Review Paper

Rationale for Triple-Combination Therapy for Management of High Blood Pressure

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The goals of antihypertensive therapy include optimal reduction in blood pressure (BP) while providing a favorable tolerability profile that promotes long-term adherence to treatment. For most patients with hypertension, these treatment goals cannot be achieved with monotherapy. When instituted early, however, combination therapy results in more rapid control of BP. This approach may facilitate improvements in long-term clinical outcomes, compared with more traditional and time-consuming stepped care and add-on algorithms for the management of hypertension. This review summarizes the rationale behind combination therapy, specifically triple-combination therapy, and discusses which combinations are most likely to result in better BP control, fewer side effects, and reduced risk of target organ damage. Supporting evidence from recent triple-combination therapy trials also is included in the review. Finally, the role of single-pill (fixed-dose) combination therapy in enhancing patient adherence is also discussed.
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Results from placebo-controlled clinical trials have firmly established that reducing blood pressure (BP) in patients with hypertension significantly reduces the risk of cardiovascular (CV) events.[1–4] In a meta-analysis of randomized trials, antihypertensive therapy reduced the risk of stroke by 35% to 40%, the risk of myocardial infarction by 20% to 25%, and the risk of heart failure by >50%.[3] Using data from the National Health and Nutrition Examination Survey Epidemiologic Follow-Up Study, Ogden and colleagues[4] determined that a sustained reduction of 10 mm Hg in systolic BP (SBP) over 10 years in patients with stage 1 hypertension and additional CV risk factors would prevent 1 death for every 11 patients treated.

The results of epidemiologic studies and landmark clinical trials have been incorporated into evidence-based guidelines for the treatment of hypertension.[5–7] These guidelines recommend that management of hypertension should be based on the severity of BP elevation and on the presence of other CV risk factors and comorbidities. In all cases, these guidelines stress that BP should be reduced to <140/90 mm Hg in patients with uncomplicated hypertension and to <130/80 mm Hg in those with diabetes or chronic kidney disease (CKD). More recent recommendations have included patients with established vascular disease and heart failure in the groups requiring the lower BP targets.[8]

Despite the availability of many effective antihypertensive agents, achieving these BP targets is difficult in many patients. BP is inadequately controlled in one third to one half of patients receiving treatment for hypertension in the United States and Canada and in 40% to 66% of patients with

concurrent hypertension and diabetes.[9–13] In the European Union, BP is inadequately controlled in more than two thirds of treated patients.[13,14] The reasons for inadequate control of BP include the multifactorial nature of hypertension, the presence of concurrent medical conditions, and/or resistant hypertension from secondary causes. Other factors include inconsistent patient adherence and the reluctance of physicians to increase therapy in response to inadequate BP control (therapeutic inertia). Another important reason is an over-reliance on monotherapy, which effectively controls BP in only 20% to 30% of the hypertensive population.[15,16]

The focus of this article is to review the rationale for combination therapy, specifically triple-combination therapy, and assess which combinations are most likely to result in better BP control, fewer side effects, and reduced risk of target organ damage. The results from recent triple-combination therapy trials will be reviewed. The role of single-pill (fixed-dose) combination therapy to enhance patient adherence is also discussed.

COMBINATION THERAPY: RATIONALE

It has been recognized since the 1980s that monotherapy does not achieve BP goals in the majority of patients with hypertension,[17] particularly those with stage 2 hypertension and those with comorbidities, such as diabetes or renal insufficiency. Most patients require $\geq$2 antihypertensive agents from complementary classes to achieve BP control,[5,18] and, in several trials, the mean number of agents required to achieve target BP was $\geq$3.[19–22]

In many cases, combination therapy using drugs with complementary mechanisms of action improves the tolerability profile of individual agents. For example, use of an angiotensin receptor blocker (ARB) or an angiotensin-converting enzyme (ACE) inhibitor with a dihydropyridine calcium channel blocker (CCB) significantly reduces the incidence of CCB-related vasodilatory edema and diuretic-related hypokalemia.[18] Agents with complementary mechanisms of action can often be combined at low doses, minimizing side effects while maintaining the same magnitude of BP reduction achieved with higher-dose monotherapy.

