Effects of Combination Olmesartan Medoxomil Plus Azelnidipine Versus Monotherapy With Either Agent on 24-Hour Ambulatory Blood Pressure and Pulse Rate in Japanese Patients With Essential Hypertension: Additional Results From the REZALT Study

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ABSTRACT

Background: In a previously reported randomized, double-blind, parallel-group study of the efficacy and tolerability of olmesartan medoxomil (OLM) and azelnidipine (AZL) combination therapy compared with monotherapy with each agent in Japanese patients with essential hypertension (the REZALT study), the use of a combination of OLM, an angiotensin II receptor blocker, plus AZL, a dihydropyridine calcium channel blocker, was associated with significantly greater reductions in office sitting blood pressure (BP) and 24-hour ambulatory BP compared with monotherapy with either agent, and was well tolerated.

Objective: This article reports the results from an a priori planned analysis and post hoc analyses of the diurnal BP and pulse rate (PR) profiles of OLM/AZL versus monotherapy with either agent from the REZALT study.

Methods: Male and female Japanese outpatients with essential hypertension were eligible if they met the following inclusion criteria: age ≥20 years; systolic BP (SBP) ≥140 to <180 mm Hg and diastolic BP (DBP) ≥90 to <110 mm Hg; and 24-hour ambulatory SBP/DBP ≥135/≥80 mm Hg. Patients were randomly assigned to receive OLM/AZL 10/8 mg, OLM/AZL 20/16 mg, OLM 20 mg, or AZL 16 mg, once daily for 12 weeks. The effectiveness of the treatments was assessed using 24-hour ambulatory BP monitoring (ABPM) and PR, analyzed by time period (BP and PR, 24 hours, daytime [7 AM–<10 PM], nighttime [10 PM–<7 AM], and early morning [6 AM–<9 AM]; PR, morning [6 AM –<11 AM]) and dipping status at baseline (dippers [(Daytime BP – Nighttime BP)/Daytime BP ≥10%] or nondippers [(Daytime BP – Nighttime BP)/Daytime BP <10%]).

Results: A total of 867 patients were enrolled, and 862 randomized patients were included in the full analysis set (590 men, 272 women; mean age, 56.6 years). A total of 839 patients had assessable ABPM data (213, 211, 206, and 209 patients in the OLM/AZL 10/8 mg, OLM/AZL 20/16 mg, OLM, and AZL groups, respectively). No clinically significant between-group differences were observed in baseline demographic and clinical characteristics. Combination therapy was associated with significantly greater antihypertensive effects on 24-hour ABPM compared with either monotherapy in all of the time periods, as follows: SBP/DBP reductions with OLM/AZL 20/16 mg in the daytime, nighttime, and early morning were –22.6/–14.1, –21.2/–12.5, and –20.6/–11.9 mm Hg, respectively (all, $P < 0.05$ vs the other 3 treatment groups). The SBP/DBP reductions with OLM/AZL 10/8 mg (daytime, –18.2/–11.0 mm Hg; nighttime, –18.1/–10.0 mm Hg; and early morning, –15.6/–9.3 mm Hg) were also significantly greater than with OLM 20 mg (–11.8/–6.7, –12.8/–7.2, and –11.0/–6.9 mm Hg, respectively; all, $P < 0.01$) and AZL 16 mg (–13.1/–7.8, –10.2/–5.5, and –9.9/–6.1 mm Hg; all, $P < 0.001$) in all of the time periods. The antihypertensive effects associated with OLM/AZL 10/8 mg or 20/16 mg

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were significantly greater than those with monotherapies regardless of dipping pattern at baseline (all, $P < 0.05$) in all of the time periods, with the exception of nighttime reduction with OLM/AZL 10/8 mg versus OLM in dippers. The numbers of patients who had any increase in BP were 12/213 (5.6%) with OLM/AZL 10/8 mg, 13/211 (6.2%) with OLM/AZL 20/16 mg, 35/206 (17.0%) with OLM, and 36/209 (17.2%) with AZL. The AZL-containing regimens were associated with reduced morning PR (mean [95% CI] changes from baseline to week 12: –1.5 beats/min [–2.5 to –0.4] with OLM/AZL 10/8 mg, –2.1 beats/min [–3.0 to –1.1] with OLM/AZL 20/16 mg, 0.4 beat/min [–0.5 to 1.3] with OLM, and –1.9 beats/min [–2.8 to –1.0] with AZL).

Conclusion: In this study in Japanese patients with essential hypertension, the reductions in daytime, nighttime, and early-morning BP assessed using 24-hour ABPM were significantly greater with combination OLM/AZL than with either monotherapy, regardless of dipping pattern at baseline. Japan Pharmaceutical Information Center registration number: JapicCTI-060286 (*Clin Ther.* 2010;32:861–881) © 2010 Excerpta Medica Inc.

Key words: ambulatory blood pressure monitoring, azelnidipine, combination therapy, essential hypertension, olmesartan medoxomil.

