In this issue of Hypertension, Calhoun et al report on a large (n=2271), short (9 weeks of treatment after 4 weeks of washout and placebo), well-designed, properly controlled, international randomized trial of a triple combination of a diuretic (D; hydrochlorothiazide [HCTZ]), a dihydropyridine calcium channel blocker (DHPCCB; amlopidine [A]), and an angiotensin receptor blocker (ARB; valsartan [V]) in volunteers who had a mean sitting (MS) diastolic blood pressure (BP; MSDBP) of ≥100 mm Hg. The results support what all would have anticipated: the use of 3 antihypertensive medications with different mechanisms of action would lead to a greater drop in BP than would combinations of any 2 of the 3 drugs given as 2-drug combinations. In fact, any other result would have been news, because combination therapy has many obvious advantages and some disadvantages compared with single-drug therapy (Tables 1 to 3).

The main result was that the triple combination reduced MS BP by 40/25 mm Hg, whereas the 2-drug combination of the ARB/D achieved a 32/20-mm Hg reduction, and the DHPCCB/D combination dropped MSBP by 31/19 mm Hg. All of these differences were highly statistically significant, thanks in part to the large sample size. More important, the differences between these regimens, a modest reduction in serum K⁺ (0.39 mmol/L in the A/D group, 0.16 mmol/L in the A/D/V group, and 0.08 mmol/L in the V/D group). A/V increased serum K⁺ by 0.04 mmol/L.

All of the combinations reduced MSDBP to <90 mm Hg but failed to lower MSSBP to <140 mm Hg. The only regimen that reduced MSSBP to <140 mm Hg and MSDBP to <90 mm Hg was the triple combination. The subjects whose MSSBP remained >140 mm Hg on 3 drugs at full or nearly full doses, one of which is a D, would be defined as having resistant hypertension by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Though some may disagree about the definition or whether the dose of D used was a full dose, a patient who is receiving these 3 classes of drugs at these doses and is still not at goal is a candidate for additional drug(s).

In many ways, this study and the benefits of triple-drug combinations return us to the dawn of the era of effective pharmacological treatment of hypertension (Figures 1 and 2). It was the triple-drug combination of reserpine, hydralazine, and HCTZ as Ser-Ap-Es (Ciba-geigy) that was the basis for the first clinical trial, the Veterans Affairs Cooperative Study, but failed to lower MSSBP to <140 mm Hg. The only regimen that reduced MSSBP to <140 mm Hg and MSDBP to <90 mm Hg was the triple combination. The subjects whose MSSBP remained >140 mm Hg on 3 drugs at full or nearly full doses, one of which is a D, would be defined as having resistant hypertension by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Though some may disagree about the definition or whether the dose of D used was a full dose, a patient who is receiving these 3 classes of drugs at these doses and is still not at goal is a candidate for additional drug(s).

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completed in 1967 and 1970, that proved that antihypertensive therapy reduced cardiovascular events, something we now take for granted.

Ser-Ap-Es was the leading-selling branded antihypertensive in the 1960s, but in subsequent decades, many authorities promoted the concept that drugs were “pharmacological probes” and that BP could be successfully reduced with 1 agent, so long as that agent interfered with the primary etiology for that individual patient’s hypertension. Thus was born the idea of sequential monotherapy, where the clinician was advised to try what seemed to be the most likely drug class to be successful and then, if BP was not “controlled,” to try a drug from a different class, one at a time. The objective of treatment here was therapeutic parsimony, getting the patient properly treated with the fewest drugs possible. Stepped care, which recommends combining drugs with complementary mechanisms of action, was ridiculed as “anti-intellectual” or “cookbook medicine.”

It is now clear that patients with stage 2 hypertension (per the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure or grade 2 or 3 per the European Society of Hypertension and the European Society of Cardiology guidelines) will need ≥2 and often ≥3 drugs to reach our targets.1–4 The current paradigm for hypertension therapy per the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure and the European Society of Hypertension and the European Society of Cardiology is to initiate treatment with 2 drugs in high-risk individuals (those ≥20/10 mm Hg above goal BP) and to treat them aggressively to reach a goal BP, arbitrarily defined as <140 mm Hg and <90 mm Hg in most hypertensive patients and <130 mm Hg systolic and <80 mm Hg diastolic in those with diabetes mellitus, chronic kidney disease, or coronary artery disease.3–5 Calhoun et al1 do not tell us how many of their volunteers had these conditions.

Another factor that Calhoun et al1 help us focus on relates to the promptness of getting to the goal BP and the profound impact that has on cardiovascular outcomes. The Valsartan Antihypertensive Long-Term Use Evaluation Study compared initial treatment with V or A in high-risk individuals.6 During the first 3 months of the trial, those randomly assigned to initial treatment with A had a greater drop in systolic BP (3.3 mm Hg) and a statistically significantly lower stroke rate. With additional time and therapy (HCTZ was the next drug in both arms, and other drugs were added later, if needed), the final result did not show a significant difference in stroke rate between these 2 regimens (P<0.08). Calhoun et al1 show us that BP can be reduced in 9 weeks close to the goal with double therapy and is even more likely to reach the goal with triple therapy, without any important adverse events.

