Review Paper

Antihypertensive Combination Therapy: Optimizing Blood Pressure Control and Cardiovascular Risk Reduction

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Treating hypertension reduces the rates of myocardial infarction, stroke, and renal disease; however, clinical trial experience suggests that monotherapy is not likely to be successful for achieving goal blood pressure (BP) levels in many hypertensive patients. In multiple recent clinical trials including various subsets of hypertensive patients, the achievement of BP goal has typically required the combination of 2 or more medications, particularly in patients with BP levels >160/100 mm Hg. When initiating combination therapy for hypertension, careful consideration must be given to the choice of medication. Clinical trial evidence has shown the efficacy of various combinations of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, and diuretics in reducing BP and cardiovascular risk. Ongoing trials should provide additional guidance on the optimal choice of combination regimens in specific clinical settings. (J Clin Hypertens. 2007;9(11 suppl 4):26–32)

The benefits of treating hypertension include reductions in the rates of myocardial infarction (MI), stroke, and renal disease. There is no doubt that these outcome benefits are in large part the consequence of reduced blood pressure (BP); the role of specific treatment agents remains a focus of controversy. In this article, the role of combination therapies in hypertension treatment is reviewed.

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IS COMBINATION THERAPY NECESSARY?

The most recent National Health and Nutrition Survey (NHANES),[1] conducted during 2003 and 2004, reported that the overall age-adjusted prevalence of hypertension was 29.3%; among those with hypertension, 66.5% were aware of their diagnosis, 53.7% were receiving treatment, and the rate of control to target was 33.1% (63.9% of those receiving treatment). Compared with data from NHANES 2001–2002, these data suggest that more individuals are becoming aware of their BP level (awareness improved from 62.5%) and receiving treatment (up from 50.1%). The improvement in BP control rates among all hypertensive patients, however, was modest (up from 30.3%); perhaps more strikingly, the control rate among treated patients was unchanged.[1]

In a more recent (January 2007) national Harris Interactive survey of 1245 hypertensive adults in the United States conducted for the Hypertension Education Foundation, >90% of respondents were aware that high BP is associated with increased risk of cardiovascular events.[2] More than 90% of those surveyed were taking medication for their hypertension; however, only 50% to 60% were involved in some form of lifestyle change to control BP. Approximately 60% of individuals reported that their BP was controlled (<140/90 mm Hg) at their previous physician visit; however, 50% reported that they were told by a health care provider at some time that their BP level remained too high. Similar data were reported from the Behavioral

Risk Factor Surveillance System, in which 98% of 24,447 hypertensive individuals from 20 American states reported taking some action to control BP; 73% reported taking BP-lowering medication.[3] Despite these positive trends, a greater effort to control hypertension is necessary if cardiovascular events are to be controlled still further.

Years ago, guidelines for hypertension management focused on treating hypertension with monotherapy, using the concept "start low, go slow" to avoid adverse effects and with an underlying belief that most individuals would respond to one particular mechanism of drug treatment. More recently, clinical trial experience suggests that this approach is not likely to be successful in most patients. In multiple recent clinical trials including various subsets of hypertensive patients (eg, those with diabetes, specific ethnic groups), the achievement of BP goal typically required 2 or more medications, despite proper titration in a controlled setting under the guidance of a protocol in which the availability of medication was not a concern.[4–9] The results of these studies made it clear that multiple-drug therapy is likely to be required in most patients, particularly in individuals with stage 2 hypertension (BP level >160/100 mm Hg).

Consensus treatment guidelines have provided practical recommendations to caregivers on when to initiate multiple-drug therapy. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)[10] suggests that antihypertensive therapy be initiated with 2 drugs when individuals present with a BP level >20 mm Hg above systolic goal and/or >10 mm Hg above diastolic BP goal. Because this recommendation is tied to specific BP targets for individual patients, it is applicable not only to isolated hypertension but also across a broad range of comorbidities, including diabetes, renal disease, and existing cardiovascular disease, for which BP goals are <140/90 mm Hg.

