Combination Therapy As First-line Treatment for Hypertension

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With the cut-off point between "normal" and "high" blood pressure (BP) being pushed increasingly downward, especially for patients with multiple cardiovascular risk factors, most hypertensives need more than one antihypertensive agent to reach their target BP. In this article, we examine the rationale for combining drugs from different classes that have synergistic or additive effects and properties that might offset one another's adverse hemodynamic and/or metabolic reactions. We suggest circumstances in which the initiation of therapy with a fixed two-drug combination might be preferable to the usual practice of starting with monotherapy followed by upward titration and addition of other agents, and we briefly review the existing fixed drug combinations. We end with the intriguing and provocative notion of the future "polypill," a fixed combination of agents addressing various components of the metabolic syndrome as well as other coexisting common risk factors in both high-risk patients with conditions requiring polypharmacy and in healthy, asymptomatic individuals.

Introduction

Hypertension is now well established as one of the most important modifiable risk factors for cardiovascular complications. However, based on reports from long-term observational and interventional studies, the definition of what constitutes hypertension has been changing in recent years. Because blood pressure (BP) levels have a continuous rather than a bimodal distribution separating normal from abnormal, the separation is arbitrary, with the cut-off point between "normal" and "high" BP being gradually set at lower levels within the population continuum. Whereas earlier epidemiologic studies defined as hypertension BPs of 160/95 mm Hg or higher, more recent studies have placed this definition at 140/90 mm Hg or higher, which is the current accepted standard. However, several large outcome trials have shown that more intensive antihypertensive therapy designed to achieve much lower BP levels offers greater protection from end-organ damage, especially for patients with more risk factors. Furthermore, longitudinal follow-up of healthy populations has shown that the risk for death from heart disease or stroke begins to rise at BP levels over 115/75 mm Hg and doubles with each increment of 20/10 mm Hg [1•]. Accordingly, the recent Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII) guidelines [2] have now defined optimal BP levels as below 120/80 mm Hg and introduced the concept of "prehypertension" for BP levels of 120–139/80–89 mm Hg. It is true that these definitions, when applied to the population at large, are controversial and have generated much debate as to their practical applicability across age groups. However, it is generally accepted that for hypertensive patients with coexisting conditions that significantly increase their cardiovascular risk, the target BP should be far below the usual epidemiologic cut-off for normality. For example, the National Kidney Foundation [3••] now recommends that hypertensive patients with diabetes and microalbuminuria should decrease their BP to below 130/80 mm Hg to minimize the risk of diabetic nephropathy as well as other cardiovascular complications.

In practice, few hypertensive patients can reach their target BP with monotherapy. It has been repeatedly shown in epidemiologic studies that less than 50% of the participants reach the cut-off 140/90 mm Hg level on monotherapy, and, by today's standards, even this level is inadequate for most hypertensives with several additional risk factors, such as chronic renal failure [3••,4]. With the exception of young subjects at the earliest stages of new-onset essential hypertension or older individuals with mild, isolated systolic hypertension, most of the hypertensive population requires treatment with two or more antihypertensive agents to achieve optimal BP control.

Rationale for Appropriate Drug Combinations

Research into the pharmacology of various classes of antihypertensive agents has provided extensive information on their mechanisms of action. This knowledge, combined with the results of studies that have clarified mechanisms of BP regulation and prevailing aberrations in different patient populations according to age, race, or other phenotypic characteristics, has led to rational drug combinations of drugs from different classes, as opposed to random accumulation of drugs.

The two main factors that characterize a rational drug combination are: 1) a synergistic action—*ie*, combined effect that exceeds the additive BP-lowering effect of each component, and 2) mechanisms of action that offset one another's side effects.

Angiotensin-inhibiting drugs and diuretics

A prime example of synergistic action is the use of a diuretic plus an angiotensin-inhibiting agent; the diuretic enhances salt excretion and—at least in the first few weeks—causes contraction of the circulating plasma volume, which stimulates the renin-angiotensin system (RAS) to the point that (especially in younger, white patients with a hyperresponsive RAS), it can maintain unchanged or minimally reduced BP; addition of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) will produce maximal antihypertensive effect in this setting.

