Clinical Trials

Limitations of Analyses Based on Achieved Blood Pressure
Lessons From the African American Study of Kidney Disease and Hypertension Trial

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See Editorial Commentary, pp 1039–1040

Abstract—Blood pressure (BP) guidelines that set target BP levels often rely on analyses of achieved BP from hypertension treatment trials. The objective of this article was to compare the results of analyses of achieved BP to intention-to-treat analyses on renal disease progression. Participants (n = 1094) in the African-American Study of Kidney Disease and Hypertension Trial were randomly assigned to either usual BP goal defined by a mean arterial pressure goal of 102 to 107 mm Hg or lower BP goal defined by a mean arterial pressure goal of ≤92 mm Hg. Median follow-up was 3.7 years. Primary outcomes were rate of decline in measured glomerular filtration rate and a composite of a decrease in glomerular filtration rate by >50% or >25 mL/min per 1.73 m², requirement for dialysis, transplantation, or death. Intention-to-treat analyses showed no evidence of a BP effect on either the rate of decline in glomerular filtration rate or the clinical composite outcome. In contrast, the achieved BP analyses showed that each 10-mm Hg increment in mean follow-up achieved mean arterial pressure was associated with a 0.35 mL/min per 1.73 m² (95% CI: 0.08 to 0.62 mL/min per 1.73 m²; P = 0.01) faster mean glomerular filtration rate decline and a 17% (95% CI: 5% to 32%; P = 0.006) increased risk of the clinical composite outcome. Analyses based on achieved BP lead to markedly different inferences than traditional intention-to-treat analyses, attributed in part to confounding of achieved BP with comorbidities, disease severity, and adherence. Clinicians and policy makers should exercise caution when making treatment recommendations based on analyses relating outcomes to achieved BP. (Hypertension. 2011;57:1061-1068.) ● Online Data Supplement

Key Words: blood pressure control ■ blacks ■ hypertension treatment ■ renal disease

A direct relationship between blood pressure (BP) and cardiovascular/renal outcomes is often shown in analyses of achieved BP in clinical trials, as well as in observational studies. Such analyses commonly document a direct, progressive relationship of BP levels with adverse outcomes at BP levels that are well below the conventional BP goal of 140/90 mm Hg BP, a level demonstrated to be beneficial in randomized trials that directly compared BP targets.1–6 Analyses of achieved BP have commonly been used to set BP treatment targets (please see Table S1 in the online Data Supplement at http://hyper.ahajournal.org). The BP guideline 130/80 mm Hg recommended for chronic kidney disease by the American Diabetes Association,7 the Joint National Committee on the Prevention, Detection, Evaluation and Treatment of High Blood Pressure,8 and the Kidney Disease Outcomes Quality Initiative9 is based on achieved BP, not...
randomized, controlled trial evidence. For example, much of the evidence for the lower systolic BP goal (<130 mm Hg) recommended for patients with diabetes mellitus, high-risk coronary heart disease, and chronic kidney disease is based on analyses of achieved BP.10–19 Interestingly, several of these trials (eg, Modification of Diet in Renal Disease and Hypertension Optimal Treatment Trial) explicitly tested the effects of 2 different BP goals, and the primary results of these trials (eg, Modification of Diet in Renal Disease and Hypertension Optimal Treatment Trial) explicitly tested the effects of 2 different BP goals, and the primary results of the intention-to-treat (ITT) analyses were null.18,20,21 Yet, the results from analyses of achieved BP were still used to guide policy despite the inconsistency with the primary ITT analyses of these trials.

The credibility of treatment recommendations based on achieved BP is a matter of continuing controversy, particularly when they conflict with ITT results from randomized, controlled trials or when such trial data are unavailable. On the surface, it may appear that analyses relating outcome to achieved BP would be more informative than ITT analyses of randomized comparisons regarding the biological effect of BP because the former, but not the latter, takes into account the patients’ actual BP levels. However, variables associated with lower levels of achieved BP may include favorable health characteristics at baseline and markers of improved prognosis during follow-up, including adherence. Hence, the apparent benefit of a lower level of achieved BP may result, in whole or in part, from confounding.

