Antihypertensive efficacy and safety of olmesartan medoxomil and ramipril in elderly patients with mild to moderate essential hypertension: the ESPORT study

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Objective To compare the efficacy and safety of the angiotensin II antagonist olmesartan medoxomil (O) and the ACE inhibitor ramipril (R) in elderly patients with essential arterial hypertension.

Methods After a 2-week placebo wash-out 1102 treated or untreated elderly hypertensive patients aged 65–89 years (office sitting diastolic blood pressure, DBP, 90–109 mmHg and/or office sitting systolic blood pressure, SBP, 140–179 mmHg) were randomized double-blind to 12-week treatment with O 10 mg or R 2.5 mg once-daily. After the first 2 and 6 weeks doses could be doubled in non-normalized (blood pressure (BP) <140/90 mmHg for nondiabetic and <130/80 mmHg for diabetic) individuals, up to 40 mg for O and 10 mg for R. Office BPs were assessed at randomization, after 2, 6 and 12 weeks of treatment, whereas 24-h ambulatory BP was recorded at randomization and after 12 weeks.

Results In the intention-to-treat population (542 patients O and 539 R) after 12 weeks of treatment baseline-adjusted office SBP and DBP reductions were greater (P<0.01) with O (17.8 (95% confidence interval: 16.8/18.9) and 9.2 (8.6/9.8) mmHg) than with R (15.7 (14.7/16.8) and 7.7 (7.1/8.3) mmHg). BP normalization rate was also greater under O (52.6 vs. 46.0% R, P<0.05). In the subgroup of patients with valid ambulatory BP recording (318 O and 312 R) the reduction in 24-h average BP was larger (P<0.05) with O [SBP: 11.0 (12.2/9.9) and DBP: 6.5 (7.2/5.8) mmHg] than with R [9.0 (10.2/7.9) and 5.4 (6.1/4.7) mmHg]. The larger blood pressure reduction obtained with O was particularly evident in the last 6 h from the dosing interval; a better homogeneity of the 24-h BP control with O was confirmed by higher smoothness indices. The proportion of patients with drug-related adverse events was comparable in the two groups (3.6 O vs. 3.6% R), as well as the number of patients discontinuing study drug because of a side effect (14 O vs. 19 R).

Conclusion In elderly patients with essential arterial hypertension O provides an effective, prolonged and well tolerated BP control, representing a useful option among first-line drug treatments of hypertension in this age group. J Hypertens 28:2342–2350 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Introduction

Development and progression of essential hypertension is associated with increasing age, with a prevalence of about 55% in men and 62% in women over 65 years [1]. Randomized trials in patients with essential arterial hypertension aged at least 65 years have shown that antihypertensive treatment is associated with a marked reduction in cardiovascular morbidity and mortality [2–10]. On the contrary, hypertensive patients, and in particular elderly individuals, are still undertreated and poorly controlled, as shown in several epidemiological studies [11–14].

Many elderly patients have multiple cardiovascular risk factors, target organ damage, associated cardiovascular conditions, and may thus need antihypertensive drugs combining improved efficacy with enhanced tolerability [15]. Furthermore, elderly hypertensive patients have a large blood pressure variability and a difficult blood pressure control in the early morning hours, which are the farthest from the last drug intake and those at higher risk of occurrence of cardiovascular events. Thus, achieving a consistent and sustained reduction in blood pressure becomes an important goal of treatment in this population [16].

Some recent meta-analyses suggest that all major classes of antihypertensive agents are equally effective in controlling blood pressure and preventing cardiovascular events at younger or older (≥65 years) age [17,18].
antihypertensive agents, angiotensin converting enzyme (ACE) – inhibitors and angiotensin II receptor blockers (ARBs) have been shown to have the best tolerability rate [19] and this has been proven to be true also in elderly patients [20]. However, large head to head comparison studies of agents of these two classes have rarely been done [21–24] and even more rarely and in relatively small studies, in elderly patients [25,26].