INTRODUCTION

Blood pressure (BP) control in the treatment of essential hypertension may require multiple drugs with different mechanisms of action because the disease involves many factors and multiple pathophysiologic mechanisms.[1] Guidelines for the management of hypertension in various countries recommend that monotherapy dose titration or a combination of antihypertensive drugs of different classes, such as angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers (ARBs), β-blockers, calcium channel blockers (CCBs), or diuretics, should be considered if adequate antihypertensive effect is not obtained with monotherapy.[2–4] The combination of an ARB plus a CCB has been reported to have additive effects on BP in patients aged >65 years with systolic hypertension.[5]

Ambulatory BP monitoring (ABPM) provides information, such as 24-hour BP (mean of BP over a period of 24 hours), patterns of diurnal BP variation, and BP variability, that is used for the assessment of the therapeutic effects of antihypertensive agents.[6] A significant association between ABPM data and cerebrovascular or cardiovascular (CV) events and organ damage has been reported previously.[7,8] Early morning and nighttime have been recognized as the periods with significantly higher prevalences of hypertensive events because BP has been associated with risks for CV events and cerebrovascular dysfunction during those time periods.[9–12] Clinical evaluation of hypertension, as monitored using ABPM, might be required for tight BP control over 24 hours and might contribute to a reduction in CV events.

Olmesartan medoxomil (OLM) has been reported to be an effective ARB.[13–16] Azelnidipine (AZL) is a dihydropyridine L-type CCB.[17] The REZALT study[18]—a randomized, double-blind, 4-arm, parallel-group study of the efficacy and tolerability of OLM/AZL combination therapy compared with monotherapy with each agent in Japanese patients with essential hypertension—reported a statistically significant difference in office sitting BP reduction and no clinically significant difference in the safety profiles of 12-week ARB/CCB combination treatment with OLM/AZL 10/8 mg or OLM/AZL 20/16 mg compared with monotherapy with either OLM 20 mg or AZL 16 mg. In the J-CORE study, a prospective, randomized, open-label, blinded end-point study in 207 patients with hypertension in Japan, OLM/AZL 20/16 mg was associated with a significant reduction in central systolic BP (SBP) ($P = 0.039$) and aortic pulse wave velocity ($P < 0.001$) compared with OLM 20 mg + hydrochlorothiazide 12.5 mg, despite the lack of a significant difference in brachial SBP reduction.[19]

In the REZALT study,[18] 24-hour ABPM was used as part of an evaluation of the effectiveness of OLM/AZL. Concerning the ABPM findings, a previously published article on REZALT[18] reported only reductions in office sitting BP and 24-hour mean BP. This article reports additional findings from a priori planned and post hoc analyses of the diurnal profile of BP and pulse rate (PR), as measured using ABPM, from the REZALT study.

PATIENTS AND METHODS

This multicenter, randomized, double-blind, 4-arm, parallel-group comparative study was conducted at 37 study sites in Japan in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. The study protocol was reviewed and approved by the institutional review board at each study site before the initiation of the study.

Study Population

Male and female outpatients with essential hypertension were eligible for participation in the study if they met the following criteria: age ≥20 years (legal adult in Japan); SBP ≥140 to <180 mm Hg and diastolic BP (DBP) ≥90 to <110 mm Hg, based on the mean of 2 sitting BP measurements during the run-in period; and 24-hour ambulatory SBP/DBP ≥135/≥80 mm Hg during the run-in period.

The main exclusion criteria were conditions such as secondary or malignant hypertension, CV disorder, or cerebrovascular disorder. Night-shift workers were also excluded.

Written informed consent was obtained from all eligible patients before study enrollment.

Study Design

The study consisted of a 4-week run-in period and a subsequent 12-week treatment period. Patients visited the study site at study weeks −4, −1, 0, 2, 4, 6, 8, 10, and 12. All enrolled patients underwent a 4-week run-in placebo washout. At screening, patients underwent BP measurement (office sitting BP and ABPM) and laboratory testing at week −1 to 0. Patients were randomly assigned to 1 of the following 4 double-blind treatment groups: OLM/AZL 10/8 mg, OLM/AZL 20/16 mg, OLM 20 mg, or AZL 16 mg, administered orally once daily between breakfast and noon, for 12 weeks. Concurrent use of any antihypertensive agents was not permitted. Changes in doses of the study drugs were also not permitted. If a patient's office sitting SBP or DBP persisted at >180 or >110 mm Hg, respectively, at >2 consecutive measurements during the study, the patient was withdrawn from the study and underwent intensified antihypertensive treatment according to the investigator's routine clinical practice. Compliance was assessed using pill counts recorded by the investigator at each study visit.

Office Sitting Blood Pressure Measurement and Ambulatory Blood Pressure Monitoring

Office sitting BP was measured in triplicate by auscultation using a standard mercury sphygmomanometer at each study visit. ABPM was conducted during the run-in period (baseline) and at the end of the treatment period (week 12). After administration of the study drug, SBP, DBP, and PR were measured and recorded every 30 minutes for ≥25 consecutive hours using a validated ABPM system (model TM-2431, A&D System Co., Ltd., Tokyo, Japan).[20] Data recorded within the first hour after the start of measurement were discarded from the analyses. A summary statistic (mean [SD]) at hourly intervals was calculated using the mean of 2 measurements taken 30 minutes apart in each hour.

Effectiveness Assessment

Effectiveness end points were changes from baseline to week 12 in 24-hour, daytime (7 AM–<10 PM), nighttime (10 PM–<7 AM), and early-morning (6 AM–<9 AM) SBP, DBP, and PR. The representative values of BP and PR in each time period were calculated as the mean of all of the readings within each time period.

Twenty-four–hour profiles of SBP, DBP, and PR at baseline and at the end of treatment were assessed graphically. Based on the patterns of diurnal SBP variation during the run-in period, patients were classified as *dippers* ([Daytime BP – Nighttime BP]/Daytime BP ≥10%) or *nondippers* ([Daytime BP – Nighttime BP]/Daytime BP <10%). For each subgroup, changes from baseline in 24-hour ambulatory BP at week 12 were evaluated, and 24-hour profiles were assessed graphically. Reductions from baseline in nighttime SBP were assessed using scatterplots. Morning PR (6 AM–<11 AM) was also assessed in the context of the 24-hour PR profile.

