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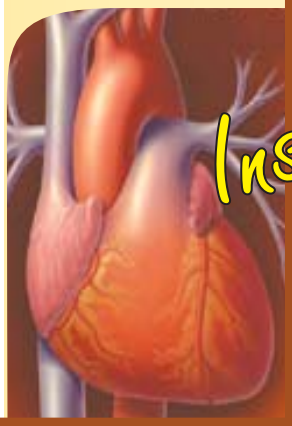

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Amlodipine/Olmesartan: A review of its use in the management of hypertension

Introduction

Arterial hypertension is the single largest contributor to global mortality, and is responsible for approximately 7.1 million deaths each year. In 2000, it was estimated that nearly 1 billion people worldwide had hypertension, and it was predicted that the prevalence would increase to over 1.5 billion by 2025. The prevalence of hypertension among people aged 35–64 years is about 30% in the US,4 and about 44% in Europe. Hypertension continues to be underdiagnosed and undertreated.

Raised blood pressure (BP) is a major risk factor for stroke, heart disease and renal failure. Many clinical trials have shown that BP reduction by a variety of strategies reduces the risk of stroke by approximately 35%, congestiveheart failure by 42%, and coronary heart disease by 28%.

Current European guidelines recommend a target systolic BP (SBP) and diastolic BP (DBP) of, 140/90 mmHg in the general population. However, despite these recommendations and the well-documented relationship between hypertension and the increased cardiovascular (CV) and renal risk, BP control rates remain poor, particularly in Europe. Therefore, the primary aim of an effective antihypertensive treatment strategy is to lower elevated BP to target levels and to achieve a maximum reduction in risk. The recent reappraisal of the European guidelines on hypertension management recommends that it may be prudent to lower BP to values within the range of 130–139/80–85 mmHg in the majority of hypertensive patients, including those with diabetes. In these guidelines, both angiotensin receptor blockers (ARBs) and calcium channel blockers (CCBs) are recommended for first-line therapy either as monotherapy or in combination. This article reviews the rationale for fixed-dose combination therapy with the ARB - olmesartan medoxomil and the CCB - amlodipine.

Fixed-dose combination therapy versus monotherapy

Among the many factors that may contribute to suboptimal BP control rates are nonadherence of patients to therapy and clinical inertia, where physicians fail to increase the dosage of existing antihypertensive medication or prescribe combinations of antihypertensive drugs when patients do not achieve their BP goal. Increasing the dose of a single antihypertensive agent in an attempt to achieve an adequate response may lead, however, to an increase in side-effects, which can lead to noncompliance and exacerbation of the BP control problem. Hypertension is a complex multifactorial condition comprising multiple pathways involved in BP control. The rationale behind combination therapy, using two or more drugs with different and complementary mechanisms of action, is the potential to improve BP control by the combined effects and, by allowing lower doses of the drugs, to reduce unwanted side-effects. A recent meta-analysis of 10,968 patients from 42 trials has shown that the average antihypertensive effect of combining two drugs from different classes (thiazides, beta-blockers, angiotensin-converting enzyme inhibitors [ACEIs] and CCBs) is approximately additive. The authors estimated that the additional reduction in BP produced by combining two drugs from different classes was approximately five times greater than that achieved by doubling the dosage of either drug. Therefore, combination therapy is a simple and effective strategy to increase antihypertensive efficacy and, therefore, control BP in hypertensive patients.

In the past, monotherapy has been the standard initial treatment approach in most patients with hypertension, with combination therapy being initiated when stepwise increases in the dose of the single agent fail to achieve the required BP reduction. More recently, a number of clinical trials have clearly demonstrated that most patients receiving antihypertensive combination therapy

are indeed able to achieve adequate BP control. The available data suggest that, overall, at least 75% of patients with hypertension will require combination therapy to achieve BP targets. Accordingly, recent European treatment guidelines recommend the use of combination therapy as an alternative to monotherapy as initial treatment, particularly in patients at high CV risk.

Single-pill combinations of two antihypertensive drugs, known as fixed-dose combinations, are now widely available, often combining an ACEI or an ARB as agents that target the renin–angiotensin system (RAS) with either a thiazide diuretic or a CCB. At low doses, fixed-dose combinations may have greater efficacy and better tolerability than the respective high-dose monotherapies. Fixed-dose combinations can simplify the treatment schedule and improve compliance and persistence with therapy compared with two antihypertensive drugs given separately. It is reasonable to expect that this may result in improvements in BP control and reduction in the incidence of CV events. Importantly, combination antihypertensive therapy comprising either an ACEI or ARB is favorable since, unlike drugs from other classes, these agents can be used at higher doses to increase efficacy without compromising tolerability. Consequently, this poses the question of "what should be combined with a RAS blocker?"

