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Efficacy and Safety of a Stepped-Care Regimen Using Olmesartan Medoxomil, Amlodipine and Hydrochlorothiazide in Patients with Moderate-to-Severe Hypertension
An Open-Label, Long-Term Study

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Abstract

Background: Treatment guidelines recommend combination therapy to control blood pressure (BP) in the majority of hypertensive patients. This long-term open-label study assessed a treatment algorithm based on olmesartan medoxomil (hereafter olmesartan), amlodipine and hydrochlorothiazide (HCTZ).

Methods: Patients with moderate-to-severe hypertension who were inadequately controlled with amlodipine 5 mg/day monotherapy and who subsequently completed 16 weeks of double-blind combination treatment with olmesartan and amlodipine entered a 28-week open-label phase in which all patients initially received olmesartan/amlodipine 40/5 mg/day. After 4, 10 and 19 weeks, patients with inadequately controlled hypertension (seated trough diastolic [DBP] and systolic [SBP] BP ≥90 mmHg and ≥140 mmHg, respectively) had their doses increased in a step-wise manner to: (i) olmesartan/amlodipine 40/10 mg; (ii) olmesartan/amlodipine/HCTZ 40/10/12.5 mg; and (iii) olmesartan/amlodipine/HCTZ 40/10/25 mg.

Results: In total, 692 patients entered the open-label phase (691 on olmesartan/amlodipine 40/5 mg). The majority of patients remained on olmesartan/amlodipine 40/5 mg without dose elevation, and, of these, 74.3% achieved goal BP at study completion or early termination. Additional patients achieved goal BP with each successive uptitration of therapy: in patients who finished the study on olmesartan/amlodipine 40/10 mg and olmesartan/amlodipine/HCTZ 40/10/12.5 mg, the respective proportions who reached goal BP were 59.0% and 47.1%. Overall, 66.9% of patients achieved the European...
Background

Hypertension is a common condition in most Western countries,[1] and the greater prevalence in older individuals means that approximately two-thirds of people aged ≥60 years are hypertensive or taking antihypertensive medication.[2] Management of the condition is an important issue, since hypertension is an independent risk factor for cardiovascular (CV) disease.[3,4]

Adequate pharmacological control of hypertension substantially reduces the risk of CV events including stroke, myocardial infarction and heart failure.[5,6] However, despite the understanding of the close link between hypertension and mortality, blood pressure (BP) control rates in hypertensive patients remain poor.[12,7,8] It is now widely acknowledged that achieving control of BP requires combination therapy with two or more antihypertensive agents.[5,9] Moreover, recent European guidelines on hypertension management place greater emphasis than previous guidelines on the key role of combination therapy.[6]

A combination involving an angiotensin II type 1 receptor antagonist (angiotensin receptor blocker [ARB]) and a calcium channel antagonist (calcium channel blocker [CCB]) represents a rational approach in the treatment of hypertension, since it combines two effective and well tolerated agents. The advent of fixed-dose ARB/CCB formulations offers potential for improving adherence to therapy, and thus optimizing control of hypertension. Therapy with an ARB or an ACE inhibitor in combination with either a CCB or a thiazide diuretic (so-called ‘A+C or A+D’) is recommended in the current UK guidelines for patients requiring combination therapy,[10] and is also acknowledged as a recommended combination in the European Society of Hypertension-European Society of Cardiology (ESH-ESC) guidelines.[6] Furthermore, preliminary results of the recent ACCOMPLISH (Avoiding Cardiovascular events through COMbination therapy in Patients Living with Systolic Hypertension) study have demonstrated that treatment with ACE inhibitor/CCB combination therapy significantly reduces CV morbidity and mortality relative to ACE inhibitor/thiazide diuretic combination therapy.[11] These results, therefore, provide further support for ‘A+C’ combination therapy.