The proportions of patients who achieved target nighttime SBP (defined as <120 mm Hg in the Japanese Society of Hypertension Guidelines for the Management of Hypertension[3]) were calculated.

Statistical Analysis

The primary analysis set was the full analysis set, which included all randomized patients who received ≥1 dose of study drug and had assessable BP data available from ≥1 time point during the treatment period.

Mean changes from baseline to week 12 in ABPM-measured SBP, DBP, and PR for each time period (24 hours, daytime [7 AM–<10 PM], nighttime [10 PM–<7 AM], and early morning [6 AM–<9 AM]) were compared between the 4 groups using ANCOVA, with baseline value, sex, and weight as covariates. Adjusted mean between-group differences and corresponding 95% CIs were estimated. Twenty-four–hour profiles of ABPM-measured SBP, DBP, and PR before and after 12-week treatment were analyzed by plotting the hourly means against time. All of the analyses were conducted a priori under blinded conditions, as specified in the protocol of the REZALT study.

The following additional analyses were conducted post hoc: 24-hour SBP profile in dippers and nondippers; and a between-group comparison of the mean changes from baseline to week 12 in ABPM-measured SBP using 1-way ANOVA by daytime and nighttime periods. Mean daytime and nighttime changes from baseline to week 12 in ABPM-measured SBP were compared using the paired *t* test. The relationships between baseline BP and reduction in nighttime SBP and morning (6 AM–<11 AM) PR were analyzed. The relationship between baseline and the reduction in nighttime SBP in each group was analyzed using a linear model. The regression line, *x*-intercept, and residual SD were calculated. Summary statistics (mean [95% CI]) were used for comparing morning and 24-hour BP and PR.

The 2-sided significance level was set at $P \leq 0.05$. All statistical analyses were conducted using SAS version 8.02 (SAS Institute Inc., Cary, North Carolina).

RESULTS

Study Population

The baseline characteristics of the patients have been described in detail elsewhere.[18] Briefly, 867 of 1206 patients who provided informed consent were randomized and entered the treatment period. The **table** shows the baseline characteristics of the 862 randomized patients included in the full analysis set (590 men, 272 women; mean age, 56.6 years). There were no clinically significant between-group differences in any of the baseline characteristics. A total of 839 patients who had assessable ABPM data available were included in the full analysis set: 213 in the OLM/AZL 10/8-mg group, 211 in the OLM/AZL 20/16-mg group, 206 in the OLM group, and 209 in the AZL group.

The proportions of patients who were compliant with treatment (defined as receiving ≥80% of assigned medications) were ≥98.6% in all of the groups at all of the time points. There were no significant differences in the proportions of compliant patients between the 4 groups at any time point.

Changes in 24-Hour Blood Pressure and Pulse Rate

Figure 1 shows the changes from baseline to week 12 in BP (SBP/DBP) measured by ABPM in each time period (24-hour, daytime, nighttime, and early morning) by treatment group. The 24-hour means are cited from the REZALT study[18] for reference. The reductions in both SBP and DBP were significantly greater in the OLM/AZL 20/16-mg group (daytime, –22.6/–14.1 mm Hg; nighttime, –21.2/–12.5 mm Hg; and early morning, –20.6/–11.9 mm Hg) than in the other 3 treatment groups in all of the time periods (all, $P < 0.05$). The BP reductions in the OLM/AZL 10/8-mg group (–18.2/–11.0, –18.1/–10.0, and –15.6/–9.3 mm Hg, respectively) were also significantly greater than in the OLM group (–11.8/–6.7, –12.8/–7.2, and –11.0/–6.9 mm Hg; all, $P < 0.01$) and in the AZL group (–13.1/–7.8, –10.2/–5.5, and –9.9/–6.1 mm Hg; all, $P < 0.001$) in all of the time periods.

The changes from baseline to week 12 in PR in each time period (24-hour, daytime, nighttime, and early morning) were –0.3, –0.7, 0.4, and –1.1 beats/min, respectively, in the OLM/AZL 10/8-mg group; –1.4, –1.4, –1.2, and –1.4 beats/min in the OLM/AZL 20/16-mg group; 1.0, 1.0, 0.9, and 0.3 beats/min in the OLM group; and –1.0, –0.8, –1.5, and –1.8 beats/min in the AZL group. The decreases in PR were significantly greater with OLM/AZL 10/8 mg, OLM/AZL 20/16 mg, and AZL compared with OLM (all, $P < 0.05$), with the exception of the comparison between OLM/AZL 10/8 mg and OLM in the nighttime period.

Profiles of 24-Hour Blood Pressure and Pulse Rate

Figure 2 shows the 24-hour profiles of ABPM-measured SBP, DBP, and PR in each of the 4 treatment groups. In all 4 treatment groups, SBP and DBP at the end of treatment were less than baseline levels throughout 24 hours. An antihypertensive effect throughout 24 hours was observed on visual inspection in all groups.

There were no major changes in the patterns of diurnal PR from baseline to week 12 in any of the treatment groups. In the groups treated with an AZL-containing regimen, differences from baseline to 12 weeks in morning PR were observed, and little or no change was observed on visual inspection over the rest of the 24-hour period. Therefore, a further analysis of morning PR changes was conducted.

