Editorial

All Thiazide-Like Diuretics Are Not Chlorthalidone: Putting the ACCOMPLISH Study Into Perspective

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In the 31 years since the first Joint National Committee (JNC) report,[1] remarkable advances have occurred in our understanding of hypertension treatment, yet our successes in improving overall population control rates have come at a slower pace. Only an estimated 38% of patients with hypertension had blood pressure (BP) that was controlled to their goal in a study from 1999 to 2004,[2] although a recent national survey suggests that this number may be as high as 50%.[3] With control rates falling short of Healthy People 2010 targets, one could surmise that ineffective drugs might be part of the problem. However, each of the conventional classes of antihypertensives—diuretics, β-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and calcium channel blockers—have consistently demonstrated overall reductions in cardiovascular (CV) outcomes in large active and placebo-controlled clinical trials, owing primarily to their ability to effectively lower BP.

Research on the pharmacotherapy of hypertension has evolved progressively from the initial question of whether pharmacologic treatment is beneficial to which agents are effective in reducing CV outcomes, which is the most effective drug, and more recently, what is the "best" combination regimen.[4,5] On the surface, the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) trial appears to address the latter question.[6] But in attempting to answer the question, an equally intriguing question has reemerged: "Is a thiazide diuretic a thiazide diuretic?"

The traditional approach to hypertension management (recommended by JNC 7) is to initiate monotherapy, typically with a thiazide-type diuretic unless compelling indications for other medications are present, and add medications sequentially to achieve goal BP.[7] In the case of patients with Stage 2 hypertension (ie, BP >160/100 mm Hg), a 2-drug regimen (which may be a fixed-dose combination agent) is recommended initially since most patients with this degree of BP elevation will require multidrug therapy to control BP. Thiazide diuretics have been recommended as the foundation of any multidrug regimen, either as initial monotherapy or as part of an initial 2-drug combination, due to their ability to enhance the antihypertensive effects of virtually all other classes of antihypertensives.

The ACCOMPLISH hypertension treatment trial, sponsored by Novartis Pharmaceuticals, compared initial therapy with 2 different fixed-dose combinations, a diuretic-based combination

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(benazepril/hydrochlorothiazide 20/12.5 mg titrated to 40/25 mg) or a nondiuretic combination (benazepril/amlodipine 20/5 mg titrated to 40/10 mg), in 11,506 high-risk patients. The hypothesis of the trial is important given that most patients typically require ≥2 antihypertensive medications to achieve goal BP, and emerging evidence that achieving control more quickly (which might occur more rapidly with 2 drugs as initial treatment rather than initial monotherapy) may confer greater benefit.[8]

To be eligible, patients had to be high-risk; be at least 55 years of age; and have a systolic BP level >160 mm Hg or currently be receiving antihypertensive therapy with evidence of CV disease, renal disease, or target organ damage. On entry, 50% were obese, 60% had diabetes, and only 37.5% had BP controlled to <140/90 mm Hg despite the use of at least 2 antihypertensive medications in most patients. The mean baseline systolic BP was approximately 145 mm Hg, a lower baseline BP than seen in many previous outcome studies. African Americans, a population considered to be highly responsive to thiazide diuretic therapy, were not as well represented (~12%) as they were in the Antihypertensive and Lipid-Lowering to Prevent Heart Attack Trial (ALLHAT).[9]

The study was stopped early, after a mean follow-up of 36 months, because of differences in primary outcome; the benazepril/amlodipine group had a hazard ratio (HR) of 0.8 (95% confidence interval [CI], 0.72–0.90; $P<0.001$) for the composite outcome of death from CV causes and CV events when compared with the other drugs. While all-cause mortality was not different between groups (HR, 0.90; 95% CI, 0.76–1.07), hard CV end points (death, stroke, myocardial infarction) were reduced by approximately 20% in the ACE inhibitor/calcium channel blocker group. The results were consistent for the primary outcome even after removal of the effect of revascularization procedures. Of interest, the ACCOMPLISH investigators chose not to include heart failure in the primary composite outcome, a condition that has consistently been reduced more with diuretic-based therapy when compared with other treatments.[9]

Although systolic BP was marginally lower in the benazepril/amlodipine group (131.6 vs 132.5 mm Hg; $P<0.001$) at the end of the study, this difference probably does not explain the 20% difference in the primary outcome. Although initial BP levels were similar between groups, a higher percentage of patients had BP that was controlled to <140/90 mm Hg in the benazepril/amlodipine group (74.5% vs 72.4%) at the end of the study. These findings are important, considering that these control rates were achieved with >50% of the patients in both groups remaining on only the original fixed-dose combination (both groups required similar and relatively low rates of add-on therapy). Equally impressive is that the differential findings between the 2 regimens were observed against a backdrop of reasonably great efforts to modify other CV risk factors, with ~67% of patients on lipid-lowering therapy (mean total cholesterol, 184.9 mg/dL) and 64% receiving antiplatelet therapy, both of which should increase the difficulty in finding a difference between the two regimens on the primary outcome.