The efficacy and tolerability of the ARB olmesartan medoxomil (hereafter olmesartan) in combination with the CCB amlodipine have already been demonstrated in multinational, randomized, controlled clinical trials in patients with hypertension ranging from mild to severe.[12-14]

Here, we describe the long-term antihypertensive efficacy and tolerability of olmesartan in combination with amlodipine in patients with moderate-to-severe hypertension, administered in an open-label setting with addition of hydrochlorothiazide (HCTZ) where needed. This study is based on the treatment algorithm recommended by the current European guidelines.[6]

Patients and Methods

Study Population and Design

This study investigated the efficacy and safety of olmesartan in combination with amlodipine, with addition of HCTZ, during 28 weeks of open-label treatment. The 28-week open-label
treatment period concluded a phase III multinational, randomized, double-blind, parallel-group study (registered on the www.clinicaltrials.gov website as: NCT00220233) conducted at 75 clinical centres in Europe. The original study was conducted to demonstrate the additional antihypertensive efficacy achieved when olmesartan was added to amlodipine monotherapy in patients with moderate-to-severe hypertension who did not respond sufficiently to monotherapy. The overall study design has been reported in detail elsewhere,[14] and is briefly described here.

The study was conducted in accordance with independent ethics committee regulations and the 1989 Declaration of Helsinki, and in compliance with the International Conference on Harmonisation Guideline for Good Clinical Practice. All patients provided written informed consent at screening.

Male and female patients aged ≥18 years with moderate-to-severe hypertension were enrolled in the trial. For newly diagnosed patients and those receiving antihypertensive medications other than amlodipine 5 mg or 10 mg and who underwent a 1- to 2-week taper-off period, key inclusion criteria were: a mean seated diastolic blood pressure (SeDBP) ≥100 mmHg, a mean seated systolic blood pressure (SeSBP) ≥160 mmHg, and 24-hour DBP as assessed by ambulatory blood pressure monitoring (ABPM) ≥84 mmHg with ≥30% of daytime DBP readings >90 mmHg. For patients on stable treatment with amlodipine 5 mg or 10 mg, key inclusion criteria were: a mean SeDBP ≥90 mmHg, a mean SeSBP ≥140 mmHg, and 24-hour DBP ≥80 mmHg with ≥30% of daytime DBP readings >85 mmHg.

Key exclusion criteria included secondary or malignant hypertension; significant cardiac, CV, cerebrovascular, renal, hepatic, gastrointestinal or haematological disease; poorly controlled diabetes mellitus; and pregnancy, planned pregnancy or breastfeeding. Women of childbearing potential who were not using an acceptable method of contraception were also excluded from the study.

The overall study design is provided in figure 1, and comprised an 8-week open-label run-in period (period I: weeks 0–8, during which eligible patients received amlodipine 5 mg/day). After 8 weeks of the open-label treatment regimen, patients who were eligible (mean SeDBP ≤115 mmHg, mean SeSBP ≤200 mmHg, and mean 24-hour DBP ≤80 mmHg with ≥30% of daytime readings >85 mmHg) were randomized to one of four treatments of 8 weeks’ duration: amlodipine 5 mg in combination with either placebo, olmesartan 10 mg, olmesartan 20 mg or olmesartan 40 mg once daily. Randomization was based on a computer-generated randomization schedule prepared prior to the

Fig. 1. Study design. All doses are in mg/day. AML = amlodipine; HCTZ = hydrochlorothiazide; OLM = olmesartan medoxomil; PCB = placebo.
start of the study. Mean SeBP at week 8 provided the baseline BP for comparative purposes throughout the ensuing double-blind and open-label study periods (weeks 8–52).

**Measurement of Blood Pressure**

BP was measured with a calibrated mercury sphygmomanometer at 4-weekly intervals throughout the trial, and at weeks 28, 34, 43 and 52 during the open-label extension phase. BP was also measured at the time of early termination in patients who failed to complete the study. This design incorporated three opportunities for up-titration and an interval of 9 weeks between the penultimate assessment (at which up-titration may have been recommended) and the final assessment.

All BP measurements were taken at trough (i.e. approximately 24 hours after the last dose of medication) with the patient in a seated position, having rested for 10 minutes. At each evaluation session, three separate BP measurements were recorded with at least 1 minute between measurements. The mean of the three measurements was used as the BP value for that visit.