Olmesartan medoxomil is an ARB inhibiting the action of renin–angiotensin system at the AT1 subtype receptor level [27,28]. Oral olmesartan medoxomil at doses ranging between 10 and 40 mg once daily is recommended for the treatment of adult patients with arterial hypertension. Extensive clinical evidence from several large well designed trials and clinical practice setting has confirmed the antihypertensive efficacy and good tolerability profile of oral olmesartan medoxomil, including elderly patients with systolic and diastolic, or isolated systolic hypertension [27–30].

The present study was designed to assess the efficacy and safety of the ARB olmesartan medoxomil in elderly patients with essential hypertension in comparison with the ACE inhibitor ramipril, which has widely been used both in clinical practice and in controlled trials, at doses between 2.5 and 10 mg once daily. To make the comparison particularly stringent, efficacy assessment was based not only on conventional office blood pressure measurements taken 24 h postdosing, but also on ambulatory monitoring over the 24 h and in particular in the early morning hours.

Methods

Study population

Elderly (age between 65 and 89 years) outpatients of both sexes, with grade 1 or 2 essential hypertension (sitting diastolic blood pressure or DBP between 90 and 109 mmHg and/or systolic blood pressure or SBP between 140 and 179 mmHg after two weeks of washout with placebo) were eligible for study participation.

The study was conducted according to Good Clinical Practice guidelines and the Declaration of Helsinki, and the protocol was approved by the Ethics Committees of the centers involved. Written informed consent was obtained from all patients prior to their inclusion into the study.

Study design

This was an Italian, multicenter (102 centers), randomized (1 : 1), double-blind, parallel group study, consisting of a 2-week wash-out period with placebo, followed by 12 weeks of treatment with olmesartan medoxomil or ramipril at the initial doses of 10 or 2.5 mg given once daily (between 0900 and 1100 h). In patients treated with antihypertensive drugs at the time of enrolment, treatment was stopped and replaced with placebo. After the first 2 and 6 weeks of active treatment the drug dose had to be doubled if office SBP was 140 mmHg or higher or office DBP was 90 mmHg or higher in non-diabetic patients and if office SBP was 130 mmHg or higher or office DBP was 80 mmHg or higher in diabetic patients, up to a maximum of 40 mg for olmesartan medoxomil and 10 mg for ramipril.

Physical examination, blood pressure and heart rate measurements were done at each visit, whereas a 12-lead ECG and blood samples for routine examinations were taken at the randomization and final visits.

Although the study also included an open-label follow-up after the double-blind phase, the present paper will only report results of the 12 weeks of double-blind period, whereas data from the open treatment phase will be reported in a separate paper.

Blood pressure and heart rate measurement

Blood pressure was measured by a physician (investigator) in the office using a standard mercury sphygmomanometer approximately 24 h after the last drug intake. The arm cuff was kept at the heart level during every blood pressure measurement. Three measurements, taken at 2 min intervals, after 5 min of rest in the sitting position were averaged and used as the office blood pressure reference value. SBP and DBP values were taken at the time of the first and fifth Korotkoff sounds, respectively. Heart rate was assessed during the 2 min interval between the last two office sitting blood pressure measurements.

Ambulatory blood pressure monitoring was performed at randomization and the final visit, noninvasively over the 24 h by oscillometric validated devices [31]. The monitoring cuff was wrapped around the nondominant arm and the patient was asked to keep her/his arm still during the automatic blood pressure measurements. The device was programmed to measure blood pressure every 15 min during daytime (from 0600 to 2200 h) and every 30 min during night-time (2200–0600 h) [32]. Each recording started in the morning, immediately after office blood pressure assessment and administration of placebo or active treatment. Patients were then sent home, asked to resume normal life, and to come back 24 h later for removal of the device.

Data analysis

The primary efficacy end-point of the study was the between-treatment comparison of sitting office SBP and DBP changes from baseline to the end of the 12 weeks of double-blind treatment.

