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ORIGINAL RESEARCH

Rationale for triple fixed-dose combination therapy with an angiotensin II receptor blocker, a calcium channel blocker, and a thiazide diuretic

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Abstract: Hypertension is a growing global health problem, and is predicted to affect 1.56 billion people by 2025. Treatment remains suboptimal, with control of blood pressure achieved in only 20%–35% of patients, and the majority requiring two or more antihypertensive drugs to achieve recommended blood pressure goals. To improve blood pressure control, the European hypertension guidelines recommend that angiotensin II receptor blockers (ARBs) or angiotensin-converting enzyme inhibitors (ACEIs) are combined with calcium channel blockers (CCBs) and/or thiazide diuretics. The rationale for this strategy is based, in part, on their different effects on the renin-angiotensin system, which improves antihypertensive efficacy. Data from a large number of trials support the efficacy of ACEIs or ARBs in combination with CCBs and/or hydrochlorothiazide (HCTZ). Combining two different classes of antihypertensive drugs has an additive effect on lowering of blood pressure, and does not increase adverse events, with the ARBs showing a tolerability advantage over the ACEIs. Among the different ARBs, olmesartan medoxomil is available as a dual fixed-dose combination with either amlodipine or HCTZ, and the increased blood pressure-lowering efficacy of these two combinations is proven. Triple therapy is required in 15%–20% of treated uncontrolled hypertensive patients, with a renin-angiotensin system blocker, CCB, and thiazide diuretic considered to be a rational combination according to the European guidelines. Olmesartan, amlodipine, and HCTZ are available as a triple fixed-dose combination, and significant blood pressure reductions have been observed with this regimen compared with the possible dual combinations. The availability of these fixed-dose combinations should lead to improvement in blood pressure control and aid compliance with long-term therapy, optimizing the management of this chronic condition.

Keywords: angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, triple therapy, hypertension

Introduction

Globally, hypertension is the most common preventable cause of death, accounting for 7.5 million deaths in 2004,[1] yet it remains an increasing health problem.[2] At the start of the 21st century, over a quarter of the world's adult population had hypertension (972 million), and this is predicted to increase by about 60% to 1.56 billion in 2025.[3] The relationship between increasing blood pressure and cardiovascular risk is well established,[4] with even modest changes in blood pressure substantially increasing cardiovascular risk.[5]

Recent hypertension guidelines, produced by the European Society of Hypertension and the European Society of Cardiology, state that the primary goal of treatment is to achieve the maximum reduction in long-term total risk of cardiovascular

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morbidity and mortality.[6] A reduction in systolic blood pressure/diastolic blood pressure to <140/90 mmHg is recommended in all patients with hypertension. More recently, the 2009 reappraisal of the European Society of Hypertension guidelines recommends that reducing blood pressure to within the range of 130–139/80–85 mmHg in all hypertensive patients may be prudent.[6,7]

Despite the widely recognized relationship between high blood pressure and cardiovascular risk, and clear hypertension guidelines, overall blood pressure control rates remain suboptimal and a growing public health concern worldwide. According to the findings of a systematic literature review conducted in established market economies, on average 20%–35% of treated hypertensive patients had their blood pressure controlled.[8,9] A significant example of poor blood pressure control is seen in epidemiological data from over 52,000 hypertensive patients in Italy, who also had a high prevalence of concomitant risk factors, including hypercholesterolemia (55.9%), obesity (36.4%), smoking (28.7%), and diabetes (15.0%),[10] putting about 50% of the overall hypertensive population at high or very high risk of cardiovascular morbidity and mortality. This is particularly relevant because overall blood pressure control has been shown to be worse in patients with increasing numbers of risk factors, as demonstrated in a review of data from over 22,000 hypertensive patients in 26 countries.[9] This is also of concern, because one would expect this higher-risk population to be receiving more intensive blood pressure control. In addition, suboptimal blood pressure control is also causing a growing economic burden, accounting for direct health care costs of US$372 billion in 2001, which are predicted to increase to US$908 billion in 2011.[11] One factor that may well be contributing to the suboptimal rates of blood pressure control is the prevailing use of monotherapy in clinical practice. Blood pressure targets are achieved in only a limited number of patients using monotherapy, while the majority require two or more antihypertensive agents.[6,7] The European guidelines recommend the use of a combination of two drugs at low doses, even as an initial treatment when hypertensive patients have marked blood pressure elevation or high blood pressure elevation in association with subclinical organ damage, diabetes, renal disease, or cardiovascular disease.[6] This approach is also recommended by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.[12] Furthermore, even though combining two drugs may significantly improve efficacy, it is estimated that for a relevant proportion of patients, this may not be enough, thus 15%–20% of patients require combination therapy with three agents to control blood pressure effectively.[7]