At week 16, patients either continued their randomized double-blind treatment for a further 8 weeks (period III: weeks 16–24) or had their medication uptitrated if their BP control was not adequate (SBP/DBP ≥140/90 mmHg). The investigators were blinded as to which combination regimen the patient received during the 8-week randomized treatment period, and remained blinded to the combination received during weeks 16–24; they were aware only that if the patient had his dose regimen titrated, the patient received a higher combination regimen between weeks 16 and 24 (figure 1).

All patients who completed double-blind therapy at week 24 (and irrespective of their dose regimen between weeks 16 and 24) entered the 28-week, open-label, extension phase of combination treatment described here. All patients were treated initially with olmesartan/amlodipine 40/10 mg; (ii) addition of low-dose (12.5 mg) HCTZ [olmesartan/amlodipine/HCTZ 40/10/12.5 mg]; (iii) increased dose (25 mg) of HCTZ (olmesartan/amlodipine/HCTZ 40/10/25 mg).

A patient was eligible for up-titration according to the stepped approach described above at any assessment during the open-label extension phase only if both mean BP values (DBP and SBP) were above the up-titration threshold of SBP/DBP 140/90 mmHg. Thus, by these stringent criteria, a patient with a mean BP of 145/85 mmHg would not undergo up-titration but would be classified as having failed to reach goal BP.

**Efficacy Assessments**

In order to evaluate the long-term safety and sustained efficacy of various combinations of olmesartan and amlodipine, the following pre-specified endpoints were evaluated using data from the open-label extension phase of the study: mean SeDBP and SeSBP at study end (week 52/early termination); mean changes in SeDBP and SeSBP in association with up-titration from one dose regimen to the next; the number and percentage of patients achieving BP goal (non-diabetic patients: DBP <90 mmHg and SBP <140 mmHg; diabetic patients, DBP <80 mmHg and SBP <130 mmHg).

**Post Hoc Analysis**

A post hoc analysis to determine (i) the cumulative proportion of patients who reached goal (non-diabetic patients: <140/90 mmHg; diabetic patients: <130/80 mmHg) during the entire study up to the end of the open-label phase, and (ii) the proportions of patients who achieved independent SBP or DBP thresholds was also conducted in the 691 patients who entered the open-label phase and received olmesartan/amlodipine 40/5 mg.

**Safety Assessments**

During the open-label extension phase, safety assessments were carried out at weeks 28, 34, 43 and 52 and, in patients who failed to complete the study, at the time of study termination. Safety data collected included any adverse events (AEs), drug-related AEs, clinical laboratory test results,
vital signs, physical examination findings and 12-lead ECG assessments. In addition, a post hoc analysis of safety in patients aged ≥65 years was conducted.

Statistical Analysis

Statistical analyses of the prespecified efficacy, safety and tolerability endpoints were conducted on the 692 patients who entered the open-label phase of the study. Descriptive statistics were used to summarize mean SeDBP and SeSBP values by treatment regimen at week 52/early termination. The additional SeDBP and SeSBP lowering achieved by doubling the dose of amlodipine to 10 mg, adding HCTZ 12.5 mg and doubling the dose of HCTZ to 25 mg was quantified and summarized using descriptive statistics. This ‘uptitration effect’ was calculated by subtracting the BP at the final assessment made while the patient was on the previous treatment regimen from the BP at the final assessment made while the patient was on the new treatment regimen. The numbers of patients on each treatment regimen who achieved BP goal (non-diabetic patients: <140/90 mmHg; diabetic patients: <130/80 mmHg) were calculated. These values were converted to percentages using as the denominator the total numbers of patients on each regimen at week 52/early termination. The number and percentage of patients on each treatment regimen who reported any AEs, serious AEs (SAEs) or discontinuations due to AEs during the open-label extension phase were presented descriptively.

Results

Patient Disposition and Baseline Characteristics

The disposition of patients to week 24 of the overall study has been previously described. A total of 692 patients with moderate-to-severe hypertension entered the long-term open-label period (weeks 24–52), and 673 patients completed the study. The patient disposition is shown in figure 2.

