EDITORIAL COMMENT

Are Renin–Angiotensin–Aldosterone System Inhibitors Lifesaving in Chronic Kidney Disease?*

Kevin Damman, MD, PHD,†‡
Hiddo J. Lambers-Heerspink, PHARMd, PHD§
Glasgow, Scotland, United Kingdom; and Groningen, the Netherlands

Renin–angiotensin–aldosterone system (RAAS) inhibition has become the cornerstone of evidence-based therapies in cardiovascular disease, including patients with hypertension, high cardiovascular risk, left ventricular dysfunction after myocardial infarction, and heart failure with reduced ejection fraction (1–3). Both angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) have been shown to improve morbidity and mortality in these populations, although evidence is more consistent with ACEI and single RAAS inhibition. However, for patients with chronic kidney disease (CKD), scarce data are available on the clinical outcome benefit with these therapies, especially in patients without diabetes. As such, a recent Cochrane review deemed the current evidence uncertain for the effectiveness of ACEIs or ARBs in patients with stage 1 to 3 CKD without diabetes (4).

The data presented by Molnar et al. (5) in this issue of the Journal are therefore of timely fashion. In this manuscript, the authors have retrospectively investigated the effect of de novo prescription of ACEI or ARB therapy in patients with nondialysis CKD on mortality in a large population.

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Data on no less than 659,546 patients with CKD were available at the start, with the primary analysis being carried out on 141,413 patients, in whom ACEI or ARB therapy was started in 18% within 1 year. Of note, this was not a randomized controlled trial, and the authors therefore had to use rigorous and elaborate statistical analysis to account for the inherent reasons that patients would be prescribed the treatment of interest. Propensity scoring, marginal structural modeling, and inverse probability of treatment and censoring weights were used. All of these statistical techniques were required to balance the treatment groups, which were clearly different at baseline. As expected, patients who were administered RAAS inhibitors were those who were supposed to be prescribed these therapies as indicated in guidelines: more frequent diabetes, higher blood pressure and hypertension, cardiovascular disease, and heart failure. When accounting for all these possible confounders, de novo ACEI/ARB treatment was associated with a significant reduction in death rates in both intention-to-treat analysis (hazard ratio: 0.81; 95% confidence interval: 0.78 to 0.84) and as-treated analysis (odds ratio: 0.37; 95% confidence interval: 0.34 to 0.41). This effect was consistent among subgroups, although nondiabetic persons tended to show less benefit. One could argue that the observed effect is even an underestimation of the true effect because the treated population clearly had a higher prevalence of cardiovascular disease, which in general should be associated with increased mortality. On the other hand, these patients may have been monitored more closely, with more intensive treatment other than RAAS inhibition, and therefore may have received better or at least more thorough medical attention, which could in part explain the results. Furthermore, there are some other important limitations to the analysis. First, although rigorous statistical methods are used, this can never totally exclude the existence of residual confounding. Second, the authors needed to exclude a large number of patients who had been exposed to RAAS inhibitors before and more than 50,000 patients who had no information on ACEI/ARB treatment, the latter comprising more than twice the number of patients who began therapy in the first year. The effects of these selection processes on the eventual outcome are unclear. Finally, the authors make no distinction between ACEI and ARB treatment, whereas mortality benefit in other populations is greater or similar for ACEI versus ARB therapy (3,6).

The recently updated Kidney Disease Improving Global Outcomes clinical practice guideline on CKD and blood pressure recommends treatment with ACEI and ARB as first-line therapy in patients with concomitant hypertension and microalbuminuria or macroalbuminuria to slow the progression of CKD (7). Because most (if not all) patients with CKD have hypertension (or blood pressures greater than the target range of 130/80 mm Hg), these therapies are indicated in the majority of patients. The guidelines make no distinction between diabetic and nondiabetic CKD. Evidence that supports the data in nondiabetic

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From the †British Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom; ‡University of Groningen, Department of Cardiology, University Medical Center Groningen, Groningen, the Netherlands; and the University of Groningen, Department of Clinical Pharmacology, University Medical Center Groningen, Groningen, the Netherlands. Dr. Damman is supported by the Netherlands Heart Institute. Dr. Lambers-Heerspink is supported by a VENI grant from the Dutch Scientific Research Organisation. Dr. Damman has reported that he has no relationships relevant to the contents of this paper to disclose. Dr. Lambers-Heerspink has consultancy agreements with the following companies: AbbVie, Astellas, Johnson & Johnson, Reata, and Vitae; all honoraria are paid to his employer/institution University of Groningen.
patients comes from the REIN (Ramipril Efficacy In Nephropathy) trials (8). In diabetic patients, the IDNT (Irbesartan Diabetic Nephropathy Trial) and RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) trials demonstrated that irbesartan and losartan slowed the progression of CKD (9,10). However, in both RENAAL and IDNT, there was no reduction in all-cause mortality, although neither was powered to answer this specific question. The current manuscript therefore differs significantly from these two randomized trials in that the observed treatment benefit was most pronounced in patients with diabetes. Of course, the power of the current study was significantly greater compared with IDNT and RENAAL together, but the latter were randomized controlled trials, and given the discrepancy between the findings, caution should be taken in the interpretation of the current data.

It is important to highlight again that the patients actually treated with ACEI/ARB were those who had comitant cardiovascular disease, and should therefore have been considered for treatment with RAAS inhibitors on the basis of that specific condition as well. Because CKD is often prevalent in diseases such as coronary artery disease, hypertension, and heart failure, and RAAS inhibitor therapy has been associated with improved cardiovascular outcomes in these populations, it is also less surprising that mortality benefit particularly was observed in these subgroups.

Last, it can be questioned whether mortality alone is the best outcome measure in patients with CKD. Although it is the most definite and therefore least-biased endpoint, other important outcomes, such as time spent off dialysis, incidence of heart failure, and quality of life, also should be considered. Approximately 2 of 3 patients with CKD actually die before they reach dialysis. A therapy that prolongs life will thus have a major impact in this population (11,12). However, any therapy in CKD that prolongs survival potentially increases the likelihood of dialysis because patients live longer and thus have a higher chance to progress to end-stage renal disease, which obviously affects quality of life. Thus, studies that evaluate the effect of interventions in CKD should analyze death (or more specifically, cardiovascular death) and end-stage renal disease together as competing events.

Overall, there is a need for more convincing mortality and outcome data in patients with CKD, not only in those with primary renal disease but also in those with conditions for which CKD is prevalent, such as hypertension, heart failure, and post-myocardial infarction. Although the present study does not give definite answers and the study design has inherent limitations, it may give a glimpse into the possible mortality benefit of ACEI/ARBs in CKD. The obvious (and right) question now is whether to conduct a properly powered phase 3 mortality trial. The most likely (and wrong) answer is that the costs, time, and generic nature of the drugs will prohibit this. It is up to the cardiovascular and nephrology research community to defy these odds.

Reprint requests and correspondence: Dr. Kevin Damman, Department of Cardiology, University Medical Center Groningen, Hanzeplein 1, 9700RB, Groningen, the Netherlands. E-mail: k.damman@umcg.nl.

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