This review will look at the rationale for using combination therapy to optimize blood pressure control, provide a summary of the evidence to support the preferred combinations, and focus on the use of angiotensin II receptor blocker (ARB)-based dual or triple combinations as examples of effective and well tolerated treatments, mostly those based on olmesartan medoxomil.

Blood pressure control: rationale for combination therapy

The most commonly used antihypertensive drugs are the renin-angiotensin system blockers, ie, angiotensin-converting enzyme inhibitors (ACEIs), ARBs, calcium channel blockers (CCBs), beta-blockers, and thiazides, and combining these classes has a number of beneficial effects. Firstly, combination therapy, which uses drugs with different and complementary mechanisms of action, can provide synergistic effects on blood pressure, thus providing higher antihypertensive efficacy than the individual components. The blood pressure-lowering effect of combination therapy can be predicted on the basis of the additive effects of the individual components, according to the findings of a meta-analysis of 42 randomized, factorial clinical trials, performed in approximately 11,000 patients with arterial hypertension.[13] According to this analysis, the blood pressure-lowering efficacy of combining two different classes is approximately five times greater than doubling the dose of one of the components. Secondly, the blood pressure-lowering efficacy of the different antihypertensive drug classes is, as expected, also accompanied by reductions in the risk of developing coronary heart disease and stroke.[14] Thirdly, a reduction in adverse events is frequently observed with specific combination strategies; adverse events are less than additive.[15] In addition, combination therapy has been associated with a lower rate of discontinuation, compared with initiating treatment with monotherapy, having the lowest rates associated with the use of renin-angiotensin system blockers.[16] Finally, combination therapy may allow dose titration of treatment without increasing pill burden, an important factor in the treatment of a condition in which compliance has important benefits for patient health,[17] and that is frequently associated with other clinical conditions, which require other drugs (antidiabetic, lipid-lowering, antiplatelet agents).

Possible combination therapies

It is possible to understand why combination therapy is so effective by considering the effects of the major classes of antihypertensive agents on the renin-angiotensin system, which is a key biological system, playing a major role in the regulation of blood pressure and in the pathophysiology of hypertension. Secretion of renin is regulated by arterial pressure, negative feedback by angiotensin II, sodium chloride delivery to the macula densa, and activity of the sympathetic nervous system.[18] Each class of antihypertensive treatment has a different effect on the renin-angiotensin system, ie, CCBs and diuretics stimulate the renin-angiotensin system to compensate for the reduced pressure in the glomerular afferent arteriolar and loss of sodium, respectively, whilst the ARBs, ACEIs, beta-blockers, and the direct renin inhibitor, aliskiren, inhibit the renin-angiotensin system at different levels, interfering with different mechanisms (Figure 1).

