Combination Therapy in Hypertension

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The goal of antihypertensive therapy is to abolish the risks associated with blood pressure (BP) elevation without adversely affecting quality of life. Drug selection is based on efficacy in lowering BP and in reducing cardiovascular (CV) end points, including stroke, myocardial infarction, and heart failure. Although the choice of initial drug therapy exerts some effect on long-term outcomes, it is evident that BP reduction per se is the primary determinant of CV risk reduction. Available data suggest that at least 75% of patients will require combination therapy to achieve contemporary BP targets, and increasing emphasis is being placed on the practical tasks involved in consistently achieving and maintaining goal BP in clinical practice. It is within this context that the American Society of Hypertension presents this Position Paper on Combination Therapy for Hypertension. It will address the scientific basis of combination therapy, present the pharmacologic rationale for choosing specific drug combinations, and review patient selection criteria for initial and secondary use. The advantages and disadvantages of single-pill (fixed) drug combinations and the implications of recent clinical trials involving specific combination strategies will also be discussed.
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The goal of antihypertensive therapy is to abolish the risks associated with blood pressure (BP) elevation without adversely affecting quality of life. Epidemiologic studies and clinical trials have been used to define individual risk and set appropriate BP targets,[1–3] recognizing that these targets reflect expert consensus based on available data and are subject to revision as additional evidence is obtained.[4] Drug selection is based on efficacy in lowering BP and in reducing cardiovascular (CV) end points, including stroke, myocardial infarction, and heart failure. Although the choice of initial-drug therapy exerts some effect on long-term outcomes, it is evident that BP reduction per se is the primary determinant of CV risk reduction. As a result, there has been a progressive lowering of BP targets in large segments of the hypertensive population, including diabetics and patients with established renal or vascular disease.[1–3,5] At the same time, increasing emphasis is being placed on the practical tasks involved in consistently achieving and maintaining goal BP in clinical practice.

It is within this context that the American Society of Hypertension presents this Position Paper on Combination Therapy for Hypertension. It will address the scientific basis of combination therapy, present the pharmacologic rationale for choosing specific drug combinations, and review patient selection criteria for initial and secondary use. The advantages and disadvantages of single-pill (fixed) drug combinations (SPCs) and the implications of recent clinical trials involving specific combination strategies will also be discussed.

COMBINATION THERAPY: A PRACTICAL NECESSITY

The ability to maintain constant or near-constant BP in response to various stressors is central to homeostasis, and the human organism has redundant physiologic mechanisms for regulating arterial pressure. BP is primarily determined by 3 factors: renal sodium excretion and resultant plasma and total body volume, cardiac performance, and vascular tone.[6] These factors control intravascular volume, cardiac output, and systemic vascular resistance, which are the immediate hemodynamic determinants of BP. Both the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS) are intimately involved in adjusting these parameters on a real-time basis. In addition, genetic makeup, diet, and environmental factors influence BP in individual patients.

Although it is occasionally possible to identify a specific cause for hypertension in some patients, BP elevation is usually multifactorial, making it very difficult, if not impossible, to normalize pressure by interfering with only a single pressor mechanism. In addition, drug therapy directed at any one component routinely evokes compensatory (counterregulatory) responses that reduce the magnitude of response, even if it was accurately directed at the predominant pathophysiologic mechanism. As a consequence, limited BP reduction is seen with all available antihypertensive agents. In a recent meta-analysis by Law and colleagues[7] of 354 randomized double-blind trials, the mean placebo-corrected reduction in BP with monotherapy was only 9.1/5.5 mm Hg. There was little difference in this regard between a diuretic, β-blocker, angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), or calcium channel blocker (CCB). Similar results were found in the Treatment of Mild Hypertension Study (TOMHS), in which comparable BP reduction was observed after long-term treatment with a diuretic, β-blocker, CCB, α-blocker, and ACE inhibitor.[8]

