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Cardiovascular disease in CKD in 2012:

Moving forward, slowly but surely

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Abstract

During 2012, an observational study confirmed the high risk of cardiovascular disease ascribed to chronic kidney disease (CKD) and again raised the question of whether CKD should be considered a cardiovascular disease risk equivalent. Several other studies evaluated methods to mitigate cardiovascular risk in CKD. Although the results of these studies have advanced the field they have also raised more questions

Nearly 10 years ago the American Heart Association (AHA) recommended that people with chronic kidney disease (CKD) should be considered in the highest-risk group for the prevention, detection, and treatment of cardiovascular risk factors.¹

Since the publication of this statement there has been debate in the literature as to whether CKD is a cardiovascular disease (CVD) risk equivalent. A 2012 observational study of 1,268,029 individuals added to this literature.² Among those without previous myocardial infarction (MI), the unadjusted rate of MI was higher in people with CKD (without diabetes) than in those with diabetes (without CKD) (6.9 per 1,000 person-years versus 5.4 per 1,000 person-years [95% CI 6.6–7.2 versus 5.2–5.7]).² When CKD was defined by an estimated glomerular filtration rate (eGFR) of <45 ml/min/1.73 m² and proteinuria (rather than the primary definition of eGFR <60 ml/min/1.73 m²), the risk of incident MI was nearly twice as high in those with CKD than in those with diabetes (12.4 per 1,000 person-years versus 6.6 per 1,000 person-years [95% CI 9.7–15.9 versus 6.4–6.9]). All-cause mortality was highest among people with diabetes and CKD, followed by those with CKD alone, then those with previous MI and those with diabetes alone. Although constrained by limitations of observational studies, the results of this study again highlights the increased CVD burden associated with CKD, especially among those with both reduced eGFR and proteinuria.

Blood pressure control remains an important modifiable risk factor for both slowing the progression of CKD and development of CVD. A *post hoc* analysis including 1,117 people from the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) and Irbesartan Diabetic Nephropathy Trial (IDNT) trials, evaluated the effect of dietary sodium (assessed by 24-hour urine sodium excretion, a surrogate for salt intake) on the efficacy of angiotensin-receptor blockers (ARBs) in preventing clinically important CKD and CVD end points compared with non-ARB therapy.³ Among those randomized to ARB therapy, the investigators noted that absolute reductions in 24-hour urinary albumin-to-creatinine ratio (ACR; measured in mmol/g) and systolic blood pressure were greatest in

those with the lowest baseline urinary sodium-to-creatinine ratio. A low sodium-to-creatinine ratio was not associated with a significant decrease in renal or CVD events among non-ARB-treated subjects; however, among those treated with ARBs, individuals in the lowest tertile of sodium-to-creatinine ratio experienced significantly fewer CVD events (hazard ratio than those in the highest tertile of sodium-to-creatinine ratio (hazard ratio 0.57 versus 1.37 [95% CI 0.39–0.84 versus 0.96–1.96]). Importantly, ARB therapy was not associated with significant reduction in systolic blood pressure, renal or CVD events among those in the highest tertiles of sodium-to-creatinine ratio. These results are consistent with those from a *post hoc* analysis of the Ramipril Efficacy in Nephropathy trials (REIN I and II) which demonstrated that low salt intake was associated with a lower risk of end-stage renal disease (ESRD) than was a higher salt intake in nondiabetic patients with proteinuria being treated with angiotensin-converting-enzyme (ACE) inhibitors.⁴ All of these findings should be considered in the context of other recent observational data (with their attendant limitations) in the general population showing a ‘J’-shaped association between salt excretion () and cardiovascular risk.⁵