Large-scale studies involving ARBs have demonstrated the efficacy of these agents in reducing cardiovascular and cerebrovascular risk in important groups of hypertensive patients. SCOPE (The Study on Cognition and Prognosis in the Elderly) showed that in elderly patients (aged 70–89 years), blood pressure-lowering with an ARB reduced major cardiovascular events as effectively as treatment with placebo (plus additional antihypertensive agents except ACEIs or ARBs).[19] Studies in high-risk patients, including those with cardiovascular disease, atrial fibrillation, recent stroke, and impaired glucose tolerance, have also shown ARB treatment to be as effective as placebo in reducing the risk of cardiovascular outcomes.[20–23] Moreover, data from the SCOPE, LIFE, (Losartan Intervention For Endpoint reduction), and the MOSES (MOrbidity and mortality after Stroke, Eprosartan compared with nitrendipine for Secondary prevention) studies provide encouraging indications that ARBs may be beneficial in reducing the risk of stroke.[19,24,25]

On the basis of their opposite effects on the renin-angiotensin system, effective antihypertensive treatment combinations are those based on the association of renin-angiotensin system blockers with CCBs or diuretics, which have stronger antihypertensive efficacy when used in combination.

In terms of the preferred combinations, outcomes data from large, randomized studies, including LIFE, ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm) and INVEST (the International Verapamil-Trandolapril Study) trials, suggest that renin-angiotensin system-based combinations may be superior to beta-blocker plus thiazide combinations in terms of cardiovascular morbidity and mortality.[25–27] Furthermore, the use of a beta-blocker in combination with a diuretic is currently not recommended in predisposed patients due to the more likely development of diabetes,[7,28] while the outcome of using a beta-blocker in combination with a CCB has not been properly investigated.[7]

Thus, the preferred combinations of antihypertensive drugs according to the European Society of Hypertension/European Society of Cardiology guidelines include ARBs and CCBs, ACEIs or CCBs, ARBs and thiazide diuretics, or ACEIs and thiazide diuretics.[6,7] The association of direct renin inhibitors and thiazide diuretics or CCBs is currently under investigation.

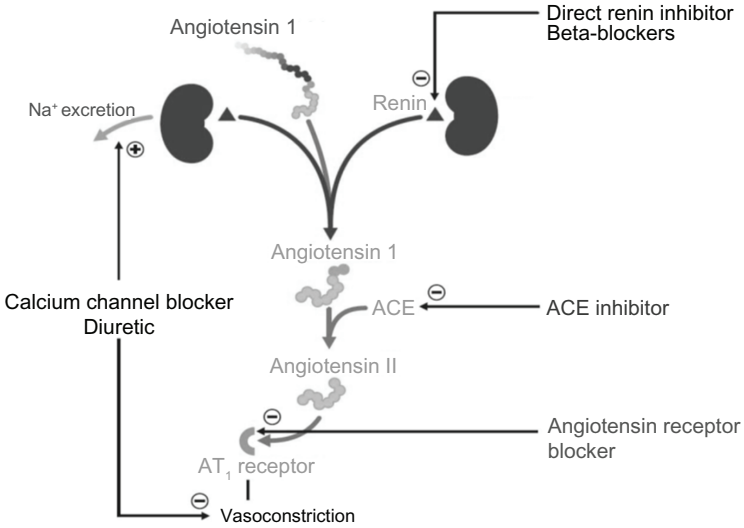

Figure 1 Effects of antihypertensive drugs that inhibit the renin-angiotensin system.[18]
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Abbreviations: ACE, angiotensin-converting enzyme; AT_1, angiotensin type 1.

Efficacy

Combining two different classes of antihypertensive drugs has been shown to provide an additive blood pressure-lowering effect,[15] and data from a large number of trials shows the efficacy of using ACEIs or ARBs in combination with CCBs or diuretics to improve blood pressure control.[7]

The blood pressure-lowering efficacy of an ACEI (perindopril) plus diuretic (indapamide) combination was more than twice that of single-drug therapy in the PROGRESS (perindopril protection against recurrent stroke) trial.[29] Similarly the antihypertensive efficacy of such a combination was confirmed in the ADVANCE (Actions in Diabetes and Vascular A reduction in disease: preterAx and diamicroN-MR Controlled Evaluation) trial and in the HYVET (HYpertension in the Very Elderly Trial).[30,31]