Open-label treatment was initiated with olmesartan/amlodipine 40/5 mg in 691 patients, and with olmesartan/amlodipine 40/10 mg in one patient. The majority of patients (n=436, 63.0%) remained on olmesartan/amlodipine 40/5 mg for the duration of the long-term study. Seventeen patients discontinued during olmesartan/amlodipine 40/5 mg treatment, and were not uptitrated. Of 174 patients not adequately controlled with this regimen, 142 (20.5% of patients starting on olmesartan/amlodipine 40/5 mg) were
uptitrated to olmesartan/amlodipine 40/10 mg, and maintained on this regimen by the end of the study. Therefore, >80% of patients completed the study on a regimen of olmesartan/amlodipine in combination and did not have HCTZ added to the regimen. Sixty-eight patients (9.8%) needed addition of HCTZ 12.5 mg to their regimen and just 27 patients (3.9%) needed addition of HCTZ 25 mg. Six patients followed a titration sequence not specified in the protocol.

Table I shows the baseline characteristics (at the start of the study – week 0) for those patients who entered the open-label extension phase. The majority of patients were male and Caucasian. Most (79%) patients were aged <65 years. The baseline characteristics of these patients were similar to those of the entire study cohort.[14]

The mean BP reported after 8 weeks of amlodipine 5 mg open-label monotherapy was 154.5/97.0 mmHg. There was a positive relationship between mean BP at week 8 and the number of successive intensifications of therapy during the open-label extension phase. The patients who were maintained throughout the open-label period on olmesartan/amlodipine 40/5 mg (the majority) were those with the lowest mean baseline BP (152.5/96.0 mmHg). Patients who needed their medications uptitrated to final regimens of olmesartan/amlodipine 40/10 mg, olmesartan/amlodipine/HCTZ 40/10/12.5 mg and olmesartan/amlodipine/HCTZ 40/10/25 mg had progressively higher mean baseline BP values of 156.5/98.1 mmHg, 160.2/99.6 mmHg, and 163.1/100.5 mmHg, respectively.

Blood Pressure Reductions and the Titration Effect

Figure 3 shows the magnitude of the mean SeSBP and SeDBP reductions achieved between baseline and the end of the open-label regimen, by end-treatment regimen. Mean BP values were <140/90 mmHg by the end of the study for all groups of patients with the exception of the group of 27 patients who needed addition of high-dose HCTZ and whose baseline mean BP was highest, despite having completed 8 weeks of open-label amlodipine therapy.

Additional BP lowering was achieved by uptitration from one dose regimen to the next. Titration from olmesartan/amlodipine 40/5 mg to olmesartan/amlodipine 40/10 mg produced an additional mean reduction in SeSBP/SeDBP of 8.8/5.5 mmHg. Addition of HCTZ 12.5 mg and 25 mg to olmesartan/amlodipine 40/10 mg produced additional mean SeSBP/SeDBP reductions of 10.2/6.3 mmHg and 3.8/3.7 mmHg, respectively.

Goal Rate and Blood Pressure Threshold Achievement

The overall goal achievement rate (non-diabetic patients: SBP/DBP <140/90 mmHg; diabetic patients: SBP/DBP <130/80 mmHg) was 66.9% at week 52/early termination. This total included only those patients who reached both DBP and SBP targets. Patients without diabetes who achieved either DBP or SBP values of <90 mmHg or <140 mmHg, respectively (but not both targets), and patients with diabetes who achieved mean BP values of <140/90 mmHg but not the diabetic goal of <130/80 mmHg were not included in the goal achievement total, nor were they uptitrated to the next level as prespecified in the trial protocol.

The goal achievement rate was 74.3% for the majority of patients who finished the study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of patients</td>
<td>692</td>
</tr>
<tr>
<td>Male [n (%)]</td>
<td>430 (62.1)</td>
</tr>
<tr>
<td>Caucasian [n (%)]</td>
<td>690 (99.7)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>55.7 (9.52)</td>
</tr>
<tr>
<td>Age group [n (%)]</td>
<td></td>
</tr>
<tr>
<td>&lt;65 y</td>
<td>547 (79.0)</td>
</tr>
<tr>
<td>65–74 y</td>
<td>137 (19.8)</td>
</tr>
<tr>
<td>≥75 y</td>
<td>8 (1.2)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.8 (3.86)</td>
</tr>
<tr>
<td>SBP/DBP at baseline on AML 5 mg/day (week 8) [mmHg]</td>
<td>154.5/97.0</td>
</tr>
</tbody>
</table>

a Values are expressed as mean (SD).