The study hypothesis was that treatment with olmesartan medoxomil was at least as effective as ramipril for the primary end-point and the two drugs had to be defined equivalent in case of a difference within 3 mmHg for SBP (common standard deviation 13 mmHg) and 2 mmHg for DBP (common standard deviation 13 mmHg) and 2 mmHg for DBP.
DBP (common standard deviation 11 mmHg). Using a two-tailed test with a 0.05 significance level and a 95% power, the estimated number of patients to be randomized was 1222 (including a 20% drop-out rate), 611 for each treatment group.

Analysis was performed on patients valid for intention-to-treat (all randomized patients receiving at least one dose of active treatment drug and having at least one office blood pressure measurement after randomization), using the last observation carried forward method for patients prematurely leaving the study. The per-protocol population (all randomized patients completing the 12-week double-blind study period without major protocol violations) was used for confirmatory analysis.

Secondary study end-points were between-treatment comparison of the percentage of normalized patients (sitting office SBP < 140 mmHg and DBP < 90 mmHg for non-diabetic patients and sitting office SBP < 130 mmHg mmHg and DBP < 80 mmHg for diabetic patients) after 2, 6 and 12 weeks of double-blind treatment; the percentage of normalized (see above) plus responder patients (sitting office SBP reduction > 20 mmHg or DBP reduction > 10 mmHg) after 2, 6 and 12 weeks of double-blind treatment; changes in 24-h, daytime and night-time average SBP and DBP after 12 weeks of treatment; hourly averages of SBP and DBP changes with treatment; SBP and DBP changes in the last 6 h of the dosing interval after 12 weeks of treatment; smoothness index of SBP and DBP after 12 weeks of treatment [33–35].

The analysis of 24-h blood pressure recordings was preceded by removal of artifacts according to previously described editing criteria [32]. Recordings were considered valid when no more than 1 h was missing over the 24 h and when at least 70% of expected measurements were available.

The smoothness index, used to assess the homogeneity of blood pressure control, was computed for each patient by dividing the average of the 24 hourly blood pressure changes after treatment by the corresponding standard deviation [33–35]. This index is characterized by a normal distribution and a greater reproducibility than the usually employed trough-to-peak ratio, thus having the advantages for the description of the consistency of the blood pressure control over the 24 h also in individual patients [34,35].

Safety analysis was applied to all randomized patients, by calculating the incidence of adverse events and changes in laboratory data or ECG during the study.

Between-treatment differences in mean sitting office and ambulatory SBP and DBP changes at week 12 were assessed by analysis of covariance, by adjusting for the baseline value. No center effect was observed in an exploratory analysis and thus it was not included in the model. Analysis of variance was used to assess differences in smoothness indices. Comparison of normalized, and normalized plus responder patients between the two treatment groups was performed by the chi-squared test.

Subgroup analysis for age groups and type of hypertension was also made. The level of statistical significance was kept at 0.05 throughout the whole study. Data are shown as mean ± SD or as mean and 95% confidence interval.

Results

Baseline demographic and clinical data

A total of 1242 patients were screened, but 140 were lost during the placebo washout period. Thus, the number of patients randomized to one of the two treatment arms was 1102; 980 of these patients completed the 12-week double-blind randomized phase, whereas 122 discontinued the study because of consent withdrawal (n = 42), lost to follow-up (n = 22), adverse events (n = 20), protocol violation (n = 14), lack of efficacy (n = 11), lack of compliance to study procedures (n = 8) or other reasons (n = 5).

Overall 1081 patients were valid for the intention-to-treat analysis (542 in the olmesartan medoxomil and 539 in the ramipril treatment group) and 917 for per-protocol analysis (468 in the olmesartan medoxomil and 449 in the ramipril treatment group). Six hundred and thirty out of 817 patients undergoing ambulatory blood pressure monitoring at baseline had valid recordings and were included in this subgroup analysis (318 randomized to olmesartan medoxomil and 312 to ramipril).