Amlodipine plus perindopril was more effective in lowering blood pressure and preventing major cardiovascular events compared with a beta-blocker and diuretic in the ASCOT-BPLA trial.[26] In INVEST, 2-year blood pressure control was similar in those patients receiving verapamil plus trandolapril compared with the combination of a beta-blocker and diuretic.[27] A similar reduction in blood pressure was also observed with amlodipine plus benazepril compared with benazepril plus hydrochlorothiazide (HCTZ) in the ACCOMPLISH (Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension) trial, whilst the ACEI plus CCB combination was more effective in reducing the primary combined cardiovascular outcome of that study.[32]

For a similar reduction in blood pressure, losartan-based therapy (initial combination with HCTZ) reduced cardiovascular morbidity and mortality to a greater extent than atenolol-based therapy in the LIFE trial.[25] In the VALUE (Valsartan Antihypertensive Long-term Use Evaluation) trial, there was no difference in cardiovascular morbidity and mortality between valsartan plus HCTZ compared with amlodipine plus HCTZ.[33] The reduction in blood pressure was substantially similar in both groups, although amlodipine-based therapy had a more pronounced blood pressure-lowering effect in the first months of therapy.

Tolerability

Unlike the additive blood pressure-lowering effects observed with combining two different classes of antihypertensive drugs, adverse effects are less than additive.[15] Moreover, the complementary mechanisms of action of the different classes of antihypertensive treatments may even lead to a reduction of some adverse events in specific cases. For example, peripheral edema is a common adverse effect of CCBs, which is reduced when a CCB is administered in combination with an ARB or ACEI.[34] A recent example of this favorable effect using ARBs is provided by the COACH (Combination of Olmesartan Medoxomil and Amlodipine Besylate in Controlling High Blood Pressure) study, described later in this review.[35]

Whilst the combinations of antihypertensive agents are generally well tolerated and consistent with the component agents, there are important differences in the adverse event profiles of the different classes. Adverse events with CCBs and thiazides are strongly dose-related, whilst those observed with ACEIs and ARBS are much less related to dose. On this basis, ACEIs and ARBs can be used at full doses in combination regimens.[15] Even though ACEIs and ARBs are well tolerated, clinical studies like ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global End-point Trial) show that ARBs have a significant tolerability advantage over ACEIs.[36] In this large study, the frequency of cough and angioedema leading to permanent discontinuation was more common in the ramipril group than in the telmisartan group (Table 1).

It should be mentioned here that, in 2011, two clinical trials reported safety issues relating to the use of olmesartan in high-risk patients. Each of these studies involved patients with type 2 diabetes who were randomized to treatment with olmesartan or placebo plus additional antihypertensive agents (except ACEIs or ARBs) as needed for blood pressure control. The ROADMAP (Randomized Olmesartan and Diabetes MicroAlbuminuria Prevention) trial involved mainly Caucasian patients with diabetes and at least one other cardiovascular risk factor, who were at risk of developing microalbuminuria. In ROADMAP, 15 (0.7%) deaths due to cardiovascular causes occurred in the olmesartan group and 3 (0.1%) in the placebo group ($P = 0.01$). The authors suggested that this difference may simply have been a chance outcome caused by the low numbers of these events.[37]

Table 1 Tolerability profiles of ramipril and telmisartan leading to permanent discontinuation in the ONTARGET study[36]

Reason for permanent discontinuation	Patients (n, %)	
	Ramipril (n = 8576)	Telmisartan (n = 8542)
Cough	360 (4.2)	93 (1.1)
Hypotensive symptoms	149 (1.7)	229 (2.7)
Renal impairment	60 (0.7)	68 (0.8)
Angioedema	25 (0.3)	10 (0.1)
Syncope	15 (0.2)	19 (0.2)
Diarrhea	12 (0.1)	19 (0.2)

The ORIENT (Olmesartan Reducing Incidence of Endstage renal disease in diabetic Nephropathy Trial) involved Eastern Asian patients with diabetes and overt nephropathy. There were 10 cardiovascular deaths (3.5%) in the olmesartan group and three (1.1%) in the placebo group, and the authors suggested that the higher number of deaths in the olmesartan group may have been related to the higher number of patients with a history of cardiovascular problems in the former group.[38]