AML = amlodipine; BMI = body mass index; SBP/DBP = systolic/diastolic blood pressure.
fewer patients entered each additional treatment step. Each successive treatment step reflected the selection of the more difficult-to-treat patients into the uptitrated groups, and delivered additional patients to goal. For patients finishing the study on olmesartan/amlodipine 40/5 mg and olmesartan/amlodipine/HCTZ 40/10/12.5 mg, 59.0% and 47.1% of patients, respectively, reached goal BP levels. Of the 27 most difficult to treat patients (those who required uptitration to olmesartan/amlodipine/HCTZ 40/10/25 mg), a further nine patients (33.3%) reached goal.

Safety

The safety profile of olmesartan/amlodipine combination therapy was consistent with that of an ARB and a dihydropyridine CCB, and no new safety concerns were identified in this open-label study. Overall, 33.0% of patients experienced an AE. The incidence of AEs considered to be drug
related was lower (6.1%) [table II]. There were no deaths and no drug-related SAEs. The incidence of drug-related dizziness, peripheral oedema and headache was low in patients on olmesartan/amlodipine 40/5 mg (table II). The incidence of drug-related peripheral oedema increased with the increase in amlodipine dose (from 0.7% with olmesartan/amlodipine 40/5 mg to 1.6% with olmesartan/amlodipine 40/10 mg) but remained low in all treatment groups. The only other drug-related AEs experienced by two or more patients on the high-dose amlodipine regimen were an increase in BP (n = 2) and arthralgia (n = 2). Addition of HCTZ to the regimen resulted in only isolated incidences (single patients) of drug-related AEs. There were no changes in laboratory parameters that represented a safety concern with any of the regimens, and no clinically meaningful changes in physical examination or ECG findings in any of the treatment groups.

Of the 145 patients in the open-label study aged ≥65 years, the majority (71.0%) remained on olmesartan/amlodipine 40/5 mg. The incidence of AEs in elderly patients was similar to that in the total population (37.2% with olmesartan/amlodipine 40/5 mg, 23.8% with olmesartan/amlodipine 40/10 mg and 18.8% with olmesartan/amlodipine/HCTZ 40/10/12.5 mg). The number of drug-related AEs in this population was low (six AEs reported in patients taking olmesartan/amlodipine 40/5 mg, and one AE reported in patients taking olmesartan/amlodipine 40/10 mg and olmesartan/amlodipine/HCTZ 40/10/12.5 mg, respectively), and there were no drug-related discontinuations. No patient aged >65 years took olmesartan/amlodipine/HCTZ 40/10/25 mg.

### Table II. Summary of adverse events (AEs) occurring after the first dose of open-label study medication and within 14 days of the last dose of open-label study medication, during treatment with olmesartan medoxomil (OLM), amlodipine (AML) and hydrochlorothiazide (HCTZ)