As shown in Table 1 the two randomization groups were not significantly different at baseline with regards to demographic and clinical characteristics. At study entry, the proportion of patients under antihypertensive medications was high as expected because of the age of the study population. Prevalence of diabetes was 20%. In the subgroup of patients included in the analysis of the ambulatory recordings there was no between-treatment difference in age (71.7 ± 5.0 years olmesartan vs. 72.0 ± 5.0 years ramipril), sex distribution (males: 55.3 vs. 52.2%), diabetes prevalence (19.5 vs. 18.6%), office systolic blood pressure (156.1 ± 9.4 mmHg vs. 156.0 ± 9.3 mmHg) and office diastolic blood pressure (91.5 ± 7.2 mmHg vs. 90.7 ± 7.3 mmHg). These demographic and clinical data were similar to those of the main study population showed in Table 1.

Dosing of randomized treatments

Proportions of patients according to drug dose and study visit are displayed in the bottom panel of Fig. 1. The full dose of olmesartan medoxomil (40 mg) was taken at the end of the study by 42.5% of patients randomized to this drug, whereas the full dose of ramipril (10 mg) by 51.6% of patients (P = 0.01). At the end of the study 25.1% and, respectively, 19.7% of patients were under the initial
doses of olmesartan and ramipril (10 and 2.5 mg), and 32.4% and 28.7% under the intermediate doses of olmesartan and ramipril (20 and 5 mg). The average study drug dose at the end of the double-blind phase was 25.9 ± 12.6 mg for olmesartan (63% of the maximal dose) and 7.1 ± 3.1 mg for ramipril (71% of the maximal dose).

In the ambulatory blood pressure monitoring subgroup the proportion of patients taking the full dose of both drugs (42.7% olmesartan and 51.6% ramipril) and the average drug dose at study end (26.0 ± 12.6 mg olmesartan and 7.1 ± 3.1 mg ramipril) was in line with the figure for the main study population.

Sitting office blood pressure and heart rate
As shown in Fig. 1, in the intention-to-treat population office sitting SBP and DBP values were progressively and significantly (p < 0.01) reduced by both treatment regimens during the study, with larger baseline-adjusted sitting office blood pressure reductions under olmesartan medoxomil than ramipril at each time-point.

As far as the primary study endpoint is regarded, at the time of the final evaluation, 12 weeks after randomization, baseline-adjusted mean sitting office SBP reduction achieved with olmesartan medoxomil was significantly (P = 0.01) greater than that observed with ramipril [17.8 (95% confidence interval: 16.8/18.9) vs. 15.7 (14.7/16.8) mmHg], the same being true for DBP [9.2 (8.6/9.8) vs. 7.7 (7.1/8.3) mmHg, P = 0.01]].

The absolute SBP and DBP values achieved at each visit were always slightly lower in the olmesartan group, and at the end of the study the olmesartan group, but not the ramipril one, achieved a mean SBP value less than 140 mmHg as recommended by guidelines.

Both SBP and DBP reductions were greater for each age group under olmesartan medoxomil than under ramipril this between-treatment difference achieved statistical significance in the 65–69 years age group for both pressure measures and in the oldest group (≥70 years) for DBP (Table 2). Overall, 68% of patients had systolic and

| Table 1 Demographic and clinical data of the patients of the intention-to-treat population at the time of randomization (n = 1081) |
|------------------------------------------|------------------------------------------|
| Olmesartan 10–40 mg (n = 542) | Ramipril 2.5–10 mg (n = 539) |
| Age (years, mean ± SD) | 72 ± 5 | 72 ± 5 |
| Males (n, %) | 278 (51) | 274 (51) |
| Height (cm, mean ± SD) | 166 ± 8 | 166 ± 8 |
| Weight (kg, mean ± SD) | 72 ± 10 | 73 ± 11 |
| BMI (kg/m², mean ± SD) | 26 ± 3 | 27 ± 3 |
| Waist circumference (cm, mean ± SD) | 95 ± 11 | 95 ± 11 |
| Concomitant diseases (n, %) | 420 (78) | 420 (78) |
| Concomitant therapies (n, %) | 308 (57) | 334 (62) |
| Previous antihypertensive treatment (n, %) | 388 (72) | 384 (72) |
| Diabetes (n, %) | 108 (20) | 105 (20) |
| Sitting office SBP (mmHg, mean ± SD) | 156 ± 10 | 156 ± 10 |
| Sitting office DBP (mmHg, mean ± SD) | 91 ± 7 | 90 ± 7 |

Data are separately shown for the two groups of randomization and reported as mean (±SD), or absolute (n) and relative frequency (%). BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure.