Agents that block the renin-angiotensin-aldosterone system, which are associated with effects on target organs that extend beyond BP reduction,[23] are usually recommended in combination therapy regimens. In the European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines, 6 preferred combinations are identified, 4 of which include an ACE inhibitor or an ARB in combination with either a CCB or a thiazide diuretic.[7]

Based on recommendations provided in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) guidelines,[5] various classes of antihypertensive agents have a compelling indication for use in specific patient subgroups (eg, β-blockers, ACE inhibitors, and aldosterone antagonists post–myocardial infarction and ACE inhibitors and ARBs in CKD). In patients without compelling indications, thiazide diuretics were recommended for most patients with stage 1 hypertension and as a component of dual-combination therapy for stage 2 hypertension. The numerous analyses derived from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) support the role for thiazide diuretics as initial antihypertensive therapy.[24] However, despite their BP-lowering efficacy and ability to influence CV morbidity and mortality, discussion and debate surrounding this particular class of agents continues in light of their adverse event (AE) profile and their metabolic side effects, including alterations in insulin sensitivity and the associated increased risk of developing diabetes.[25]

Despite extensive clinical trial experiences with chlorthalidone, hydrochlorothiazide (HCTZ) remains the more popular diuretic choice among clinicians in the context of developing single-pill antihypertensive combinations. Chlorthalidone has a longer duration of action compared with HCTZ and is a more effective antihypertensive agent over 24 hours.[26] Because it was the agent used in most of the US-based hypertension outcome trials, including ALLHAT, preferred use of chlorthalidone over HCTZ has been advocated by some authorities. This controversy has increased since the publication of the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) trial,[27] in which first-line therapy with the combination of an ACE inhibitor and a CCB provided superior end point reduction compared with therapy based on an ACE inhibitor/HCTZ combination. At present, however, there is no conclusive evidence favoring the use of one or another of the thiazide-type diuretics.

TRIPLE-COMBINATION THERAPY: RATIONALE

As Black notes in a recent editorial,[27] the use of triple-combination therapy originated in the Veterans Affairs Cooperative Studies conducted in the late

1960s and early 1970s. Another triple-combination formulation of amlodipine, olmesartan, and HCTZ was approved in July 2010. However, triple-combination therapy fell out of use in subsequent decades in favor of the stepped-care approach.[27] We have now come full circle, with the recognition that hypertension is a complex disorder involving several interrelated physiologic systems, making it difficult to control BP in most patients without interfering with multiple mechanisms. Indeed, guidelines from the United States,[5] Canada,[6] and the European Union[7] now recommend a combination of 2 first-line agents, either as separate doses or in single-pill combinations, as initial treatment in patients with stage 2 hypertension, in those whose BP is ≥20/10 mm Hg above target BP, or, in the case of the ESH/ESC guidelines, whenever the total CV risk score of a patient is high.

The recognition that triple-combination therapy is frequently a necessity is based on large-scale studies. In the Study on Cognition and Prognosis in the Elderly (SCOPE) of 4964 elderly patients with stage 2 hypertension (BP: 160–179/90–99 mm Hg), 49% of patients were receiving ≥3 antihypertensive agents by the end of the study.[19] Similarly, in the International Verapamil SR and Trandolapril Study (INVEST) involving patients with hypertension (mean BP: 150/86 mm Hg) and coronary artery disease, about half of the patients assigned to receive a CCB or a β-blocker were receiving ≥3 antihypertensive medications at the end of the 2-year follow-up period.[20] In ALLHAT, ≥3 antihypertensive agents were necessary for 24% of black patients and 24% of nonblack patients initially assigned to receive chlorthalidone, for 41% and 31%, respectively, initially assigned to receive lisinopril, and for 28% and 25%, respectively, of those initially assigned to receive amlodipine.[21] At study end point in ACCOMPLISH, 32% of the 11,506 patients with hypertension at high risk for CV disease were receiving at least 1 other antihypertensive agent in addition to initial therapy with either benazepril/amlodipine or benazepril/HCTZ.[22]