I have some quibbles with this study. To the cynics among us, it is simply an industry-sponsored marketing study done to register a triple combination, should such a product be in development. It is not important who sponsored the trial and for what purpose. What is important is whether the design is credible, whether the study addresses an important question, and whether the ethics, performance, and analysis of the trial are appropriate.

It is regrettable that the enrollment criteria were based on MSDBP, rather than MSSBP. Our major unmet need is to develop better drugs or drug combinations that reduce systolic BP safely and effectively.7 In this trial, the diastolic BP goal was reached by all of the combinations, but only the triple combination reduced average MSSBP to the systolic BP goal.

Why HCTZ and not chlorthalidone? Only 3 fixed-dose combinations currently available in the United States include chlorthalidone (Tenoretic, Clorpres, and Combipres), none of which are combined with an angiotensin receptor blocker or angiotensin-converting enzyme inhibitor (Table 4). There is increasing appreciation that chlorthalidone is a more effective thiazide-like diuretic, one that is underused by most physicians. The benefits of chlorthalidone in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial

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**Table 3. Disadvantages of a Fixed-Dose Combination as Antihypertensive Therapy**

<table>
<thead>
<tr>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of dose flexibility</td>
</tr>
<tr>
<td>Fixed-dose combinations may not contain appropriate doses when treating hypertension and a comorbid condition</td>
</tr>
<tr>
<td>Increased risk of dose-independent reactions</td>
</tr>
</tbody>
</table>

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**Figure 1. Development of antihypertensive therapy.** DHP indicates dihydropyridine; ETa, endothelin A receptor blocker; VPI, vasopeptidase inhibitor.
and the Systolic Hypertension in the Elderly Program are clear, and one can speculate that even more dramatic results would have been achieved in this trial had chlorthalidone been the D rather than HCTZ.8,9

The international nature of this study points out issues in terminology, especially in classification and stratification of our patients. In the United States, we speak of “stages” of hypertension, whereas the Europeans use the term “grade.”2,4 In both systems, the writers of the guidelines are attempting to help the practicing clinician appreciate the risks associated with the level of BP, and so the argument is more semantic than scientific. Also, the terms “moderate” and “severe” hypertension that are used in this article, along with other archaic stratification terms, eg, “mild” hypertension, should be abandoned now and forever. No one ever speaks of having “mild” cancer.

As we approach the publication of a new US guideline, studies such as the one by Calhoun et al1 provide important support to what is likely to be addressed in that document. This study demonstrates that multidrug therapy can be given safely and that triple combinations, when chosen wisely, can be effective at getting BP close to or at our goals and can do so promptly. This study demonstrates again that such combinations can reduce both the metabolic and clinical adverse reactions associated with monotherapy with the mainstays of our therapies (less edema with DHPCCB when given with a blocker of the renin-angiotensin-aldosterone system and less hypokalemia when a Di sgiven with a renin-angiotensin-al-
dosterone system blocker). It shows that using drug classes with complementary mechanisms of action can get more patients to goal without concern about demography or eth-
nicity. Using single pills will simplify therapy and should result in better BP control. However, it is also clear that, even with well-chosen double and triple combinations, there will still be a substantial number of patients who will need additional antihypertensive therapy, if we are to effectively deal with the worldwide cardiovascular epidemic.

**Table 4. Fixed-Dose Antihypertensive Combinations Available in the United States**

<table>
<thead>
<tr>
<th>Class</th>
<th>Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretic</td>
<td>Butiserpine (reserpine/butalbital)</td>
</tr>
<tr>
<td>Diuretic</td>
<td>Hypnex (hexamethonium/hydralazine)</td>
</tr>
<tr>
<td>Diuretic</td>
<td>Hypotenin A, B, &amp; C (pentolinium/hydralazine/resperine)</td>
</tr>
<tr>
<td>Diuretic</td>
<td>Renir (reserpine/ephedrine)</td>
</tr>
<tr>
<td>Diuretic</td>
<td>Verapene (rauwolfa/veratrum)</td>
</tr>
<tr>
<td>Diuretic</td>
<td>Thiazide/K+-sparing diuretic</td>
</tr>
<tr>
<td>Diuretic</td>
<td>Clonidine/thiazide</td>
</tr>
<tr>
<td>Diuretic</td>
<td>ACE inhibitor/thiazide</td>
</tr>
<tr>
<td>Diuretic</td>
<td>ACE inhibitor/CCB</td>
</tr>
<tr>
<td>Diuretic</td>
<td>ARB/thiazide</td>
</tr>
<tr>
<td>Diuretic</td>
<td>Low-dose β-blocker/thiazide</td>
</tr>
<tr>
<td>Diuretic</td>
<td>ARB/CCB</td>
</tr>
<tr>
<td>Diuretic</td>
<td>DRI/thiazide</td>
</tr>
</tbody>
</table>

ACE-I indicates angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker.

**Figure 2. Development of fixed-dose combinations for antihypertensive therapy.**

- ACE inhibitor/thiazide
- ACE inhibitor/CCB
- ARB/thiazide
- ARB/CCB
- DRI/thiazide

**Disclosures**

H.R.B. is a consultant to Novartis, Merck Sharp & Dohme, Daiichi-Sankyo, and Boeringer-Ingelheim. In the past 2 years, he has been on the Bristol-Myers Squibb and Novartis speakers bureaus. He has no stock or stock options and is not an employee of Novartis or any other pharmaceutical company.

**References**


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