Antihypertensive Efficacy of Aliskiren
Is Hydrochlorothiazide an Appropriate Benchmark?

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The thorough prospective, randomized, double-blind trial of Schmieder et al.1 in the current issue of *Circulation* convincingly documents that aliskiren treatment provided significantly greater blood pressure (BP) reduction than hydrochlorothiazide. The study is well done; the number of patients (n = 1124) is impressive; and the efficacy variables were analyzed, as is appropriate for an intention-to-treat population, with the last observation carried forward method. The authors concluded that aliskiren provided “more effective BP lowering than a thiazide-type diuretic, the drug class recommended by JNC 7 [Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure] guidelines2 as first-line therapy for the treatment of hypertension.” Indeed, not only JNC 7 but also JNC VI, V, IV, III, and I have recommended a thiazide-type diuretic, most commonly hydrochlorothiazide in the United States, as first-line therapy. Thus, over the years and decades, the JNC has elevated hydrochlorothiazide to the gold standard of antihypertensive therapy. Not surprisingly, therefore, hydrochlorothiazide remains the most prescribed drug in the United States. In 2007, >130 million prescriptions for hydrochlorothiazide, either alone or in combination, were written in this country. The doses of hydrochlorothiazide almost exclusively prescribed are 12.5 and 25 mg/d. This begs the question as to how solid the evidence is that hydrochlorothiazide in the dose of 12.5 to 25 mg reduces cardiovascular events (ie, stroke and heart attacks). A thorough scrutiny of the literature reveals little, if any, outcome evidence for low-dose hydrochlorothiazide. All outcome studies were done with higher doses, with hydrochlorothiazide in fixed combinations with a potassium-sparing diuretic, or with chlorthalidone, which obviously is an entirely different antihypertensive drug.3 Hydrochlorothiazide was compared with and found to be inferior to enalapril in the Australian National Blood Pressure 2 study, but the dose is not specified.4 Thus, we have to conclude that for the most prescribed drug in the United States, outcome evidence is paltry.

In the study of Schmieder et al.1 outcome was not the issue, but the authors document better efficacy of aliskiren compared with hydrochlorothiazide with regard to the surrogate end point (ie, millimeters of mercury). Therefore, the question to ask is, what is the antihypertensive efficacy of hydrochlorothiazide in the dose of 12.5 to 25 mg/d? In another thorough, double-blind, placebo-controlled, factorial-design trial in 2776 hypertensive patients, the maximum dose of aliskiren (300 mg) lowered BP by 8.0/3.4 mm Hg compared with a meager 6.8/2.5 mm Hg with 25 mg hydrochlorothiazide (after subtraction of placebo).5 With aliskiren, 63.9% of patients reached goal BP (<140/90 mm Hg); with hydrochlorothiazide 25 mg, 59.0% reached goal BP; and with placebo, 45.8% achieved goal BP. Similarly, in the study of Schmieder et al, the fall in BP with placebo was substantial, reducing the placebo-subtracted BP decrease to 7.7/3.4 mm Hg with aliskiren and to merely 4.7/1.6 mm Hg with hydrochlorothiazide at week 6. Thus, the seemingly impressive fall in BP seen with both aliskiren and hydrochlorothiazide at the end of the study have to be reassessed in light of a (missing) placebo comparison. The recent thorough Cochrane meta-analyses of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and aliskiren provide a reality check by putting the findings of the present study into an objective context and illustrate 2 important points (the Figure6–8: No significant difference in antihypertensive efficacy can be found between the 3 classes of renin-angiotensin system (RAS) blockers, and the fall in BP with RAS blockade is disappointingly small when corrected for placebo. However, what also becomes increasingly clear is that hydrochlorothiazide in the dose of 12.5 to 25 mg is a suboptimal antihypertensive drug. The poor antihypertensive efficacy of low-dose hydrochlorothiazide has previously been documented9 and seems to be even more pronounced when assessed by 24-hour ambulatory BP monitoring.10 At higher doses (50 to 100 mg), its BP-lowering effect may be equivalent to that of most other antihypertensive drugs. At that dose, however, adverse effects such as hypokalemia, hyponatremia, hyperuricemia, and insulin resistance, all of which are dose dependent, preclude the use of hydrochlorothiazide as monotherapy in many patients.11 Of greater concern is the finding of an increased risk of sudden cardiac death with higher doses of hydrochlorothiazide,12 which was documented in a case-control study of hypertensive patients. Compared with low-dose (25 mg/d) hydrochlorothiazide therapy, moderate-dose therapy (50 mg/d) was found to be associated with a 70% higher risk of sudden cardiac death (odds ratio, 1.7; 95% confidence interval, 0.7 to 4.5), and high-dose therapy (100
mg/d) increased this risk by >3-fold (odds ratio, 3.6; 95% confidence interval, 1.2 to 10.8; \(P\) for trend=0.02).\(^\text{12}\)