The Canadian treat-to-goal Simplified Therapeutic Intervention To Control Hypertension (STITCH) study compared a simplified combination therapy treatment-to-goal algorithm based on initial therapy with an ACE inhibitor or ARB/diuretic combination, followed by a CCB, if needed, to achieve target BP.[10] This strategy was compared with conventional care based on the Canadian Hypertension Education Program (CHEP) guidelines in a population of 2048 patients with uncontrolled hypertension. At the end of the study, approximately 30% of patients assigned to receive initial combination therapy required 3 agents; 65% achieved their target BP. These results are noteworthy because of the substantial proportion of patients who required triple-combination therapy, even though they had uncomplicated and nonsevere hypertension (mean BP: approximately 154/88 mm Hg) at baseline. In addition, the study showed that a regimen using an ACE inhibitor or ARB, a thiazide diuretic, and a CCB was effective and well tolerated in a broad patient population. Further, this simplified strategy was more effective in achieving target BP than was a treatment model based on CHEP guidelines.

TRIPLE-COMBINATION THERAPY: RECENT CLINICAL TRIALS

In May 2009, the US Food and Drug Administration (FDA) approved a single-pill, triple combination of amlodipine, valsartan, and HCTZ. Another triple-combination formulation of amlodipine, olmesartan, and HCTZ was approved several months later. The approval of the amlodipine/valsartan/HCTZ combination was based on the recently completed factorial study reported by Calhoun and colleagues (Table).[28–36] This prospective, randomized, double-blind study assessed the safety and efficacy of once-daily, triple-combination therapy vs the component 2-drug combinations (amlodipine/valsartan, valsartan/HCTZ, or amlodipine/HCTZ). The study included 2271 patients with stage 2 hypertension (mean BP: 170/107 mm Hg at baseline) who were randomized to receive 5 weeks of treatment with amlodipine/valsartan/HCTZ 10/320/25 mg or 1 of the 3 dual therapies indicated previously herein. At the end of the study, SBP and diastolic BP (DBP) were reduced to a significantly greater extent in patients receiving triple-combination therapy (mean BP reduction: 39.7/24.7 mm Hg) than in patients receiving any of the dual therapies ($P<.0001$ for all 3 comparisons). Only triple-combination therapy reduced the mean SBP to <140 mm Hg and the mean DBP to <90 mm Hg. The differences in final BP levels between the triple-combination therapy group and the 3 dual-therapy groups were clinically relevant (8/5 mm Hg vs valsartan/HCTZ; 6/3 mm Hg vs amlodipine/valsartan; 8/5 mm Hg vs amlodipine/HCTZ).[27] The proportion of patients achieving the target BP (<140/90 mm Hg) was significantly greater in the triple-combination group (70.8%) than in the dual-component groups (48.3% with valsartan/HCTZ, 54.1% with amlodipine/valsartan,

