Editorial

Venous Thromboembolism
Yet Another Cardiovascular Complication of Chronic Kidney Disease?

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It has long been recognized that patients with end-stage renal disease experience high mortality rates and high rates of cardiovascular disease.1 During the past 10 to 15 years, heightened attention has been paid to the risks of death and cardiovascular disease experienced by patients with non–dialysis-requiring chronic kidney disease (CKD), with many studies showing significant increases in risk associated with modest reductions in kidney function, typically classified by the estimated glomerular filtration rate (eGFR). For example, Go et al2 showed adjusted relative hazards of 1.2, 1.8, and 3.2 for mortality and 1.4, 2.0, and 2.8 for cardiovascular events in persons with eGFR 45 to 59, 30 to 44, and 15 to 29 mL/min/1.73m² relative to people with normal or near normal kidney function (eGFR ≥60 mL/min/1.73m²). Most studies have highlighted the risks of ischemic heart disease, heart failure, stroke, and structural cardiac abnormalities, including left ventricular hypertrophy.2–6 Few have addressed the association between CKD and venous abnormalities.

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In this issue of Circulation, Mahmoodi et al7 examined the association between mild-to-moderate CKD and the incidence of venous thromboembolism (VTE). Motivated by relatively low event rates and conflicting data from individual cohort studies, possibly related to insufficient power, the authors pooled 5 community-based cohort studies—3 from Europe and 2 from the United States. The search selection criteria were reasonable, with the exception that all included studies were required to have data on both eGFR and urinary albumin excretion, which may have excluded large population studies in which urinary albumin was not measured or was determined semiquantitatively (eg, by dipstick only). Nevertheless, the authors should be congratulated for the impressive collaborative effort required to integrate patient level data from 5 established cohorts to explore a clinical issue that, owing to relatively low event rates, would obligate nearly 600 000 person-years of observation. The investigative team included members from multiple clinical and methodological disciplines, a poignant example of a team science approach.

The authors used conventional definitions of CKD, incorporating reduced eGFR or micro- or macroalbuminuria. The KD-EPI equation was used as the primary GFR-estimating equation. It is important to recognize the CKD definitions typically include—in addition to evidence of impaired kidney function or urinary albumin excretion—evidence of prolonged (≥3 months) duration; in the pooled analysis, only a single determination of CKD was required, likely resulting in an overestimation of CKD prevalence and misclassification above and beyond that expected as a result of the limitations of GFR estimating equations. Readers should interpret with caution any results referring to eGFR spline data above the range of 60 to 75 mL/min, where the accuracy and precision of GFR estimating equations are suspect.8 Venous thromboembolism was limited to events that were symptomatic, in contrast to some clinical trials in which routine screening for deep venous thrombosis or pulmonary embolism might have been performed. Limitations of the analysis not specifically addressed include relatively poor representation of racial and ethnic minorities and sparse inclusion of people with diabetes mellitus, one the most important causes of impaired kidney function and albuminuria in the adult population worldwide. The European cohorts were relatively young, which may partially explain the modest number of VTE events. As with all pooled analyses, selection or publication bias could also be operative.

Although the authors claim that their “comprehensive analysis” provided evidence for a “clear association of eGFR and albuminuria with risk of VTE,” the findings should not be considered definitive. The pooled hazard ratios were modest (≈1.5-fold, with lower limits of the 95% confidence interval barely above unity), and the dose–response relationship was not clear. Moreover, given the paucity of factors for which the authors were able to adjust, and the modest elevation in risk, the findings could be explained by chance or residual confounding. Nevertheless, the observation linking CKD with VTE is important and worthy of consideration and further study.

The authors propose several mechanisms that might be operative. They remind us that certain patients with nephrotic syndrome—particularly those afflicted with membranous nephropathy—experience a marked increase in the risk of VTE, presumably related to the urinary loss of anticoagulant proteins.9 However, the majority of VTE events occurred in patients with little to no albuminuria, and the urinary protein loss seen in patients with nephrotic syndrome and VTE are typically at least 3 orders of magnitude higher than what was observed in these cohorts. Although platelet abnormalities

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are well described among patients on dialysis, it is unclear whether platelet function per se is abnormal in patients with mild to moderate CKD. Rather, heightened states of oxidative stress and inflammation, associated with or directly caused by impaired kidney function and albuminuria, are a more likely mechanism explaining VTE.\textsuperscript{10,11}

The authors are correct that if the risk of VTE were truly increased in (and attributable to) CKD, CKD might be an important and as yet unrecognized risk factor for VTE in the adult population. Given this possibility, clinicians should be mindful of common behaviors (eg, sedentary lifestyle, long-distance travel) and therapeutics (eg, oral contraceptives) that may increase VTE risk. Obesity may be a particularly important confounding factor; even in the absence of diabetes mellitus, obesity is a well established clinical correlate of CKD\textsuperscript{12} and is strongly associated with CKD progression.\textsuperscript{13} Moreover, although the safety of erythropoiesis-stimulating agents in CKD was questioned after the results of the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) trial showed a 2-fold increase in the risk of stroke,\textsuperscript{14} which was widely publicized, the same placebo-controlled trial showed a near doubling of the risk of VTEs in patients treated with erythropoiesis-stimulating agents (2.0\% versus 1.1\%, \textit{P}=0.02), which failed to attract the same attention.

Although perhaps not definitive, the study by Mahmoodi et al raises the distinct notion that patients with CKD should be carefully evaluated not only for abnormalities related to hypertension, athero- and arteriosclerosis, left ventricular hypertrophy, and arrhythmia, but also for abnormalities on the venous side of the vasculature. This important contribution to the literature provides more reason for close cooperation among cardiologists and nephrologists and an extension of the long list of cardiorenal syndromes.

Disclosures
None.

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