Clinical trials document that achieving BP targets is usually not possible with a single agent. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), only 26% of patients achieved goal BP with monotherapy—despite the fact that the target BP for diabetics (36% of the patient population) was <140/90 mm Hg rather than the <130/80 mm Hg mandated by current guidelines.[9] In the Hypertension Optimal Treatment (HOT) trial, 33% of patients achieved their BP target (diastolic only) with monotherapy, 45% required 2 drugs, and 22% needed ≥3 agents.[10] Systolic BP at the end of the study averaged 141 mm Hg, indicating that even a higher percentage of patients would have required combination therapy according to current treatment standards. In the Losartan Intervention for Endpoints Reduction (LIFE) trial, in which treatment to goal (<140/90 mm Hg) was aggressively pursued in patients with left ventricular hypertrophy and a mean baseline BP of 175/98 mm Hg, more than 90% required at least 2 antihypertensive agents.[11]

The importance of blocking multiple physiologic pathways is underscored by studies using a treatment strategy known as "sequential monotherapy." This approach is based on the observation that BP response to different antihypertensive medications is often quite variable, and BP control should be more readily achieved with monotherapy if patients are exposed to multiple drugs and then treated with the most effective agent.[12] In the Strategies in Treatment of Hypertension (STRATHE) study, treatment initiated with a low-dose combination was compared with a monotherapy arm in which patients were first treated with a β-blocker but could be switched to an ACE inhibitor or a CCB if BP remained >140/90 mm Hg. At the end of 9 months, a significantly higher percentage of patients randomized to the low-dose combination achieved target BP compared with those receiving sequential monotherapy (62% vs 49%, P=.02).[13]

The aggregate of available data suggests that at least 75% of patients will require combination therapy to achieve contemporary BP targets. This estimate reflects the results of previous studies, the lower BP targets now in place for large segments of the hypertensive population, and the rapidly increasing prevalence of obesity. The latter is important as the presence of obesity further elevates pretreatment BP and increases the magnitude of BP reduction needed to achieve therapeutic targets.[14]

The importance of achieving goal BP in individual patients cannot be overemphasized. In major clinical trials, small differences in on-treatment BP

frequently translate into major differences in clinical event rates. Recent data also suggest that inadequate BP control is itself an independent risk factor for the development of diabetes in hypertensive patients.[15]

COMBINATION THERAPY: THEORETIC CONSIDERATIONS

Efficacy

Rational combination therapy is based on the deliberate coadministration of ≥2 carefully selected antihypertensive agents. Inclusion of drugs known to reduce the long-term incidence of CV end points is highly preferred. A fundamental requirement of any combination is evidence that it lowers BP to a greater degree compared with monotherapy with its individual components. This is achieved by combining agents that either interfere with distinctly different pressor mechanisms or effectively block counterregulatory responses. Combining 2 drugs may result in partial or complete additivity of their BP-lowering effects, depending on the degree to which their pharmacologic effects are distinct and complimentary. Fully additive combinations are more effective in terms of BP reduction. In general, combining drugs from complementary classes is approximately 5 times more effective in lowering BP than increasing the dose of one drug.[16] Another important requirement of a combination is pharmacokinetic compatibility (ie, combined-drug administration results in smooth and continuous BP reduction throughout the dosing interval).[17] These principles apply regardless of whether agents are included in an SPC or are coadministered as separate drugs.

Tolerability

Improving the overall tolerability of treatment is a key element in designing rational drug combinations. This beneficial effect will occur whenever side effects associated with a particular agent are neutralized by the pharmacologic effects of an added drug.[17] Because most antihypertensive agents produce dose-dependent side effects, high-dose monotherapy may lead to adverse events. In this circumstance, a lower dose of the initial agent in combination with another antihypertensive may be preferable to minimize dose-dependent side effects even if no additional BP reduction is achieved. An example is the use of a low-dose combination of an ACE inhibitor and a dihydropyridine CCB in a patient who develops edema at a higher CCB dose. In this instance, reducing the CCB dose and adding an ACE inhibitor will produce comparable BP reduction, but will generally do so without the side effects previously observed.[18]

