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Recent Update on Fixed Combinations of Antihypertensive Agents

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ABSTRACT

The amlodipine/atorvastatin single tablet has been shown to improve patients' achievement of national guideline recommended blood pressure and lipid target levels and exhibits a safety profile consistent with the parent compounds. The single tablet formulation has the potential to improve adherence and decrease prescription costs. These potential benefits are associated with important implications because hypertensive patients with additional risk factors represent a large proportion of those at risk for cardiovascular events. Combination low-dose drug treatment increases efficacy and reduces adverse effects. Fixed low-dose combination drug treatment increases efficacy and reduces adverse effects. This combination has greater potency and a similar side effect profile to monotherapy and represents a highly effective approach for attaining goal blood pressure levels using a therapeutic strategy that very effectively lowers blood pressure, is well-tolerated, and minimizes increasing doses of monotherapy-induced metabolic effects. **(Korean Circ J 2008;38:237-243)**

KEY WORDS: Combination drug therapy; Amlodipine; Atorvastatin; Risk reduction.

Introduction

Hypertension is the leading risk factor for cardiovascular disease (CVD) mortality, which accounts for approximately 30% of all deaths worldwide. According to an analysis based on the Framingham data, 78% of hypertensive males and 82% of hypertensive females have at least one other cardiovascular (CV) risk factor.[1] The Health Survey for England reported in 1998 that 19% of males and 26% of females with hypertension also had high total cholesterol levels.[2]

Patients with hypertension are also more likely to have associated CV risk factors; for example, approximately 50% of patients with hypertension have hypercholesterolaemia and 20-40% of patients with hypertension have hyperglycaemia. The presence of multiple risk factors increases the risk of CV events associated with hypertension. The most common risk factors for CVD include advanced age (> 55 years for males and >65 years for females), smoking, dyslipidaemia, family history of premature CVD, abdominal obesity, abnormal C-reactive protein levels, and clinical conditions, such as diabetes and renal disease.[3]

For the appropriate control and improving compliance in hypertensive patients, fixed-dose combination therapy for better blood pressure (BP) and risk control are currently recommended.

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Benefits of multifactorial intervention

Recent evidence suggests that large-scale reductions in cardiovascular events are observed when hypertension and dyslipidemia are treated. For example, it has been calculated that almost one-half of the coronary heart disease events occurring in hypertensive patients could be prevented by controlling BP and lipid levels. However, several different medications with varying frequencies of dosing are important contributory factors to poor compliance, particularly in elderly patients. Therefore, efforts should be made to simplify drug regimens to reduce the frequency of drug administration, as well as the number of tablets to be taken. This can be achieved using long-acting agents and fixed-dose combinations. For example, a single tablet, such as an amlodipine/atorvastatin compound to treat hypertension and dyslipidemia, can be taken by everyone at increased risk for CVD or stroke.

Adherence to medication

Blood pressure and low density lipoprotein-cholesterol (LDL-C)-lowering are key therapeutic strategies for preventing cardiovascular events in hypertensive patients with additional risk factors. However, this approach is confounded by poor patient adherence to

antihypertensive and lipid-lowering medications. Pill count is an important issue for hypertensive patients that are less likely to refill their antihypertensive and lipid-lowering prescriptions as their total number of prescriptions increases.[4] Synchronizing the initiation of antihypertensive and lipid-lowering therapy also improves adherence in comparison to patients starting one therapy more than 30 days prior to the other,[5] and adherence decreases as the time between initiation of antihypertensive and lipid-lowering therapies is prolonged. Patient adherence to medication has also been shown to be significantly greater with a single-pill regimen compared to a two-pill regimen for antihypertensive therapy alone.[6] Recently, the increased cost of multiple prescriptions has been reported to have a large impact on adherence.[7] Physicians may therefore be able to significantly improve medication adherence by initiating antihypertensive and lipid-lowering therapy concomitantly, thereby reducing pill burden and costs.

Caduet® (fixed-dose combination of amlodipine and atorvastatin)

Amlodipine/atorvastatin (Caduet®) is a once-daily fixed-dose combination of the dihydropyridine calcium channel antagonist, amlodipine, and the HMG-CoA reductase inhibitor, atorvastatin. It is indicated for the management of hypertension and dyslipidemia in patients in whom treatment with both agents is appropriate.

