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Lowering Blood Pressure to Lower the Risk of Cardiovascular Events in CKD

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Blood pressure control is one of the most important aspects of cardiovascular disease management because numerous studies have demonstrated the benefits of lowering blood pressure to prevent stroke, heart failure, and other cardiovascular events.¹ Persons with chronic kidney disease (CKD) frequently have hypertension,² and recent guidelines from KDIGO (Kidney Disease: Improving Global Outcomes) and the Eighth Joint National Committee (JNC 8) address the issues of antihypertensive agents and blood pressure targets.^{1,3,4} JNC 8 recommends a blood pressure goal, 140/90 mm Hg for patients with CKD, whereas KDIGO recommends a target blood pressure, 130/80 mm Hg for patients with CKD with proteinuria.³ JNC 8 guidelines recommend renin-angiotensin system antagonists as the preferred agents in all patients with CKD,¹ whereas KDIGO recommends them as preferred agents only in patients with proteinuria.^{3,4} Recommendations for different blood pressure targets and agents in patients with CKD are based largely on evidence from trials demonstrating their efficacy in slowing kidney disease progression, rather than reducing the risk of cardiovascular events.^{5–7} Some experts have expressed concern about the lower targets given higher risks of adverse drug-related events in individuals with CKD. Moreover, questions also remain regarding the comparative efficacy of different classes of antihypertensive medications.

WHAT DOES THIS IMPORTANT STUDY SHOW?

A recent meta-analysis conducted by the Blood Pressure Lowering Treatment Trialists' Collaboration⁸ helps inform some heretofore unanswered questions. In this analysis, investigators searched for randomized clinical trials completed between 1995 and 2012 that compared 2 or more active blood pressure–lowering medications, active medications with placebo, or different targets for blood pressure lowering. The investigators were able to obtain patient-level data from 25 studies of 152,290 individuals, of whom 20% (N 5 30,295) had an estimated glomerular filtration rate (eGFR; calculated using the MDRD [Modification of Diet in Renal Disease] Study equation), 60 mL/min/1.73 m². Of these more than 30,000 individuals, only 439 (0.3% of total cohort) had eGFRs, 30 mL/min/1.73 m² at baseline. As such, results should be considered generalizable to only patients with CKD stage 3, rather than to all patients with CKD irrespective of stage.

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The primary outcome of the meta-analysis was major cardiovascular events, defined as the first episode of stroke, coronary heart disease, heart failure, and cardiovascular death. Active treatment with an angiotensin-converting enzyme (ACE) inhibitor compared with placebo resulted in a 19% (95% confidence interval [CI], 10%–27%) lower risk of the primary outcome, whereas calcium channel antagonists compared with placebo (3 studies; N 5 6,107) led to a 28% (95% CI, 11%–42%) lower risk. After accounting for the larger reduction in blood pressure in trials that used calcium channel antagonists, the relative risk reduction for ACE inhibitors versus placebo (hazard ratio [HR], 0.83; 95% CI, 0.79–0.87) was nearly identical to the relative risk reduction for calcium channel antagonists versus placebo (HR, 0.84; 95% CI, 0.75–0.94). When the efficacy of different medication classes was compared head to head, no significant differences were observed for ACE inhibitors versus calcium channel antagonists or for comparisons of either of these 2 medication classes versus diuretic- or b-blocker-based regimens. Taken together, these results suggest that among the classes of medications included in this meta-analysis, no one class of antihypertensive agent is superior to any other for preventing cardiovascular events.

The investigators further examined whether baseline kidney function modified the relative efficacy of different antihypertensive medication classes by conducting analyses after stratifying the cohort by baseline eGFR (< 60 vs. ≥ 60 mL/min/1.73 m²) or treating eGFR as a continuous outcome. No evidence of effect modification by baseline eGFR was seen. Importantly, because patients with lower eGFRs have higher event rates, the absolute benefit of active treatment was larger in patients with lower eGFRs, with 28 major cardiovascular events prevented per 1,000 patients treated with an ACE inhibitor or calcium channel antagonist versus placebo when eGFR was < 60 mL/min/1.73 m², compared with 19 cardiovascular events prevented in patients with eGFR ≥ 60 mL/min/1.73 m². In the 17,635 patients with information for proteinuria (of whom 1,730 had proteinuria), the presence or absence of proteinuria did not modify the benefit of treatment with an ACE inhibitor or calcium channel antagonist versus placebo on cardiovascular events.

Only 5 studies in 19,546 participants compared higher or lower blood pressure targets. No statistically significant benefit was seen with a lower blood pressure target (HR, 0.93; 95% CI, 0.80–1.07) and no significant effect modification by baseline eGFR was observed.