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diastolic hypertension, 31.5% had isolated systolic hypertension and only 0.5% had diastolic hypertension. In the systolic and diastolic hypertension group blood pressure reductions were significantly greater under olmesartan medoxomil than under ramipril, whereas differences observed in the patients with isolated systolic hypertension did not achieve statistical significance (Table 2).

At study end sitting office heart rate was slightly decreased by both olmesartan (from 70.3 ± 9.2 bpm to 69.0 ± 8.5 bpm) and ramipril (from 70.3 ± 9.6 bpm to 69.6 ± 8.9 bpm), with no statistically significant between-treatment difference (P = 0.24).

**Normalized and responder patients**

As shown in Fig. 2, the rate of patients with SBP and DBP normalized with monotherapy progressively increased with increased doses during the study, with percentages always greater in the olmesartan medoxomil treatment group. Sitting office blood pressure normalization was achieved by the end of the 12 weeks of double-blind treatment in 52.6% of patients treated with olmesartan medoxomil and in 46.0% of patients treated with ramipril, with a statistically significant between-treatment difference (P = 0.03).

At study end, also the proportion of normalized or responder patients was significantly larger in the olmesartan medoxomil treatment group (59.0 vs. 52.9% of ramipril; P = 0.04) (Fig. 2), whereas the rate of responder and not normalized patients was very small (6.4% under olmesartan and 6.9% under ramipril).

At study end, office blood pressure normalization rates achieved with olmesartan medoxomil were significantly higher than under ramipril treatment in the systolic and diastolic hypertension group (53.2 vs. 44.7%; P = 0.02), whereas only a nonsignificant difference was observed in patients with isolated systolic hypertension (50.3% olmesartan medoxomil vs. 47.0% ramipril; P = 0.54). Proportion of normalized or responder patients was 62.2% (olmesartan medoxomil) vs. 54.1% (ramipril; P = 0.03) in the systolic and diastolic group and 31.0 vs. 49.2% (P = 0.74) in the isolated systolic hypertension group.

Results of analysis of office blood pressure and heart rate, normalized and responder patients on the intention-to-treat population were confirmed by performing per-protocol analysis (data not shown).

**Table 2** Baseline-adjusted systolic (SBP) and diastolic blood pressure (DBP) reductions after 12 weeks of treatment with olmesartan or ramipril by age subgroups and by type of hypertension

| Age (years) | SBP (mmHg) | DBP (mmHg) | P |
|-------------|------------|------------|
|             | Olmesartan 10–40 mg | Ramipril 2.5–10 mg | Olmesartan 10–40 mg | Ramipril 2.5–10 mg | P |
| 65–69 (n = 222/216) | 18.3 (16.7/19.9) | 15.2 (13.6/16.8) | 0.01 | 9.0 (8.1/9.9) | 7.5 (6.5/8.4) | 0.02 |
| ≥70 (n = 290/283) | 17.8 (16.1/18.8) | 16.1 (14.7/17.5) | 0.17 | 9.3 (8.5/10.1) | 7.9 (7.1/8.7) | 0.01 |
| Type of hypertension | | | | | |
| Systolic and diastolic (n = 378/351) | 19.3 (18.1/20.5) | 16.7 (15.4/18.0) | 0.01 | 11.4 (10.7/12.1) | 9.8 (9.1/10.5) | 0.01 |
| Isolated systolic (n = 155/183) | 15.1 (12.9/17.2) | 14.0 (11.9/16.0) | 0.47 | 4.4 (3.2/5.5) | 3.1 (2.1/4.2) | 0.12 |