Reductions From Baseline in Morning Pulse Rate

The arithmetic mean (95% CI) changes in morning PR from baseline to week 12 were –1.5 beats/min (–2.5 to –0.4) with OLM/AZL 10/8 mg, –2.1 beats/min (–3.0 to –1.1) with OLM/AZL 20/16 mg, 0.4 beat/min (–0.5 to 1.3) with OLM, and –1.9 beats/min (–2.8 to –1.0) with AZL. The mean differences between morning and the rest of the 24-hour–period PR were –1.5 beats/min (95% CI, –2.6 to –0.5; $P = 0.006$) with OLM/AZL 10/8 mg, –1.3 beats/min (95% CI, –2.3 to –0.4;

Table. Baseline demographic and clinical characteristics of the population in a study of combination olmesartan medoxomil/azelnidipine (OLM/AZL) versus monotherapy with either agent for essential hypertension in Japanese patients.*

Characteristic	OLM/AZL 10/8 mg (n = 221)	OLM/AZL 20/16 mg (n = 214)	OLM 20 mg (n = 211)	AZL 16 mg (n = 216)
Age, mean (SD), y	56.6 (9.9)	55.7 (10.4)	57.4 (11.0)	56.7 (10.6)
Sex, no. (%)				
Male	146 (66.1)	152 (71.0)	145 (68.7)	147 (68.1)
Female	75 (33.9)	62 (29.0)	66 (31.3)	69 (31.9)
Dipping pattern of nighttime BP, no. (%)				
Dippers†	85 (38.5)	79 (36.9)	84 (39.8)	95 (44.0)
Nondippers‡	136 (61.5)	135 (63.1)	127 (60.2)	121 (56.0)
Office measurements, mean (SD)				
SBP, mm Hg	154.4 (9.6)	154.1 (9.8)	153.7 (9.8)	154.5 (9.5)
DBP, mm Hg	97.1 (5.4)	97.2 (5.5)	97.1 (5.4)	97.7 (5.7)
PR, beats/min	70.9 (8.2)	70.1 (7.8)	71.1 (9.4)	71.0 (7.5)
24-Hour ambulatory measurements, mean (SD)				
24-Hour[18]				
SBP, mm Hg	157.6 (11.8)	157.7 (11.5)	157.3 (12.6)	158.1 (12.3)
DBP, mm Hg	96.5 (8.1)	96.9 (8.0)	96.6 (8.2)	96.6 (8.1)
PR, beats/min	70.2 (7.9)	69.5 (7.7)	70.1 (9.1)	69.8 (7.9)
Daytime§				
SBP, mm Hg	162.9 (11.5)	162.8 (11.3)	162.3 (12.3)	163.6 (12.3)
DBP, mm Hg	100.1 (8.6)	100.3 (8.1)	100.2 (8.6)	100.3 (8.2)
PR, beats/min	74.3 (8.7)	73.3 (8.4)	74.0 (9.8)	73.9 (8.6)
Nighttime‖				
SBP, mm Hg	148.8 (15.1)	149.0 (14.9)	148.9 (15.8)	148.7 (15.3)
DBP, mm Hg	90.3 (9.2)	91.1 (9.7)	90.6 (9.3)	90.5 (9.5)
PR, beats/min	63.5 (8.2)	63.1 (8.2)	63.7 (9.2)	63.1 (8.3)
Early morning¶				
SBP, mm Hg	157.8 (16.2)	156.4 (17.2)	155.7 (17.2)	157.8 (16.2)
DBP, mm Hg	97.2 (11.1)	96.9 (10.6)	96.7 (11.1)	97.7 (9.8)
PR, beats/min	66.8 (9.1)	66.0 (9.1)	66.4 (9.9)	66.3 (9.2)

BP = blood pressure; SBP = systolic BP; DBP = diastolic BP; PR = pulse rate.
*No significant between-group differences were found.
† Dippers: (Daytime BP – Nighttime BP)/Daytime BP ≥10%.
‡ Nondippers: (Daytime BP – Nighttime BP)/Daytime BP <10%.
§ 7 AM to <10 PM.
‖ 10 PM to <7 AM.
¶ 6 AM to <9 AM.