Studies have shown that combination therapy with an ACEI (benazepril) and a CCB (amlodipine) provides superior BP-lowering efficacy compared with either agent as monotherapy. Subsequently, the ACCOMPLISH (Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension) trial was one of the first major studies to investigate the effects of fixed dose combination therapy and demonstrated the benefits of combination treatment comprising a RAS blocker/CCB and RAS blocker/thiazide diuretic by the achievement of very high levels of BP control. In this large, randomized, double-blind clinical trial, the effects of benazepril plus amlodipine were compared with those of benazepril plus the thiazide diuretic hydrochlorothiazide (HCTZ) in reducing CV morbidity and mortality in approximately 11,500 patients at high risk of CV events. The study drugs were taken as a single-capsule formulation. Drug doses were force-titrated to attain recommended BP goals. BP control (<140/90 mmHg) was achieved by 75.4% of patients receiving benazepril/amlodipine and 72.4% of patients receiving benazepril/HCTZ. Notably, the primary composite endpoint, including death from CV causes and CV events, were significantly ($P < 0.001$) reduced by approximately 20% in the benazepril/amlodipine arm compared with the benazepril/HCTZ arm. However, these results should not be extrapolated to the general hypertensive population in regard to assuming that a RAS blocker/CCB combination is per se superior to a RAS blocker/thiazide diuretic combination since the patient population in ACCOMPLISH was not typical of the general hypertensive population: there was a high level of obesity and approximately 60% of patients were diabetic. Nonetheless, the combination of a RAS blocker plus a CCB was undoubtedly an effective combination in these patients, and supports the use of combination therapy comprising a RAS blocker and CCB to control BP and reduce CV risk in patients with hypertension, especially those with features of the metabolic syndrome such as obesity and diabetes.

Another randomized trial, ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial), demonstrated that the ARB telmisartan was equally as effective as the ACEI ramipril in reducing the incidence of CV events in high-risk patients. Importantly, there was a lower incidence of cough and angio-edema in patients who received telmisartan compared with those who received ramipril. This result is consistent with a large scale observational study of more than 195,000 patients in the US Veterans Affairs Health Care System who initiated ACE therapy. The study found an increase in the incidence of angioedema associated with the use of ACEIs (1.97 cases/1000 person years) compared with other antihypertensive medications (0.51 cases/1000 person years), and that the risk of angioedema remained elevated with longer-term use, even beyond one year. Taken together these findings support the rationale for combining an ARB and a CCB as an antihypertensive strategy. This notion is reflected by the recent European hypertension treatment guidelines in which combination therapy with an ARB or ACEI plus a CCB is indeed a recommended strategy.

Amlodipine/Olmesartan combination therapy

Since ARBs inhibit the activity of the RAS by blocking the angiotensin II type 1 (AT_1) receptor, the efficacy of the ARBs depend upon their ability to inhibit AT_1 receptor activation by angiotensin II. Pharmacodynamic studies have shown that ARBs, when given in their recommended doses, differ in their ability to block the AT_1 receptor. These differences in AT_1 receptor blockade may translate into differences between ARBs in their ability to control BP over 24 hours. This is in line with an independent meta-analysis of studies which used ambulatory BP monitoring (ABPM) to measure 24-hour BP control with ARBs. This meta-analysis found that the size of reduction in ambulatory SBP depended upon the drug used, and that the dose used affected the duration of the antihypertensive activity for both systolic and diastolic BP.

In this regard, the ARB olmesartan medoxomil (hereafter referred to as olmesartan) is of interest since it has been shown in pharmacodynamic studies to produce a strong level of AT_1 receptor blockade in relation to dose. Furthermore, direct comparison with several other ARBs has shown that olmesartan produces robust antihypertensive efficacy over 24 hours, the daytime, night-time, and end-of-dosing interval periods relative to losartan, candesartan or valsartan monotherapy, and was at least as

efficacious as irbesartan.

Clinical data suggest that olmesartan may protect against end-organ damage and, in this regard, renoprotective and anti-atherosclerotic effects have been reported in clinical and experimental studies. As with other members of this drug class, olmesartan has shown excellent, placebo-like tolerability in clinical studies. Taken together, the efficacy and excellent tolerability of olmesartan make it highly suitable for use in combination therapy.

Fixed-dose combination formulations of olmesartan and amlodipine (olmesartan/amlodipine 20/5 mg, 40/5 mg or 40/10 mg) are approved in several European countries for once-daily administration in patients with essential hypertension who have responded inadequately to either drug as monotherapy, or who are receiving separate tablets as combination therapy. Like olmesartan, amlodipine provides effective BP control and exhibits organ-protective properties.

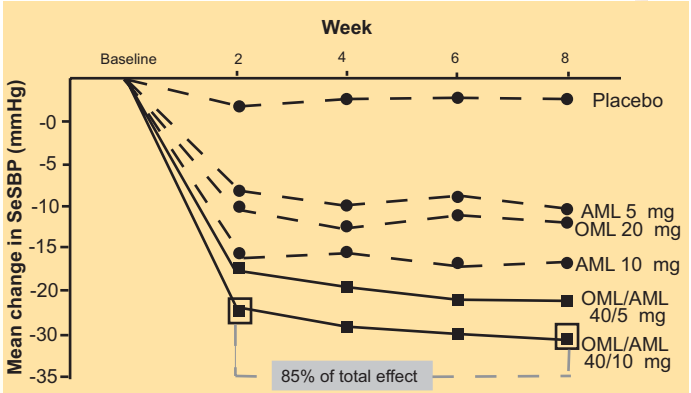

Figure 1: Mean change in seated systolic blood pressure (SeSBP) from baseline to weeks 2, 4, 6 and 8 with olmesartan (OLM) and amlodipine (AML) monotherapy and olmesartan/amlodipine combination therapy.

