Initial Choice of Antihypertensive on Long-Term Cardiovascular Outcomes in CKD

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Hypertension contributes substantially to the risk for long-term cardiovascular disease (CVD) outcomes such as stroke, ischemic heart disease, and heart failure, especially in persons with CKD (1). In this regard, BP reduction is an important CVD risk reduction strategy, especially in persons with CKD. Our understanding of targets for BP reduction and choice of agents has evolved in the last few years, given the results of the Action to Control Cardiovascular Risk in Diabetes Trial and the African American Study of Kidney Disease and Hypertension (AASK), which called into question the conventional systolic targets of 130 mmHg and choice of antihypertensive for those with diabetes and CKD (2,3). However, as we wait for the much anticipated eighth report of the Joint National Committee (JNC) recommendations, we continue to be guided by recommendations of the JNC-7 (4). Much of the primary pharmacologic treatment recommendations for the general population from JNC-7 was driven by findings from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Findings from the ALLHAT indicated that lisinopril and amloidipine were not superior to chlorthalidone in reducing heart disease in those high-risk participants with hypertension, in the context of achieving comparable reductions in BP between treatment groups. Since completion, the collaborative group has explored the cohort post hoc for various outcomes and has reported kidney and CVD outcomes at 5 (5) and 6 years (6). In this issue of Cjasn, Rahman et al. (7) report data on ~9 years of follow-up from the original cohort.

The authors collected passive post-trial morbidity and mortality data derived by cross-referencing participants from 2002 to 2006 to national databases after the end of the trial. Barring exclusion of the veteran population and non-Medicare recipients, because morbidity data were not available after the trial, the authors included the majority of the original cohort (31,350 of 33,357) using a designated a priori outcome of composite cardiovascular mortality. The authors stratified the population by baseline estimated GFR (eGFR) using both the Modification of Diet in Renal Disease (MDRD) and the CKD Epidemiology Collaboration formula (CKD-EPI) equations because the majority of participants had normal eGFR (≥90 ml/min per 1.73 m²) or a mild (60–89 ml/min per 1.73 m²) reduction in eGFR. These investigators further stratified the participants by the presence or absence of diabetes, in an attempt to capture a population with, or at risk for, proteinuria; the original cohort did not include measures of proteinuria. Following all modeling and clinical adjustments, the authors main observation is that participants with more advanced kidney disease, or lower eGFR, have a proportionally higher risk for cardiovascular mortality. This is not entirely novel, as numerous population-based cohorts have previously reported this; however, there are multiple nuances when considering the data in aggregate that have significant clinical meaning.

Considering the authors’ designation of cardiovascular mortality stratified by baseline eGFR as the outcome of interest, there have been few large clinical studies to date that address CVD mortality in those with established kidney disease. Most of our current working knowledge of reducing the burden of CVD in those with CKD has been extrapolated from population-based studies that only support the graded relationship between advancing kidney disease and increased incident CVD. The discussion on actual risk reduction began with the UK Prospective Diabetes Study Group (UKPDS) (8) and other investigative groups that support BP reduction as the predominant strategy to prevent kidney disease and CVD outcomes in those with diabetes. However, the UKPDS did not provide insight into risk reduction in those with established CKD or whether the choice of antihypertensive strategy mattered. In subsequent years, numerous trials such as the Heart Outcomes Prevention Evaluation, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan, and Irbesartan Diabetic Nephropathy Trial have explored whether choice of antihypertensive mattered in cardiovascular risk reduction in those with CKD (9–11). Data from these trials have fueled a healthy discussion on choice of antihypertensive and appropriate targets for BP reduction. However, data from these studies have yielded conflicting results. Despite these data, conventional wisdom has been that inhibitors of the renin-angiotensin system (RAS) should take priority as a CVD risk reduction strategy in those with CKD, largely because of their extended benefit on CKD progression.

It should be noted the inconsistency among the trials is derived from differences in primary outcome
and target BP. The primary outcomes have ranged from CVD to CKD progression to primary prevention studies using incident proteinuria and BP with systolic targets ranging from the low to mid-130s to 140s (mmHg). The variation between trials has driven discussion on whether the observed risk reduction was BP independent and caused by the choice of antihypertensive (class) or whether the findings were purely because of differential BP reductions. The variable targets have also led to speculation on what level of control is appropriate for optimal CVD risk reduction in those with CKD. The current data from the ALLHAT collaborative group continues to be critical information in the discussion on reducing the burden of CVD in those with CKD.