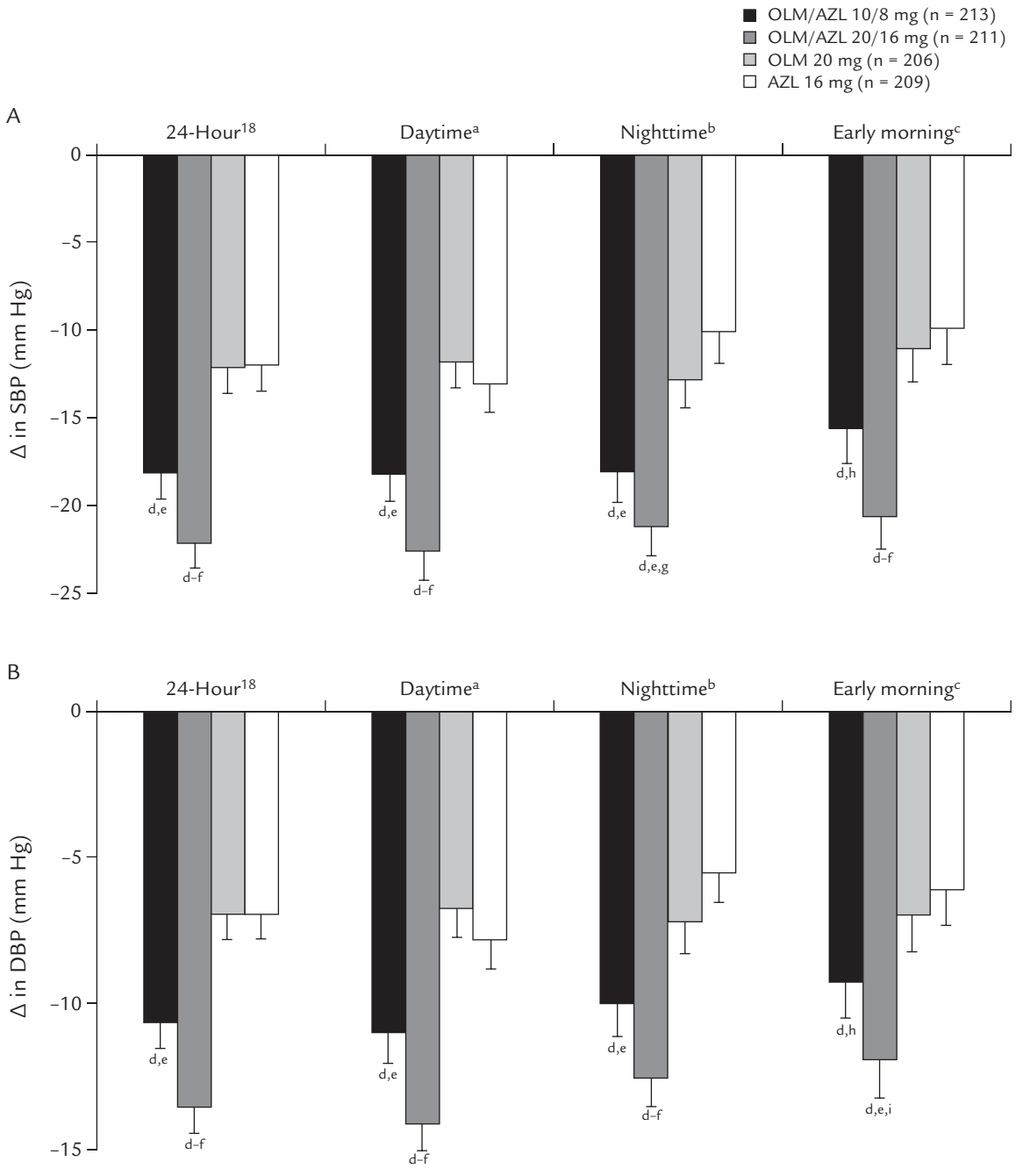

Figure 1. Adjusted mean (95% CI) changes from baseline in (A) systolic blood pressure (SBP) and (B) diastolic blood pressure (DBP) at 12 weeks of treatment with combination olmesartan medoxomil/azelnidipine (OLM/AZL) versus monotherapy with either agent for essential hypertension in Japanese patients. The results were adjusted by covariates of baseline value, sex, and body weight. [a]7 AM to <10 PM; [b]10 PM to <7 AM; [c]6 AM to <9 AM; [d]$P < 0.001$ versus AZL; [e]$P < 0.001$ versus OLM; [f]$P < 0.001$ versus OLM/AZL 10/8 mg; [g]$P < 0.05$ versus OLM/AZL 10/8 mg; [h]$P < 0.01$ versus OLM; [i]$P < 0.01$ versus OLM/AZL 10/8 mg (ANCOVA).

