the majority of major bleeding events in those patients with eGFR <60 ml/min occurred on GP IIb/IIIa inhibitors. However, it is unknown whether it was the GP IIb/IIIa inhibitor or concomitant unfractonated

Figure 1. The classification of chronic kidney disease (CKD) according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative. Increased rates of adverse effects are generally seen below an estimated glomerular filtration rate of 60 ml/min/1.73 m². CHF = congestive heart failure; CV = cardiovascular; ESRD = end-stage renal disease; GFR = glomerular filtration rate; MI = myocardial infarction. Adapted from reference 3.

Figure 2. Freedom from cardiovascular death after angioplasty or bypass surgery in the Bypass Angioplasty Revascularization Investigation (BARI) Trial and Registry, n = 3,608. CKD = chronic kidney disease; DM = diabetes mellitus. Adapted from reference 7.
heparin that was the culprit, given that both have renal-dependent clearance mechanisms and both have graded increased bleeding risks in those with low eGFR (12). Cardiologists need to understand how to use conventional antithrombotics, including unfractionated heparin, low-molecular-weight heparin, GP IIb/IIIa inhibitors, and bivalirudin in the settings of acute coronary syndromes and percutaneous coronary intervention. These sources of data will be best derived from future, prospective randomized trials in the CKD population. A substantial number of other drugs require dose adjustment or special precautions in CKD, including antiarrhythmics, intravenous inodilators (milrinone), and digoxin. From the reported outcomes studies, it is unknown how often these CKD-related drug adverse events contribute to hard outcomes. Lastly, despite their proven benefit in CKD and congestive heart failure, agents that block the RAS may hasten the progression to ESRD and cause problems with hyperkalemia; hence, their underuse in the most advanced CKD patients results in a lack of cardioprotection.

ABNORMAL VASCULAR BIOLOGY IN CKD

As renal function declines, there are a host of abnormalities that develop, including changes in coagulation, fibrinolysis, lipids, endothelial dysfunction, homocysteine, anemia, calcium/phosphorus balance, and many other factors that have been related to CVD (Fig. 3) (13). The leading hypotheses include hyperactivation of the RAS leading to adverse cardiac remodeling, accelerated atherosclerosis, and symptomatic events (13). There is a growing body of evidence that erythropoietin deficiency and anemia are related to adverse ventricular remodeling and cardiac failure (14). Hyperhomocysteinemia is an obvious therapeutic target for future trials in ACS given its predictable elevation in CKD, known association with adverse outcomes, and its reduction with high doses of folic acid (15). Lastly, advanced atherosclerosis related to abnormal vascular calcification driven by an elevated calcium-phosphorous product (CPP) is an attractive hypothesis in ESRD, where recent studies suggest that not only is CPP related to coronary calcification, but that lowering of the CPP may reduce or stabilize the coronary calcification process (16).

CONCLUSIONS

Chronic kidney disease is the most important factor in predicting adverse outcomes after virtually all cardiac events including acute coronary syndromes. Hence, CKD is really a “spoiler” for the expected benefit of many treatments in cardiovascular medicine. A combination of excess comorbidities, therapeutic nihilism, therapy-related toxicity, and a unique vascular pathobiology accounts for this observation. Through intense and systematic study of these mechanisms, new diagnostic and therapeutic targets will be discovered, which will enhance the cardiac care of patients with CKD, and perhaps attenuate the powerful risks we are seeing today.
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