Until recently, few randomized trials specifically compared BP targets. As more randomized clinical trials comparing BP targets are becoming available, BP treatment recommendations can be based on the ITT comparisons of randomized groups rather than analyses of achieved BP. The African American Study of Kidney Disease and Hypertension (AASK) Trial provides a unique opportunity to document differences in results by randomized group versus achieved BP on renal outcomes and to explore potential reasons.

AASK is a completed trial that randomized blacks with hypertensive kidney disease to 2 different BP goals. As reported previously, the ITT analyses documented that there was no significant difference in renal outcomes between the randomized BP goals during the trial.22 In this report, we compare analyses based on achieved levels of BP to the original ITT analyses and consider whether differences in the results of these 2 types of analysis can be explained by the relationship of achieved BP with baseline and follow-up variables.

**Methods**

The AASK Trial design and procedures have been described previously.22,23 The institutional review board at each study site approved the study protocol. Written informed consent was obtained from each participant. Trial participants were blacks, aged 18 to 70 years, with hypertensive chronic kidney disease, as defined by a diastolic BP >95 mm Hg and a glomerular filtration rate (GFR) between 20 and 65 mL/min per 1.73 m² measured by 125I-iothalamate clearance. Individuals were randomly assigned in a 2×3 factorial design to 1 of 2 BP goals, usual BP goal with a mean arterial BP (MAP) goal of 102 to 107 mm Hg or lower BP goal with MAP goal of <92 mm Hg. In addition, they were randomly assigned to an initial drug therapy with the angiotensin-converting enzyme inhibitor, ramipril; the calcium channel blocker, amlodipine; or the β-blocker, metoprolol.22 Figure 1 displays the allocation of participants to the 2 randomized BP goals, as well as an overview of analyses.

**BP and Renal Function Outcomes**

Three consecutive seated BPs were measured at each study visit with a Hawksley random 0 sphygmonanometer after 5 minutes of rest.23,24 The means of the last 2 BP readings were recorded. GFR
was measured by the renal clearance of $^{125}I$-iothalamate twice at baseline then at months 3, 6, and every 6 months thereafter. Mean follow-up BP levels were computed as the mean of all of the study BP measurements (except for BP measured at GFR visits) starting in month 4 of follow-up through each participant’s final BP measurement. Because the study protocol required titration of BP based on MAP, we regard the mean follow-up MAP as the primary measure of achieved BP.

This report focuses on 2 main renal outcomes, the chronic GFR slope and a clinical composite defined by a confirmed decline in GFR by $>$50% or $>$25 mL/min per 1.73 m$^2$ from the baseline GFR, end stage renal disease (ESRD; dialysis or transplantation), or death. The chronic GFR slope is defined by the rate of change in GFR beginning at 3 months after randomization, when the maximal hemodynamic effect on GFR resulting from antihypertensive treatment is achieved. The chronic slope corresponds with the long-term rate of progression of renal disease.

**Statistical Analyses**

Participant characteristics were summarized by randomized BP group and by level of mean follow-up BP using means and SDs for continuous variables and by frequencies and percentages for categorical variables. ANOVA or $\chi^2$ tests were used as appropriate to compare patient characteristics between the BP subgroups. Kernel density curves were used to compare the distributions of mean follow-up MAP between the randomized BP groups.

We applied 2 approaches for analyses relating achieved BP to renal outcomes. In the first approach, we applied an as-treated strategy to relate renal outcomes to each participant’s level of achieved BP, irrespective of the participant’s randomized BP assignment. In the as-treated approach, which mimics analyses of achieved BP in observational studies and previous randomized trials, the total variation in achieved BP between participants reflects a combination of the separation between the 2 BP intervention groups and differences among participants achieved BP levels within each BP group. The phrase “as-treated” indicates that the analysis relates outcomes to the treatment (BP) actually received (achieved), in contrast to ITT analyses, which compare outcomes according to randomized assignment.

In the second approach, we compared outcomes between participants who achieved the same BP level in spite of being randomized to different BP interventions. Here we took advantage of the fact that some participants randomized to the lower BP goal had achieved MAP levels at or near the target range of the usual BP goal (see Figure 2). By comparing renal outcomes for participants with the same achieved MAP that was out of range for low-goal participants but in range for the usual BP goal participants, we could examine whether failure to attain a given BP target might itself be associated with poor renal outcome, independent of biological effects of BP.