In clinical trials, the fixed-dose combination of amlodipine/atorvastatin effectively manages two important risk factors simultaneously in hypertensive patients at risk of CVD or in those patients with concomitant hypertension and dyslipidemia. The combination is bioequivalent to amlodipine and atorvastatin given alone, and does not modify the efficacy of either single agent. Amlodipine/atorvastatin is generally well-tolerated, with a tolerability profile consistent with that of each single agent. Compared with the co-administration of each single agent, the convenience of single-tablet amlodipine/atorvastatin has the potential to improve patient adherence and the management of cardiovascular risk in selected patients, thereby improving clinical outcomes.

Amlodipine is a dihydropyridine calcium channel blocker (CCB) that inhibits extracellular calcium influx into vascular smooth muscle via blockade of L-type calcium channels, causing relaxation of vascular smooth muscle and leading to a reduction in BP. Atorvastatin is a HMG-CoA reductase inhibitor that impedes mevalonic acid formation, which subsequently reduces cholesterol formation and increases the rate of LDL-C clearance from plasma.[8] Atorvastatin (40 mg /day) increases flow mediated dilation (FMD) and decreases the carotid-radial pulse wave velocity (PWV) at 8 weeks of administration in patients with moderate hypercholesterolemia (total cholesterol: 200-250 mg/dL). The combined administration of amlodipine and atorvastatin may have an additive or potentially synergistic beneficial effect on atherosclerotic plaque formation and some molecular markers of endothelial function (Table 1).

Administration of the fixed-dose combined amlodipine/atorvastatin tablet does not alter the rate or extent of absorption of either agent. The pharmacokinetic and pharmacodynamic properties of amlodipine and atorvastatin make them well-suited for combination in a single tablet to manage CV risk.[9] The half-lives of both agents facilitate once-daily dosing, and both can be administered at any time of the day with or without food.[10] Randomized, controlled trials, such as Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), Valsartan Antihypertensive Long-term Use Evaluation (VALUE), Comparison of Amlodipine versus Enalapril to Limit Occurrences of Thrombosis (CAMELOT), and Anglo-Scandinavian cardiac outcomes trial-blood pressure lowering arm (ASCOT-BPLA), have demonstrated that amlodipine reduces CV events and deaths in patients with hypertension and reduces CV events in normotensive patients with coronary artery disease (CAD). Statins have been unequivocally established as first-line pharmacotherapy for the majority of patients with dyslipidemia.[11] Moreover, atorvastatin has demonstrated clinical efficacy in inhibiting atherosclerosis and preventing cardiovascular events in randomized, controlled trials in patients with diabetes. The co-administration of amlodipine and atorvastatin has been demonstrated to be safe and effective for lowering both BP and LDL-C in patients with concomitant hypertension and dyslipidemia (Fig. 1).[12] The fixed-dose combination of amlodipine/atorvastatin is generally well-tolerated in patients with hypertension with or without dyslipidemia, with an overall tolerability profile similar to each single agent. In clinical trials, the most common treatment-related adverse events

Table 1. Summary of the pharmacodynamic effects of amlodipine (AML), atorvastatin (ATO), or a combination of AML and ATO on endothelial cell function and atherosclerotic plaque

Parameter	Effect		
	AML	ATO	AML/ATO
Nitric oxide release	↑	↑	↑↑
Arterial wall compliance (small vessels)	↑	↑	↑↑
Arterial wall compliance (large vessels)	↑	↑	↑
Markers of inflammation	↔	↓	↓
Insulin resistance	↓	↓	↓↓
PAI-1	↓	↓	↓
t-PA	↑	↑	↑↑
Atherosclerotic lesion area	↔	↓	↓
Calcified lesion area	↓	↓	↓

PAI-1: plasminogen activator inhibitor type 1, t-PA: tissue plasminogen activator, ↑: indicates an increase, ↓: indicates a decrease, ↑↑ or ↓↓: indicates an additive effect, ↔: indicates no change

associated with amlodipine and atorvastatin administered as a fixed-dose combination or concomitantly as separate agents were peripheral edema, myalgia, and sinusitis. Most adverse events were mild-to-moderate in severity. Neither drug has any adverse effects on the other's efficacy or tolerability (Fig. 2).[13]

Amlodipine/atorvastatin is the first single-tablet therapy available for the treatment of more than one CV risk factor. Single-tablet amlodipine/atorvastatin may provide an important strategy to help narrow the existing practice-outcome gap for CV risk reduction.