Therapeutic efficacy of amlodipine/olmesartan

The efficacy of amlodipine/olmesartan has been evaluated in three key randomized, double-blind trials. The factorial Combination of Olmesartan Medoxomil and Amlodipine Besylate in Controlling High Blood Pressure (COACH) trial evaluated the efficacy of dual combination therapy with olmesartan/amlodipine compared with its component monotherapies in patients with mild-to-severe hypertension. Two add-on trials evaluated the efficacy of olmesartan plus amlodipine in patients with moderate-to-severe hypertension who responded inadequately to amlodipine or olmesartan monotherapy.

Two other studies have evaluated the efficacy of olmesartan/amlodipine-based titration regimens in patients with hypertension. The BP-CRUSH (Blood Pressure Control in All Subgroups with Hypertension) trial was a study that evaluated rates of BP goal achievement in patients who responded inadequately to antihypertensive monotherapy and were switched to olmesartan/amlodipine-based therapy. The AZTEC (AZOR Trial Evaluating Blood Pressure Reduction and Control) study used ABPM to determine the efficacy of a fixed-dose combination of olmesartan/amlodipine over the 24-hour dosing interval in patients with hypertension who did not respond adequately to amlodipine monotherapy.

Only treatment regimens involving olmesartan/amlodipine dosages approved for use in Europe are reviewed here with regard to the results obtained in the overall population in each study, respectively.

Table 1: The COACH trial – change in seated diastolic blood pressure (SeDBP) and seated systolic blood pressure (SeSBP) from baseline to week 8 in the intent-to-treat population (last observation carried forward)

Treatment group	No. of patients	Mean (SD) change in SeDBP, mmHg	Mean (SD) change in SeSBP, mmHg
Olmesartan			
10 mg	160	-8.3 (9.28)**	-11.5 (15.23)**
20 mg	159	-9.2 (9.73)**	-13.8 (15.90)**
40 mg	160	-10.2 (10.69)**	-16.1 (16.58)**
Amlodipine			
5 mg	161	-9.4 (8.25)**	-14.9 (14.95)**
10 mg	163	-12.7 (8.25)**	-19.7 (16.52)**
Olmesartan/amlodipine			
20 mg/5 mg	160	-14.0 (9.07)**	-23.6 (14.86)**
40 mg/5 mg	157	-15.5 (8.15)**	-25.4 (14.70)**
40 mg/10 mg	161	-19.0 (8.90)**	-30.1 (15.91)**
Placebo	160	-3.1 (10.67)**	-4.8 (18.70)*

Notes: *P <0.05; **P < 0.001.
Abbreviation: SD, standard deviation.

COACH trial

The COACH trial was a multicenter, randomized, doubleblind, placebo-controlled study with a factorial design. Eligible patients were aged >18 years, were naïve to antihypertensive therapy or underwent a 2-week washout period, and had a seated DBP (SeDBP) of 95–120 mmHg. Patients (n = 1940) were randomized to eight weeks of olmesartan monotherapy (10, 20 or 40 mg/day), amlodipine monotherapy (5 or 10 mg/day), each possible combination of the corresponding olmesartan and amlodipine doses, or placebo. The primary endpoint was the change from baseline in mean trough SeDBP (measured before taking the daily dose of study medication) after eight weeks of treatment in the intent-to treat (ITT) population (patients with a BP measurement at baseline and at least one BP measurement after taking at least one dose of study medication) with last-observation-carried-forward (LOCF) imputation. Secondary endpoints included change from baseline in seated SBP (SeSBP), and the proportion of patients achieving the BP target (<140/90 mmHg for patients with uncomplicated hypertension; <130/80 mmHg for patients with diabetes). BP was recorded at weeks 2, 4, 6 and 8 respectively.

Table 2: The COACH trial – patients achieving the blood pressure target (<140/90 mmHg for patients with uncomplicated hypertension; <130/80 mmHg for patients with diabetes) after eight weeks of treatment (last observation carried forward)

Treatment group	No (%)
Olmesartan	
10 mg (n = 160)	32 (20.0)
20 mg (n = 159)	42 (26.4)
40 mg (n = 160)	58 (36.3)
Amlodipine	
5 mg (n = 161)	34 (21.1)
10 mg (n = 163)	53 (32.5)
Olmesartan/amlodipine	
20 mg/5 mg (n = 160)	68 (42.5)*,†
40 mg/5 mg (n = 157)	80 (51.0)*,†
40 mg/10 mg (n = 161)	79 (49.1)*,†
Placebo (n = 160) 14 (8.8)	

Notes: *P < 0.005 vs olmesartan monotherapy at the same dosage; †P < 0.001 vs amlodipine monotherapy at the same dosage.