Data are shown for the intention-to-treat population and reported as mean and 95% confidence interval. The P-value refers to the statistical significance of the between-treatment difference.
Ambulatory blood pressure monitoring
Also in the population of patients with valid ambulatory recordings, sitting office SBP and DBP reductions were greater with olmesartan medoxomil [19.3 (18.0/20.6) and 10.1 (9.4/10.8) mmHg] than with ramipril [16.8 (15.5/18.1) and 8.4 (7.7/9.2) mmHg; *P* = 0.01 for SBP and *P* = 0.01 for DBP]. Treatment-induced blood pressure reductions on 24-h, daytime and night-time average SBP and DBP values under olmesartan medoxomil were greater than under ramipril, with between-treatments differences always statistically significant, except for night-time DBP (Table 3).

As shown in Fig. 3, both drugs reduced blood pressure during every period in which the 24 h were divided; however, in the last 6 h period from the dosing interval, covering the last part of the night sleep and the hours of awakening, significantly greater SBP and DBP reductions were achieved with olmesartan medoxomil [10.5 (11.8/9.0) mmHg SBP and 6.1 (7.0/5.3) mmHg DBP] than with ramipril [7.3 (8.7/5.9) and 4.5 (5.3/3.6) mmHg; *P* = 0.01 for SBP and *P* = 0.01 for DBP].

Assessment of the homogeneity of the blood pressure control by the smoothness index, showed significantly greater values for olmesartan medoxomil for both SBP (0.82 ± 0.98 vs. 0.62 ± 0.89 ramipril; *P* = 0.01) and DBP (0.68 ± 0.80 vs. 0.51 ± 0.74; *P* = 0.01), thus indicating a greater and more persistent antihypertensive efficacy of the former drug over the 24 h.

Heart rate was not changed over the 24 h by olmesartan [baseline-adjusted reduction and 95% confidence interval: 0.4 (1.1/0.3) bpm] and ramipril [0.1 (0.8/0.7) bpm, *P* = 0.52 between-treatments].

Safety and tolerability
Laboratory and safety analyses were carried out in all randomized patients (*n* = 1102). A total number of 136 (12.3%) patients reported adverse events (75 in the olmesartan medoxomil and 61 in the ramipril treatment group) for an overall number of 175 adverse events

Table 3  Average ambulatory systolic (SBP) and diastolic blood pressure (DBP) at randomization, at final double-blind visit (±SD), and baseline-adjusted reductions after treatment (mean and 95% confidence interval)

|                | SBP (mmHg) | DBP (mmHg) |
|----------------|------------|------------|
|                | Olmesartan 10–40 mg | Ramipril 2.5–10 mg | Olmesartan 10–40 mg | Ramipril 2.5–10 mg |
| 24-h           | *n* = 318  | *n* = 312  | *n* = 318  | *n* = 312  |
| Baseline       | 141.2 ± 13.9 | 140.6 ± 12.8 | 140.9 ± 9.2 | 140.6 ± 9.4 |
| End of 12 weeks of treatment | 130.0 ± 12.5 | 129.7 ± 12.6 | 140.8 ± 12.9 | 131.7 ± 12.8 |
| Reduction with treatment | 11.0 (12.2/9.9) | 9.0 (10.2/7.9) | 6.5 (7.2/5.8) | 6.5 (7.2/5.8) |
| *P*            | 0.02       | 0.03       | 0.03       | 0.03       |
| Daytime        | 0.02       | 0.02       | 0.02       | 0.02       |
| Baseline       | 145.6 ± 13.8 | 144.3 ± 13.0 | 84.2 ± 9.4 | 83.3 ± 9.7 |
| End of 12 weeks of treatment | 131.7 ± 12.8 | 125.0 ± 12.9 | 77.1 ± 8.1 | 77.9 ± 8.6 |
| Reduction with treatment | 11.5 (12.7/10.3) | 9.7 (10.9/8.5) | 6.9 (7.6/6.1) | 5.7 (6.4/4.9) |
| Night-time     | 0.03       | 0.02       | 0.02       | 0.02       |
| Baseline       | 131.8 ± 16.9 | 132.2 ± 15.2 | 73.8 ± 10.4 | 74.2 ± 10.6 |
| End of 12 weeks of treatment | 122.2 ± 14.8 | 124.8 ± 14.4 | 68.3 ± 8.6 | 69.4 ± 9.1 |
| Reduction with treatment | 9.7 (11.0/8.3) | 7.3 (9.7/6.0) | 5.6 (6.4/4.8) | 4.7 (5.5/3.9) |
| *P*            | 0.02       | 0.15       | 0.02       | 0.15       |