Table. Recent Triple-Combination Therapy Studies With ARBs

Study	Study Design	Treatment	Response Rate	SBP/DBP, mm Hg
Calhoun et al[28]	Multinational, randomized, double-blind, parallel-group		Patients with BP <140/90 mm Hg, %	Change from baseline in mean sitting BP
	Forced-titration			
	Patients had SBP ≥145 and DBP ≥100 mm Hg	V/H 320/25 mg	58.3	−32.0/−19.7 (+7.6/+5.1 vs A/V/H; *P*<.0001)
		V/A/320/10 mg	54.1	−33.5/−21.5 (+6.2/+3.3 vs A/V/H; *P*<.0001)
		A/H 10/25 mg	44.8	−31.5/−19.5 (+8.2/+5.3 vs A/V/H; *P*<.0001)
		V/A/H 320/10/25 mg	70.8	−39.7/−24.7
Val-DICTATE[29]	Multicenter, randomized, active-controlled, parallel-group		Estimated cumulative % (actual step % [No./No.]) with BP <140/90 mm Hg	
	Four-week double-blind phase (H 25 mg or V/H 160/12.5 mg), followed by 16-week open-label stepped-care starting with V/H 160/25 mg (if BP ≥140/90 mm Hg):			
	Uptitration of V →	H 25 mg	16 (16 [23/145])	
	Addition of A →	V/H 160/12.5 mg	37 (37 [53/145])	
	Uptitration of A	V/H 160/25 mg	64 (64 [125/195])	
	Patients had SBP >150 and <180 mm Hg and DBP >95 and <110 mm Hg	V/H 320/25 mg	78 (64 [75/118])	
		V/A/H 320/5/25 mg	84 (57 [42/74])	
		V/A/H 320/10/25 mg	89 (42 [16/38])	
EX-STAND[30]	Randomized, double-blind, parallel-group, active-controlled, multicenter		Patients with BP <140/90 mm Hg, %	Change from baseline (∼ SBP)
	Forced-titration in combination arm, with add-on H at week 8 (either arm) if SBP ≥130 mm Hg	Week 8		
		A 10 mg	30.2	−27/−11.2
	Patients were black with SBP ≥160 and <200 mm Hg	V/A 320/10 mg	49.8; *P*<.0001	−34/−14.0; *P*<.001
		Week 12 (opt. H)		
		A/H 10/12.5 mg	35.9	−30/−12.8
		V/A/H 320/10/12.5 mg	57.2; *P*<.0001	−37/−16.2; *P*<.001

Table. Recent Triple-Combination Therapy Studies With ARBs (Continued)

Study	Study Design	Treatment	Response Rate	SBP/DBP, mm Hg
EX-EFFeCTS[31]	Multinational, randomized, double-blind, parallel-group Forced-titration, with add-on H at week 4 if SBP ≥130 mm Hg Patients had SBP ≥160 and <200 mm Hg		Patients with BP <140/90 mm Hg, %	Change from baseline and incremental reduction with optional H
		Week 4		
		A 10 mg	23.8	−23.5/−8.6 (change from baseline)
		V/A 160/10 mg	45.3	−30.1/−12.5 (change from baseline)
		Week 8		
		A/H 10/12.5 mg	31.1	−3.1/NR (incremental reduction)
		V/A/H 160/10/12/5 mg	53.0	−6.9/NR (incremental reduction)
EX-FAST[32]	Multinational, randomized, double-blind, parallel-group Fixed-dose, with add-on H at week 8 and uptitration at week 12 if BP ≥140/90 mm Hg or ≥130/80 mm Hg (latter if diabetes) Patients had SBP <180 and DBP <110 mm Hg (<160 and <100 mm Hg in diabetes) on monotherapy		Patients with BP <140/90 mm Hg (non-DM) or BP <130/80 mm Hg (DM), %	
		Week 8		
		V/A 160/5 mg	71.1	−16.5/−9.3
		V/A 160/10 mg	76.4	−19.2/−11.3; $P<.001$
		Week 16		
		V/A/H 160/5/12.5–25 mg	72.7	−17.5/−10.4
		V/A/H 160/10/12.5–25 mg	74.8	−20.0/−11.6; $P<.001$

Table. Recent Triple-Combination Therapy Studies With ARBs (Continued)