More recently, the impact of the OLIVUS (OLmesartan on progression of coronary atherosclerosis: evaluation by intraVascular UltraSound) study looked at Japanese patients with stable angina pectoris and established coronary artery disease who were randomized to treatment with olmesartan or placebo plus additional antihypertensive agents (except ACEIs or ARBs). This study found no difference in the rate of cardiovascular or cerebrovascular events between the two groups, although a composite event rate of cardiovascular and cerebrovascular deaths, myocardial infarction, stroke, angina, and heart or renal failure was significantly lower in the olmesartan group ($P = 0.041$).[39] Further insights into the safety of olmesartan may come from the OSCAR (OlmeSartan and Calcium Antagonists Randomized) study which is comparing the effects of olmesartan monotherapy with an olmesartan plus CCB combination on cardiovascular morbidity and mortality in elderly Japanese hypertensive patients at increased cardiovascular risk.[40] Perhaps the final point in this regard is that the United States Food and Drug Administration carried out an investigation into the safety data from the ROADMAP and ORIENT studies, found no safety concerns, and concluded that the benefits of olmesartan continue to outweigh its potential risks for the treatment of high blood pressure.[41]

ARB-based combination therapy

Recent European guidelines highlighted the need to overcome the persistent prevailing use of monotherapy in the treatment of hypertension and recommend the use of combination therapy in the majority of patients. In this regard, the 2009 reappraisal of the guidelines highlights the benefits of renin-angiotensin system-based combinations.[6,7]

The efficacy of ARBs is based on their ability to antagonize selectively the binding of angiotensin II to the angiotensin II type 1 (AT_1) receptor; the differences reported between class members are mostly explained by differences in dosing.[42] For example, olmesartan 20 mg and irbesartan 300 mg have been shown to block the blood pressure response to exogenous angiotensin II completely, whilst the effect was blocked to a lesser extent with valsartan 160 mg and losartan 100 mg.[43] Such differences in the ability to block the AT_1 receptor appear to translate into differences in duration of antihypertensive efficacy. An independent meta-analysis of studies that used ambulatory blood pressure monitoring showed that the magnitude of blood pressure reductions depended upon the agent used.[44] This is in line with the results of direct head-to-head clinical comparisons, which have shown that some members of the ARB class, particularly olmesartan medoxomil, provide highly effective blood pressure reductions over 24 hours.[45–47] This observation suggests that dual or triple fixed-combination therapies based upon olmesartan can provide effective and sustained control of blood pressure levels. The increased blood pressure-lowering efficacy of a dual fixed-dose combination of olmesartan with either amlodipine or HCTZ has been confirmed in a number of clinical studies.[35,48–52]

The COACH study provides a good example of the beneficial effects of combination therapy. In this 8-week, randomized, double-blind, factorial study, the antihypertensive efficacy of olmesartan (10 mg, 20 mg, or 40 mg) in combination with amlodipine (5 mg, 10 mg) was compared with component monotherapies in 1940 patients with mild-to-severe hypertension.[35] Significantly greater dose-dependent reductions in seated diastolic blood pressure and systolic blood pressure were observed with olmesartan plus amlodipine compared with the component monotherapies ($P < 0.001$). Blood pressure reductions were greater with olmesartan 20 mg in combination with amlodipine 5 mg (–22.6/–14.6 mmHg, respectively), compared with monotherapy with olmesartan 20 or 40 mg (–12.8/–9.9 and –15.4/–10.9 mmHg, respectively) and compared with amlodipine 5 or 10 mg (–14.3/–10.0 and –18.9/–13.3 mmHg, respectively). These results provide a practical demonstration of the principle that combination therapy is superior to monotherapy, and that combining two agents at a lower dose produces larger blood pressure reductions than titrating the dose of monotherapy. The proportion of patients achieving their blood pressure goal (<140/90 mmHg, or <130/80 mmHg for patients with diabetes) showed a similar pattern of response, with all doses of combination therapy showing higher rates of goal achievement compared with the same dose of each monotherapy. The combination was well tolerated, and as highlighted earlier, showed particular benefits in terms of reducing the occurrence of peripheral edema, an adverse event frequently associated with amlodipine 10 mg. In this study, combining amlodipine 10 mg with olmesartan (10 mg, 20 mg, or 40 mg) reduced the frequency of edema seen

