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EDITORIAL

# Targeting Cardiovascular Disease in Patients with Chronic Kidney Disease: Is Primary Prevention with Aspirin Ready for Prime Time?

## Editorial to: "Aspirin for Primary Prevention of Cardiovascular Disease and Renal Disease Progression in Chronic Kidney Disease Patients: A Multicenter Randomized Clinical Trial (AASER Study)" by M. Goicoechea et al.

Roy O. Mathew[1] · Elvira O. Gosmanova[2] · Mandeep S. Sidhu[3]

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Kidney failure requiring renal replacement therapy is one of the most feared complications among patients with chronic kidney disease (CKD). However, it is often underappreciated that the risks of cardiovascular and all-cause mortality exceed many folds of the risk of end-stage kidney disease in these patients [1–3]. Over a decade ago, Go et al., in a study that evaluated close to a million patients, found an independent, graded, and inverse association between falling levels of renal function and all-cause and cardiovascular mortality [4]. Since that time, it has become well accepted that CKD is a state of heightened cardiovascular disease (CVD) risk which entails the increased risk of ischemic heart disease.

Two roadblocks stand in the way of adequately mitigating this risk of CVD in the CKD population. The first is the differential pathophysiology of ischemic heart disease in patients with CKD, as compared to the general population. In the latter group, unstable plaque rupture with subsequent thrombosis and thrombus propagation is central to the pathophysiology of acute coronary syndromes. In the former group, additional elements may play a greater role such as vascular calcification, altered vascular reactivity, coronary microvascular dysfunction, and myocardial hypertrophy [5]. Second is that, despite the heightened CVD risk in CKD, patients with CKD have been excluded or underrepresented in cardiovascular therapeutic trials. In this issue of *Cardiovascular Drugs and Therapy*, Goicoechea et al. [6] seek to rectify the absence of clinical trial data on pharmacologic interventions in this population by studying aspirin administration as a primary prevention tool against CVD in patients with stage 3 and 4 CKD.

In the general population, the United States Preventive Services Task Force recommends that persons aged 50–69 years of age with a > 10% lifetime risk of developing CVD, with a life expectancy of at least 10 years, and who are willing to take low-dose aspirin for at least 10 years should be offered low-dose aspirin therapy (100 mg or less) for the prevention of CVD and/or colorectal cancer [7]. In addition, the American Diabetes Association also advocates the use of low-dose aspirin for primary prevention in diabetic patients aged > 50 years with an additional CVD risk factor and low risk of bleeding complications [8]. Therefore, overall, primary prevention recommendations are currently limited to those who are at a high risk for CVD. Increased CVD risk in the CKD population makes a primary prevention study of aspirin therapy within this population appropriate and timely. On the other hand, prevalent CVD in CKD patients may pose a challenge for the patient recruitment for a trial assessing primary CVD prevention, as evident by the lack of prior randomized controlled trials in this population. The secondary analysis of the HOT trial [9] demonstrated favorable risk-to-benefit ratio of aspirin use in patients with CKD, and moreover, beneficial effects of aspirin in patients with estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m$^2$ were more pronounced, as compared with patients with preserved renal function. However, the analysis of aspirin effectiveness for primary versus secondary prevention was not performed. Impaired antiplatelet effects of aspirin in CKD patients have been reported [10] but might be explained by increased number of underlying comorbidities in patients with CKD rather than CKD itself

✉ Mandeep S. Sidhu
sidhum@amc.edu

[1] Department of Medicine, Division of Nephrology, William Jennings Bryan Dorn VAMC, Columbia, SC, USA

[2] Nephrology Section, Stratton VA Medical Center and Division of Nephrology, Department of Medicine, Albany Medical College, Albany, NY, USA

[3] Division of Cardiology, Albany Medical Center and Department of Medicine, Albany Medical College, 47 New Scotland Ave, Albany, NY 12208, USA

[11]. In addition to concerns about reduced antiplatelet effect of aspirin in CKD, its use can be associated with major and minor bleeding; although, the bleeding risk does not appear to differ in patients with and without CKD [9]. Lastly, a retrospective observation study from Korea involving 3768 patients with CKD and the average baseline eGFR 43.5 ml/min/1.73 $m^2$, patients on aspirin were propensity-score matched with aspirin non-users [12]. Not only did aspirin fail to prevent CVD events in CKD patients, the doubling of serum creatinine and renal death were significantly higher in aspirin users. Therefore, given the uncertainty of benefit and the possibility of harm, the current KDIGO guidelines recommend against using aspirin for primary CVD prevention in CKD patients [13].