A total of 1923 patients were included in the primary efficacy analysis, of which 1689 completed the 8-week treatment period. All combination and monotherapy dosages and placebo were associated with statistically significant reductions in SeDBP from baseline to week 8 (P < 0.001) (Table 1). The reductions in SeDBP at week 8 seen with each monotherapy increased as the dosage of monotherapy rose. The combinations of olmesartan/amlodipine also produced dose-dependent reductions in SeDBP at week 8, and these were significantly greater than those achieved with the equivalent doses of olmesartan or amlodipine monotherapy (P < 0.001). Changes in SeSBP from baseline to week 8 followed a similar pattern to the changes in SeDBP (Table 1). The largest reductions in SeDBP and SeSBP were achieved after two weeks of active treatment (Figure 1). Thus, about 85% of the maximum BP reductions observed at the end of the 8-week treatment period had been observed after two weeks of treatment (Figure 1). The benefits of combination therapy were observed irrespective of baseline hypertension stage. Furthermore, prior use of antihypertensive agents did not appear to affect efficacy.

Significantly greater proportions of patients receiving olmesartan/amlodipine achieved the BP target at week 8 than patients receiving monotherapy (Table 2). The proportions of patients reaching the BP goal were 42.5%, 51.0% and 49.1% for olmesartan/amlodipine 20/5 mg, 40/5 mg and 40/10 mg, respectively.

At the end of the 8-week randomized phase of the COACH trial, 1684 patients entered a 44-week openlabel extension period in which they received olmesartan/amlodipine 40/5 mg once-daily initially. Uptitration to olmesartan/amlodipine 40/10 mg, followed by addition of HCTZ 12.5 mg and then 25 mg, was permitted if patients did not achieve the BP goal. Back-titration was also possible. Mean BP decreased from 164/102 mmHg at baseline to 131/82 mmHg at the end of this open-label extension period, while overall 66.7% of patients achieved the BP goal.

A total of 525 patients remained on olmesartan/amlodipine 40/5 mg throughout the extension period, and 80.0% of these achieved the BP goal. Uptitration to olmesartan/amlodipine 40/10 mg alone was necessary in 378 patients, of whom 70.6% achieved the BP goal. Addition of HCTZ at a dose of 12.5 mg/day (n = 287) or 25 mg/day (n = 419) resulted in 66.6% and 46.3% of the respective patients achieving their BP goal. Thus, treatment with olmesartan/amlodipine and up-titration as necessary, with or without HCTZ, allowed the majority of patients to achieve BP control.

Trial in patients with inadequate response to amlodipine monotherapy

This randomized, double-blind, multicenter study evaluated the efficacy of olmesartan/amlodipine in patients aged ≥18 years with moderate-to-severe hypertension who failed to respond adequately to amlodipine monotherapy. Patients received open-label amlodipine 5 mg/day monotherapy for eight weeks. At the end of the monotherapy phase, patients with BP ≥140/90 mmHg were randomized to eight weeks of double-blind daily treatment with amlodipine 5 mg plus placebo or olmesartan/amlodipine 10/5 mg, 20/5 mg or 40/5 mg. At the end of the double-blind period, patients who had achieved the target BP of ≤140/90 mmHg continued on randomized therapy for a further eight weeks. Patients with BP ≥140/90 mmHg had their medication uptitrated to olmesartan/amlodipine 20/5 mg, 40/5 mg or 40/10 mg during this period.

The primary endpoint was the change in mean trough SeDBP from the end of the open-label run-in period (baseline) to the end of double-blind treatment (week 8) in the ITT population (defined as in the COACH trial) with LOCF imputation. Key secondary endpoints included the

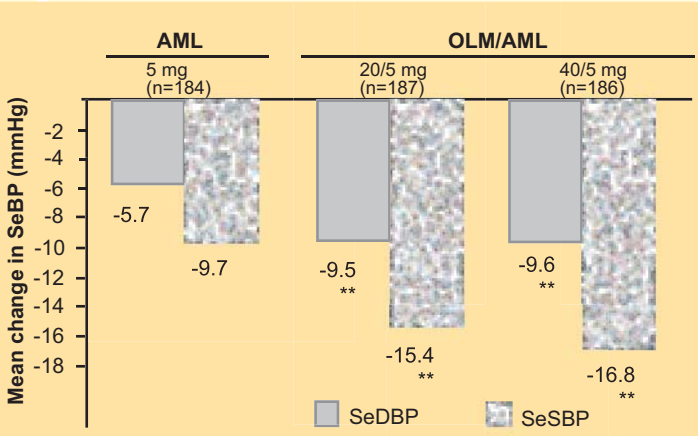

Figure 2: Olmesartan/amlodipine combination therapy versus amlodipine monotherapy - mean change from baseline in seated blood pressure after eight weeks of randomized, double-blind treatment.
Notes: *p < 0.05; **p < 0.0001 vs AML 5 mg monotherapy.
Abbreviations: AML, amlodipine; OLM, olmesartan; SeBP, seated blood pressure; SeDBP, seated diastolic blood pressure; SeSBP, seated systolic blood pressure.