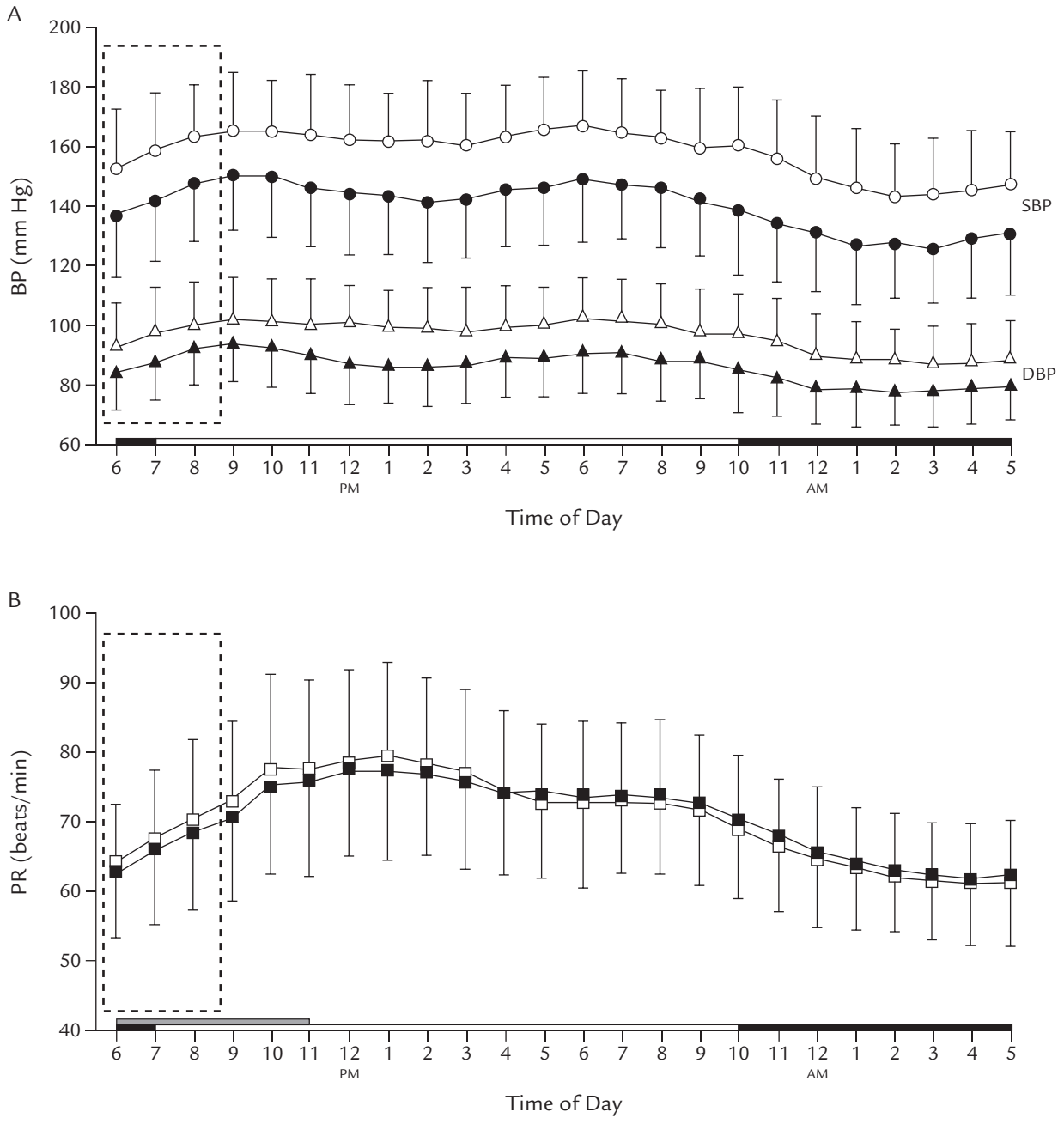

Figure 2. Twenty-four–hour profiles of arithmetic mean (SD) (A) systolic blood pressure (SBP) and diastolic blood pressure (DBP) and (B) pulse rate (PR) before (open symbols) and after (solid symbols) 12-week treatment with combination olmesartan medoxomil/azelnidipine (OLM/AZL) 10/8 mg for essential hypertension in Japanese patients (n = 213). The white, grey, and black areas of the horizontal scales represent daytime (7 AM–<10 PM), morning (6 AM–<11 AM), and nighttime (10 PM–<7 AM), respectively. The early-morning period (6 AM–<9 AM) is indicated by the dashed lines.

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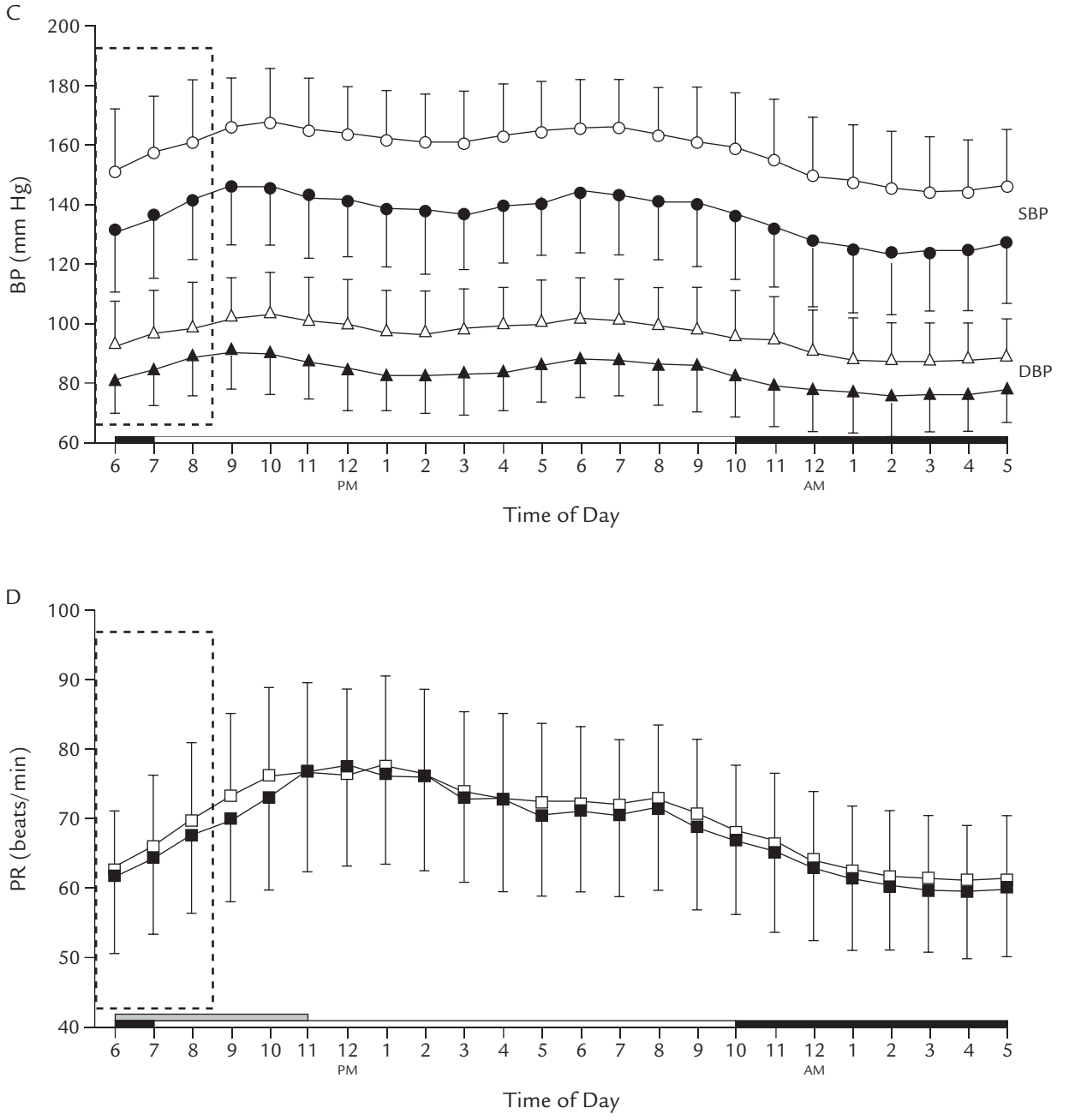

