

# Early Antihypertensive Efficacy of Olmesartan Medoxomil

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*The authors assessed the early antihypertensive efficacy of olmesartan medoxomil (OM) in a 12-week prospective observational study. Of 2221 patients with untreated hypertension who received OM (mainly 10 or 20 mg), 331 patients whose blood pressure (BP) was measured at 1 week after initiation of treatment were defined as the “early BP determination group,” whereas the remaining 1890 patients were defined as the “standard BP determination group.” Baseline characteristics, doses of OM, concomitant drugs used, and BP during treatment did not differ between the 2 groups. The achievement rate of BP target (<140/90 mm Hg) was 28.4% at 1 week in the early BP determination group and 28.3% at 2 weeks in the standard BP determination group (P=NS). Rates of adverse drug reactions in the 2 groups were similar. The present study suggests that OM is safe and effective in reducing BP at an early time point of treatment. J Clin Hypertens (Greenwich). 2008;10:930–935. ©2008 Le Jacq*

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Large-scale clinical studies have demonstrated that lowering blood pressure (BP) in hypertensive patients reduces the incidence of cardiovascular events; results of some studies have suggested that prompt and more effective BP control may be important for the prevention of cardiovascular events.<sup>1–3</sup>

There is a perception that calcium channel blockers (CCBs) have a relatively rapid-onset antihypertensive effect, whereas angiotensin II type 1 (AT<sub>1</sub>) receptor blockers (ARBs) may have a slower-onset effect.<sup>4</sup> Olmesartan medoxomil (OM) is an ARB with high affinity<sup>5–7</sup> and selectivity toward AT<sub>1</sub> receptors.<sup>8</sup> OM has been shown to elicit more potent antihypertensive effects at 2 weeks after starting treatment compared with other ARBs tested.<sup>9–16</sup>

While previous studies have suggested that OM lowers BP levels as early as 1 week after commencing treatment,<sup>17,18</sup> the early treatment effects of OM have not been studied in a large number of patients.

The present study is a secondary analysis of a previously reported 12-week prospective observational study in hypertensive patients who received OM in the setting of daily clinical practice in Japan between July 2004 and September 2005.<sup>19,20</sup> In this report, we assessed BP levels at early time points (1 or 2 weeks) of treatment with OM monotherapy in 2221 patients.

## METHODS

### Study Design and Participants

This study followed an open, prospective cohort design. The study protocol was approved by the In-House Ethical Committee of Sankyo (presently Daiichi Sankyo following merger) and was based on

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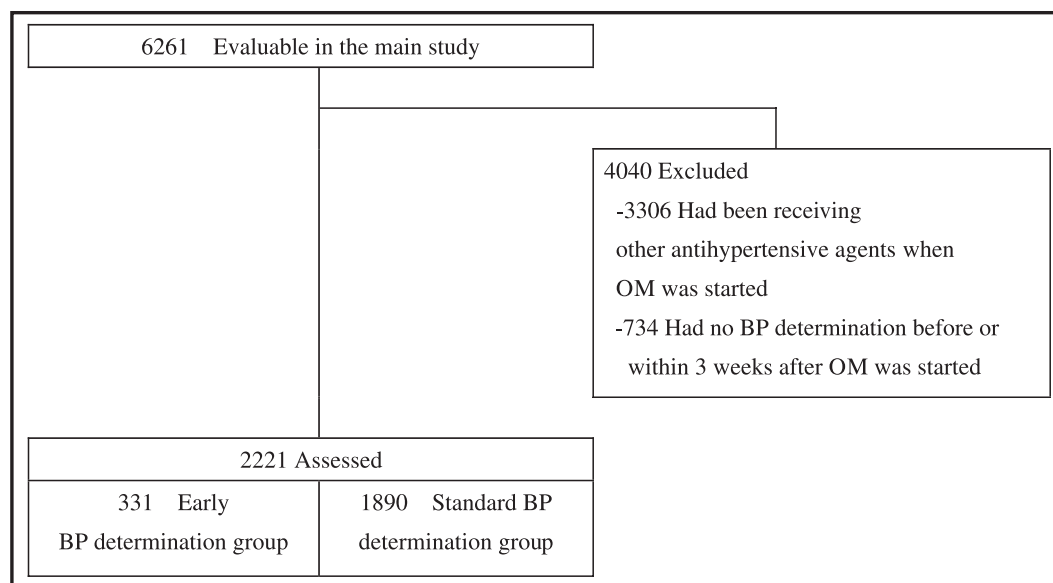