Adherence

Long-term adherence to treatment is necessary to control BP, and combination regimens can facilitate this objective, both in reducing the number of medications and the frequency of dosing required. A recent study of approximately 85,000 patients from Kaiser Permanente found that adherence was inversely related to the number of medications prescribed. In this study, antihypertensive medication adherence levels were 77.2%, 69.7%, 62.9%, and 55% in patients receiving 1-, 2-, 3-, or 4-drug regimens.[19] Other studies have found that adherence drops even more dramatically with increasing number of doses taken per day, from 71% with once-daily dosing to 61%, 50%, and 31% with 2, 3, or 4 daily doses of antihypertensive medication.[20] In many patients, SPCs promote adherence by reducing pill burden and simplifying the treatment regimen. In a meta-analysis of 9 studies comparing administration of SPCs or their separate components, the adherence rate was improved by 26% in patients receiving SPCs.[21]

It should be emphasized that simplification of the treatment regimen is only one strategy for improving adherence. For many patients, cost is a critical issue. Branded combinations that are not generically available are often more expensive and can, in some cases, result in significant co-payments that adversely affect medication adherence. It should be noted that many SPCs that combine an ACE inhibitor with a diuretic are generic, as is one ACE inhibitor/CCB combination. Physicians should be aware of these generic preparations and use them when necessary. They should not assume that an SPC improves adherence in every situation, particularly if its use increases direct patient expenditure or does not significantly reduce pill burden because the patient is receiving multiple other medications.

SPECIFIC DRUG COMBINATIONS

There are 7 major classes of antihypertensive drugs and multiple members of each class; therefore, the number of possible combinations is quite large. In this position paper, 2-drug combinations involving classes of pharmacologic agents that reduce CV end points (diuretics, CCBs, ACE inhibitors, ARBs, β-blockers) are emphasized. Combinations of ≥3 drugs are not reviewed. Specific combinations are designated as preferred or acceptable based on the considerations previously outlined. Combinations that are less effective on the basis of efficacy, safety, or tolerability concerns are also identified.

RAAS Inhibitor + Diuretic

The combination of an ACE inhibitor, ARB, or direct renin inhibitor with a low-dose thiazide-type diuretic results in fully additive BP reduction.[22–26] Diuretics initially reduce intravascular volume and activate the RAAS, leading to vasoconstriction as well as salt and water retention. In the presence of a RAAS inhibitor, this counterregulatory response is attenuated. Addition of a RAAS inhibitor to a thiazide-type diuretic also improves its safety profile by ameliorating diuretic-induced hypokalemia,[27] but can result in hyperkalemia in susceptible patients. Based on their safety, efficacy, and favorable performance in long-term trials, combinations of an ACE inhibitor or an ARB with a low-dose diuretic are classified as preferred. Most FDCs containing a diuretic use hydrochlorothiazide (HCTZ). Because chlorthalidone is more effective than other diuretics in reducing BP over 24 hours[28] and was the agent used in all but one large US-based hypertension outcome trial, some authorities favor its use over HCTZ. Because it is not currently aligned in any SPC with an ACE inhibitor or ARB, it can be administered as a separate agent.

RAAS Inhibitor + CCB

The combination of an ACE inhibitor or ARB with a CCB results in fully additive BP reduction.[29–31] Addition of either of these 2 RAAS inhibitors significantly improves the tolerability profile of the CCB. Through their antisympathetic effects, RAAS inhibitors blunt the increase in heart rate that may accompany treatment with a dihydropyridine-type CCB. In addition, RAAS inhibitors partially neutralize the peripheral edema, which is a dose-limiting side effect of these CCBs.[32] The cause of the edema is believed to be arteriolar dilation, resulting in an increased pressure gradient across capillary membranes in dependent portions of the body. RAAS blockers are thought to counteract this effect through venodilation.

The Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) trial tested whether initial fixed-dose combination therapy with an ACE inhibitor and CCB differs from initial fixed-dose combination therapy with an ACE inhibitor and diuretic on clinical outcomes in high-risk hypertensive patients. Despite comparable BP reduction, the ACE inhibitor/CCB combination reduced the combined end point of CV death, myocardial infarction, and stroke by 20% compared with the ACE inhibitor/diuretic combination.[33] Of note, 60% of patients were diabetic and a large percentage had evidence of underlying ischemic heart disease.[34] These results suggest the superiority of a CCB over a diuretic when used in conjunction with a RAAS blocker in this high-risk population. ACE inhibitor/CCB combinations are classified as preferred. In view of end point studies demonstrating comparability between ACE inhibitors and ARBs, ARB/CCB combinations are considered to be equivalent.[35]

RENIN INHIBITOR + ARBS

The combination of a renin inhibitor with an ARB produces partially additive BP reduction and is well tolerated. In a study in which maximum approved doses of valsartan and aliskiren were combined, a 30% additional BP response was observed compared with either monotherapy.[36] The side effect profile of this acceptable combination was comparable with placebo. There are no CV outcome data with this combination to date.

CCBs + Diuretics

The combination of a diuretic and a CCB results in partially additive BP reduction.[37,38] Presumably, this partial effect reflects overlap in the pharmacologic effects of the 2 drugs. CCBs increase renal sodium excretion, albeit not to the same extent as diuretics. Moreover, long-term treatment with both classes is associated with vasodilation, given that volume depletion does not occur with diuretics. From an end point perspective, this combination performed well in the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial in which HCTZ was added as a second step in patients randomized to amlodipine.[39] As opposed to ACE inhibitor/CCB or ARB/CCB combinations, the CCB + diuretic has no favorable effect on either drug's side effect profile. These combinations are classified as acceptable.

β-Blockers + Diuretics

Although β-blockers reduce CV end points in placebo-controlled trials, meta-analyses (based primarily on the performance of atenolol) suggest that they are less effective than diuretics, ACE inhibitors, ARBs, and CCBs.[40–42] The antihypertensive effects of β-blockers are mediated through reduction in cardiac output and suppression of renin release.[43] As with the ACE inhibitors and ARBs, β-blockers attenuate the RAAS activation that accompanies the use of thiazide diuretics, and their combination results in fully additive BP reduction.[44–46] Addition of diuretics also improves the effectiveness of β-blockers in black patients and

others with low-renin hypertension.[47] These combinations are classified as acceptable, recognizing that their use is associated with increased risk of glucose intolerance, fatigue, and sexual dysfunction.

Thiazide Diuretics + Potassium-Sparing Diuretics

Hypokalemia is an extremely important dose-related side effect of thiazide diuretics. By attenuating hypokalemia, the combination of HCTZ with a potassium-sparing diuretic such as triamterene, amiloride, or spironolactone improves its safety profile.[48] Because of the risk of hypokalemia that can lead to cardiac arrhythmias and sudden death, HCTZ 50 mg and chlorthalidone 25 mg should generally be used in combination with a potassium-sparing agent (or an inhibitor of the RAAS). Given the latest data demonstrating the importance of aldosterone blockade in obese patients and the efficacy of aldosterone blockade in helping achieve BP goals, the spironolactone/HCTZ combination is particularly well suited in such individuals.[49] The addition of amiloride to HCTZ reduces hypokalemia and results in variable BP reduction.[50,51] These combinations are classified as acceptable in people with relatively well-preserved kidney function (ie, estimated glomerular filtration rate >50 mL/min/1.73 m^2). At glomerular filtration rate levels below this, the risk for hyperkalemia increases and the diuretic efficacy of HCTZ starts to diminish.[52]

CCBs + β-Blockers

The pharmacologic effects of these 2 drug classes are complementary, and their combination results in additive BP reduction. In one study, a low-dose combination of felodipine extended-release (ER) and metoprolol ER produced BP reduction comparable to maximum doses of each agent with an incidence of edema similar to placebo.[53,54] The combination of a β-blocker and a dihydropyridine CCB is acceptable. β-Blockers should not generally be combined with nondihydropyridine CCBs such as verapamil or diltiazem because their additive effects on heart rate and atrioventricular conduction may result in severe bradycardia or heart block.