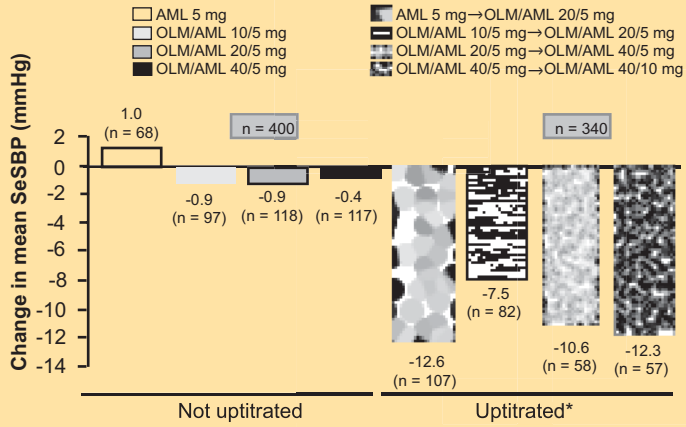

Figure 3: Olmesartan/amlodipine combination therapy versus amlodipine monotherapy . mean change from baseline in seated systolic blood pressure after eight weeks of randomized, double-blind, uptitrated treatment.
Notes: *Uptitration of non-responders: patients whose BP was not adequately controlled (SeDBP ≥90 mmHg and SeSBP ≥140 mmHg) during randomized treatment in Period II.
Abbreviations: AML, amlodipine; OLM, olmesartan; SeSBP, seated systolic blood pressure.

mean changes in trough SeDBP (baseline to week 4) and trough SeSBP (baseline to weeks 4 and 8), and the additional mean changes in SeDBP and SeSBP that occurred with further double-blind treatment (week 8 to week 16). The proportions of patients achieving the BP goal (defined as in the COACH trial) at weeks 8 and 16 of the double-blind phase were assessed.

A total of 755 patients were randomized to double-blind treatment, and 746 were included in the primary efficacy analysis. Compared with patients who were randomized to continue with amlodipine 5 mg, patients who were randomized to each olmesartan/amlodipine regimen showed significantly greater reductions in mean SeDBP from baseline to week 8 of the double-blind phase. The additional reductions in SeDBP achieved with olmesartan/amlodipine 20/5 and 40/5 mg compared with amlodipine 5 mg were 3.7 and 3.8 mmHg respectively (P <0.0001) (Figure 2). Patients receiving olmesartan/ amlodipine also experienced greater reductions in mean SeSBP from baseline to week 8 of the double-blind phase. The additional reductions in SeSBP achieved with olmesartan/amlodipine 20/5 and 40/5 mg compared with amlodipine 5 mg were 5.8 and 7.1 mmHg respectively (P < 0.0001) (Figure 2). All treatment regimens demonstrated a reduction in mean SeDBP and SeSBP after four weeks of double-blind treatment. In the second half of the double-blind phase, patients who had not achieved BP control had their treatment uptitrated and showed further significant increases in BP reduction by the end of this second 8-week treatment phase. Uptitration of amlodipine 5 mg to olmesartan/amlodipine 20/5 mg, olmesartan/amlodipine 20/5 to 40/5 mg, and olmesartan 40/5 to 40/10 mg resulted in further mean reductions of SBP (Figure 3) and DBP: -8.2, -6.2 and -8.2 mmHg respectively.

The proportion of patients reaching their BP goal at week 8 of double-blind treatment was significantly higher for olmesartan/ amlodipine 20/5 mg (54%) and 40/5 mg (51%) compared with amlodipine monotherapy (30%) (P < 0.0001). Continuation of combination therapy for an additional eight weeks, without uptitration, resulted in BP goal achievement by over 70% of patients. Uptitration of medication resulted in an additional 36%–47% of patients achieving their BP goal. Overall, 469 of 746 patients (63%) achieved their BP goal at the end of 16 weeks of double-blind therapy, with or without uptitration.

This study also included ABPM measurements at the start and end of the first 8-week, double-blind phase, and after the additional eight weeks of randomized treatment with uptitration as necessary. During the first 8-week, double-blind period, each dose of olmesartan/amlodipine significantly reduced 24-hour, daytime and night-time DBP and SBP, compared with amlodipine 5 mg plus placebo. In patients who did not achieve their BP goal with their initial dosage of combination therapy, uptitration led to further reductions in 24-hour, daytime and night-time BP. Taken together, the ABPM measurements were in agreement with the scheduled office BP measurements. Moreover, the