Figure 1. Study population and patient disposition. OM indicates olmesartan medoxomil; BP, blood pressure.

the pharmaceutical affairs law in Japan. The protocol was submitted to and approved by the Ministry of Health, Labour and Welfare of Japan before study commencement. This study was carried out in medical institutions registered according to good postmarketing surveillance practice in Japan.

Participants were OM-naïve and had essential hypertension. Physicians in several medical institutions were asked to select and register patients at the registration center within 14 days of starting OM therapy. The registration period was 1 year, from July 2004 to June 2005. OM (mainly 10 or 20 mg) was administered at each participating physician's discretion. Neither prior treatment nor combination drugs were restricted. The standard observation period was 12 weeks. BP, clinical laboratory data, and adverse events were recorded.

In this secondary analysis, we selected patients with untreated hypertension who received OM monotherapy and whose BP was determined before and within 3 weeks (4–21 days) of starting OM treatment. Patients were divided into 2 groups, those whose BP was and those whose BP was not measured at 1 week (7±3 days) after starting OM (“early BP determination group” and “standard BP determination group,” respectively). The main efficacy variable was the change from baseline in BP and achievement rate of BP target (<140/90 mm Hg) at the earliest time point measured (1 or 2 weeks).

#### Statistical Analysis

Continuous variables and categorical variables were expressed as mean±SD and rate (%), respectively,

and were compared between the 2 groups by *t*-test and Fisher's exact test as appropriate. The time course of changes in BP was analyzed by Dunnett's multiple comparison test. Multiple logistic regression analysis adjusted for baseline characteristics of the patients was used to test whether BP determination at 1 or 2 weeks affected the achievement rate of the BP target at the end of the study. The covariate factors used were sex, age (younger than 65, 65–74, and 75 years or older), presence or absence of comorbid conditions, and systolic BP (SBP)/diastolic BP (DBP) before treatment with OM.

*P* values <.05 were defined as significant. Statistical analyses were performed using SAS System Release 8.2 (SAS Institute Inc., Cary, NC).

## RESULTS

### Patient Disposition

Of 6261 patients included in the main study, those who had been receiving other antihypertensive agents when treatment with OM was started (n=3306) and those whose BP was not determined before or within 4 to 21 days after initiation of OM treatment (n=734) were excluded. Hence, 2221 patients were analyzed in the present study. The early BP determination and standard BP determination groups comprised 331 and 1890 of the 2221 patients, respectively. The patient disposition is shown in Figure 1.

### Baseline Characteristics and Drug Administration

Baseline characteristics of the 2 groups are shown in Table I. No significant difference was noted between the 2 groups at baseline, except mean age.

**Table I.** Baseline Characteristics of Patients

	EARLY BP DETERMINATION GROUP (N=331)	STANDARD BP DETERMINATION GROUP (N=1890)
Women	176 (53.2)	1027 (54.3)
Age, y	62.2±11.9	63.8±11.7 <sup>a</sup>
Age range, y		
<65	182 (55.0)	961 (50.8)
65–74	101 (30.5)	571 (30.2)
≥75	48 (14.5)	358 (18.9)
BMI, kg/m <sup>2</sup>	24.5±3.5	24.2±3.5
SBP, mm Hg	169.0±16.7	168.2±16.8
DBP, mm Hg	95.6±12.5	95.2±12.0
Pulse rate, beats/min	73.7±10.2	75.0±10.5
Comorbid conditions	204 (61.6)	1200 (63.5)
Hyperlipidemia	129 (39.0)	629 (33.3)
Diabetes mellitus	37 (11.2)	268 (14.2)
Heart disease	16 (4.8)	133 (7.0)
Cerebrovascular disorder	10 (3.0)	92 (4.9)
Liver disease	39 (11.8)	171 (9.0)
Renal disease	7 (2.1)	57 (3.0)

Abbreviations: BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure. Values are mean ± SD or No. (%). <sup>a</sup>*P*<.05.