The *P*-value refers to the statistical significance of the between-treatment difference.

![Fig. 3](image_url)

Average baseline-adjusted 6 h systolic (SBP) and diastolic blood pressure (DBP) changes after 12 weeks of treatment with olmesartan (O) 10–40 mg (*n* = 318, open bars) and ramipril (R) 2.5–10 mg (*n* = 312, striped bars), for the group of patients with valid ambulatory blood pressure recordings. Asterisks refer to the statistical significance of between-treatment differences (**P* < 0.01; *P* < 0.05).

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(98 under olmesartan medoxomil and 77 under ramipril). Most of the events (68.6%) were of a mild intensity; 33 (3.0%) patients were withdrawn from the study owing to adverse events (14 in the olmesartan medoxomil and 19 in the ramipril group).

Events attributed to study treatment were 40 and occurred in 40 patients. Most of them were of mild intensity and only one was serious. Rate of patients with drug-related adverse events was comparable between the two treatment groups (Table 4). The most common drug-related adverse events were cough (more prevalent in the ramipril group with 13 vs. two episodes in the olmesartan medoxomil group), dizziness or vertigo, asthenia, hypertensive crisis or hypotension. All these side-effects are usually observed with these classes of drugs, in particular cough for ACE inhibitors.

Treatment was accompanied either by no change or only small and meaningless changes in the laboratory values considered in the study.

**Discussion**

In our elderly hypertensive patients the blood pressure reduction achieved after 12 weeks of treatment with olmesartan medoxomil 10–40 mg once daily was larger than that obtained with ramipril 2.5–10 mg once daily. This effect was already evident 2 weeks after initiation of treatment, thus confirming rapid onset of action of olmesartan medoxomil also in elderly patients [28–30]. In addition, the antihypertensive effect of olmesartan medoxomil progressively increased throughout the study and was achieved by using less frequently the highest drug dosage (40 mg/day) as compared with the ramipril group (10 mg/day) (43 vs. 52%; final dose 63 vs. 71% of the maximal one).

Also the proportion of patients attaining blood pressure normalization (<140/90 mmHg in case of absence of diabetes and less than 130/80 mmHg in presence of diabetes) was greater under treatment with olmesartan, as well as the number of normalized or responder patients. This result is clinically relevant, because it is well known from population studies that in this age range fewer than one treated patient out of three (30–40%) [11,12] has a good blood pressure control with monotherapy: in our study the rate of controlled patients was 59%, namely more than one out of two patients.