Fixed-Dose Combination Antihypertensive Drugs

Blood pressure control and achievement of guideline goals

It is difficult to achieve adequate BP control with monotherapy in most patients, even when the dose is optimised.[14] Response rates with any class of antihypertensive administered as monotherapy range from 30-60%; however, no monotherapy has been shown to achieve target BP in more than 20-30% of the overall hypertensive population (Fig. 3).[15]

By contrast, combining two complementary antihypertensive agents has been shown to improve the response rate to 75-90%. Compared with high-dose monotherapy, combination therapy is associated with fewer adverse effects. Guidelines advocate combination therapy with once daily treatment regimens that provide 24-h efficacy.[16] Firstline combination treatment is recommended in Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC)-7[17] for patients with a BP >20 mmHg above the systolic goal or 10 mmHg above the diastolic goal. Hypertension guidelines from the International Society on Hypertension in Blacks (ISHIB)[18] suggest the use of combination therapy when BP is >15 mmHg above the systolic goal and/or >10 mmHg above the diastolic goal.

Fixed-dose combination antihypertensive drugs have been available for the treatment of hypertension for over 40 years. Reserpine/dihydralazine/hydrochloro-

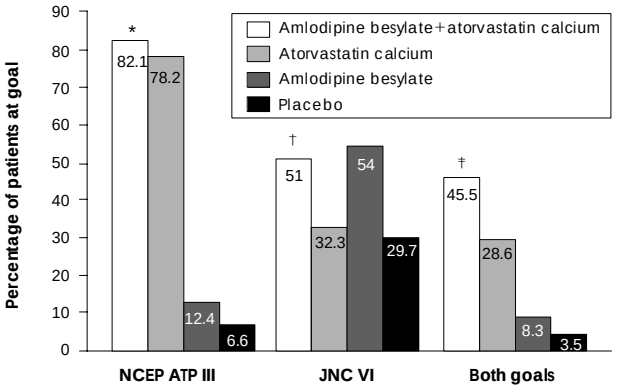

Fig. 1. Efficacy of amlodipine/atorvastatin compared with single-agent therapy or placebo in patients with concomitant hypertension and dyslipidemia. *p=.225 versus atorvastatin; p<.001 versus amlodlpine, †p<.001 versus atorvastatin; p=.520 versus amlodipine, ‡p<.001 versus atorvastatin; p<.001 versus amlodlpine. NCEP ATP III: national cholesterol education program adult treatment panel guideline III, JNC: Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.

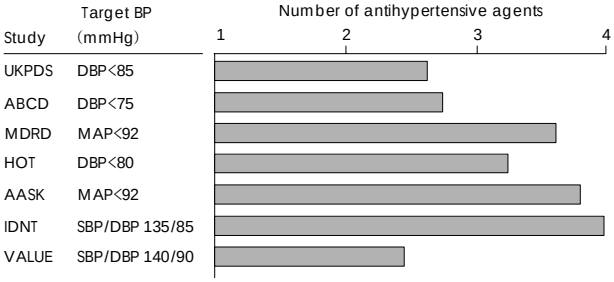

Fig. 3. Two-to-four antihypertensive agents are required to achieve effective BP control to target levels. BP: blood pressure, DBP: diastolic blood pressure, MAP: mean arterial pressure, SBP: systolic blood pressure.