Captopril + hydrochlorothiazide was the first such combination, and has become the reference against which newer ACE inhibitors plus diuretics are compared. Several such trials have been reported in the past few years [5–8]. The same mechanism is true for ARB + diuretic combinations [9–12]. An added advantage of these combinations is that the ACEI or ARB tends to offset not only the compensatory hormonal reactions, but also the dysmetabolic effects of thiazides (hypokalemia, hyperuricemia, accentuated insulin resistance). Furthermore, the addition of diuretic to an ACEI or ARB permits control of BP for patients who would otherwise have been resistant to the angiotensin-inhibiting drug alone, such as black hypertensives, and who can still benefit from the long-term, end-organ protection of angiotensin inhibition that is widely believed to offer benefits beyond BP-lowering. Notably, losartan was shown to have an additional uricosuric effect unrelated to its ARB properties, which enables it to compensate more effectively for the hyperuricemic effects of the diuretics.

Angiotensin-converting enzyme inhibitors and calcium channel blockers

The ACE inhibitors and calcium channel blockers (CCBs) are another example of a synergistic combination. Dihydropyridine-type CCBs cause vasodilation that stimulates both the RAS and the sympathetic nervous system (causing reflex vasoconstriction and tachycardia), both of which tend to blunt their efficacy. Angiotensin-inhibiting drugs will minimize both of these reactions and maximize the BP-lowering effect. They also offset the tendency of CCBs to retain salt and water, as well as their tendency to cause dependent edema [13–17], and they were shown to be particularly effective in the prevention or reversal of diabetic nephropathy [18] and left ventricular hypertrophy [19]. Combinations of ACEI with nondihydropyridine CCBs, such as trandolapril with sustained-release verapamil, have also been used successfully [20].

Diuretics + β-adrenergic receptor blockers

Diuretics + β-adrenergic receptor blockers may have more than additive BP-lowering effects but may also accentuate one another's adverse effects (*eg*, accelerated onset of glucose intolerance, sexual dysfunction). In this respect, however, it should be noted that one of the main benefits of using a drug combination is the fact that lower doses of each agent are needed to reach the BP target, which diminishes the probability and the intensity of dose-dependent side effects. One such low-dose combination is bisoprolol + hydrochlorothiazide [21]. Several fixed combinations of diuretics with β-blockers were reported in the literature of earlier years [22], including fixed three-drug combinations [22,23].

Kaliuretic + potassium-sparing diuretics

Kaliuretic + potassium-sparing diuretics is one of the oldest and most widely used combinations. Although they probably have no additive BP-lowering action, combinations of thiazides + spironolactone or amiloride improve the tolerability of the thiazide by reducing hypokalemia [24–26].

β-blockers + calcium channel blockers

β-Blockers + CCBs of the dihydropyridine type may have less than additive antihypertensive action, but they still complement each other in terms of their effects on peripheral vascular resistance and cardiac output and minimize each other's adverse effects: β-blockers suppress the RAS and sympathetic stimulation caused by the vasodilatory effect of the CCB, whereas the CCB minimizes the peripheral vasoconstricting action of the β2-adrenergic blockade. Several such combinations have been used successfully [27–29].

Finally, there are combinations that are undesirable or inappropriate, either because they have little additional BP-lowering effect than each component alone (*eg*, CCB and diuretic) or, worse still, because their adverse effects might be additive to the point of becoming dangerous (*eg*, verapamil + β-adrenergic blocker, which can lead to excessive bradycardia and depressed myocardial contractility, leading to heart block or congestive heart failure).

A helpful mnemotechnic is what Brown *et al.* [30] have proposed as the "AB/CD rule": angiotensin-inhibiting (A) or β-blocking (B) drugs are best combined with calcium blockers (C) or diuretics (D). However, they also note the diabetogenic potential of older "B" and "D" combinations, and recommend "A" + "C" + "D" as preferable for standard triple therapy for resistant hypertension.

Accordingly, the choice of optimal drug combinations requires a judgment call, taking into account individual clinical circumstances relevant to mechanisms of BP maintenance (age, ethnicity, dietary habits) and to coexisting conditions (*eg*, diabetes, obesity, gout, ischemic heart disease). Whether the chosen combination is prescribed as separate drugs or as a fixed drug combination requires another judgment call.