LESS-EFFECTIVE COMBINATIONS

ACE Inhibitors + ARBs

Although sometimes useful for proteinuria reduction and in the treatment of symptomatic patients with heart failure, the combination of an ACE inhibitor and an ARB is not recommended for the treatment of hypertension. ACE/ARB combinations produce little additional BP reduction compared with monotherapy with either agent alone. In the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET), patients receiving the ACE inhibitor/ARB combination showed no improvement in CV end points despite additional BP reduction averaging 2.4/1.4 mm Hg.[35] There were also more side effects with the combination than with individual agents. These combinations are classified as less effective.

RAAS Inhibitors + β-Blockers

These drug classes are both cardioprotective and frequently coadministered to patients with coronary heart disease or heart failure. When these agents are combined, however, they produce little additional BP reduction compared with either monotherapy.[55] For this reason, they constitute a less effective combination when BP reduction is the principal goal. They can, however, be used together in patients with coronary artery disease or heart failure when outcome improvement is the primary objective.

β-Blockers + Centrally Acting Agents

β-Blockers and centrally acting agents (eg, clonidine, a-methyldopa) interfere with the sympathetic nervous system. The degree to which they produce additive BP reduction has not been studied. When used together, their combination may result in severe bradycardia or heart block. In addition, when abruptly discontinued, patients receiving these drugs in combination may exhibit severe rebound hypertension.[56] For this reason, they constitute a less-effective combination.

CLINICAL APPLICATION

Patient Selection: Initial Therapy

Because most patients with hypertension will require 2 or 3 drugs to achieve BP control, the pivotal questions for initial therapy are as follows.

- Should treatment be started with monotherapy or a combination?
- If 2 drugs are initiated, should they be administered as single entities or an SPC?

Although there is limited scientific evidence to definitively answer these questions, several considerations support the use of initial combination therapy in most patients with hypertension. Initiation of multiple drugs targets multiple physiologic pathways, making it more likely that those making a significant contribution to BP elevation will be inhibited. By beginning with combination therapy, counterregulatory responses will be reduced. The

result is an increase in the percentage of responders as well as increased magnitude of response in any population of hypertensive patients.

Recent studies also suggest an important correlation between the time taken to achieve goal BP and clinical outcome. In the VALUE trial, a post hoc analysis indicated that patients who reached target BP within 6 months of entering the protocol demonstrated substantially better outcomes throughout the 5-year duration of the study, regardless of assigned treatment.[57] Likewise, in the International Verapamil SR-Trandolapril (INVEST) study, lower CV risk was documented in patients who spent a larger fraction of the time with BP <140/90 mm Hg.[58,59] It is therefore prudent to adopt therapeutic approaches designed to achieve goal BP within several months whenever possible.

Several studies have documented that BP control is more rapidly achieved using an initial combination strategy. Weir and colleagues[60] compared the time to achieve goal BP with fixed doses of the ARB, valsartan, alone and in combination with HCTZ in a meta-analysis of 9 randomized trials that included patients with either stage 1 or 2 hypertension. After 8 weeks of treatment, 48% of patients begun on monotherapy with the usual starting dose of valsartan achieved their Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) 7 target compared with 75% begun on a combination of HCTZ with the same dose of valsartan.[60] In the ACCOMPLISH study, the first major end point trial in which treatment was initiated with an SPC, BP was reduced to <140/90 mm Hg in 73%of patients after 6 months.[61] The Simplified Treatment Intervention to Control Hypertension (STITCH) study compared the effectiveness of a treatment algorithm using an initial SPC (ACEI/HCTZ or ARB/HCTZ) to a guideline-based approach that included initial monotherapy in 45 Canadian family practices. In this "real-world" study, the proportion of patients who achieved target BP within 6 months was 65% in those initiated with the SPC compared with 53% receiving guideline-based treatment. Patients initiated on the SPC experienced no additional side effects.[62]