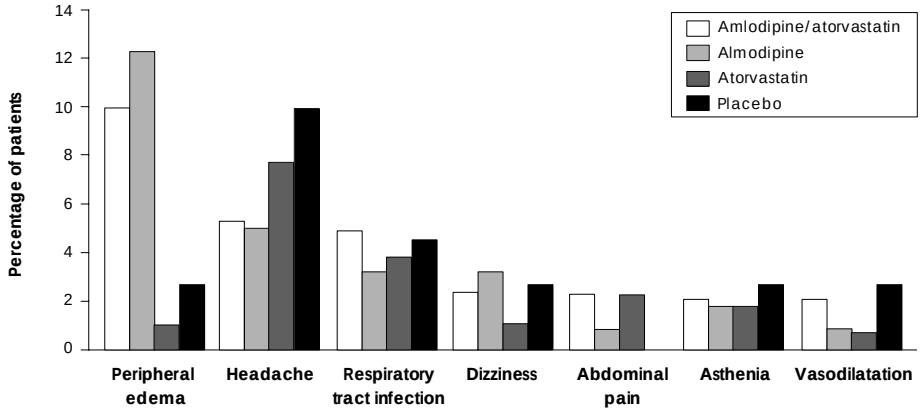

Fig. 2. Tolerability of amlodipine/atorvastatin compared with single-agent therapy or placebo. The graph shows adverse events in patients with co-existing hypertension and dyslipidemia who were randomized to once-daily amlodipine plus atorvastatin (any of eight dose combinations; n=885), amlodipine (5 or 10 mg alone; n=221), atorvastatin (10, 20, 40, or 80 mg alone; n=443), or placebo (n=111) in the double-blind, double-dummy, multicenter RESPOND trial.

thiazide (Unipres®) and methyldopa/hydrochlorothiazide (Aldoril®) were marketed in the 1960s. Fixed-dose combination antihypertensive drugs subsequently lost popularity because of a perception of increased toxicity compared to monotherapy. However, a large variety of fixed-dose combination agents have been developed in recent years for patients requiring multiple antihypertensive agents for BP control (Table 2).[19]

Fixed low-dose combination therapy: advantages and disadvantages (Table 3)

The advantages of combination therapy include improved adherence to therapy[20] and minimization of BP variability. In addition, combining two antihypertensive agents with different mechanisms of action may provide greater protection against major CV events and the development of end-organ damage.[16] The challenge remains

Table 2. Fixed low-dose combination therapy: advantages and disadvantages

Advantages of fixed-dose combination therapy
Increased compliance, simplified titration, and convenience of use
Potentiation of antihypertensive effects of a single compound
Additive or synergistic effect
Enhancing effect in specific populations
Diuretic with an ACE inhibitor, ARB, or β-blocker
Attenuation in adverse events
Decrease in diuretic-induced metabolic changes with ACE inhibitors or ARBs
Decrease in CCB-related peripheral edema with ACE inhibitors
Improved overall results, greater BP response, and lower cost when co-payments and pharmacy filling fees are considered
Disadvantages of fixed-dose combination therapy
May not be well-tolerated in patients at risk for orthostatic hypotension, such the elderly, diabetic patients, and persons with autonomic dysfunction
Some combinations do not contain sufficient doses of the constituent drugs to provide BP control
Lack of flexibility in titrating doses of individual components

ACE: angiotensin converting enzyme, ARB: angiotensin II receptor blockers, CCB: calcium channel blocker

Table 3. Currently available fixed-dose combination antihypertensives

Class	Combination	Trade name
ACE inhibitors and diuretics	Benazepril (5-20 mg)/HCTZ (6.25-25 mg)	Lotensin HCT
	Captopril 25-50 mg/HCTZ 15-25 mg	Capozide
	Enalapril 5-10 mg/HCTZ 12.5-25 mg	Vaseretic
	Lisinopril 10-20 mg/HCTZ 12.5-25 mg	Zestoretic; Prinzide
	Fosinopril 10-20 mg/HCTZ 12.5 mg	Monopril HCT
	Quinapril 10-20 mg/HCTZ 12.5-25 mg	Accuretic
	Moexipril (7.5-15 mg)/HCTZ (12.5-25 mg)	Uniretic
ARBs and diuretics	Losartan (50 mg)/HCTZ (12.5-25 mg)	Hyzaar
	Valsartan (80-160 mg)/HCTZ (12.5-25 mg)	Diovan HCT
	Irbesartan (150-300 mg)/HCTZ (12.5 mg)	Avalide HCT
	Telmisartan (40-80 mg)/HCTZ (12.5-25 mg)	Micardis HCT
	Olmesartan (20-40 mg)/HCTZ (12.5-25 mg)	Benicar HCT
	Candesartan (16-32 mg)/HCTZ (12.5 mg)	Atacand HCT
	Eprosartan (600 mg)/HCTZ (12.5-25 mg)	Teveten HCT
Potassium-sparing diuretics and HCTZ	Amiloride (5 mg)/HCTZ (50 mg)	Moduretic (5-50)
	Spironolactone (25-50 mg)/HCTZ (25-50 mg)	Aldactazide
	Triamterene (37.5-75 mg)/HCTZ (25-50 mg)	Dyazide; Maxzide
Calcium channel blockers and ACE inhibitors	Amlodipine (2.5-10 mg)/Benazepril (10-20 mg)	Lotrel
	Felodipine (5 mg)/Ramipril (5 mg)	Triapin
	Felodipine (2.5-5 mg)/Enalapril (5 mg)	Lexxel
	Verapamil (180-240 mg)/Trandolapril (1-4 mg)	Tarka
Calcium channel blockers and ARBs	Amlodipine (5 mg)/Valsartan (80-160 mg)	Exforge
	Olmesartan (20-40 mg)/HCTZ (12.5-25 mg)	
Beta blockers and diuretics	Atenolol (50-100 mg)/Chlorthalidone (25 mg)	Tenoretic
	Bisoprolol (2.5-10 mg)/HCTZ (6.25 mg)	Ziac
	Nadolol (40-80 mg)/Bendroflumethiazide (5 mg)	Corzide
	Propranolol (40-80 mg)/HCTZ (25 mg)	Inderide