Goicoechea et al. should be commended for attempting to address the knowledge gap in using aspirin for primary CVD prevention in CKD patients. The authors randomized 111 patients to either receive low-dose aspirin (100 mg daily) or to receive standard of care without aspirin. Fifty(50) patients were assigned to the active intervention arm with aspirin therapy and sixty one(61) to the standard treatment arm. After a mean of 64.8 months of follow-up, no significant difference was detected between the groups in the primary composite outcome of fatal or non-fatal CV events, consisting of congestive heart failure, acute coronary syndrome, peripheral vascular disease, or stroke: In the aspirin group, 10% (5/50) of patients had a primary event, and in the control group, 28% (17/61) of patients had a primary event (hazard ratio 0.396, 95% confidence interval 0.146–1.076, $p$ value = 0.069). Additionally, 13% (8/61) patients in the control group experienced fatal or non-fatal coronary event, as compared with no acute coronary syndrome events in the aspirin group. Although, aspirin appears to reduce coronary events, the results should be interpreted with caution given the study's small sample size and low rate of CVD events in the aspirin arm, which raises a concern for incomplete ascertainment of CVD events.

The other critically important finding of this study is a significant reduction in renal events in aspirin-treated patients. Among the 61 patients assigned to the standard therapy, nine required initiation of renal replacement therapy (RRT), and eight patients reached a doubling of serum creatinine; while among the 50 aspirin-treated patients, two patients started dialysis, and only one patient experienced a doubling in serum creatinine ($p$ = 0.016 for difference between groups). The high rate of RRT events as compared with doubling of serum creatinine is puzzling, and it questions whether patients experienced acute kidney injury requiring RRT rather than true CKD progression. The standard treatment group had non-significant but approximate 3 ml/min/1.73 $m^2$ lower eGFR than the aspirin-treated group, and the multivariate analysis demonstrated that there was an 8% lower risk of renal events per 1 ml/min/1.73 $m^2$ higher eGFR. In addition, albuminuria is a well-recognized and important risk factor for both cardiovascular and renal events in patients with CKD. The standard therapy arm had a higher proportion of patients with a higher degree of proteinuria (albumin-creatinine ratio > 300 mg/g); however, the authors did not include proteinuria in the adjustment for the analysis of renal events. It was encouraging, that in addition to reduced renal events, the rates of major and minor bleeding events were low and were not increased with aspirin therapy in this primary prevention cohort.

In conclusion, Goicoechea et al. found that primary prevention with aspirin therapy for 5 years in patients with CKD stages 3–4 was not associated with reduction in fatal and non-fatal CVD events; moreover, it was associated with a slower decline of renal function and was not associated with an increase in bleeding risk. In light of the relatively modest sample size in this study, a larger RCT should be conducted and to include stage 5 CKD as well, before aspirin can be uniformly recommended for patients with severe CKD. The exclusion of patients with low GFR now represents an anachronism of clinical trial conduct and should only be done for true cause—such as true harm due to medication pharmacokinetics. The expectation of a negative finding, challenges in event ascertainment, or difficulties in recruitment or retention are no longer valid arguments to exclude CKD patients. Goicoechea and colleagues have made an important first step in attempting to answer this important question for prevention in this high-risk population. Now, the medical community needs to take the baton and build upon this effort in seeking an evidence base to better inform patients and providers.

## Compliance with Ethical Standards

**Conflict of Interest** Drs. Mathew and Gosmanova are employees of the US Department of Veterans Affairs. Opinions expressed in this paper are those of the authors' and do not necessarily represent the opinion of the Department of Veterans Affairs. Dr. Sidhu declares no conflict of interest.

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