<table>
<thead>
<tr>
<th>Type of AE</th>
<th>OLM/AML 40/5 mg (n = 691)</th>
<th>OLM/AML 40/10 mg (n = 243)</th>
<th>OLM/AML/HCTZ 40/10/12.5 mg (n = 93)</th>
<th>OLM/AML/HCTZ 40/10/25 mg (n = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>228 (33.0)</td>
<td>60 (24.7)</td>
<td>17 (18.3)</td>
<td>7 (25.0)</td>
</tr>
<tr>
<td>Drug-related AE</td>
<td>42 (6.1)</td>
<td>11 (4.5)</td>
<td>3 (3.2)</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>Maximum severity of AEs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mild</td>
<td>136 (19.7)</td>
<td>32 (13.2)</td>
<td>11 (11.8)</td>
<td>2 (7.1)</td>
</tr>
<tr>
<td>moderate</td>
<td>85 (12.3)</td>
<td>27 (11.1)</td>
<td>5 (5.4)</td>
<td>5 (17.9)</td>
</tr>
<tr>
<td>severe</td>
<td>7 (1.0)</td>
<td>1 (0.4)</td>
<td>1 (1.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Any serious AE</td>
<td>9 (1.3)</td>
<td>1 (0.4)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>AE leading to discontinuation</td>
<td>7 (1.0)</td>
<td>2 (0.8)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Drug-related AE leading to discontinuation</td>
<td>6 (0.9)</td>
<td>1 (0.4)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>AEs that occurred in ≥1% of any group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dizziness</td>
<td>12 (1.7)</td>
<td>1 (0.4)</td>
<td>1 (1.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>peripheral oedema</td>
<td>12 (1.7)</td>
<td>6 (2.5)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>elevated blood uric acid</td>
<td>0 (0.0)</td>
<td>1 (0.4)</td>
<td>0 (0.0)</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>headache</td>
<td>27 (3.9)</td>
<td>4 (1.6)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>pruritus</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (1.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Drug-related AEs that occurred in ≥1% of any group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dizziness</td>
<td>9 (1.3)</td>
<td>1 (0.4)</td>
<td>1 (1.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>peripheral oedema</td>
<td>5 (0.7)</td>
<td>4 (1.6)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>elevated blood uric acid</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>pruritus</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (1.1)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

a Patients who had AEs with an onset date under more than one dose regimen were summarized under all relevant treatment regimens. Data are given as n (%).

b Definitely, probably or possibly related to study treatment, as judged by the investigator.

c AEs selected for those considered to be of most relevance; list is not comprehensive.
Discussion

This study has shown that a stepped-care open-label regimen based on the olmesartan/amlo
dipine combination with addition of HCTZ as necessary controls BP to the levels recommended by current treatment guidelines (non-diabetic patients: <140/90 mmHg; diabetic patients: <130/80 mmHg) in 67% of patients with moderate-to-severe hypertension. The majority of patients (453 of 692, 65%) remained on their starting regimen of olmesartan/amloidipine 40/5 mg until their final study visit, and BP goal was achieved in 74% of these patients.

Although this long-term study concluded a randomized controlled trial, the stepped-care open-label nature of the design of the long-term phase reported here was reflective of real clinical practice, and the goal achievement rates represent a marked improvement on those typically reported in epidemiological studies. In this study, uptitration and/or addition of HCTZ was based on a predefined threshold of SBP ≥140 mmHg and DBP ≥90 mmHg, rather than goal achievement. If the real clinical practice of uptitration for all patients not at goal had been implemented, it might be expected that even more patients would have reached goal.

Each increase in dose regimen was associated with further decreases in BP, and brought additional patients to goal. The additional reductions in BP were significant and of a magnitude that is clinically relevant in terms of reduction in CV risk. Mean SeDBP was <90 mmHg on all four treatment regimens by the end of open-label treatment, and mean SeSBP was <140 mmHg in all but the highest dosage group (representing the most difficult to treat patients). Moreover, in the group that finished the study on the initial treatment regimen (olmesartan/amloidipine 40/5 mg), mean BP at the end of the study approached the more stringent level required in diabetic patients (<130/80 mmHg). Few clinical trials have achieved this level of BP control.

The study design meant that patients whose hypertension was not easily controlled by medication were selected for progressive treatment intensification. The stepped-care approach therefore brought additional, more difficult to treat patients to goal, including patients who required uptitration to the high-dose triple combination regimen. Overall, impressive goal rate achievement was observed against the stringent dual-goal definition.

Because only those patients who did not reach the uptitration threshold of both DBP <90 mmHg and SBP <140 mmHg were uptitrated, patients who achieved either the DBP or SBP threshold, but not both, and diabetic patients whose BP was <140/90 mmHg, but who were not at the diabetic goal of 130/80 mmHg, remained on their previous treatment. In the primary analysis, these patients were excluded from both the goal-achievement population and the uptitrated population. Therefore, a post hoc analysis of achievement of BP thresholds of <140/90 mmHg and <130/80 mmHg of independent DBP and SBP targets was conducted to determine these outcomes for the entire patient population in the study, inclusive of those patients who were not uptitrated and who were not at goal.