ACE: angiotensin converting enzyme, HCTZ: hydrochlorothiazide, ARB: angiotensin II receptor blockers

Table 4. Efficacy: blood pressure-lowering effects of drugs when used at one-half standard dose separately and in combination. The reductions with two and three drugs are based on an additive effect

	Blood pressure reduction* (95% CI)		
	One drug	Two drugs	Three drugs
Systolic blood pressure (mmHg)	6.7 (6.1 to 7.2)	13.3 (12.4 to 14.1)	19.9 (18.5 to 21.3)
Diastolic blood pressure (mmHg)	3.7 (3.1 to 4.3)	7.3 (6.2 to 8.3)	10.7 (9.1 to 12.4)

*Reductions in blood pressure adjusted to a usual pretreatment blood pressure of 150/90 mmHg (the average blood pressure in people 50-69 years of age who have a stroke or ischaemic heart disease event). CI: confidence interval

Table 5. Adverse effects of drugs: percentage of people with one or more symptoms attributable to treatment, according to category of drug and dose, in randomised trials

Category of drug	No of trials	Percentage (95% CI) with symptoms (treated minus placebo)*		
		Half standard dose	Standard dose	Twice standard dose
Thiazides	59	2.0 (-2.2 to 6.3)	9.9 (6.6 to 13.2)	17.8 (11.5 to 24.2)
β-blockers	62	5.5 (0.3 to 10.7)	7.5 (4.0 to 10.9)	9.4 (3.6 to 15.2)
ACE inhibitors	96	3.9 (-3.7 to 11.6)	3.9 (-0.5 to 8.3)	3.9 (-0.2 to 8.0)
Angiotensin II receptor antagonists	44	-1.8 (-10.2 to 6.5)	0 (-5.4 to 5.4)	1.9 (-5.6 to 9.3)
Calcium channel blockers	96	1.6 (-3.5 to 6.7)	8.3 (4.8 to 11.8)	14.9 (9.8 to 20.1)

*Most common symptoms: thiazides, dizziness, impotence, nausea, and muscle cramps; β-blockers, cold extremities, fatigue, and nausea; ACE inhibitors, cough; CCB, flushing, ankle oedema, and dizziness. CI: confidence interval, ACE: angiotensin converting enzyme, CCB: calcium channel blocker

to translate the evidence and recommendations outlined in the current hypertension management guidelines into clinical practice, as combination therapy remains underused, especially in high-risk patients. Table 4 shows the expected reduction in blood pressure with one, two, and three BP-lowering drugs used at one-half standard doses.[21] The reductions with two and three drugs are based on the additive effect.