Current guidelines suggest that 2 drugs be used for initial therapy if there is a 20/10-mm Hg elevation in BP above goal (BP >160/100 mm Hg for patients with uncomplicated hypertension or >150/90 mm Hg for those with diabetes and other comorbid conditions).[1–3] For patients with stage 1 hypertension, it is often reasonable to start with monotherapy. Recent data, however, suggest that the advantages of initial combination treatment may extend to stage 1 hypertension. In the meta-analysis by Weir and colleagues, the magnitude of effect in terms of time-specific achievement of goal BP was greater in the stage 1 compared with the stage 2 subgroup. Among patients who had stage 1 hypertension, 72% achieved their JNC 7 target by week 8 if initiated on valsartan 160 mg monotherapy vs 92% who received initial therapy with the same dose of valsartan in combination with HCTZ.[60] With regard to tolerability, the percentage of patients complaining of dizziness was higher in the combination treatment group, but the number who discontinued therapy from adverse events was similar.

Single-Pill Combinations

SPCs may be used as initial treatment in a patient in whom multidrug therapy is likely to be needed, as the "second step" in a patient partially controlled on monotherapy, or as a substitute for independently titrated doses of individual components. Convenience is the major advantage of using an SPC. It is easier for the patient to comply with a regimen that includes fewer pills.[63] In addition, it takes less time for a physician to achieve BP control in a group of patients using a combination that is known to be safe, effective, and well tolerated.[62,64] On the other hand, SPCs may significantly increase the cost to the patient compared with adding individual generic drugs and may affect the pharmacokinetics of administered agents. The same or better control rates and medication costs as SPCs can be achieved through the use of a labor-intensive, knowledge-based approach. For example, in the Collaborative Management of Hypertension study, a physician/pharmacist team achieved an 89% BP control rate within 9 months using such an approach.[65] Although some form of combination treatment is a necessity, similar treatment results are achievable with or without the routine use of SPCs. The choice can be made based on the individual practice setting and the resources available to both patient and physician.

Combination Therapy: Partially Treated Patients

In patients who are taking antihypertensive therapy but do not have their BP controlled, additional treatment is indicated. The selection of specific combinations should be made from those that are listed as preferred or acceptable in the Table. Less-effective combinations should generally be avoided

Table. Drug Combinations in Hypertension: Recommendations

Preferred
ACE inhibitor/diuretic[a]
ARB/diuretic[a]
ACE inhibitor/CCB[a]
ARB/CCB[a]
Acceptable
β-Blocker/diuretic[a]
CCB (dihydropyridine)/β-blocker
CCB/diuretic
Renin inhibitor/diuretic[a]
Renin inhibitor/ARB[a]
Thiazide diuretics/K+-sparing diuretics[a]
Less effective
ACE inhibitor/ARB
ACE inhibitor/β-blocker
ARB/β-blocker
CCB (nondihydropyridine)/β-blocker
Centrally acting agent/β-blocker

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker. [a]Single-pill combinations available in the United States.

or used with caution. The choice of specific combinations will be dictated by individual patient considerations including demographics, comorbid conditions, response to previous treatments, and cost, as well as physician preference. The goal is always a cost-effective, long-term treatment that controls BP using agents that are safe, effective, and well tolerated.

SUMMARY RECOMMENDATIONS

- Routinely use combination therapy to achieve BP targets
- Use only preferred or acceptable 2-drug combinations (Table)
- Routinely initiate combination therapy in patients who require ≥20/10-mm Hg BP reduction to achieve target BP
- Initiate combination therapy in stage 1 patients (at the physician's discretion), especially when the second agent will improve the side effect profile of initial therapy
- Use SPCs rather than separate individual agents in circumstances where convenience outweighs other considerations.

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