To investigate possible sources of differences in renal outcomes between participants achieving the same MAP in the 2 BP groups, we used $t$ tests or $\chi^2$ tests as appropriate to compare baseline characteristics between usual BP goal and lower BP goal participants whose mean follow-up MAP was between 100 and 107 mm Hg. Here we broadened the MAP range to 100 to 107 mm Hg from the usual BP goal target of 102 to 107 mm Hg to increase the sample size.

To investigate the sensitivity of the results to the selection of the outcome variable and to the statistical model, we considered the following: (1) analyses of an exclusively renal composite including only GFR events and ESRD, while censoring deaths; (2) multivariable models not including baseline MAP as a covariate; (3) extended models including adjustment for additional baseline covariates; and (4) “step-function” models (rather than splines) with follow-up MAP subdivided by MAP $<$92 mm Hg, 92 to 102 mm Hg, 102 to 107 mm Hg, and $>$107 mm Hg.

**Figure 2.** Mean follow-up achieved blood pressure (BP) was defined as an average of achieved BP throughout follow-up from visit 4. Data restricted to 1065 participants with non-missing follow-up achieved mean arterial pressure (MAP). In the low BP goal, 45% with mean follow-up MAP $<$92 mm Hg, 6% with mean follow-up MAP 102 to 107 mm Hg. In usual BP goal, 6% with mean follow-up MAP $\leq$92 mm Hg, 51% with mean follow-up MAP 102 to 107 mm Hg.
lower prevalence of left ventricular hypertrophy than those who were above their BP goal. Participants in the lower BP group, who achieved goal BP, were also more adherent (92.6 ± 7.66% versus 83.0 ± 14.7%; P<0.001) to antihypertensive medications and required fewer antihypertensive medications than those who failed to achieve their goal. Similarly, in the usual BP group those participants whose achieved BPs were at or below their MAP goal also had fewer comorbidities and antihypertensive medications, lower mean baseline BPs, lower prevalence of left ventricular hypertrophy, and greater adherence to antihypertensive medications than those who failed to achieve their goal. 

As-Treated Analyses (Based on Achieved BP)

Figure 3 compares the results of ITT and achieved BP analyses of GFR slope and clinical outcomes. The ITT analyses showed no evidence of a BP effect on either the chronic GFR slope (Figure 3A) or the clinical composite outcomes. The achieved BP analyses, however, showed a significant difference in the chronic GFR slope between participants whose achieved BPs were at or below their MAP goal and those whose achieved BPs were above their MAP goal (P<0.001). Similarly, the achieved BP analyses showed a significant difference in the composite clinical outcomes between participants whose achieved BPs were at or below their MAP goal and those whose achieved BPs were above their MAP goal (P<0.001).

Results

Participant Characteristics

Figure 2 displays the distribution of mean follow-up achieved MAP by randomized BP group. Although the distribution is bimodal, there was substantial overlap in achieved MAP between the randomized groups. The baseline characteristics of the participants stratified by randomized BP group assignment and whether the mean achieved BP was at goal is shown in Table 1. As reported previously, there were no significant differences in the baseline characteristics between the 2 randomized groups.22

In contrast, when we compared participants within each randomized group for which achieved BPs were at goal versus out of goal, there were significant differences in several important baseline demographic and clinical characteristics. Participants in the lower BP group who achieved the BP goal (in goal) had fewer comorbidities, lower baseline mean systolic and diastolic BPs, and lower prevalence of left ventricular hypertrophy than those who were above their BP goal. Participants in the lower BP group, who achieved goal BP, were also more adherent (92.6 ± 7.66% versus 83.0 ± 14.7%; P<0.001) to antihypertensive medications and required fewer antihypertensive medications than those who failed to achieve their goal. Similarly, in the usual BP group those participants whose achieved BPs were at or below their MAP goal also had fewer comorbidities and antihypertensive medications, lower mean baseline BPs, lower prevalence of left ventricular hypertrophy, and greater adherence to antihypertensive medications than those who failed to achieve their goal. 