Whether warfarin is associated with a reduced risk of stroke among patients with CKD, especially those on dialysis with nonvalvular atrial fibrillation, remains controversial. A 2012 study of 132,372 people with atrial fibrillation included in Danish national registries noted that although individuals with CKD had an increased risk of stroke compared with those without kidney disease, this risk was significantly attenuated by the use of warfarin (hazard ratio 0.76; 95% CI 0.64–0.91).⁶ The reduction in stroke risk seen with warfarin was even stronger when the analysis was limited to patients on dialysis (hazard ratio 0.44 [95% CI 0.26–0.74]). Bleeding complications associated with warfarin were more frequent in individuals with CKD than in those without CKD (hazard ratio 1.33 [95% CI 1.16–1.53]). These results are in contrast to those from an earlier observational study of patients on dialysis, which indicated that those treated with warfarin are in fact at an increased risk of stroke.⁷ The older age of the dialysis patients (mean 72 years versus 66 years) and the high number of patients on warfarin without international normalized ratio (INR) monitoring (27%) in the earlier study, together with differences in the ascertainment of stroke outcomes, may account for some of the differences. A high-quality randomized trial of warfarin in patients on dialysis with atrial fibrillation would help answer the question of whether warfarin has a beneficial effect on the risk of stroke. Given the known benefit of warfarin in the general population, however, conducting such a trial and deciding in which patient group sufficient clinical equipoise exists to perform a randomized trial would be challenging. Until further data are available, we suggest that in CKD patients with an elevated risk of stroke according to CHADS₂ score, treatment with warfarin should be considered on an individual basis and only given with close INR monitoring and after weighing the increased risk of bleeding.

2012 also saw the publication of results from two clinical trials targeting abnormalities in mineral metabolism in patients with CKD. Thadhani and colleagues evaluated the effect of treatment with paracalcitriol versus placebo in 227 individuals with a serum parathyroid hormone level between 50 pg/ml and 300 pg/ml and an eGFR in the range 15–60 ml/min/1.73 m² and mild to moderate left ventricular hypertrophy (LVH).⁸ At 48 weeks, no differences

were seen between the two groups in left ventricular mass index or any of the 10 other assessed parameters of cardiac structure or function. Although earlier studies in rat models had demonstrated that vitamin D supplementation was associated with a decrease in LVH, Thadhani *et al*'s results indicate that active vitamin D supplementation has no role in altering cardiac structure in patients with CKD.

In the EVOLVE (Effect of Cinacalcet on Cardiovascular Disease in Patients Undergoing Dialysis) trial, 3,883 dialysis patients with secondary hyperparathyroidism were randomly assigned to receive cinacalcet or placebo. In the nonadjusted intention-to-treat analysis, cinacalcet was not associated with a reduction in the composite primary outcome of death, MI, hospitalization for unstable angina, heart failure, or a peripheral vascular event (hazard ratio 0.93 [95% CI 0.85–1.02]).⁹ Interestingly, after adjustment for baseline characteristics, a significant reduction in the relative hazard of the composite end point was noted in the cinacalcet group (hazard ratio 0.88 [95% CI 0.79–0.97]); however, such an adjustment was not pre-specified for the primary outcome. The trial may also have been biased towards the null given that commercial cinacalcet was used in nearly 20% of the placebo group. Therefore although some aspects of the trial are suggestive of a beneficial effect of cinacalcet, the primary outcome was negative and the conclusions are nondefinitive.

Despite many recent negative results from randomized controlled trials in patients with CKD, there does seem to be light at the end of the tunnel. In fact, mortality adjusted for age, gender, race, and comorbid conditions among prevalent ESRD patients has fallen 28.4% since 1995.¹⁰ Although the exact reasons for this finding remain unclear, it is encouraging. Several simultaneous interventions are probably required for a reduction in risk to be demonstrated, given the high burden of different forms of cardiovascular disease and multiple traditional and nontraditional cardiovascular disease risk factors in this patient population.

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Key Advances

- Observational data support the hypothesis that individuals with kidney disease, especially those with proteinuria, are at extremely high risk of adverse cardiac events²
- A low-sodium diet in individuals treated with an angiotensin-receptor blocker may be synergistic in treating hypertension, preventing a decline in kidney function and reducing the risk of cardiovascular events³
- Warfarin may be associated with a reduced risk of stroke in patients with chronic kidney disease (CKD) and atrial fibrillation, but more studies are required in this patient population⁶
- Activated vitamin D⁸ and calcimimetic agents⁹ have not conclusively been shown to reduce the risk of cardiovascular disease in CKD