This meta-analysis has important strengths. The large number of trials and patients included in the analysis provides substantial power to assess whether treatment outcomes differ by eGFR. In addition, the investigators had individual patient data from most trials, which enabled them to assess treatment outcomes stratified by eGFR consistently across trials. The analysis also has some limitations, most of which were acknowledged by the authors. First, the majority of patients with CKD had eGFRs of 45–60 mL/min/1.73 m²; thus, the findings may not apply to patients who have more advanced CKD, even those with CKD stage 3b (30–44 mL/min/1.73 m²). Moreover, very few of the trials included in the meta-analysis had information for proteinuria, which also might modify the effect of alternative antihypertensive agents or alternative blood pressure targets. In addition, the meta-analysis did not evaluate treatment with angiotensin receptor blockers (ARBs) or regimens based on b-blockers or diuretics alone. Some important trials, such as ACCOMPLISH (Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic

Hypertension) and ACCORD-BP (Action to Control Cardiovascular Risk in Diabetes—Blood-Pressure-lowering arm), were not included for unspecified reasons (and are discussed in greater detail next). Finally, although the meta-analysis evaluated the effects of alternative treatment strategies on cardiovascular outcomes, these results do not advance our knowledge about the effects of alternative antihypertensive treatment strategies on noncardiovascular outcomes, including kidney function, cognition, frailty, and health-related quality of life.

HOW DOES THIS STUDY COMPARE WITH PRIOR STUDIES?

There are no randomized trials comparing different classes of antihypertensive agents conducted exclusively in patients with CKD that were powered to examine cardiovascular events as the primary outcome. As such, this meta-analysis provides important evidence to support the safety and efficacy of treating hypertension in patients with stage 3 CKD to prevent subsequent cardiovascular events with any of the following classes of antihypertensive medications: ACE inhibitors, calcium channel antagonists, b-blockers, or diuretics. However, the ACCOMPLISH trial, which was not included in the meta-analysis, showed that treatment with benazepril plus amlodipine was superior to benazepril plus hydrochlorothiazide.⁹ In that study of 11,506 high-risk hypertensive participants, despite, 1 mm Hg difference in achieved systolic blood pressure between the 2 groups, patients randomly assigned to receive benazepril plus amlodipine experienced a 20% (95% CI, 10%–28%) lower risk of cardiovascular morbidity or mortality than patients randomly assigned to benazepril plus hydrochlorothiazide. Approximately 18% of the ACCOMPLISH cohort had eGFRs, 60 mL/min/1.73 m², but an analysis stratified by eGFR was not reported.

The meta-analysis did not show a benefit of lower blood pressure targets. This finding is consistent with the ACCORD-BP trial,¹⁰ which randomly assigned 4,733 patients with type 2 diabetes mellitus to a target systolic blood pressure target, 120 versus, 140 mm Hg (ACCORD-BP was not included in the meta-analysis). ACCORD-BP did not find a significant benefit of the lower blood pressure target on the composite end point of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death (HR, 0.88; 95% CI, 0.73–1.06), although the effect on stroke was nominally significant (HR, 0.59; 95% CI, 0.39–0.89). Patients with serum creatinine concentrations. 1.5 mg/dL or protein excretion. 1 g/24 h were excluded. A recent systematic review found in patients with CKD that targeting blood pressure to, 130/80 mm Hg also did not slow CKD progression more than targeting blood pressure to, 140/90 mm Hg, although there may have been some benefit associated with targeting lower blood pressure in patients with heavy proteinuria.¹¹ Given the low event rates, effects on cardiovascular events were inconclusive in that review.

WHAT SHOULD CLINICIANS AND RESEARCHERS DO?

This meta-analysis provides evidence of a clear benefit of treating hypertension to reduce the risk of cardiovascular events in patients with mild to moderate CKD, but does not support the use of one particular class of medication over another for the goal of reducing cardiovascular events. As mentioned, it is noteworthy that trials designed to evaluate the effects of antihypertensive agents on progression of CKD (ie, dialysis or doubling of serum creatinine level) were not included in the meta-analysis. For example, IDNT (Irbesartan

Diabetic Nephropathy Trial)⁶ and the RENAAL (Reduction of Endpoints in NIDDM With the Angiotensin II Antagonist Losartan) Study⁵ both showed ARBs to have benefit in slowing CKD progression. Thus, although the recent guidelines for treating hypertension in CKD advocate including an ACE inhibitor or ARB in the antihypertensive regimen to slow CKD progression,^{1,3} this meta-analysis provides convincing data that for the goal of reducing the risk of cardiovascular event, agents other than ACE inhibitors and ARBs can be used successfully in patients with CKD.

This meta-analysis does not provide additional clarity on optimal blood pressure targets in patients with or without CKD. Results from SPRINT (Systolic Blood Pressure Intervention Trial; NCT01206062), which enrolled nondiabetic patients with hypertension and a large proportion with CKD (eGFR, 20–60 mL/min/1.73 m²), should provide more definitive guidance on blood pressure targets in CKD upon its completion in 2018. In the meantime, clinicians should continue treating hypertensive patients to achieve blood pressures, 140/90 mm Hg with a variety of lifestyle interventions (exercise, weight loss, and dietary modification) or antihypertensive medications.

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