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outcome (Figure 3B). In contrast, the results of the achieved BP analyses show that, at progressively higher levels of achieved BP, mean GFR decline steepened (Figure 3C), and the rate of the clinical composite outcome increased (Figure 3D). In the achieved BP analyses, each 10-mm Hg increment in follow-up MAP was associated with a 0.35 mL/min per 1.73 m² (95% CI: 0.08 to 0.62 mL/min per 1.73 m²; \( P = 0.01 \)) faster mean GFR decline. Each 10-mm Hg increment in mean follow-up MAP was associated with a 17% (95% CI: 5% to 32%; \( P = 0.006 \)) increased risk of the clinical composite outcome.

### Joint Analyses of Randomized BP Group and Achieved MAP

Figure 4 displays the results of analyses relating chronic GFR slope to both randomized BP group and achieved MAP. As shown, for participants assigned to the lower BP goal, where MAP ≤92 mm Hg was in range and MAP >92 was out of range, higher MAP levels were associated with faster GFR decline. In contrast, among participants assigned to the usual BP goal, renal outcomes appeared similar in participants with achieved MAP near the usual goal target range of 102 to 107 mm Hg and participants who achieved lower MAP levels. Importantly, within the 102 to 107 mm Hg range, after adjusting for the prespecified baseline covariates, the chronic GFR slope was steeper among lower BP goal participants than usual BP goal participants, at the same level of achieved MAP. At the midpoint of this interval, at 104.5 mm Hg, the adjusted mean (±SE) GFR slope was 0.99±0.41 mL/min per 1.73 m² per year faster among lower BP goal participants than among usual BP goal participants (\( P = 0.02 \)); the difference in adjusted mean slope tended to increase further toward
Comparison of Participants With MAP of 100 to 107 mm Hg

We compared the clinical and demographic characteristics of participants with achieved mean MAP of 100 to 107 mm Hg between the 2 BP groups (Table 2). Among participants whose achieved mean MAP was 100 to 107 mm Hg, those assigned to the lower BP group had greater prevalence of left ventricular hypertrophy and higher baseline BP and required more antihypertensive medication as compared with those in the usual BP group. Antihypertensive medication adherence was also lower among those in the lower BP group.

Sensitivity Analyses

Similar results to those summarized above were observed for the renal composite including only ESRD or declining GFR events, with death censored, and for multivariable models in which baseline MAP was not included as a covariate. In step function models comparing lower and usual BP goal participants with MAP between 102 and 107 mm Hg, the mean chronic slope was 1.52 mL/min per 1.73 m² steeper (95% CI: 0.13 to 2.90 mL/min per 1.73 m²; \( P = 0.03 \)) for participants assigned to the lower BP goal, and the hazard ratio of the clinical composite, including GFR events, ESRD, and death, was 2.15 (95% CI: 1.27 to 3.63; \( P = 0.004 \)). Similar results were also obtained in the extended models, including covariate adjustment for randomized treatment assignment and baseline left ventricular hypertrophy on ECG, smoking, fasting glucose, and history of cardiovascular disease, in addition to the prespecified covariates. Using the linear spline models, with more extensive covariate adjustment, the adjusted mean GFR slope at MAP of 104.5 mm Hg was 1.09±0.41 mL/min per 1.73 m² per year faster in the low than the usual BP group (\( P = 0.008 \)), and the hazard ratio for the clinical composite outcome was 1.58 (95% CI: 1.10 to 2.29; \( P = 0.01 \)) for the low versus the usual BP group.


Discussion

This report illustrates the challenges of using analyses of achieved BP to guide treatment recommendations. The AASK Trial is one of a few studies that directly compared different BP goals and is ideally suited to this evaluation. In this article, we document that analyses based on achieved BP lead to markedly different inferences than ITT analyses. Specifically, ITT analyses comparing randomized groups documented that the rate of decline in kidney function did not differ between the lower and usual BP goal groups. However, in analyses based on achieved BP, lower levels of BP were associated with more favorable renal outcomes. Further analyses documented that the likely reason for this discrepancy was confounding of achieved BP with comorbidities and adherence. When results were stratified by achieved MAP, participants in the lower BP group who were above goal had a faster decline in renal function than did participants in the usual BP group who were within goal but had the same achieved MAP. However, this group also had poorer prognostic factors at baseline and worse adherence during follow-up.