Analysis of the 691 patients treated with olmesartan/amloidipine 40/5 mg at the outset of the open-label phase showed that throughout the entire study, the cumulative proportion of patients achieving goal BP (<140/90 mmHg and <130/80 mmHg in patients with diabetes) was 79.5%. Moreover, 87.6% of patients reached a DBP of <90 mmHg, with 34.2% reaching <80 mmHg. Analysis of SBP threshold achievement yielded similar proportions; 85.1% of patients reached a SBP of <140 mmHg, and 51.5% reached <130 mmHg.

This study has shown that the BP-lowering effects of olmesartan/amloidipine combination therapy achieved in double-blind controlled trials are maintained during long-term open-label treatment. Among patients who had received olmesartan/amloidipine 40/5 mg during the earlier double-blind period of the study and who completed open-label therapy on the same dose combination (n = 115), the mean BP was 129.8/83.2 mmHg at entry to the open-label phase and 132.3/84.1 mmHg at the end of the open-label phase. Here it should be remembered that in order for patients to be uptitrated they had to...
have both their SBP and DBP levels above the SBP and DBP thresholds of 140 and 90 mmHg, respectively. This means that patients with an SBP ≥140 mmHg would not have been uptitrated if their DBP had been <90 mmHg, and vice versa. Thus, BP levels may have shown a degree of variability over time since the study did not have the aim or design of treating patients to achieve the lowest possible level of BP. The small size of the difference and the fact that mean SBP and DBP levels in this group were below the respective 140 and 90 mmHg targets at the start and end of open-label treatment suggest that the antihypertensive effects of olmesartan/amlo- dipine in combination are maintained in the long-term open-label setting, which approximates to daily clinical practice.

This study did not identify any unexpected AEs, and the overall incidence of AEs was low in all treatment groups. Therefore, long-term treatment with olmesartan/amlo- dipine combination therapy in an open-label setting, with HCTZ added when needed, was a safe and well tolerated strategy in the management of patients with moderate-to-severe hypertension in an open-label setting. In addition, olmesartan/amlo- dipine combination therapy was similarly well tolerated during long-term treatment in patients aged ≥65 years. This is of importance given the increased prevalence of hypertension in elderly individuals.

ARBs have a side effect profile similar to that of placebo. Moreover, in a recent study, ARB therapy was shown to be as effective as ACE inhibitor therapy for reducing CV outcomes, but with a significantly reduced incidence of cough and angioedema. CCBs, although well tolerated drugs, are associated with a relatively high incidence of peripheral oedema. In the current study, doubling the dose of amlo- dipine from 5 mg/day to 10 mg/day increased the incidence of this adverse effect from 0.7% to 1.6%. The overall absolute incidence of peripheral oedema remained low, however, and it is likely that this was due to co-administration of olmesartan, as recently shown.

Current European guidelines indicate the preferred combinations of antihypertensive agents, and this includes the combination of an ARB and a CCB. Such a combination is rational not only in terms of minimization of adverse effects, but also because the antihypertensive efficacy of CCBs may be affected by activation of the sympathetic and renin-angiotensin systems that occurs secondary to CCB-induced vasodilation. The renin-angiotensin system blockade provided by co-administration of an ARB should negate this effect. Thus, in addition to providing potent antihypertensive efficacy in their own right, ARBs allow co-administered CCBs to exert their full antihypertensive effect. The results of this study provide further support for the use of a regimen based on ARB/CCB combination therapy, following encouraging results in previous studies.

Conclusion

This open-label extension phase of a randomized, double-blind study has demonstrated that olmesartan/amlo- dipine ± HCTZ combination therapy is safe and well tolerated. Moreover, the stepped-care regimen described is highly effective in lowering BP in patients with moderate-to-severe hypertension, and in allowing patients to achieve their BP goals. The BP-lowering effects of olmesartan/amlo- dipine combination therapy observed during earlier double-blind treatment, reported elsewhere, were well maintained during long-term treatment.

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