Figure 2 (continued). Twenty-four–hour profiles of arithmetic mean (SD) (C) SBP and DBP and (D) PR before (open symbols) and after (solid symbols) 12-week treatment with combination OLM/AZL 20/16 mg for essential hypertension in Japanese patients (n = 211). The white, grey, and black areas of the horizontal scales represent daytime (7 AM–<10 PM), morning (6 AM–<11 AM), and nighttime (10 PM–<7 AM), respectively. The early-morning period (6 AM–<9 AM) is indicated by the dashed lines.

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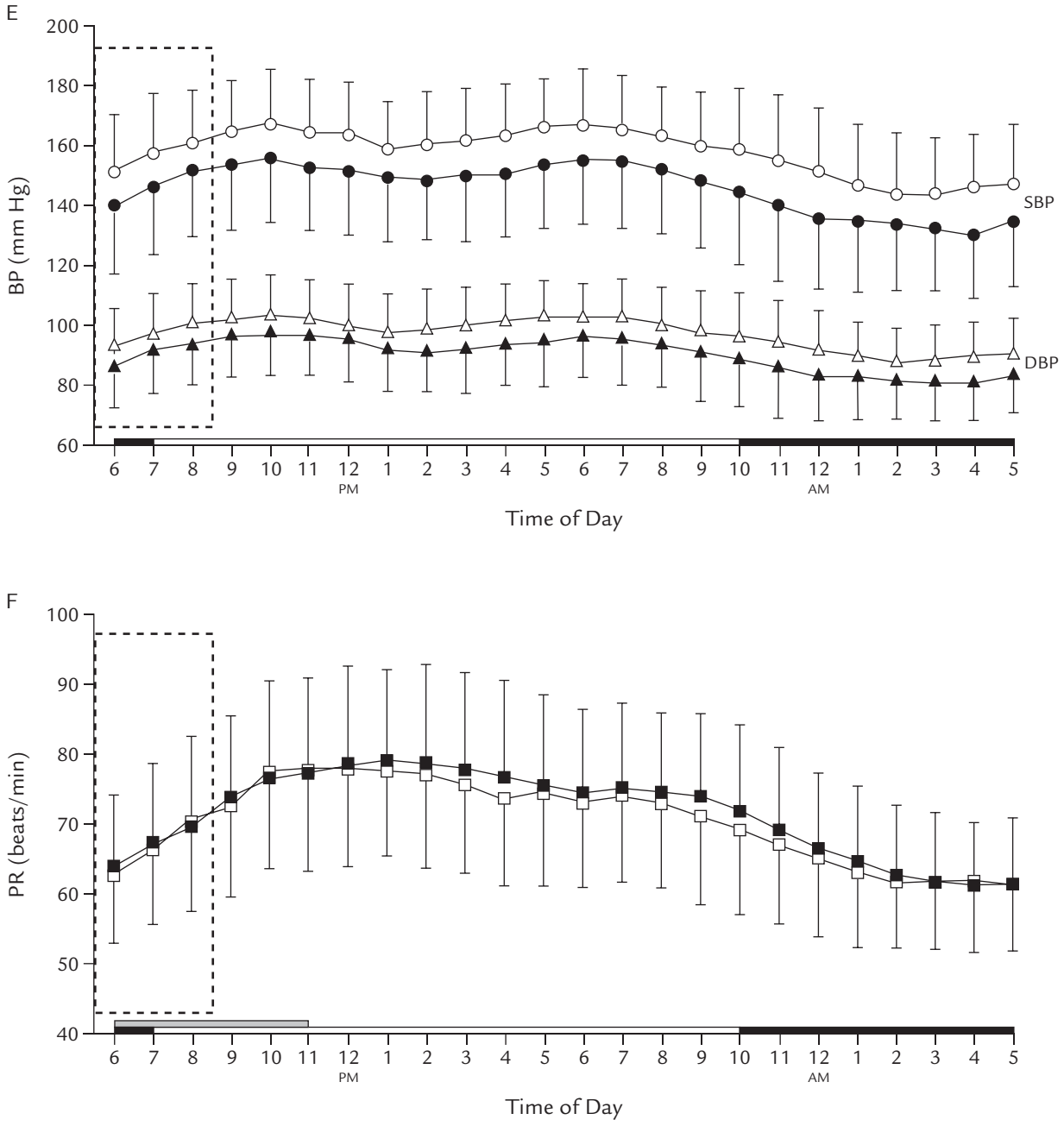

Figure 2 (continued). Twenty-four–hour profiles of arithmetic mean (SD) (E) SBP and DBP and (F) PR before (open symbols) and after (solid symbols) 12-week treatment with monotherapy with OLM 20 mg for essential hypertension in Japanese patients (n = 206). The white, grey, and black areas of the horizontal scales represent daytime (7 AM–<10 PM), morning (6 AM–<11 AM), and nighttime (10 PM–<7 AM), respectively. The early-morning period (6 AM–<9 AM) is indicated by the dashed lines.