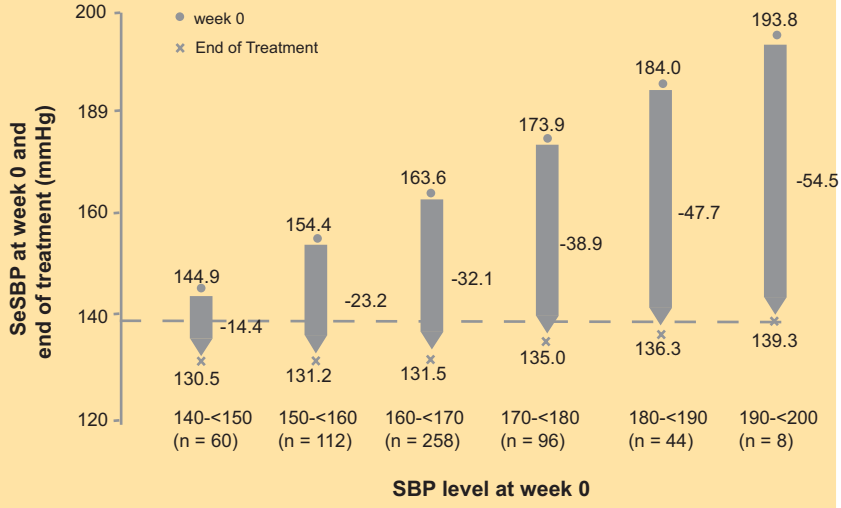

Figure 4: Mean levels of seated systolic blood pressure (SeSBP) at the start (week 0) and end of treatment (week 52) according to baseline SeSBP in all patients treated with olmesartan/amlodipine combination therapy in a randomized, double-blind study.
Note: Adapted with permission from Mourad and Le Joune. Effective systolic blood pressure reduction with olmesartan medoxomil/amlodipine combination therapy. Clin Drug Investig. 2009;29(6):419–425.

detected BP reductions were consistent over the 24-hour dosing interval.

Patients who completed the 16 weeks of double-blind combination therapy entered a 28-week, open-label phase in which they received olmesartan/amlodipine 40/5 mg once daily (n = 691). After 4, 10 and 19 weeks in the open-label phase, patients with inadequately controlled BP had their doses increased in a stepwise manner, with addition of HCTZ as necessary, to: olmesartan/ amlodipine 40/10 mg; olmesartan/amlodipine/HCTZ 40/10/12.5 mg; and olmesartan/amlodipine/HCTZ 40/10/25 mg. The majority of patients remained on olmesartan/amlodipine 40/5 mg without uptitration, and 74.3% of these patients achieved their BP goal. Additional patients achieved with each successive uptitration. Overall, 66.9% of patients achieved their BP goal during this 28-week, open-label phase. Analysis of the final reductions in SBP, observed at the end of the overall active treatment period of 52 weeks, revealed that SBP reductions were related to the initial SBP level at the start of the study.

Thus, patients with higher baseline SBP levels achieved larger reductions in SBP (Figure 4). Furthermore, despite the substantial reductions in BP achieved with olmesartan/ amlodipine in this study, it is notable that the incidence of treatment-related hypotension was very low. Among the 578 patients who completed the 28-week, open-label phase, and received olmesartan/amlodipine 40/5 mg or 40/10 mg without the addition of HCTZ, there were four reports of hypotension (0.7%), all involving patients receiving olmesartan/ amlodipine 40/5 mg.

Trial in patients with inadequate response to olmesartan monotherapy

Findings of a multicenter, randomized, double-blind trial conducted in patients aged >18 years with moderate-to-severe hypertension demonstrated that the addition of amlodipine to olmesartan lowered BP to a greater extent and enabled more patients to achieve their BP goal compared with olmesartan monotherapy.

After eight weeks of randomized, double-blind treatment, the additional reduction in SeDBP and SeSBP achieved with olmesartan/amlodipine 20/5 mg compared with olmesartan 20 mg monotherapy was 2.7 mmHg (P = 0.0006) and 5.3 mmHg (P < 0.0001), respectively. Furthermore, the proportion of patients achieving their BP goal was significantly higher for olmesartan/amlodipine 20/5 mg (44.5%) compared with olmesartan 20 mg monotherapy (28.5%) (P = 0.0011).

AZTEC and BP-CRUSH – efficacy of amlodipine/ olmesartan- based titration regimens

AZTEC and BP-CRUSH are postregistration studies designed to obtain further information on the efficacy of olmesartan/ amlodipine, both of which used tight BP control and forced titration regimens.

The AZTEC study was an open-label, multicenter, single-arm, dose-titration study in 185 patients with hypertension, consisting of a 3–4-week placebo run-in period and a 12-week active treatment period. Initially, patients received amlodipine 5 mg/day. If SeBP remained ≥120/80 mmHg, as assessed using conventional office-based BP measurements, medication was uptitrated at 3-weekly intervals to olmesartan/amlodipine 20/5, 40/5 and 40/10 mg. The change from baseline in mean 24-hour ambulatory SBP/DBP at week 12 (the primary endpoint), as assessed by ABPM, was –21.4/–12.7 mmHg (P < 0.0001 vs baseline). The reduction in BP was consistent across the 24-hour dosing interval. The proportions of patients achieving the prespecified mean 24-hour ambulatory BP target of <130/80 mmHg was 70.9%. Dose-dependent reductions in office-based SeBP from baseline were observed with the stepwise olmesartan/ amlodipine treatment algorithm, with the largest reductions in SeBP seen with the olmesartan/amlodipine 40/10 mg combination for which, cumulatively, 76.8% of patients achieved a SeBP goal of <140/90 mmHg.