A similar approach to treatment initiation has been taken by the Hypertension in African Americans Working Group (HAAWG).[11] African American patients represent the highest-risk ethnic group in the United States—hypertension develops at earlier ages than among whites and is associated with rates of fatal stroke, fatal heart disease, and end-stage renal disease (ESRD) that are 1.8 times, 1.5 times, and 4.2 times greater, respectively, than in white patients. The overall death rate from hypertension in this population is >3 times that in white Americans. In 2004, the age-adjusted death rate from hypertension was 15.6 and 14.3 per 100,000 for white men and women, respectively, compared with 49.9 and 40.6 per 100,000 for African American men and women, respectively.[12] In recognition of these risks, the HAAWG suggested that a more intensive approach was warranted in these patients, involving initiation of 2 drugs when BP exceeds goal by >15 mm Hg systolic and/or >10 mm Hg diastolic.[11] Therefore, 2 consensus panels have concluded that treatment initiation with 2 drugs is strongly supported and justified in many cases of hypertension management.

COMBINATION THERAPY OPTIONS

Recent clinical trials have provided data on mortality and morbidity outcomes with respect to different combination therapies for hypertension. The Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm (ASCOT-BPLA)[13] was a prospective, randomized, open-label, blinded end point trial in which 19,257 hypertensive adults aged 40 to 79 years with ≥3 other cardiovascular risk factors received either the calcium channel blocker (CCB) amlodipine plus the angiotensin-converting enzyme (ACE) inhibitor perindopril if necessary or the β-blocker atenolol with the thiazide diuretic bendroflumethiazide added if necessary to lower BP. (ASCOT-BPLA incorporated a 2 × 2 factorial design in which patients with moderately elevated cholesterol received placebo or atorvastatin; the lipid-lowering component was discontinued early because of the significant benefit of atorvastatin.)

The BP component of ASCOT-BPLA was stopped prematurely after 5.5 years of median follow-up because there was significantly less risk of secondary end points, including nonfatal MI, total cardiovascular end points, all-cause mortality, stroke, and heart failure in patients treated with amlodipine/perindopril compared with those treated with atenolol/bendroflumethiazide.[13] There was also a nonsignificant trend toward reduced risk for the primary end point (nonfatal and fatal MI) favoring amlodipine/perindopril treatment.[13] A subsequent analysis, adjusting for mean BP level, demonstrated reductions of 13% (P<.014) and 17% (P<.018), respectively, in risks for the primary end point and stroke.[14]

Another major trial of combination antihypertensive therapy is under way, with cardiovascular mortality and morbidity as the primary outcome. The Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET)[15] is designed to test whether the angiotensin II receptor blocker (ARB) telmisartan,