Initial mean dosage of OM in the early and standard BP determination groups was 16.8±4.8 and 17.1±4.8 mg/d, respectively; approximately 70% and 30% of patients in both groups started OM at 20 and 10 mg/d, respectively.

In the early BP determination group, 330/331 (99.7%) and 161/186 patients (86.6%) remained on OM monotherapy at 1 and 12 weeks of treatment. Similarly, 1856/1890 (98.2%) and 1187/1372 patients (86.5%) in the standard BP determination group remained on OM monotherapy at 2 and 12 weeks, respectively. Thus, roughly the same proportion of patients remained on OM monotherapy at the end of the study in both groups (Table II). The most frequently added antihypertensive drug class was CCBs, which were given to 10.8% (20/186 patients) and 10.5% (144/1372 patients) in the 2 groups, respectively (Table II).

### Efficacy

Changes of BP from baseline at the earliest time point measured (1 or 2 weeks) and at 12 weeks are shown in Figure 2. Mean±SD change in SBP/DBP from baseline was 21.9±17.1/10.0±10.9 mm Hg at 1 week in the early BP determination group and 21.7±18.1/10.4±10.8 mm Hg in the standard

BP determination group (*P*=NS). No significant difference was detected between the 2 groups. Achievement rate of the BP target (<140/90 mm Hg) in patients in the early BP determination group before OM administration was 0.3%, while the rates at 1 and 12 weeks after initiation of OM were 28.4% and 52.2%, respectively. In the standard BP determination group, the rates before and at 2 and 12 weeks were 1.1%, 28.3%, and 50.5%, respectively. No significant difference was detected between the achievement rate at 1 week in the early BP determination group and that at 2 weeks in the standard BP determination group (*P*=.947).

The time course of changes in BP is shown in Figure 3. SBP and DBP in the early BP determination group were significantly (*P*<.0001) reduced to 147.0±15.7/85.6±10.5 mm Hg at 1 week. Likewise, SBP and DBP in the standard BP determination group were significantly (*P*<.0001) and comparably reduced to 146.5±17.3/84.7±11.0 mm Hg at 2 weeks. SBP and DBP in the 2 groups were not significantly different at 4, 8, and 12 weeks of OM administration (*t*-test).

The odds ratio for achieving the BP target at the end of the study in the early BP determination vs standard BP determination group was 1.071 (95% confidence interval, 0.837–1.370), indicating no significant difference between the 2 groups.

### Safety

The incidence rates of adverse drug reactions in the early BP determination group and the standard BP determination group were 2.7% (9/331 patients) and 3.7% (70/1890 patients), respectively, indicating that there was no significant difference between groups. Furthermore, incidence rates of adverse drug reactions associated with excessive BP lowering such as dizziness, postural dizziness, and hypotension were 0.6% (2/331 patients) and 1.0% (18/1890 patients) in the early BP determination group and in the standard BP determination group, respectively, again indicating no significant difference between groups. All patients recovered from their adverse drug reactions.

### DISCUSSION

This report describes a secondary analysis of efficacy data from a previously published 12-week prospective observational study of the antihypertensive effects of OM.<sup>19,20</sup> The present study indicates that OM monotherapy provided significant and safe BP reduction as early as the first week of treatment. The achievement rate of the BP target was

**Table II.** Patients' Distribution According to Number and Class of Additional Antihypertensive Drugs Being Taken at Each Time Point of BP Determination (1 or 2 and 12 Weeks of Treatment)