with the higher dose of this CCB, with a statistically significant reduction observed for olmesartan 20 mg/amlodipine 10 mg ($P = 0.032$) and olmesartan 40 mg/amlodipine 10 mg ($P = 0.011$). A further illustration of the benefits of combination therapy comes from a randomized study of the effects of adding olmesartan (10–40 mg) in 755 patients with moderate-to-severe hypertension who had not shown an adequate response to 8 weeks of treatment with amlodipine 5 mg.[52] Significant reductions in blood pressure were observed after 8 weeks of double-blind treatment with all doses of olmesartan and amlodipine combination therapy compared with patients randomized to continue receiving amlodipine 5 mg ($P < 0.03$). The benefits of combination therapy were also seen in the significantly higher level of blood pressure goal achievement with olmesartan 40 mg/amlodipine 5 mg (51%) and olmesartan 20 mg/amlodipine 5 mg (54%) compared with the group that continued on amlodipine 5 mg (30%; $P < 0.0001$). In each of these studies, olmesartan in combination with amlodipine was well tolerated.

In regard to the combination of olmesartan with HCTZ, greater reductions in seated diastolic blood pressure and systolic blood pressure were observed with olmesartan (10 mg, 20 mg, or 40 mg) plus HCTZ (12.5 or 25 mg) than monotherapy with either component at 8 weeks in a randomized, double-blind, factorial design study in 502 patients with grade 2 hypertension.[48] Blood pressure reductions with olmesartan 20 mg plus HCTZ 12.5 mg were greater than monotherapy of either olmesartan 20 mg or HCTZ 12.5 mg. Moreover, blood pressure reductions in the group that received the 20/12.5 mg combination were larger than the blood pressure reductions seen in the groups that received monotherapy at higher doses (olmesartan 40 mg and HCTZ 25 mg, respectively), again highlighting the benefits of combination therapy over titration of monotherapy. In a secondary analysis of this study, the proportion of patients achieving their blood pressure goals was also found to be greater in those receiving combination therapy compared with monotherapy.[49] A recent addon study in patients with moderate-to-severe hypertension (n = 972) who had inadequate blood pressure control with olmesartan 40 mg provides further support for the efficacy of combination therapy. Compared with patients randomized to continue with olmesartan 40 mg alone, those randomized to receive HCTZ (12.5 mg and 25 mg) showed significant dose-related reductions in clinic systolic blood pressure and diastolic blood pressure ($P < 0.0001$), as well as significant reductions in ambulatory systolic blood pressure and diastolic blood pressure and improvements in goal rate achievement.[53]

The benefits of combination therapy with the inclusion of dose titration are illustrated by a treat-to-target study that used a stepwise treatment intensification algorithm. The efficacy of a 12-week olmesartan-based regimen was investigated in 276 patients with grade 1 and 2 hypertension in a randomized, double-blind, placebo-controlled, titration study.[51] Patients received olmesartan 20 mg for 3 weeks after which those who did not achieve an adequate level of blood pressure control were uptitrated to 40 mg for 3 weeks, and then in the two following 3-week periods, HCTZ 12.5 mg was added and uptitrated to 25 mg. Blood pressure reductions occurred in a progressive treatment-related and dose-related manner. The reductions in seated diastolic blood pressure and systolic blood pressure increased at each dose titration step, with the greatest reductions observed in patients who received olmesartan 40 mg plus HCTZ 25 mg. These studies have also shown that the olmesartan/HCTZ combination is well tolerated, with adverse events of mild-to-moderate severity.[48,51,53]

These studies highlight the benefits of combining two antihypertensive agents from different classes, but there are some patients, estimated to represent around 15%–20% of the patient population, who cannot be controlled with two drugs, and who require a combination of three or more antihypertensive agents. For such patients, the 2009 reappraisal of the European guidelines suggests that a combination containing a renin-angiotensin system blocker, CCB, and thiazide diuretic is rational.[7] Recent clinical studies bear this out and have shown that triple therapy with an ARB, CCB, and a diuretic significantly reduces blood pressure compared with dual combination therapy.[54,55]