Table 1. Advantages and disadvantages of fixed drug combinations

Advantages	Disadvantages
Fewer pills	Loss of flexibility
Low individual doses	Difficult to titrate
Better tolerability	Unclear cause of adverse reactions
Improved compliance	Increased potential for adverse interactions
Convenience	
Lower cost	

Fixed Drug Combinations

Much has been written in recent years about the advantages and disadvantages of using fixed drug combinations [5–11,13,15,17–29]. There are also arguments relevant to the proper timing of instituting a chosen fixed combination—that is, as first choice upon initiation of drug therapy or upon reaching the BP goal, after which no further changes are likely to be needed [31–35]. Table 1 summarizes the pros and cons of these choices. Table 2 presents a list of common marketed fixed combinations. Obviously, only drugs with synergistic or additive effects and no serious adverse interactions are offered in such formulations.

Clearly, the advantages of a fixed drug combination derive from the ability to attack the BP via two or more mechanisms using low doses of drugs with synergistic actions. Taking fewer pills enhances compliance because of greater convenience, favorable psychological impact, better acceptance of the need for life-long therapy, less probability of dose-dependent adverse effects, and lower cost if the patient is responsible for full pay or co-pay. Several surveys have demonstrated that essentially healthy patients tend to miss routinely scheduled doctor's visits and to stay on the originally prescribed regimen, as long as they feel well. In such patients, initiating antihypertensive therapy with a low-dose, two-drug combination to avoid need of upward titration is a reasonable first choice, as it is more likely to bring them on target with fewer visits.

Several of the combinations listed in Table 2 are available in multiple-dose combinations, especially regarding the diuretic dosing, thus permitting some flexibility if upward titration becomes necessary. On the negative side, of course, it is often difficult to maximize the dose of one component—for example, the ACEI or ARB, when this becomes desirable—without maximizing the other, which may be undesirable for fear of adverse effects. In such a case, switching to separate prescriptions might be upsetting or confusing to the patient. This is one of the main reasons that many practitioners prefer to switch to the fixed combinations for chronic maintenance, after the drugs have been titrated, the target BP has been obtained, and no further changes are anticipated. Another is the eventuality of an adverse reaction. If a side-effect occurs that is related to the drugs' mechanism combination, such as cough from an ACE inhibitor–containing combination or ankle edema from a dihydropyridine-containing combination, the diagnosis is easy. But if the patient develops an allergic reaction or a gastrointestinal disturbance, it is impossible to figure out which component is the culprit, and both agents are likely to be discarded. Despite this (rather infrequent) disadvantage, the fixed combination, especially starting at higher doses, is also an appropriate first choice for the high-risk patient with more severe hypertension, for whom rapid attainment of a safe, if not quite optimal, BP level is desirable, and monotherapy is deemed unlikely to be sufficient. A common example is the hypertensive diabetic with compromised renal function and elevated cardiovascular risk, who is likely to require three or more drugs before reaching target BP [3••].

Fixed combinations appropriate for initiation of therapy are usually those that include a thiazide-type diuretic, because diuretics are always recommended as first or second choice. Indeed, one of the main criticisms on the design of the recent Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) trial [36••] was the fact that addition of diuretic was precluded in patients not responding to an ACE-inhibitor monotherapy, thus depriving them of an optimal drug combination, whereas those not responding to thiazide monotherapy had the benefit of optimizing their response by adding a β-adrenergic blocker, which is a rational combination. Exceptions are the patients in whom thiazides are contraindicated (*eg*, because of coexisting gout or hyperparathyroidism) or are no longer effective because of chronic renal failure. In such a case, loop diuretics, indapamide, or metolazone are appropriate.

Additionally, as a note of caution: The unquestionable benefits of antihypertensive therapy have been demonstrated in large, randomized trials, in which the doses of drug combinations have been individually adjusted to compare outcomes of therapy based mostly on an agent from one class versus another. It was correctly pointed out that there are really no outcome trials comparing fixed-dose combinations [37], and, although intuitive clinical wisdom suggests which fixed combinations might be optimal, there are no hard data to guide evidence-based choices. A new, ongoing clinical trial entitled Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) is designed to directly compare cardiovascular morbidity and mortality between two fixed-dose combination therapies [38•].

The Future: The Polypill?