	EARLY BP DETERMINATION GROUP		STANDARD BP DETERMINATION GROUP	
	1 WEEK (N=331)	12 WEEKS (N=186)	2 WEEKS (N=1890)	12 WEEKS (N=1372)
	No.			
0	330 (99.7)	161 (86.6)	1856 (98.2)	1187 (86.5)
1	1 (0.3)	20 (10.8)	33 (1.7)	163 (11.9)
2	0 (0.0)	5 (2.7)	1 (0.1)	21 (1.5)
3	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
≥4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Class				
Diuretic	0 (0.0)	5 (2.7)	9 (0.5)	35 (2.6)
α-Blocker	0 (0.0)	2 (1.1)	1 (0.1)	10 (0.7)
β-Blocker	0 (0.0)	1 (0.5)	1 (0.1)	14 (1.0)
CCB	1 (0.3)	20 (10.8)	23 (1.2)	144 (10.5)
ACE inhibitor	0 (0.0)	0 (0.0)	1 (0.1)	4 (0.3)
ARB	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	2 (1.1)	0 (0.0)	0 (0.0)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II type 1 receptor blocker; BP, blood pressure; CCB, calcium channel blocker. Values are No. (%). The patients' distribution represents that in 1 day prior to BP determination at 1, 2, and 12 weeks.

28.4% at 1 week and 28.3% at 2 weeks after initiation of OM treatment.

To assess whether the results achieved at 1 week of treatment in 331 patients could be extrapolated to 1890 previously untreated patients whose BP was not assessed at 1 week, a comparison was made between the 2 groups regarding baseline characteristics, efficacy, safety, and BP target achievement rates. No significant difference in these parameters was detected between the 2 groups, with the exception of the mean age of the patients. It is considered unlikely that the small difference of age would affect the pharmacokinetics of OM in the 2 groups; thus, it is concluded that BP findings at 1 week in the early BP determination group might possibly be extrapolated to the standard BP determination group.

Furthermore, we tested whether determination of BP level at 1 week affected the achievement rate of the BP target at the end of the study using multiple logistic regression analysis. The odds ratio of achieving the BP target in the early vs standard BP determination group was 1.071, suggesting that measuring BP at 1 week vs at 2 weeks does not predict a different outcome of achieving BP target.

Several factors contribute to the prompt BP-lowering effects of OM, including high affinity and persistent binding to AT<sub>1</sub> receptors and

	Early BP Determination Group		Standard BP Determination Group	
	1 Week	12 Weeks	2 Weeks	12 Weeks
Change in SBP From Baseline, mm Hg	-21.9±17.1	-31.6±19.7	-21.7±18.1	-29.6±18.1
Change in DBP From Baseline, mm Hg	-10.0±10.9	-16.7±12.2	-10.4±10.8	-15.0±11.6

Figure 2. Changes from baseline in blood pressure (BP) at early time point measured (1 or 2 weeks) and at 12 weeks. SBP indicates systolic blood pressure; DBP, diastolic blood pressure.

favorable pharmacokinetics. Angiotensin II levels are increased shortly after administration of an ARB due to the blockade of normal feedback inhibition of renin release. Thus, administration of ARBs with weak AT<sub>1</sub> receptor affinity may not sufficiently antagonize the stimulated AT<sub>1</sub> receptors, resulting in gradual BP lowering. However, ARBs with a high affinity for AT<sub>1</sub> receptors, such as OM, may achieve more complete blockade of AT<sub>1</sub> receptors, thereby causing more rapid BP lowering. It may be possible that BP reduction at 1 week is achievable with other antihypertensive agents.