The ACCOMPLISH results imply that there could be an advantage in favor of the ACE inhibitor/calcium channel blocker combination when compared with the ACE inhibitor/thiazide diuretic as the preferred initial therapy in a high-risk hypertensive population. With similar rates of BP control, the findings suggest that there may be explanations beyond differences in BP that favor the ACE inhibitor/calcium channel blocker combination. However, as others have argued, we believe that lowering BP remains the key to explain most of the benefits noted in hypertension treatment studies.[10] Examination of specific pharmacokinetic and pharmacodynamic differences between the drugs used in this trial reveals what appears to be a stacked deck in favor of the amlodipine/benazepril combination; differences in the choice of antihypertensive agents and doses used may have ultimately been responsible for the difference in outcome findings.

Benazepril is a prodrug that is rapidly converted to an active metabolite, benazeprilat. The elimination half-life of benazeprilat is 22 hours, but there is conflicting evidence as to whether it should truly be a once-daily dosed drug, as it achieves a trough: peak ratio of only 0.4.[11,12] This is less than the ratio of 0.5 that the US Food and Drug Administration currently recommends for once-daily antihypertensive agents.[13] Despite these characteristics, benazepril is most often used once daily, as it was in ACCOMPLISH. With benazepril included in both regimens, the comparison of interest in ACCOMPLISH appears to be between amlodipine and hydrochlorothiazide. Hydrochlorothiazide, when used chronically, has a half-life of 8 to 15 hours and a duration of action that is only slightly longer.[14] The addition of hydrochlorothiazide may prolong the duration of action of the ACE inhibitor; however, the underlying pharmacokinetic and pharmacodynamic differences between hydrochlorothiazide and amlodipine favor the amlodipine-based regimen

for the optimal once-daily duration of effect. Amlodipine is one of the longest-acting antihypertensive agents available. It has a half-life of 38 to 50 hours and full 24-hour duration of action that maintains a trough:peak ratio of 57.7, even 72 hours following abrupt withdrawal.[15,16] Combining amlodipine with any other agent, including benazepril, easily carries the BP-lowering effect throughout the 24-hour period. With these characteristics in mind, it is surprising that the differences in BP reduction were not greater in favor of the amlodipine-benazepril combination than those actually observed in ACCOMPLISH.

In analyzing the findings of ACCOMPLISH, an important consideration is the selection of hydrochlorothiazide as the diuretic. Although it is the most commonly prescribed thiazide-type diuretic and is available in several fixed-dose combinations, the weight of the clinical trial evidence supporting thiazide-type diuretics in the management of hypertension in the United States is largely based on studies using chlorthalidone.[9,17–21] Chlorthalidone-based regimens have proven effective in reducing CV events in every clinical trial in which they have been studied. Chlorthalidone more closely resembles amlodipine in its comparative pharmacokinetic profile, pharmacodynamic profile, and antihypertensive efficacy, with a half-life of 45 to 60 hours when used chronically.[22] This is believed to be due to significant partitioning into red blood cells and an ability to backleak into plasma and prevent the late period of antidiuresis (the "braking" effect).[23]

Chlorthalidone and hydrochlorothiazide differ in potency;[14] this has direct implications on both dosing equivalence and kaluresis. Studies have consistently demonstrated the ability of monotherapy with chlorthalidone 12.5 to 25 mg/d to lower systolic BP by 15 to 20 mm Hg from baseline, while similar reductions for hydrochlorothiazide appear to require 25 to 50 mg/d.[14,24] Extrapolation to the ACCOMPLISH trial suggests the possibility that a chlorthalidone-based regimen (using the same 12.5–25-mg dosing used for hydrochlorothiazide) would have resulted in similar, if not possibly lower, clinic BP values than those observed in the hydrochlorothiazide arm of the trial. However, the more important differences between these 2 drugs may relate to their ability to affect nighttime BP control. Direct comparison of the antihypertensive efficacy of both agents reveals that at half the dosage of hydrochlorothiazide (ie, 25 mg/d compared with 50 mg/d), chlorthalidone is more effective in lowering BP throughout the full 24-hour dosing period. This difference is most pronounced during nighttime hours while the reduction in serum potassium between the agents remains equivalent.[24]