The clinical benefit (seated diastolic blood pressure reduction ≥2 mmHg) of triple combination therapy with olmesartan 40 mg, amlodipine 10 mg, and HCTZ 25 mg has been compared with that of dual combination therapy with the individual components in TRINITY (the TRIple therapy with olmesartan medoxomil, amlodipine, and hydrochlorothiazide in hyperteNsIve patienTs studY), conducted in 2492 patients with moderate-to-severe hypertension.[54] After 12 weeks, seated diastolic blood pressure and systolic blood pressure reductions were significantly greater with triple combination therapy compared with dual combinations ($P < 0.001$), ie, least squares mean reductions in seated diastolic blood pressure of –21.8 versus –15.1 to –18.0 mmHg; least squares mean reductions in seated systolic blood pressure of –37.1 versus –27.5 to –30.0 mmHg. Also, a significantly greater proportion of patients using triple therapy reached target blood pressures ($P < 0.001$ versus

dual combinations). Significantly greater reductions in mean 24-hour blood pressure were also observed for the triple combination compared with dual therapy ($P < 0.0001$), showing that duration of action is increased as well as magnitude of effect.[56] Triple combination therapy was well tolerated, with the majority of adverse events being mild-or-moderate in severity. There was no difference in the incidence of treatment-emergent adverse events between triple and dual combination therapies.

A further insight into the potential of combination therapy comes from the BP-CRUSH (Blood Pressure ContRol in all sUbgroupS with Hypertension) study which used a stepwise, treat-to-target based approach.[57] The study involved 999 patients uncontrolled on monotherapy who received olmesartan plus amlodipine 20/5 mg for 4 weeks after which those who did not meet a specified blood pressure target had their treatment intensified after intervals of 4 weeks by titration to 40/5 mg, and then 40/10 mg by the addition of HCTZ 12.5 mg and finally by titration of this to 25 mg. At the end of the dual combination phase after 12 weeks, the cumulative percentage of patients who had achieved the primary end point of seated systolic blood pressure <140 mmHg (<130 mmHg in diabetics) was 75.8%, and at the end of the triple combination phase after 20 weeks, the cumulative percentage who had achieved this end point was 90.3%.[57]

It should also be pointed out that a triple combination based upon the ARB valsartan has also become available and shown promising efficacy in clinical studies. In one study, 408 patients with grade 2 hypertension were randomized to 8 weeks of treatment with valsartan plus amlodipine 160/10 mg or amlodipine 10 mg. After 4 weeks, HCTZ 12.5 mg was added if mean systolic blood pressure was >130 mmHg. By the end of the 8-week study, patients who had received valsartan plus amlodipine plus HCTZ showed significantly greater mean seated blood pressure reductions from baseline (30.5/13.8 mmHg) than those who received amlodipine plus HCTZ (24.3/8.3 mmHg, $P < 0.0001$). Significant reductions in ambulatory blood pressure were also seen in a subanalysis of 283 subjects from a separate study of patients with moderate-to-severe hypertension who had received 6 weeks of randomized treatment with valsartan plus amlodipine plus HCTZ 320/10/25 mg or each component dual combination. In the first phase of this study, each group received a lower-dose dual combination and HCTZ was added to one group after a week with all doses being titrated before the final 6 weeks. At the end of the study, the mean reduction from baseline in 24-hour mean ambulatory systolic blood pressure/diastolic blood pressure was 30.3/19.7 mmHg with amlodipine plus valsartan plus hydrochlorothiazide, and 18.8–24.1/11.7–15.5 mmHg with the dual combinations ($P < 0.01$ for each triple versus dual comparison).[58]