Study	Study Design	Treatment	Response Rate	SBP/DBP, mm Hg
Volpe et al[33]	Multicenter, open-label Stepped-care: Uptitration of A → Addition of H → Uptitration of H Eligibility by pretreatment: Newly diagnosed or A-naïve with SBP, DBP, and 24-hour DBP ≥160, ≥100, and ≥84 mm Hg (30% of daytime values >90 mm Hg) A-pretreated with SBP, DBP, and 24-hour DBP ≥140, ≥90, and ≥80 mm Hg (with 30% of daytime values >85 mm Hg)	 O/A 40/5 mg O/A 40/10 mg O/A/H 40/10/12.5 mg O/A/H 40 10/25 mg	Cumulative % (step % [No./No.]) with BP <140/90 mm Hg (non-DM) BP <130/80 mm Hg (DM) 48.6 (74.3 [336/452]) 60.8 [59.0 [85/144]) 65.5 (47.1 [32/68]) 66.9 (33.3 [9/27])	Incremental change in BP (end point BP) NA (131.4/83.1) −8.8/−5.5 (135.0/85.4) −10.2/−6.3 (138.3/87.3) −3.8/−3.7 (145.6/89.7)
Gomes et al[34]	Multicenter, open-label Stepped-care: Addition of H → Uptitration of O and H → Addition of A Patients had SBP ≥140 and <180 mm Hg and DBP ≥90 and <110 mm Hg	 O 20 mg O/H 20/12.5 mg O/H 40/25 mg O/A/H 40/5/25 mg	Cumulative % (step % [No./No.]) with BP <130/85 mm Hg 26 (26 [37/144]) 49 (31 [33/106]) 74 (49 [36/73]) 86 (59 [19/32])	Change from baseline in patients achieving a BP <130/85 mm Hg −30.5/−19.1 −34.8/−21.6 −34.2/−19.8 −44.4/−20.0
Neutel et al[35]	Multicenter, open-label Stepped-care: Uptitration of O → Addition of H → Uptitration of H → Addition of A → Uptitration of A Patients had DBP 90–109 mm Hg and SBP <200 mm Hg	 O 20 or 40 mg O/H 40/12.5 or 40/25 mg O/A/H 40/25/5 or 40/25/10 mg	Cumulative % with BP <140/90 mm Hg (BP <130/85 mm Hg) 58.7 (35.2) 83.2 (69.3) 93.3 (87.7)	Change from baseline −17.7/−10.7 −29.3/−16.1 −33.7/−18.2

Table. Recent Triple-Combination Therapy Studies With ARBs (Continued)

Study	Study Design	Treatment	Response Rate	SBP/DBP, mm Hg
Neutel et al[36]	Multicenter, open-label subgroup of study above		Stage 1 HTN: Cumulative % with BP <140/90 mm Hg (BP <130/85 mm Hg)	Stage 1 HTN: Change from baseline
		O 20 or 40 mg	79.7 (55.7)	−16.7/−11.6
		O/H 40/12.5 or 40/25 mg	93.7 (88.6)	−24.8/−15.8
		O/A/H 40/25/5 or 40/25/10 mg	97.5 (96.2)	−26.4/−16.5
			Stage 2 HTN: Cumulative % with BP <140/90 mm Hg (BP <130/85 mm Hg)	Stage 2 HTN: Change from baseline
		O 20 or 40 mg	42.0 (19.0)	−18.4/−10.0
		O/H 40/12.5 or 40/25 mg	75.0 (54.0)	−32.7/−16.3
		O/A/H 40/25/5 or 40/25/10 mg	90.0 (81.0)	−39.1/−19.4

Abbreviations: A, amlodipine; ARBs, angiotensin receptor blockers; BP, blood pressure; DBP, diastolic blood pressure; DM, diabetes mellitus; EX-EFFeCTS, the Exforge Efficacy and Control in Treatment of Stage 2 Hypertension trial; EX-FAST, the Exforge in Failure After Single Therapy trial; EX-STAND, Exforge Evaluation in Stage 2 Hypertensives of African Descent trial; H, hydrochlorothiazide; HTN, hypertension; NA, not applicable; NR, not reported; O, olmesartan; SBP, systolic blood pressure; V, valsartan; Val-DICTATE, the Valsartan Hydrochlorothiazide Diuretic for Initial Control and Titration to Achieve Optimal Therapeutic Effect trial.

and 44.8% with amlodipine/HCTZ; $P<.0001$ for all 3 comparisons).