Table. Fixed-Dose Combination Drug Options

Drug	Trade Name
Diuretics and potassium-sparing agents	
Amiloride 5 mg/hydrochlorothiazide 50 mg	Moduretic
Spironolactone 25 or 50 mg/hydrochlorothiazide 25 or 50 mg	Aldactazide
Triamterene 37.5, 50, or 75 mg/hydrochlorothiazide 25 or 50 mg	Dyazide, Maxzide
β-Blockers and diuretics	
Atenolol 50 or 100 mg/chlorthalidone 25 mg	Tenoretic
Bisoprolol 2.5, 5, or 10 mg/hydrochlorothiazide 6.25 mg	Ziac
Metoprolol 50 or 100 mg/hydrochlorothiazide 25 or 50 mg	Lopressor HCT
Nadolol 40 or 80 mg/bendroflumethiazide 5 mg	Corzide
Propranolol 40 or 80 mg/hydrochlorothiazide 25 mg	Inderide
Propranolol (extended-release) 80, 120, or 160 mg/hydrochlorothiazide 50 mg	Inderide LA
Timolol 10 mg/hydrochlorothiazide 25 mg	Timolide
ACE inhibitors and diuretics	
Benazepril 5, 10, or 20 mg/hydrochlorothiazide 6.25, 12.5, or 25 mg	Lotensin HCT
Captopril 25 or 50 mg/hydrochlorothiazide 15 or 25 mg	Capozide
Enalapril 5 or 10 mg/hydrochlorothiazide 12.5 or 25 mg	Vaseretic
Fosinopril 10 or 20 mg/hydrochlorothiazide 12.5 mg	Monopril HCT
Lisinopril 10 or 20 mg/hydrochlorothiazide 12.5 or 25 mg	Prinzide; Zestoretic
Moexipril 7.5 or 15 mg/hydrochlorothiazide 12.5 mg	Uniretic
Quinapril 10 or 20 mg/hydrochlorothiazide 12.5 mg	Accuretic
ARBs and diuretics	
Candesartan 16 or 32 mg/hydrochlorothiazide 12.5 or 25 mg	Atacand HCT
Irbesartan 150 or 300 mg/hydrochlorothiazide 12.5 or 25 mg	Avalide
Losartan 50 or 100 mg/hydrochlorothiazide 12.5 or 25 mg	Hyzaar
Valsartan 80 or 160 mg/hydrochlorothiazide 12.5 or 25 mg	Diovan HCT
CCBs and ACE inhibitors	
Amlodipine 2.5 or 5 mg/benazepril 10 or 20 mg	Lotrel
Diltiazem 180 mg/enalapril 5 mg	Teczem
Felodipine 2.5 or 5 mg/enalapril 5 mg	Lexxel
Verapamil (extended release) 180 or 240 mg/trandolapril 1, 2, or 4 mg	Tarka
CCBs and ARBs	
Amlodipine 5 or 10 mg/valsartan 160 or 320 mg	Exforge
Amlodipine 5 or 10 mg/olmesartan 20 or 40 mg	Azor
Other combinations	
Clonidine 0.1, 0.2, or 0.3 mg/chlorthalidone 15 mg	Combipres
Hydralazine 25, 50, or 100 mg/hydrochlorothiazide 25 or 50 mg	Apresazide
Methyldopa 250 or 500 mg/hydrochlorothiazide 15, 25, 30, or 50 mg	Aldoril
Reserpine 0.10 mg/hydralazine 25 mg/hydrochlorothiazide 15 mg	Ser-Ap-Es
Reserpine 0.125 mg/hydrochlorothiazide 25 or 50 mg	Hydropres

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker.

the ACE inhibitor ramipril, or the combination confers cardioprotection independent of BP lowering in high-risk patients whose BP is well-controlled. ONTARGET has enrolled 25,620 high-risk patients (mean age, 66.9 years) with either a history of cardiovascular disease (coronary artery disease, peripheral arterial disease, or cerebrovascular disease) or diabetes with documented end-organ damage. The primary end point of ONTARGET is a composite of cardiovascular death, nonfatal MI, stroke, or hospitalization for heart failure. Patient follow-up is planned for 3.5 to 5.5 years. At randomization, 68.3% of the study population had hypertension, and mean BP was 134/77 mm Hg. Results are anticipated in 2008.

There are several studies assessing the BP, renal, and heart failure outcomes of ACE inhibitor and ARB combination therapy; however, ONTARGET

is the only ongoing investigation of cardiovascular mortality and morbidity. The rationale for ONTARGET is based on the concept that although both ARBs and ACE inhibitors reduce BP by inhibiting the effects of the renin-angiotensin system (RAS) on the vasculature, these drug classes target different aspects of the RAS and their action may therefore be complimentary. ACE inhibitors block the formation of angiotensin II from angiotensinogen via inhibition of ACE; however, because angiotensinogen may be converted to active angiotensin II by non-ACE pathways, RAS blockade is incomplete. ARBs block the angiotensin receptor type 1 (AT_1), reducing the effects of angiotensin at this site. Other angiotensin receptor subtypes, however, may still interact with angiotensin II; moreover, both ARBs and ACE inhibitors may induce a compensatory increase in the level of angiotensin II.