BP-CRUSH was an open-label, multicenter, singlearm, dose-titration study with a 20-week active-treatment period, the aim of which was to demonstrate that patients with hypertension who had previously failed to achieve BP control on monotherapy were able to achieve their BP goal with an olmesartan/amlodipine-based treatment regimen, which also included the addition of HCTZ. On day 1, patients (n = 999) were switched from antihypertensive monotherapy to olmesartan/amlodipine 20/5 mg. If BP

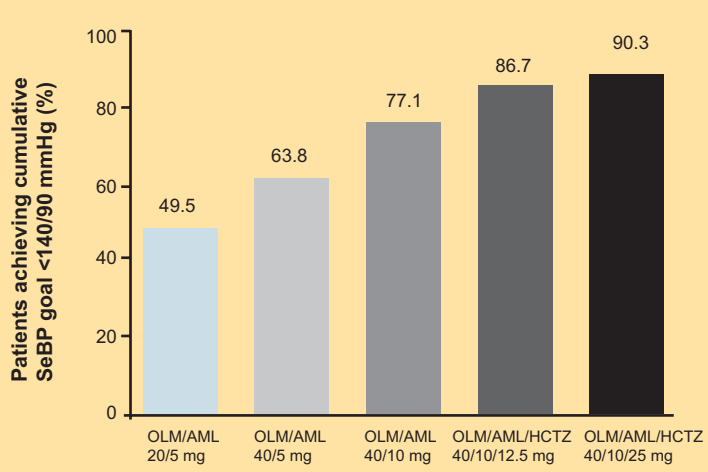

Figure 5: Proportion of patients who achieved the cumulative seated blood pressure (SeBP) goal of 140/90 mmHg in the BP-CRUSH study.
Abbreviations: AML, amlodipine; HCTZ, hydrochlorothiazide; OLM, olmesartan.

remained >120/70 mmHg, medication was uptitrated at 4-weekly intervals to olmesartan/amlodipine 40/5 mg, olmesartan/ amlodipine 40/10 mg, olmesartan/ amlodipine/ HCTZ 40/10/12.5 mg and olmesartan/ amlodipine/ HCTZ 40/10/25 mg. The primary efficacy endpoint, the proportion of patients achieving the SeBP goal (<140 mmHg; <130 mmHg for patients with diabetes) at the end of 12 weeks of olmesartan/amlodipine therapy, was 75.8%. Mean changes from baseline in BP at the end of each titration period ranged from -14.2/-7.7 mmHg for olmesartan/amlodipine 20/5 mg to -25.1/-13.7 mmHg for olmesartan/ amlodipine/ HCTZ 40/10/25 mg. The BP goal (<140/90 mmHg) was achieved by 90.3% of patients who received olmesartan/amlodipine/HCTZ 40/10/25 mg (Figure 5). ABPM measurements taken in a subgroup of patients (n = 243) at baseline and 12 and 20 weeks after treatment showed that BP reductions were sustained throughout the 24-hour dosing interval.

Tolerability of olmesartan/amlodipine

Olmesartan/amlodipine was generally well tolerated in clinical trials in patients with mild to severe hypertension. In the COACH trial, 521 of the 1940 randomized patients (26.9%) experienced a drug-related treatment-emergent adverse event (TEAE), with an overall incidence of 19.9% to 33.1% across the active-treatment groups receiving approved dosages and 29.6% for placebo-treated patients. The majority of these adverse events were mild in severity. Peripheral edema was the most common TEAE, affecting 385 of the 1940 patients (19.8%). Other commonly reported TEAEs were headache (130/1940 [6.7%]), dizziness (76/1940 [3.9%]) and fatigue (62/1940 [3.2%]), with no consistent differences between the active-treatment groups. Headache occurred most frequently in the placebo group (23/162 [14.2%]). Overall, 3.8% (74/1940) of patients were withdrawn from the trial because of drug-related TEAEs. The only serious drug-related TEAE was a nonfatal cerebrovascular accident occurring in a patient receiving olmesartan 20 mg/day, in whom BP was not fully controlled. Hypotension was reported in 0.5% (9/1940) of patients across the treatment groups. Seven patients had drug-related hypotension, of which two were withdrawn from the trial because of moderate or severe hypotension. In the 44-week open-label extension of the COACH trial, the adverse event profile was similar to that observed during the double-blind phase.

In the trials comparing olmesartan/amlodipine with the respective monotherapies, drug-related TEAEs were reported in 5.3%–7.7% of patients receiving approved dosages of olmesartan/amlodipine compared with 7.4% and 8.9% of patients receiving amlodipine or olmesartan monotherapy, respectively.49,50 Few patients receiving combination therapy in either trial discontinued due to a drug-related TEAE, and no serious drug-related TEAEs were observed in either trial.

Peripheral edema represents a common side effect of CCBs such as amlodipine, because these drugs may increase capillary pressure in peripheral tissues by inducing precapillary vasodilation of resistance arteries.60 Peripheral edema may be ameliorated by coadministration of an ARB or ACEI, as these agents may lower capillary pressures by decreasing postcapillary resistance in veins. The COACH trial assessed patients specifically for peripheral edema, rating its presence on a 5-point severity scale at all scheduled clinic visits. At baseline, 264 of the 1940 randomized patients (13.6%) had peripheral edema, which was predominantly graded as mild.46 During the 8-week, randomized, double-blind treatment phase, the frequency of edema was greatest among patients receiving amlodipine 10 mg monotherapy (60/163 [36.8%]), and affected 12.3% (20/162) of patients receiving a placebo. As expected, the frequency of peripheral edema was lower in the olmesartan/amlodipine 40/10 mg group (38/162 [23.5%]) than in the amlodipine 10 mg group (P = 0.011). Most cases of edema were mild or moderate in severity. Severe edema occurred in one patient (0.6%) in the amlodipine 5 mg group, two patients (1.2%) in the amlodipine 10 mg group and one patient (0.6%) in the olmesartan/ amlodipine 40/10 mg group. Edema was also reported in the trials comparing olmesartan/ amlodipine with the respective monotherapies, but the frequencies were lower than in the COACH trial.