The finding of different efficacy between the 2 agents using ambulatory blood pressure monitoring (ABPM) may provide biologic plausibility for the experience observed in the Multiple Risk Factor Intervention Trial (MRFIT).[18] MRFIT was a large primary prevention trial in 12,866 men aged 35 to 57 years in the upper 10% to 15% Framingham risk for coronary heart disease. They were randomly allocated to a special intervention (SI) group (diet modification, smoking cessation, stepped-care diuretic-based treatment for hypertension) or a usual care group. The choice of hydrochlorothiazide or chlorthalidone for the stepped-care treatment in the SI clinics was left to the discretion of the individual physician. A midstudy recommendation was made by the data and safety monitoring board to switch all SI MRFIT participants who were then taking 50 or 100 mg of hydrochlorothiazide to 50 mg of chlorthalidone because mortality rates were significantly higher in clinics using hydrochlorothiazide compared with chlorthalidone. This mortality pattern was reversed after the change in protocol; clinics predominately using chlorthalidone from the very beginning continued to experience significantly lower death rates. The ACCOMPLISH findings would be much more compelling had chlorthalidone been the agent selected for the diuretic-based regimen.

The ACCOMPLISH BP differences reported are based on office BP; it is likely that many BP readings were done several hours after patients took their early morning dose of medication. This is a time in which the medications would likely be exerting their optimal antihypertensive effects. Differences in antihypertensive efficacy between hydrochlorothiazide and amlodipine would therefore be minimized. In the case of hydrochlorothiazide, it has been reported that office BP overestimates the antihypertensive response, compared with ABPM.[25] This has been observed when directly comparing hydrochlorothiazide to chlorthalidone; significantly lower nighttime BP has been found with chlorthalidone even though daytime and clinic BP were similar between the two.[24] This raises the question in ACCOMPLISH of whether 24-hour ABPM findings (the focus of an important ACCOMPLISH substudy) will reveal differences between the regimens, particularly with regard to nighttime BP. Any differences in nighttime BP should not be underestimated, as it is known to be one of the best predictors of CV risk.[26] One of the reasons for the better outcomes in the ACE inhibitor addition

group observed in the Heart Outcomes Prevention Evaluation (HOPE) study was the possible differences in nighttime BP.[27] The findings of ACCOMPLISH may be entirely explainable and consistent with epidemiologic evidence if a significant difference in nighttime BP of as little as 5 to 8 mm Hg between the 2 treatment groups is determined.

An equally important point about the choice of diuretic is that no randomized controlled outcome trial has demonstrated benefits of hydrochlorothiazide (compared with placebo or usual care) with doses that were as low as in the ACCOMPLISH trial. The dose of hydrochlorothiazide in ACCOMPLISH was 12.5 to 25 mg, a relatively low dose, but the doses of benazepril and amlodipine were maximal and similar to previous trials demonstrating benefit. While the doses of hydrochlorothiazide employed in ACCOMPLISH are most commonly recommended in clinical practice and available in fixed-dose combinations, the lowest doses of hydrochlorothiazide demonstrating equivalence or superiority in large outcome-based comparative trials have actually been 25 to 50 mg/d.[28–31] Chlorthalidone has been used in doses as low as 12.5 to 25 mg in clinical trials (Systolic Hypertension in the Elderly Program [SHEP] and ALLHAT), but research findings have suggested that these doses may be more clinically effective than 25- to 50-mg doses of hydrochlorothiazide.[14,24] With regard to hydrochlorothiazide, perhaps the pendulum has swung too far in the direction of advocating "low" doses, the definition of which should be reevaluated depending on the thiazide chosen.