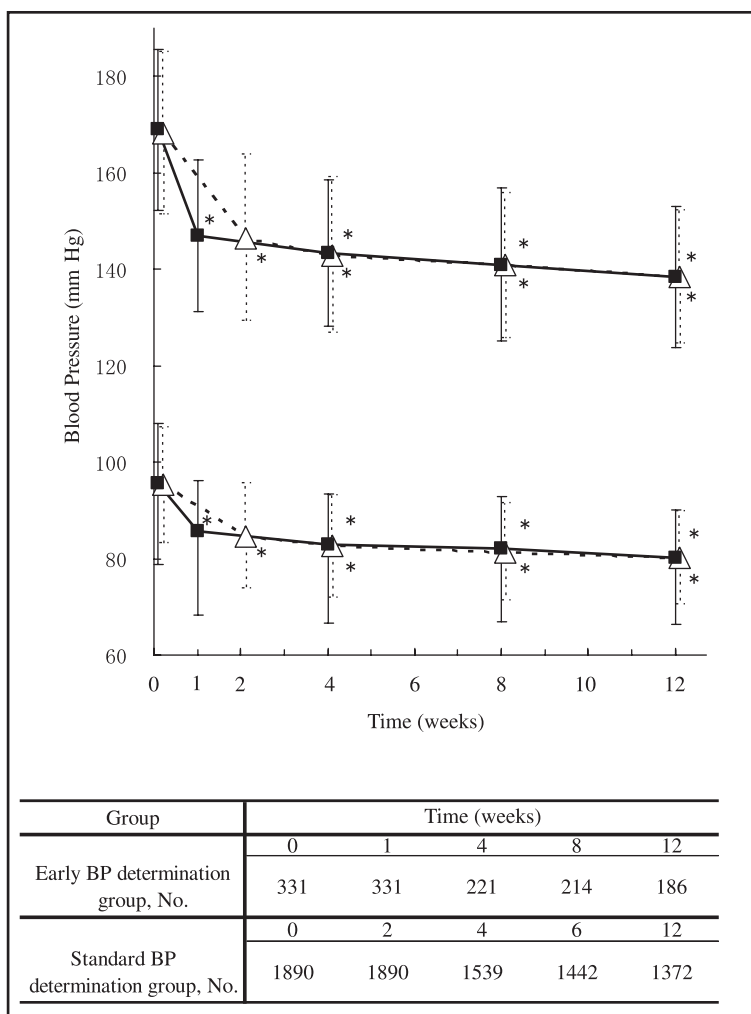


Figure 3. Time course of changes in blood pressure (BP). Upper and lower symbols represent changes in mean (SD) systolic BP and diastolic BP, respectively. Filled small squares and open large triangles were values obtained from the early determination group and standard determination group, respectively. \*Significant ( $P < .0001$ ) difference vs before treatment by Dunnett's multiple comparison test. The table at the bottom of the figure shows the number of patients whose BP was determined at each time point.

The incidence rate of adverse drug reactions in the early BP determination group was 2.7%, whereas that in the standard BP determination group was 3.7% ( $P = \text{NS}$ ). Furthermore, adverse drug reactions associated with excessive BP lowering occurred in 0.6% in the early BP determination group and 1.0% in the standard BP determination group ( $P = \text{NS}$ ). These similar results further underscore the contention that patients in the 2 groups responded identically to OM treatment.

The BP-lowering efficacies of various ARBs at early time points have been reported previously. In the study by Kassler-Taub and associates,<sup>21</sup> achievement rates of the DBP target ( $< 90$  mm Hg) at 1 week were 48% with irbesartan 300 mg, 31% with losartan potassium 100 mg, and 26% with placebo. In an analysis of the BP-lowering efficacy

of incremental doses of valsartan given either alone or together with hydrochlorothiazide, the achievement rates of the BP target ( $< 140/90$  mm Hg) at 1 week were 5% to 28%.<sup>22</sup>

Successful early reduction of BP may confer additional benefit over slower BP reduction.<sup>1-3</sup> Moreover, it is believed that rapid reduction of BP as early as the first week of treatment may improve patient adherence, thereby enhancing reduction of cardiovascular risk.<sup>23</sup>

Some limitations of this study should be considered. The design of the study was to represent the "real world" of clinical practice, and consequently patients were not blinded to treatment and no placebo comparison was used. Moreover, this is a secondary analysis of existing clinical trial data that was not designed to assess early antihypertensive

efficacy. It was not possible to compare BP at 1 week and at 2 weeks in the same patient because the number of patients with BP determinations at both time points was limited.

In conclusion, the present study suggests that OM monotherapy is safe and effective in producing rapid BP reduction in the first week of treatment.

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