A further recent development is the availability of dual and triple combinations based on the direct renin inhibitor, aliskiren. This was demonstrated by a study of 412 patients with grade 2 hypertension who were randomized to 8 weeks of treatment with aliskiren plus amlodipine (150/5 mg) or amlodipine (5 mg), force titrated to aliskiren plus amlodipine plus HCTZ (300/10/25 mg) or aliskiren plus amlodipine (300/10 mg). Both treatments reduced mean seated blood pressure, but the reductions seen with the triple combination were larger and enabled 72.6% of patients to achieve blood pressure goal, compared with 53.2% of dual combination recipients.[59]

Further analyses of these studies and new studies with triple combination therapy should help to make clear the patient populations in which triple combinations are most suitable. Here it may be informative to look at the long-term extension phase of the COACH study during which HCTZ could be added to olmesartan plus amlodipine, with all three agents titrated according to the investigators' discretion. Not surprisingly, it could be seen at the end of the study that the patients who had required HCTZ had the higher blood pressure levels at baseline than patients who had reached the end of the study on the olmesartan plus amlodipine dual combination.[60] Thus, some of the patients who will likely benefit from the use of the triple combination will be those with more severe forms of hypertension.

Fixed-dose combination therapy

A further important issue related to the use of combination therapy is that represented by the choice of single-pill fixed-dose combinations. In those patients who require two or more drugs to control blood pressure, the use of fixed-dose combination of two drugs is recommended in European guidelines.[6,7] In this regard, the major role played by compliance with therapy for effective management of high blood pressure is widely recognized. Indeed, poor compliance is common in the treatment of chronic diseases such as hypertension, with an estimated 30%–50% of patients not complying with antihypertensive therapy.[61] As the number of daily administrations increases, compliance with treatment decreases and, thus, the lack of compliance represents a common and major problem in the clinical management of hypertension. Therefore, the use of fixed-dose combination therapy can help to simplify treatment regimens and to ensure higher compliance with therapy.[62]

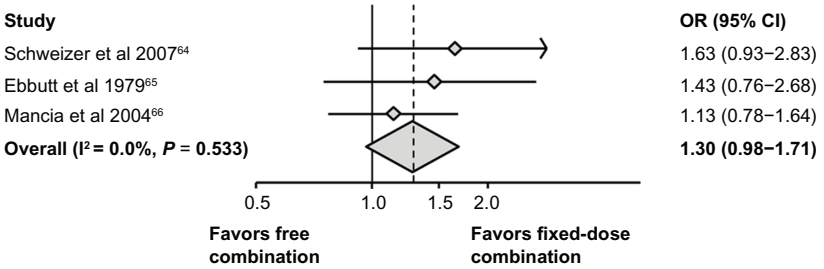

Figure 2 Comparison of the blood pressure normalization ratios of fixed dose versus free dose combinations of the same antihypertensive agents.

Abbreviations: OR, odds ratio; CI, confidence interval.

A meta-analysis of nine studies using fixed-dose combination therapies, including four in hypertensive patients, found a 26% decrease in risk of noncompliance compared with a free-drug component regimen.[63] The risk of noncompliance decreased by 24% with fixed-dose combination therapy in the four studies of hypertensive patients ($P < 0.0001$). The use of fixed-dose combination therapy may also be associated with improved blood pressure control. A meta-analysis of three studies with fixed-dose combinations of antihypertensive drugs, which reported normalization of blood pressure, has shown a trend towards greater blood pressure control, compared with the corresponding free drug combination (Figure 2).[17]

Various dual combinations of ARBs with HCTZ or amlodipine are available as fixed-dose combinations. Recently two fixed-dose combinations of three agents including an ARB have become available, ie, valsartan with amlodipine and HCTZ, and olmesartan with amlodipine and HCTZ. The development of ARB-based triple fixed-dose combinations like these may be helpful to improve blood pressure control and compliance in clinical practice.

Conclusion

Hypertension is a growing public health concern, and the use of combination therapy can aid treatment optimization and improve blood pressure control. ARB-based dual and triple combinations, such as those based upon olmesartan, provide greater reductions in blood pressure than the component monotherapies and dual therapies, respectively, are well tolerated, and can also help to improve compliance.

Disclosure

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