The ALLHAT collaborative group has previously reported on 6-year outcomes (6) suggesting that initial antihypertensive choice did not convey additional CVD benefit at any level of GFR with similar BP control. In the current analysis, Rahman et al. again report at roughly 9 years of follow-up that initial choice may not provide additional CVD benefit with similar level of BP control at trial cessation (e.g., systolic BP = 134–136 mmHg between groups), irrespective of level of kidney function. The data in aggregate from this follow-up again suggest initial antihypertensive choice may not be as important in those with mild or moderate reductions in eGFR in primary prevention of CVD mortality. These findings are important to the current discussion on cardiovascular risk reduction in those with CKD; however, this should not be confused as representative of an established CKD cohort.

It should be noted that the primary design of ALLHAT did not include measures of proteinuria and excluded individuals with more advanced kidney disease (serum creatinine >2 mg/dl). Considering that a minority of individuals with diabetes and an eGFR ≥60 ml/min per 1.73 m² will have overt proteinuria (12), the observation that the vast majority of participants (~82%) had normal to mild reductions in eGFR ≥60 ml/min per 1.73 m² limits extrapolation of conclusions to established CKD cohort. The authors control for this by stratifying the cohort based on the presence or absence of diabetes to capture a population either with, or at risk for, proteinuria. Furthermore, the authors use the CKD-EPI as a comparator to the MDRD equation in estimating GFR to minimize misclassification at this level of kidney function. In recent years, the CKD-EPI equation has been shown to be better for estimating measured GFR, for detecting CKD, and for assessing risk than the MDRD study equation, particularly at higher levels of GFR (13,14). Incorporation of the diabetic population and the utilization of the CKD-EPI in this population enhance capture of the CKD population within the ALLHAT. The authors’ observation that there were no differences between the diabetic and nondiabetic population and there was no misclassification between the CKD-EPI equations represents optimal conditions given the limitations of the design.

The authors then contrast their findings to those of the MDRD and AASK cohorts as relative comparator CKD cohorts. It should be noted for discussion that the study populations were vastly different, wherein investigators from AASK/MDRD included established CKD (e.g., GFR <60 ml/min per 1.73 m²) and targeted a systolic BP goal of <130 mmHg. Although the premise behind ALLHAT focused on initial choice in the general population with hypertension at high risk for heart disease, the differences in design are compelling and should be noted when weighing the data. The true value of the current report is in the comparison with AASK on long-term outcomes.

The AASK collaborative group included a post-trial cohort phase with active observation and management relative to the current ALLHAT passive approach by cross-reference to national databases such as the National Death Index, Center for Medicare and Medicaid Services, and the US Renal Data System. Investigators attempted to control for the passive approach with time-dependent regression models and report no differences between in-trial and post-trial periods. Of significant interest, the authors report on cumulative survival analysis at 10 years, extending their previous report that neither lisinopril nor amlodipine was superior to chlorthalidone; however, the authors were unable to incorporate proteinuria in this approach. In this context, findings from AASK suggest proteinuria is a potential effect modifier (3,15), supporting the notion that those with proteinuria may derive improvements in kidney disease progression or even CVD outcomes by targeting a systolic BP <130 mmHg. Interestingly, data from a recent report from AASK attempted to answer the question of choice of antihypertensive (15) on CVD outcomes and, similar to the current report from ALLHAT, found no evidence that choice of class had an effect.

In summary, the current report from ALLHAT represents a significant piece of contemporary information on optimal antihypertensive treatment for CVD outcomes in those with CKD. The main finding from the current report of the ALLHAT continues to support that reductions in eGFR are associated with a significant burden of CVD and initial choice of antihypertensive may not impact CVD mortality in earlier stages of CKD. However, findings from the current report should be examined in the context of other CKD cohorts and weighed in the context of the primary study design, lack of proteinuria measures, and passive post-trial follow-up.

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References
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