Adverse effects

Single drugs

The dose-response relationship is clear for thiazides, β-blockers, and calcium channel blockers. Thiazides and CCB infrequently cause symptoms (2.0 and 1.6%, respectively) at one-half the standard doses, but commonly (9.9 and 8.3%, respectively) at standard doses ($p<0.001$). β-blockers cause symptoms in 5.5% of patients at one-half standard doses and in 7.5% at standard doses ($p=0.04$). Cough (3.9%) was virtually the only symptom with angiotensin converting enzyme (ACE) inhibitors and did not vary with dose, a finding consistent with earlier studies.[12][13] No excess symptoms occurred at standard doses or one-half standard doses with angiotensin II receptor blockers (ARB) (Table 5).[21]

Combinations of drugs

In 66 trial arms, single drugs caused symptoms in 5.2% (3.6-6.6%) of participants on average (prevalence in the treated group minus prevalence in the placebo-treated group). In 33 trial arms, 2 drugs together caused symptoms in 7.5% (5.8-9.3%), which is significantly lower than the value of 10.4% (5.2%×2) expected with an additive effect ($p<0.03$). One drug does not therefore potentiate the adverse effects of another. Many antihypertensive agents work by affecting fluid and sodium balance, blocking the renin-angiotensin-aldosterone system (RAAS), or the sympathetic nervous system, and decreasing systemic vascular resistance by blocking L-type calcium channels. Combinations of ACE inhibitors, ARB, diuretics, and CCB have additive effects in controlling BP and minimizing adverse effects of individual components. Combination therapy using ARB with hydrochlorothiazide (HCTZ) provides greater potency and fewer side effects than higherdose monotherapy with either agent, and potentially offers benefits beyond those of BP-lowering alone, particularly in high-

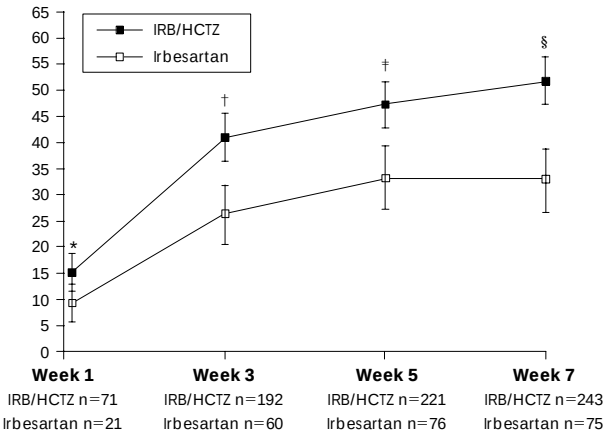

Fig. 4. Comparison of the antihypertensive effects of irbesartan/HCTZ (150/12.5 mg) and valsartan/HCTZ (80/12.5 mg) in hypertensive patients in the COmparative Study of Efficacy of Irbesartan/HCTZ with Valsartan/HCTZ Using Home Blood Pressure Monitoring in the TreAtment of Mild-to-Moderate Hypertension (COSIMA) study.[22] *p=0.0317, †p=0.0002, ‡p=0.0005, §p<0.0001. Error bars represent 95% Confidence Intervals. n: number controlled, HCTZ: hydrochlorothiazide.

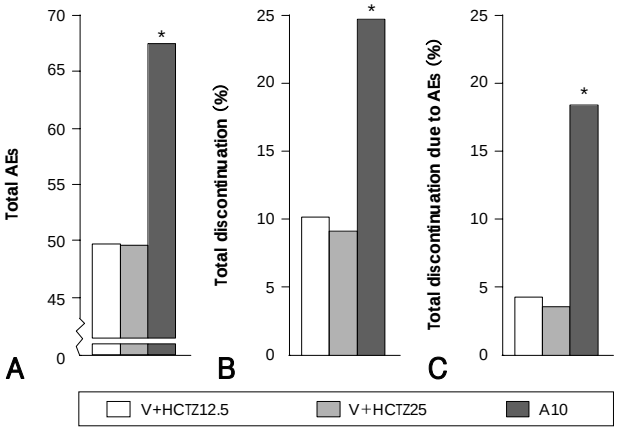

Fig. 5. Rates of (A) total AEs, (B) total discontinuations, and (C) total discontinuations as a result of AEs in the groups that received valsartan (160 mg) plus hydrochlorothiazide (12.5 mg [V+HCTZ12.5]), valsartan (160 mg) plus HCTZ (25 mg [V+HCTZ 2S]), and amlodipine (10 mg [A10]). *p<0.05 vs. combination-therapy groups. HCTZ: hydrochlorothiazide.