Interestingly, in recent years, combinations have been proposed that would include not only antihypertensives from different classes but also drugs not related to BP—for example, a statin or aspirin. Because most hypertensives are likely to have several components of the metabolic syndrome in

Table 2. Common marketed fixed drug combinations

Old drug combinations
Clonidine + HCTZ (*Clorpres*)
Methyldopa + HCTZ (*Aldoril*)
Hydralazine + HCTZ (*Hydra-Zide*)
Rauwolfia + HCTZ (Rauzide, Serpasil-Esidrex)
Three-drug: rauwolfia + hydralazine + HCTZ (Serapes)
Diuretics
HCTZ + spironolactone (*Aldactazide*, Al-tazide, Al-daciazinc)
HCTZ + amiloride (*Moduretic*)
HCTZ + triamterene (*Dyazide*, *Maxzide*)
β-blocker + diuretic
Atenolol + HCTZ (*Tenoretic*)
Bisoprolol +HCTZ (*Ziac*)
Timolol + HCTZ (*Timolide*)
Propranolol +HCTZ
Nadolol + bendroflumethiazide (*Corzide*)
Three-drug: HCTZ + amiloride + timolol (*Moducren*)
ACEI + diuretic
Benazepril + HCTZ (*Lotensin*-HCT)
Captopril + HCTZ (*Capozide*)
Enalapril + HCTZ (*Vaseretic*)
Lisinopril + HCTZ (*Zestoretic*, *Prinzide*)
Quinapril + HCTZ (*Accuretic*)
Moexipril + HCTZ (*Uniretic*)
Delapril + indapamide
Fosinopril + HCTZ
Perindopril + indapamide
Cilazapril + HCTZ
Ramipril + HCTZ
ARB + diuretic
Losartan + HCTZ (*Hyzaar*)
Irbesartan + HCTZ (*Avalide*)
Valsartan + HCTZ (*Diovan*-HCT, Co-Diovan)
Eprosartan + HCTZ (*Teveten*-HCT)
Telmisartan + HCTZ (*Micardis*-HCT)
Candesartan + HCTZ (*Atacand*-HCT)
Olmesartan + HCTZ (*Benicar*-HCT)
ACEI + CCB
Benazepril + amlodipine (*Lotrel*)
Enalapril + felodipine (*Lexxel*)
Trandolapril + verapamil SR (*Tarka*)
CCB + β-blocker
Felodipine + metoprolol (*Logimax*)
Nifedipine + atenolol

Italics denote brand names marketed in the United States.
ACEI—angiotensin-converting enzyme inhibitor; ARB—angiotensin II–receptor blocker; CCB—calcium-channel blocker; HCTZ—hydrochlorothiazide.

addition to hypertension, including a hypercoagulable state, glucose intolerance, and hypercholesterolemia, all requiring their own specific treatment, a so-called "polypill" might include several low-dose drugs. Such a combination of six agents was recently proposed, including an ACE inhibitor, a β-adrenergic blocker, a diuretic, a statin, low-dose aspirin, and folic acid (for suppression of homocysteine) [39•], thus permitting control of several common hemodynamic and metabolic aberrations with a single pill. This provocative and intriguing novel idea has elicited many comments, some of them sarcastic or cynical, but it may well have some merit for certain populations. Indeed, it was recently reported [40] that a "tetrapill," containing an ACE inhibitor, a β-adrenergic blocker, a statin, and aspirin, substantially improved the survival of patients with recent heart attacks or unstable angina.

Conclusions

Numerous large, longitudinal, antihypertensive drug outcome trials in recent years have established the facts that 1) desirable BP targets are at least 140/90 mm Hg and lower for diabetics or other patients at increased cardiovascular risk (*eg*, patients with chronic renal insufficiency), and 2) that such patients can rarely reach and maintain their target BP on monotherapy. Starting therapy with a combination of drugs with synergistic mechanisms and/or the capacity to cancel out one another's adverse effects is a reasonable alternative to the usual monotherapy with stepwise upward titration and subsequent addition of other drugs in many such patients. Fixed-dose combinations of drugs with complementary properties have the advantage of simplicity, tolerability, convenience, and cost-effectiveness, leading to improved compliance. As such, they may be appropriate as first choice for both the otherwise healthy subjects with mild hypertension, for whom an easy regimen with few follow-up visits is important, and for the more severely hypertensive patient with multiple risk factors, for whom intensive therapy with several drugs is needed to obtain optimal BP control. These benefits have to be weighed against the diminished dosing flexibility and the potential confusion if adverse reactions arise, requiring reevaluations and separate prescriptions.

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