Conclusion

In randomized, double-blind trials, olmesartan/amlodipine has demonstrated greater efficacy than the respective monotherapies in reducing BP, including a reduction within two weeks of initiation in the COACH trial, and achieving their BP goals, including over 24 hours, in patients with moderate-to-severe hypertension who had responded inadequately to olmesartan or amlodipine monotherapy. Up to 54% of patients who had failed to respond adequately to olmesartan or amlodipine monotherapy achieved their BP goal during eight weeks of treatment with olmesartan/amlodipine. Uptitration of olmesartan/amlodipine provided additional BP reductions, allowing even more patients to achieve their BP goal, while the incidence of hypotension remained very low. Furthermore, treat-to-target studies have demonstrated the power of olmesartan/amlodipine-based treatment in achieving high BP goal rates. Olmesartan/ amlodipine was generally well tolerated over short- and long-term therapy and this observation was not affected by uptitration. Peripheral edema was significantly less common with olmesartan/amlodipine 40/10 mg than with amlodipine 10 mg monotherapy. In Europe, a fixed-dose combined olmesartan/amlodipine formulation is available in three dosages (20/5, 40/5 and 40/10 mg), allowing flexible dosing and uptitration.

Ref:Olmesartan/amlodipine: a review of its use in the management of hypertension . R Kreutz. Vascular Health and Risk Management 2011:7 183–192.

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Cardiology News

PCI Safe in Patients With Severe Aortic Stenosis

Short-term mortality after percutaneous coronary intervention is no higher than usual when patients have severe aortic stenosis. The finding has significant implications for managing severe coronary artery disease in patients being considered for transcatheter aortic valve replacement (TAVR). Typically, such patients undergo a combined surgery to replace the aortic valve and construct coronary artery bypass grafts (CABG). With the availability of TAVR, PCI has been suggested as alternative to CABG - but relatively few patients with severe aortic stenosis have undergone PCI. The team used data in the Cleveland Clinic Interventional Registry to find 254 patients with severe aortic stenosis who underwent PCI between 1998-2008. They further identified 508 propensity-matched PCI patients without aortic stenosis. The rate of the primary endpoint of 30-day mortality was 4.3% vs 4.7% with and without aortic stenosis, respectively. In the aortic-stenosis cohort, the 30-day mortality rate was 5.4% when the ejection fraction was <30% compared 1.2% with a higher EF. Mortality was also higher with an STS (Society of Thoracic Surgeons) score <10 compared to a score of 10 or more (10.4% vs 0%). Thus a higher risk combined valve/CABG procedure can be converted into two potentially lower risk procedures i.e. PCI for coronary artery disease and isolated AVR with (a) minimally invasive approach.

Circulation 2012.

Stent Thrombosis at Coronary Bifurcations Carries Worse Prognosis

A new study confirms what many cardiologists would probably guess: stent thrombosis at coronary bifurcations is a bad problem. Data from the University of California's stent thrombosis registry show that patients in this situation are more likely to die or suffer major adverse cardiovascular events (MACE) than patients with restenosis in non-bifurcating stents. In-hospital mortality was significantly higher when the stent was in a bifurcation (20% vs 2%; p<0.0001). During a median 2.3-year follow-up, long-term mortality was 3.3-fold higher, and risk of MACE was 2.2-fold higher, among patients with bifurcation stent thrombosis. The increased risk of death and MACE persisted after the researchers adjusted for the type of thrombosed stent and the involved vessel.

J Am Coll Cardiol Intv 2012;5:57-63.

Benefits of Statins Outweigh Musculoskeletal Effects

In a cohort of people without arthritis, musculoskeletal pain, most often in the legs and lower back, was reported 33% more often by those using statins. Although the majority of people who use statins do not experience statin-associated musculoskeletal side effects, about 6% (or one out of every 17 people) without arthritis have pain associated with statin use. Statin although generally well tolerated, musculoskeletal side effects, including muscle aches, pain, weakness, cramps or creatine kinase elevations are the most common adverse effects of statins. The 33% relative increase in risk translates to a few additional patients feeling discomfort for every 100 treated. This study should not deter patients from taking their medication - or shake their faith in the powerful risk reduction effect of statins - but people with these complaints should talk with their doctors.

Am J Med 2012;125:176-182.

Editorial Note

Dear Doctor,

We are happy to present the 24th issue of "Insight Heart". It is a small endeavor to provide you compiled & updated information on cardiovascular diseases and its management. This issue is focused on " ***Combination therapy in hypertension***". We will appreciate your thoughtful comments.

Thanks and regards.