This pattern has been seen in other trials comparing the effect of BP goals on clinical outcomes. A similar discrepancy between the ITT comparison of randomized BP groups and analyses of achieved BP occurred in the Modification of Diet in Renal Disease Trial, in which participants were randomly assigned to lower BP goal group (MAP \( \leq 92 \) mm Hg) or a usual BP goal group (MAP \( \leq 107 \) mm Hg and \( <113 \) mm Hg in those age \( >61 \) years). As in the AASK analyses, when the randomized groups were combined and analyzed by achieved mean MAP, there was an association between higher levels of mean MAP during follow-up and decline in GFR, even after controlling for baseline characteristics.

No difference in cardiovascular disease or renal outcomes was noted in the overall cohort in the Hypertension Optimal Treatment Trial, a large clinical trial (n=18 790) that included a subset of hypertensive participants with mild renal disease at baseline randomized to 1 of 3 diastolic BP goal groups, \( \leq 90 \) mm Hg, \( <85 \) mm Hg, and \( \leq 80 \) mm Hg. In contrast to the ITT analysis, lower levels of achieved diastolic BP were associated with a reduced risk of cardiovascular disease in this trial, although there was not a significant difference in serum creatinine after 3.8 years of follow-up. Of note, this study randomized participants based on diastolic rather than systolic BP goals, and only 2 serum creatinine measurements were available (baseline and final visit).

The limitations of as-treated analyses, in which outcomes are related to treatment received rather than randomized treatment assignment, have been documented in the nephrology and general clinical trials literature. This report demonstrates these limitations in the setting of analyses of achieved BP. Recently, the Action to Control Cardiovascular Risk in Diabetes Trial documented that a systolic BP goal \(<120\) mm Hg did not significantly lower the rate of composite or cardiovascular events compared with a traditional systolic BP goal of \(<140\) mm Hg in patients with type 2 diabetes mellitus. Such results will likely encourage post hoc analyses to identify those that may have benefited from the lower systolic BP goal. However, in view of results from AASK, we urge caution, especially if analyses based on achieved BP are conducted. A trial similar to Action to Control Cardiovascular Risk in Diabetes Trial, the Systolic Blood Pressure Invention Trial, in nondiabetic hypertensive patients (40% with chronic kidney disease), which is underway by National Heart, Lung, and Blood Institute, will offer similar appeal.

An important issue is the extent to which confounding may account for the relationship of BP with clinical outcomes in observational studies. Our sense is that the problem of confounding, although potentially present in observational studies, is magnified in the setting of achieved BP analyses conducted in the setting of a clinical trial. Although their effects might be reduced, the confounding relationships demonstrated in the AASK as-treated analyses seem likely to also occur in the observational setting, where national and international standards stipulate maximum acceptable BP levels. If such a bias does exist, then, regardless of where BP targets are set, patients with higher observed BP levels may always seem to do worse. When BP level is explicitly targeted, as in the AASK Trial, variations in comorbidities and behavioral factors may account for a greater proportion of the variation in achieved BP than in the observational setting, where observed BP level also depends on variations in practice patterns, access to treatment, and other factors. Thus, the degree of confounding in achieved BP analyses from the AASK Trial is likely amplified because of the controlled conditions of the trial. Nonetheless, residual confounding likely occurs in observational analyses, especially recent studies in which there are substantial efforts to control BP to recommended BP goals.

The AASK Trial, with distinct randomly assigned BP goals but partially overlapping achieved BP levels, provided a unique opportunity to investigate potential biases in analyses of achieved BP by comparing patients with similar BP levels who were in goal for one treatment arm but out of goal for the other. Potential limitations include reduced statistical power in analyses based on subgroups of participants. However, major strengths include a well-characterized study population with extensive data on potential confounders, both at baseline and during follow-up; a long duration of follow-up; and a large, sustained contrast in BP between randomized groups.

Perspectives

In summary, analyses based on achieved BP can lead to markedly different inferences than traditional ITT analyses. A major reason for this discrepancy appears to be confounding of achieved BP with comorbidities, disease severity, and adherence. Clinicians and policy makers should exercise caution when making treatment recommendations based on analyses relating outcomes to achieved BP.

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References
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Running Title: Pitfalls of Achieved BP Analyses

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References for Table S1


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* Guidelines for Black patients
† Accepted ADA and KDOQI guidelines as only evidence
‡ Consensus recommendation after review of other available guidelines