The rates of AEs were similar between treatment groups. Peripheral edema was among the most common AEs, which occurred less frequently in patients receiving triple-combination therapy (4.5%) than in those receiving CCB-based dual therapies (8.7%). This finding apparently represents an advantage attributable to the inclusion of the ARB in the regimen; it is also possible that the diuretic contributed to this outcome. Other common AEs included headache (4.3% with triple therapy; 4.9%–7.0% with dual therapy) and dizziness (7.7% with triple therapy; 2.3%–7.0% with dual therapy). The incidence rates of hypotension ($\leq$1.5%), syncope (<1.0%), postural dizziness, exertional dizziness, and orthostatic hypotension (each <0.5%) were low across all treatment groups. Reductions in SBP were greatest in patients with severe hypertension (SBP: $\geq$180 mm Hg) at baseline (−49.6 mm Hg with triple therapy vs −39.9 mm Hg to −43.6 mm Hg with dual-component therapy). Reduction in BP with use of triple-combination therapy was independent of age, sex, race, and ethnicity.

Three other recently conducted studies showed higher control rates with amlodipine/valsartan/HCTZ than with monotherapy or dual therapy.[30–32] Each was a titration-to-effect study, in which patients whose hypertension was not controlled with use of dual therapy with amlodipine/valsartan were eligible to receive additional HCTZ treatment. This titration-to-effect approach is regularly used in the clinic setting. Consistent with the triple-combination therapy (amlodipine/valsartan/HCTZ 10/320/25 mg) control rates reported by Calhoun and colleagues,[28] in the Exforge in Failure After Single Therapy (Ex-FAST) trial,[32] BP control was achieved in 73% to 75% of patients who received amlodipine/valsartan/HCTZ 5/160/12.5 or 10/160/12.5 mg after it remained uncontrolled with use of amlodipine/valsartan. BP was reduced by up to 20.0/11.6 mm Hg. In the Exforge Evaluation in Stage Two Hypertensives of African Descent (Ex-STAND) study, 57% of black patients with stage 2 hypertension (a population subgroup that has a high fraction of resistant hypertension) who were treated with amlodipine/valsartan/HCTZ 10/320/12.5 mg achieved BP control.[30]

Several recent studies have also assessed the efficacy of triple-combination therapy with olmesartan, amlodipine, and HCTZ. In a treat-to-goal study conducted by Volpe and colleagues,[33] 692 patients with stage 2 hypertension initially received open-label treatment with 40/5 mg olmesartan/amlodipine. Patients whose BP was not controlled (ie, patients who did not achieve BP <140/90 mm Hg for those without diabetes or <130/80 mm Hg for those with diabetes) with this regimen received step-up treatment with 40/10 mg olmesartan/amlodipine followed by 40/10/12.5 mg olmesartan/amlodipine/HCTZ and then 40/10/25 mg olmesartan/amlodipine/HCTZ. For those patients whose BP was not controlled with 40/5 mg olmesartan/amlodipine, sequential step-up therapy resulted in incremental reductions in BP of 8.8/5.5 mm Hg, 10.2/6.3 mm Hg, and 3.8/3.7 mm Hg, respectively. At the end of the study, mean BP values were <140/90 mm Hg in all treatment groups, except for 27 patients who had the highest BP at baseline and required step-up treatment to 40/10/25 mg olmesartan/amlodipine/HCTZ. In patients who ended the study taking olmesartan/amlodipine 40/10 mg or olmesartan/amlodipine/HCTZ 40/10/12.5 mg, 59% and 47%, respectively, reached goal BP (patients without diabetes, <140/90 mm Hg; patients with diabetes <130/80 mm Hg). Triple-combination therapy was well tolerated.

Two smaller open-label studies also showed the effectiveness of olmesartan/amlodipine/HCTZ treatment for hypertension.[34–36] One of the studies was a clinical, practice-based trial that evaluated a step-wise drug algorithm of these 3 agents in patients with either stage 1 or 2 hypertension (titrated to a maximal dose of olmesartan/amlodipine/HCTZ 40/10/25 mg). At study end (week 24), 93% of patients achieved BP goal of $\leq$140/90 mm Hg, with 88% achieving the more stringent goal of $\leq$130/85 mm Hg.[35] When patients with stage 1 and stage 2 hypertension were separately evaluated, 98% and 90%, respectively, achieved the $\leq$140/90 mm Hg goal and 96% and 81%, respectively, achieved the $\leq$130/85 mm Hg goal.[36] In another study that evaluated a similar type of step-wise algorithm in patients with stage 1 and 2 hypertension (titrated to a maximal dose of olmesartan/amlodipine/HCTZ 40/5/25 mg), 86% of patients achieved BP goal (<130/85 mm Hg) at the end of the treatment algorithm.[34]

WHERE DO WE GO FROM HERE?