Overall, the long-term effects of these alterations of the RAS remain unclear. In preclinical studies of ACE inhibitors and ARBs, RAS blockade was shown to suppress markers of atherosclerosis, inflammation, and oxidative stress.[16–18] In addition, receptor blockade with ARBs may promote the interaction of angiotensin II with an alternate receptor, AT_2, which has been shown to inhibit the proliferation of endothelial cells (which is thought to contribute to the progression of hypertension).[16]

Although clinical studies of properly dosed ACE inhibitor and ARB combinations have not shown impressive benefits with respect to BP reduction, they have demonstrated significant improvement with regard to target organ damage, specifically heart failure and proteinuria. For example, in the Combination Treatment of Angiotensin II Receptor Blocker and Angiotensin-Converting Enzyme Inhibitor in Nondiabetic Renal Disease (COOPERATE) trial,[19,20] 336 patients with nondiabetic renal disease were treated with the ACE inhibitor trandolapril, the ARB losartan, or the combination. Combination therapy did not lower BP to a significantly greater degree than either monotherapy; however, the incidence of a composite renal outcome (doubling of serum creatinine level or progression to ESRD was reduced by about 60% with combination therapy relative to both monotherapies. Similarly, in the Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) pilot study[21] of patients with heart failure, in which patients received the ARB candesartan, the ACE inhibitor enalapril, or the combination, combination therapy tended to have a more beneficial effect on cardiac volumes and ejection fraction. This finding was not related to a reduction in BP; there were no significant differences observed among groups for changes in BP.

In the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM)-Added trial,[22] the ARB candesartan or placebo was added to preexisting ACE inhibitor therapy in 2548 patients with congestive heart failure and a left ventricular ejection fraction <40%. Compared with placebo, candesartan was associated with significant reductions in cardiovascular death (by 16%; *P*=.029) and hospital admission for heart failure (by 17%; *P*=.014). By 6 months, BP was lowered from baseline by 4.6 mm Hg systolic (*P*=.007) and 3.0 mm Hg diastolic (*P*=.004) more in the candesartan group than in the placebo group. Across the entire CHARM program, candesartan provided significant benefit, compared with placebo, with respect to cardiovascular death and heart failure hospitalization, regardless of whether patients were receiving an ACE inhibitor at baseline; however, the effect of candesartan on all-cause mortality was not significant.[23] Thus, it is possible that vascular and cardioprotective benefits may be significantly improved by the addition of other agents. Whether the noted benefit resulted from the BP differences or were a result of specific therapy can be debated.

Another investigation of combination antihypertensive treatment evaluating cardiovascular morbidity and mortality is the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) trial.[24] The ACCOMPLISH trial is the first blinded and randomized study that will prospectively compare the effects of 2 antihypertensive combinations, the ACE inhibitor benazepril plus the diuretic hydrochlorothiazide (force-titrated to 40/12.5 mg, with the option to raise to 40/25 mg) and benazepril plus amlodipine (force-titrated to 40/5 mg, with the option to raise to 40/10 mg) on a composite cardiovascular mortality and morbidity end point. Eligibility criteria include systolic hypertension (systolic BP ≥160 mm Hg or currently on antihypertensive therapy) and a history of risk factors (target organ damage, kidney disease, or diabetes) for cardiovascular events. More than 12,000 patients (mostly elderly) from the United States and Europe were randomized into the study from 2003 to 2005, and the study is expected to be completed in October 2008.

The ACCOMPLISH study is based on the premise that although ACE inhibitors, thiazide diuretics, and CCBs each reduce cardiovascular disease

through BP reduction, there is evidence that ACE inhibitors improve cardiac and renal disease beyond BP-lowering effects.[25] This has led to the recommendation that ACE inhibitors should be used as initial therapy for patients with renal disease, diabetes, and high-risk conditions.[10] Although thiazides enhance the effectiveness of ACE inhibitors through the reduction of sodium and plasma volume, thereby increasing renin levels, their effects on other components of vascular disease in hypertension, such as oxidative stress and endothelial dysfunction, are less clear. Alternatively, CCBs improve nitric oxide availability, which may improve endothelial dysfunction; however, less is known about their effect on oxidative stress. In addition, CCBs have a high response rate and strong vasodilatory effect. The results of the ACCOMPLISH trial should help clarify whether thiazide diuretics or CCBs are superior combination partners in high-risk patients with hypertension.