It is little surprise, then, that in patients whose BP was not controlled in the study of Schmieder et al.,\(^\text{1}\) amlodipine had to be added more often in the hydrochlorothiazide arm than in the aliskiren arm and that the fall in BP with the combination was greater in the latter. Calcium antagonist/RAS blocker combinations are used extensively and have an additive or even synergistic effect,\(^\text{13}\) whereas calcium antagonist/thiazide combinations are generally avoided in clinical practice. It is little surprise also that hypokalemia was much more common with the calcium antagonist/hydrochlorothiazide combination (17.9 versus 0.9%; \(P<0.0001\)); if anything, amlodipine stimulates the RAS, thereby further promoting potassium loss, whereas RAS blockers such as aliskiren have the opposite effect (ie, mitigate the potassium-wasting effect of hydrochlorothiazide). Indeed, in the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial,\(^\text{14}\) hypokalemia (6.2% versus 3.5%; \(P<0.0001\)) and, probably as a consequence, new-onset diabetes mellitus (16.4 versus 13.1%; \(P<0.001\)) occurred more often in the amlodipine than in the valsartan arm; hydrochlorothiazide was the first add-on drug in both treatment strategies in this study.

The fact that hydrochlorothiazide in commonly used doses is a suboptimal antihypertensive drug should not detract from its being exceedingly useful in combination with an RAS blocker such as an angiotensin-converting enzyme inhibitor, an angiotensin receptor blocker, or even a direct renin inhibitor like aliskiren. When combined with any of these drug classes, hydrochlorothiazide elicited a distinct incremental fall in BP. Thus, hydrochlorothiazide seems to be more useful as an “enhancer” of the antihypertensive effect of RAS blockers than as a monotherapeutic agent. However, even when combined with a RAS blocker, hydrochlorothiazide is inferior to amlodipine, as we learned in the recent Avoiding Cardiovascular Events in Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) study.\(^\text{15}\)

This landmark trial was stopped prematurely because combination treatment with benazepril and amlodipine reduced cardiovascular morbidity and mortality (cardiovascular death, fatal/nonfatal myocardial infarction, fatal/nonfatal stroke, hospitalization for unstable angina, and coronary revascularization) 20% better than combination treatment with benazepril and hydrochlorothiazide. Because BP was lowered to the same extent in both arms, the ACCOMPLISH results indicate either that amlodipine confers benefits independent of its BP-reducing effects or, mutatis mutandis, that hydrochlorothiazide has BP-independent, detrimental effects on cardiovascular morbidity and mortality.

One may appropriately ask at this juncture what other comparator should be selected if hydrochlorothiazide can no longer be considered the benchmark by which antihypertensive drugs are judged. The question is important because many pharmaceutical companies tend to go down the path of the least resistance (ie, select an antihypertensive drug that can be beaten easily with regard to efficacy and safety). For many years, the prototype of such a weak comparator has been atenolol, which not only is a poor antihypertensive agent but also has never been shown to reduce cardiovascular events better than placebo.\(^\text{16,17}\) However, solid and substantial outcome data are available with chlorthalidone\(^\text{18,19}\) and amlodipine.\(^\text{20}\) Therefore, future comparative trials should consider either chlorthalidone or amlodipine as the benchmark by which other antihypertensive drugs are judged.

In summary, the authors and the sponsor are to be congratulated that in the present study aliskiren beat hydrochlorothiazide with regard to the surrogate end point (ie, BP). Aliskiren seems to exert antihypertensive efficacy that is similar to other RAS blockers. However, neither for BP reduction nor for outcome should low-dose (ie, 12.5 to 25 mg) hydrochlorothiazide be considered an acceptable benchmark. Although hydrochlorothiazide is the most commonly prescribed antihypertensive drug, its BP-lowering effect is paltry, and no morbidity and mortality data have been provided at low doses. At higher doses, adverse effects preclude the monotherapeutic use of hydrochlorothiazide in many patients. The only 2 drugs that fulfill benchmark criteria for both antihypertensive efficacy and outcome data are chlorthalidone and amlodipine. The JNC recommendation to use “thiazide-type” diuretics as initial therapy has been proven to be deceptive and should be amended.

**Disclosures**

Dr Messerli is an ad hoc consultant/speaker for the following organizations: GSK, Novartis, Boehringer Ingelheim, Forest, Daiichi
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