There is no question that the combination of an ACE inhibitor and calcium channel blocker is an effective one that is now generically available in fixed-dose combination or as single agents. Thus, the fundamental question posed by ACCOMPLISH is relevant, timely, and important. However, the notion that the ACCOMPLISH findings should challenge current thiazide diuretic–based recommendations for initial therapy is concerning and potentially detrimental; it is clear that one of the most important interventions to achieve goal BP is the addition or optimization of the diuretic.[32–34] Dissemination of ALLHAT findings helped reverse some of the "diuretic phobia" that was promulgated for many years by concerns about adverse electrolyte and metabolic effects that are more pronounced with use of historically very high doses. Overemphasis of the ACCOMPLISH results could halt this progress and send a confusing message to clinicians who may not appreciate the subtle, yet important, differences within the diuretic class. Importantly, the mean BP at entry in ACCOMPLISH was 145/80 mm Hg with over one-third of patients requiring three or more agents to achieve this level. Until the debate over ACCOMPLISH can be adequately addressed with 24-hour BP data, even if clinicians do choose an ACE inhibitor and calcium channel blocker regimen as the first two agents, we strongly urge that the next agent added be chlorthalidone, which is widely available generically.

So what can we learn from ACCOMPLISH? The practitioner who bases decisions on evidence from randomized trials expecting to see similar benefit in practice should use the doses of antihypertensive drugs that were used in trials. In most cases, it is often 75% to 80% of the maximum dose of a drug, while in ACCOMPLISH, the maximum allowable dose for the thiazide diuretic was 50% of what was used in trials that demonstrated a reduction in events. Unfortunately, many practitioners have been inappropriately convinced that there is a flat dose-response curve for thiazide diuretics above 25 mg/d, that dosing and efficacy between agents are interchangeable, and that expected outcomes are a "class" effect. Contributing to this is the fact that nearly all available combination products that include hydrochlorothiazide include only 12.5 to 25 mg of the thiazide. However, up-titration to higher doses of hydrochlorothiazide in an attempt to achieve doses used in the clinical trials that have demonstrated benefit must be done cautiously due to the potential for hypokalemia. Since the lowest effective dose of hydrochlorothiazide in previous clinical trials demonstrating benefit was 25 to 50 mg/d and chlorthalidone 25 mg/d appears to be more effective in antihypertensive efficacy with no increased hypokalemia, we believe that 12.5 to 25 mg/d of chlorthalidone (as used in SHEP and ALLHAT) should be the preferred thiazide-type diuretic and the standard for comparison in clinical trials.

If ACCOMPLISH is to be considered an important trial comparing a thiazide diuretic combination–based regimen to a non–thiazide-based combination regimen, it must be done so with a cautionary note. The choice of hydrochlorothiazide was convenient since it is the most commonly prescribed thiazide diuretic. The dose was rationalized on the basis that it is most commonly used; however, this should not be used as primary justification for its selection if a true evidence-based trial was intended. Unfortunately, ACCOMPLISH shares similar characteristics to other pharmaceutical industry–sponsored trials that choose an inferior

comparator at a suboptimal dose. Selection of chlorthalidone would have been the more appropriate choice, considering that there are more than 3 decades of evidence favoring its use. To address the question posed earlier, "if you've seen one thiazide diuretic, you've seen only one thiazide diuretic." We implore the pharmaceutical industry to consider this when designing future thiazide-based fixed-dose antihypertensive combination agents, and until proven otherwise, all thiazide-like diuretics are NOT chlorthalidone.

SUMMARY

- Hydrochlorothiazide 12.5–25 mg/d is the most commonly prescribed thiazide-type diuretic and is widely available in fixed-dose combinations. The dose-response curve for thiazide diuretics, however, does not entirely flatten above 25 mg/d, and the 12.5–25 mg dose may be viewed as a compromise between the dose-response curve for antihypertensive and kaliuretic effects.
- Doses of $\leq$25 mg/d of hydrochlorothiazide may be too low to demonstrate the benefits in outcomes observed in previous clinical trials (the lowest dose of hydrochlorothiazide showing effectiveness in previous trials demonstrating benefit was 25–50 mg/d).
- Chlorthalidone has been the standard thiazide-like diuretic used in most landmark United States outcome trials in which unequivocal benefits have been reported. Although considered a thiazide-like diuretic, it possesses several important pharmacokinetic and pharmacodynamic differences when compared with other thiazides.
- At doses of 12.5–25 mg, chlorthalidone lowers blood pressure more effectively than hydrochlorothiazide 25–50 mg with no difference in the occurrence of hypokalemia. Chlorthalidone's longer duration of action permits control of blood pressure throughout the 24-hour period, including nighttime hours.
- Chlorthalidone should become the standard for future diuretic comparisons in outcome-based hypertension trials and should be utilized preferentially whenever new diuretic fixed-dose combination agents are developed.

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