Several studies have investigated the effects of combination therapies on surrogate disease markers. Combination therapy with a CCB and an ACE inhibitor improves renal proteinuria more than ACE inhibitor or CCB monotherapy.[26] In addition, the increase in proteinuria seen in early treatment with CCBs is offset when these agents are given in combination with an ACE inhibitor.[26] The combination of an ACE inhibitor and an ARB has demonstrated improvement in proteinuria and reduction in the progression to ESRD, compared with ACE inhibitor or ARB monotherapy in nondiabetic renal disease.[20] Similar studies are ongoing, using similar combinations in diabetic and nondiabetic proteinuria.[27] Other studies have shown the benefit of combination therapy on cognition with the ACE inhibitor perindopril plus the diuretic indapamide.[28] A more recent trial in which elderly patients with hypertension were treated with telmisartan plus hydrochlorothiazide suggested that an ARB plus a diuretic also protects cognitive function.[29] An open-label study in which amlodipine, benazepril, and the combination were evaluated in hypertensive patients showed that measures of vascular compliance and function are improved significantly with ACE inhibitor plus CCB combination therapy compared with monotherapy with either agent.[30] These trials all suggest that therapy with 2 agents is superior to monotherapy in improving surrogate end points.

FIXED-DOSE COMBINATIONS

Combination therapy is not only supported scientifically; it also has practical benefits. A major barrier to BP control is poor adherence to therapy. In the context of combination treatment, it has been shown that reducing the number of pills prescribed has a positive effect on adherence; it may also reduce the resource allocation and cost associated with antihypertensive therapy at both the health care system and individual patient level.[31,32] The Table lists some currently available fixed-dose antihypertensive combinations, including the recently approved CCB/ARBs.

WHAT TO DO WHEN 2-DRUG THERAPY IS NOT ENOUGH

Clinical trial data indicate that a number of patients will require a third or fourth drug to adequately manage BP, which raises the question of how to proceed when a 2-drug combination fails to reduce the BP level to target. Several considerations, beginning with an assessment of the patient's response and underlying conditions, may help direct the selection of additional therapies.

Selecting an agent from a different class than the initial 2 drugs in the combination therapy is a reasonable option. In resistant hypertension, the addition of the aldosterone inhibitor spironolactone may significantly improve BP control, even at low doses and without producing significant hyperkalemia.[33] It remains important to assess potassium levels, however, and renal function should be assessed before and following initiation of therapy. Although direct vasodilators such as minoxidil and hydralazine can provide the necessary potency, they frequently require high-dose diuretics for volume control and β-blockers to attenuate reflex heart rate increases. Some concurrent conditions (such as pulmonary hypertension or aortic valvular disease), however, may specifically indicate the need for these agents. Labetalol and carvedilol are possible options, particularly for labile hypertension, as they offer both β-blockade and vasodilation based on their α-blocking action. Because of significant adverse effects, the centrally acting agents clonidine, guanfacine, and methyldopa should be reserved as a last resort. In particular, careful consideration of heart rate suppression must be given when using these agents in the setting of concurrent β-blocker use.

In isolated systolic hypertension, the addition of isosorbide nitrates has been shown to improve BP control.[34] The recent introduction of a direct renin inhibitor (aliskiren) offers yet another add-on option, although there are only preliminary data with respect to its use in combination therapy, demonstrating additional BP reduction when added to ARB therapy.[35] Additional clinical trials are needed to provide guidance on the management of patients with hypertension that is resistant or refractory to

medical therapy. Secondary hypertension should be considered in patients who fail to respond to multidrug antihypertensive regimens, especially if a 4-drug combination is ineffective.

CONCLUSIONS

Antihypertensive therapy has clear benefits; however, achievement of BP control is fraught with significant challenges that impede success. Combination therapies offer clinicians a better chance to reach goals in the patients they treat but require careful consideration with respect to the choice of agents. New clinical trials should provide additional guidance on the optimal choice of combination regimens (ACE inhibitor plus ARB, ACE inhibitor or ARB plus CCB, ACE inhibitor or ARB plus diuretic) in specific clinical settings. It is encouraging, however, that combination therapy has been found to be safe and well-tolerated, with evidence of clinical benefit in most studies of hypertension treatment.

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