This is also the first head-to-head trial clearly showing a greater antihypertensive efficacy of an ARB compared with an ACE inhibitor in a large sample of the elderly population. As a matter of fact most of the studies evaluating antihypertensive efficacy of ARBs in the elderly have been carried out against dihydropyridine calcium channel blockers [36–38] or diuretics [39]. The only two double-blind, randomized studies published so far and directly comparing an ARB and an ACE inhibitor failed to demonstrate a superiority of one drug on the other [25,26]. One study assessed the comparative efficacy and tolerability of 8 weeks of irbesartan 150–300 mg once daily and enalapril 10–20 mg once-daily treatment in 141 patients at least 65 years of age with a sitting diastolic blood pressure between 95 and 110 mmHg [25]. At study end the mean reduction from baseline in diastolic blood pressure was 9.6 mmHg with irbesartan and 9.8 mmHg with enalapril; the mean reduction in sitting systolic blood pressure was 10.1 and 11.6 mmHg. Normalization rates did not differ between drugs. Irbesartan was associated with a significantly lower incidence of cough than was enalapril. The other study compared the efficacy and safety of eprosartan 600–800 mg once daily and enalapril 10–20 mg once daily to lower systolic blood pressure in 334 elderly patients aged more than 65 years with essential hypertension (sitting systolic blood pressure ≥160 mmHg and diastolic blood pressure between 90 and 114 mmHg) [26]. After 12 weeks of double-blind treatment mean reductions from baseline in sitting diastolic blood pressure were 9.4 mmHg with eprosartan and 9.6 mmHg with enalapril, whereas the corresponding figures for sitting systolic blood pressure were 18.0 and 17.4 mmHg. Normalization and response rates were also similar in the two groups, whereas adverse events were more frequent in the enalapril group [26]. In these studies ARBs were as effective as ACE inhibitors, but better tolerated. In our study olmesartan showed a greater antihypertensive efficacy than ramipril with a reduced incidence of cough.

The efficacy of olmesartan medoxomil was not negatively influenced by increasing age the drug being equally effective in providing blood pressure control in patients aged 65–69 years or at least 70 years. Olmesartan medoxomil also proved to be effective in controlling blood pressure in a relatively small subgroup of high-risk patients such as those with isolated systolic hypertension.
though no statistically significant and clinically relevant difference was observed as compared with ramipril. The good office blood pressure control obtained with olmesartan medoxomil was confirmed over the 24 h by ambulatory monitoring. In particular, the antihypertensive effect of olmesartan medoxomil was smoother and more long lasting than that of ramipril, this ensuring a better control of blood pressure variability and 24-h blood pressure coverage in the hours farthest from the last drug intake. These results are in line with previous studies based on ambulatory blood pressure monitoring carried out in younger individuals with this drug [40–42]. They also confirm in a large sample of elderly hypertensive patients what was recently shown in an open-label study comparing efficacy of 14-week telmisartan 80 mg and ramipril 5–10 mg treatment in 1613 grade 1–2 hypertensive patients aged 18 years or older [22]. In this open-label study long-term treatment with an ARB was superior to ramipril in reducing blood pressure over the 24 h and particularly during the last 6 h of the once-daily dosing interval.

Both olmesartan medoxomil and ramipril were well tolerated, but the former was associated with a lower rate of cough, which was indeed the most common among the treatment-emergent adverse events recorded in the ramipril group. Other adverse-drug reactions were well balanced between the two groups, and thus olmesartan medoxomil seems to match a better tolerability in terms of class side-effects and a greater effectiveness in controlling blood pressure.

Our study has also some limitations. First, the study design did not foresee measurement of standing blood pressure, a parameter that is clinically relevant in elderly treated hypertensive patients. However, we recorded only three cases of symptomatic hypotension: all of them were reported by patients treated with olmesartan at the three possible study doses. In addition, very low blood pressure values were never observed during ambulatory blood pressure monitoring. Second, the antihypertensive effect of the maximum dose of ramipril employed in our study (10 mg) might not correspond to that of olmesartan (40 mg). It is likely that ramipril at a higher dose than 10 mg may have a greater antihypertensive effect, but comparison had been made up to the maximum doses currently recommended for ramipril and olmesartan.

In conclusion, this large-scale pharmacological trial demonstrated that olmesartan medoxomil provides effective, prolonged and well tolerated control of hypertension in elderly patients with essential systolic and diastolic or isolated systolic hypertension. Therefore, olmesartan medoxomil might be considered as an effective and useful option among first line drug treatments of elderly patients with essential arterial hypertension.

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Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEEP). SHEEP Cooperative Research Group. JAMA 1991; 266:2925–2926.

Medical Research Council trial of treatment in hypertension of older adults: principal results. MRC Working Party. BMJ 1999; 320:405–412.

Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEEP). SHEEP Cooperative Research Group. JAMA 1991; 266:2925–2926.

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Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEEP). SHEEP Cooperative Research Group. JAMA 1991; 266:2925–2926.