The use of combination therapy is a practical necessity for the majority of patients with hypertension because of the multifactorial nature of hypertension, the limitations in the potency of individual agents, and the increased incidence of obesity and

diabetes in the hypertensive population. New guidelines for the treatment of hypertension (eg, JNC 8, updated International Society on Hypertension in Blacks [ISHIB] guidelines) are expected to increase focus on the use of combination therapy, including expanding indications for initial treatment in appropriate patients.[37] The focus today is less on identification of the best *drug* for hypertension and more on the identification and use of preferred combinations.

It is logical to postulate that the best combinations will contain agents that have been shown to be most effective in long-term reduction of CV end points. Of the available classes of antihypertensive agents, β-blockers, ACE inhibitors, ARBs, diuretics, and CCBs all have been shown to reduce the occurrence of CV events in placebo-controlled trials. Several studies, including Losartan Intervention For Endpoint reduction in hypertension (LIFE) and the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), have indicated that the β-blocker atenolol is less effective in this regard than ARBs, ACE inhibitors, or CCBs. Low-dose diuretics have performed well in ALLHAT, the Hypertension in the Very Elderly Trial (HYVET), and other recent studies. In summary, the consensus of available evidence favors the use of ACE inhibitors and ARBs, low-dose diuretics, and CCBs as the preferred classes of antihypertensive drugs.

The studies reviewed in this article contributed to the recognition of the significant benefits of combining therapies into a single tablet. By reducing pill count and the number of times daily that patients are required to take medications, these preparations increase convenience, adherence, and long-term effectiveness. This has led to the development of single-pill, 2-drug combinations that involve almost all the newer classes of antihypertensive agents. Generic preparations of several combinations are also available. Therefore, the recent development of triple-combination therapy, including the 3 preferred classes of antihypertensive agents, is a logical development.

In clinical practice, triple-combination therapy may be used in a number of ways. In most patients, therapy will be initiated with a single agent (stage 1) or dual combination (stage 2) depending on the baseline BP.[18] In patients in whom the response to monotherapy with a diuretic, ARB, or CCB is such that the patient's BP remains >20/10 mm Hg above target, a rational "second step" might involve up-titration directly to triple-combination therapy. In other circumstances, patients receiving dual combinations of an ARB, CCB, and diuretics whose BP remains uncontrolled will be switched to triple-combination therapy. Finally, it may be used as a substitute for independently titrated doses of individual components. It is difficult to determine the exact fraction of patients who will ultimately require ≥3 antihypertensive agents to achieve target BP according to current guidelines. A reasonable estimate based on available data is that triple-combination therapy is needed in at least 25% of hypertensive patients. In any event, it is clear that triple-combination therapy of this type constitutes an effective, well-tolerated regimen that is capable of achieving BP targets in a large majority of patients with hypertension.

CONCLUSIONS

The majority of patients require ≥2 hypertensive agents to control BP. Combination therapy using drugs with complementary mechanisms of action can improve treatment tolerability, leading to improved patient compliance. Use of once-daily, single-pill combinations can also improve compliance by lowering pill count and obviating frequent dosing. In clinical trials, triple-combination therapy with amlodipine/valsartan/HCTZ reduced SBP/DBP by up to 39.7/24.7 mm Hg, and up to 75% of patients met BP goal. The occurrence of peripheral edema was less frequent with amlodipine/valsartan/HCTZ than with dual-component therapy, and hypotension-related AEs were infrequent. These titrate-to-effect results show the treatment potential and applicability of triple-combination therapy in the clinic setting.

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