risk hypertensives. The combination of an ARB and HCTZ has been reported to be effective in difficult-to-treat and severely hypertensive patients for several ARB, including losartan, candesartan, telmisartan, and eprosartan. A high fixed-dose combination of irbesartan (300 mg)/HCTZ (25 mg) given once daily was also effective and well-tolerated in patients with previously uncontrolled hypertension. As well as significantly reducing BP measured in the clinic in anambulatory setting, 12 weeks of treatment preserved the circadian profile, as shown by trough-to-peak ratios and smoothness index values for systolic and diastolic BP (Fig. 4).[22] No metabolic changes were observed at these doses, and no patients discontinued the study because of treatment-related side effects. Fixed-dose combinations of HCTZ and ARBs provide effective, simple, aggressive, and well-tolerated BP control and are now rapidly gaining acceptance with physicians. The usefulness of ARB/HCTZ combinations in hypertension has now been demonstrated in clinical trials for most of the ARBs.[23] Some of the most detailed recent data have been obtained with valsartan. In a recent double-blind, multicenter study of 24 weeks duration involving 1,088 patients, fixed-dose combinations of valsartan (160 mg) with HCTZ (15.5 or 25 mg) were found to reduce BP to a similar degree to amlodipine alone (10 mg).[24] However, adverse events were significantly less frequent with the ARB/HCTZ combination and discontinuation rates as a result of adverse events were 4.2%, 3.5%, and 18.2% in the valsartan/HCTZ (12.5 mg), valsartan/HCTZ (25 mg), and amlodipine groups, respectively (Fig. 5).[24]

Calcium Channel Blocker in Combination Therapy

Calcium channel blockers effectively and safely lower BP and reduce long-term CV risk in a wide range of patient populations. As CCBs have a different mode of action to commonly used inhibitors of the RAAS pathway (such as ACE inhibitors and ARB), combinations with these agents should provide synergistic or complementary effects compared with using two agents that inhibit the same pathway.[25]

The Avoiding Cardiovascular events through COMbination therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) study is the first outcomes trial to compare initial therapy with two different combinations. Patients will be randomized to amlodipine/benazepril (5/20 mg) or benazepril/HCTZ (20/12.5 mg), and will have their doses force-titrated to standard maintenance doses of amlodipine/benazepril (5/40 mg) and benazepril/HCTZ (40/12.5) mg during the first 2 months. The doses can be increased to 10/40 mg or 40/25 mg, respectively, and after 3 months, other antihypertensive agents (excluding the drug classes involved in the primary treatments) can be added to achieve a BP <140/90 mmHg (<130/80 mmHg for patients with diabetes or renal insufficiency). Investigators will be strongly encouraged to reach target blood pressure in all patients.

Patients will be seen at 3 and 6 months, and thereafter at 6-month intervals until the end of the trial (mean, 39 months). The amlodipine/benazepril-treated group showed 20% less CV mortality/morbidity compared with the benazepril/HCTZ-treated group. The ACCOMPLISH trial will provide compelling evidence for initial combination therapy with angiotensin converting enzyme inhibitor (ACEI)/calcium channel blocker (CCB) and challenge current diuretic-based guidelines.

Conclusions

Global risk reduction is very important for prevention of CV event in patients with hypertension. Single-tablet amlodipine/atorvastatin (Caduet®) is the first single-tablet therapy available for the treatment of more than one CV risk factor, and increases compliance, decreases multiple CV risk factors, and decreases morbidity and mortality with CAD. Caduet may provide an important strategy to help reduce the existing practice-outcome gap for CV risk reduction.

Fixed low-dose combination therapy of antihypertensive agents whose mechanisms of action are complementary is an effective, safe, and cost-effective method of decreasing BP in most patients with essential hypertension. Because many neurohormonal and cellular mechanisms cause hypertension, defining a specific etiology and creating a cause-specific treatment plan is difficult. Reduction in BP is only about 20% less at one-half standard dose than at standard dose, but adverse effects are much less common.

The efficacy of drugs in combination is additive, but the prevalence of adverse effects is less than additive. Fixed-low dose combinations of two or three drugs at low dose are therefore preferable to one or two drugs at standard dose to improve compliance and reduce cost, consequently to help improve CV outcome.

Acknowledgments

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