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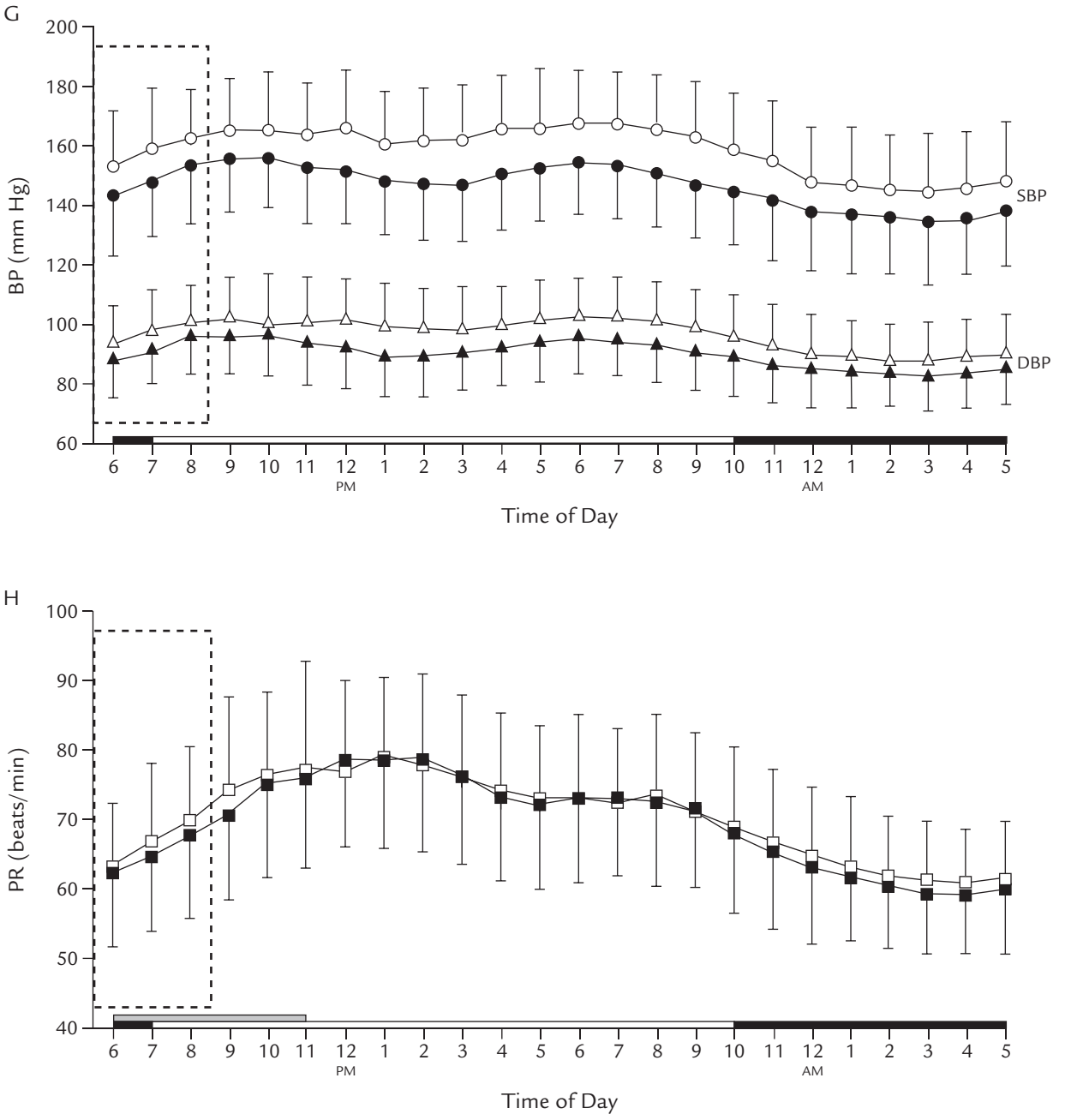

Figure 2 (continued). Twenty-four–hour profiles of arithmetic mean (SD) (G) SBP and DBP and (H) PR before (open symbols) and after (solid symbols) 12-week treatment with monotherapy with AZL 16 mg for essential hypertension in Japanese patients (n = 209). The white, grey, and black areas of the horizontal scales represent daytime (7 AM–<10 PM), morning (6 AM–<11 AM), and nighttime (10 PM–<7 AM), respectively. The early-morning period (6 AM–<9 AM) is indicated by the dashed lines.

$P = 0.007$) with OLM/AZL 20/16 mg, –0.9 beat/min (95% CI, –1.8 to 0.0; P = NS) with OLM, and –1.3 beats/min (95% CI, –2.3 to –0.3; $P = 0.008$) with AZL. The proportions of patients who had increases from baseline in morning PR were 40.4% (86/213), 35.5% (75/211), 48.5% (100/206), and 34.0% (71/209) of patients in the OLM/AZL 10/8-mg, OLM/AZL 20/16-mg, OLM, and AZL groups, respectively. In contrast, the proportions of patients who had a decrease or no change in PR compared with baseline were 59.6% (127/213), 64.5% (136/211), 51.5% (106/206), and 66.0% (138/209). The antihypertensive effects on morning SBP/DBP were statistically significant in each of the treatment groups (mean [95% CI] reductions: SBP, –15.6 [–17.5 to –13.7], –20.5 [–22.4 to –18.6], –10.0 [–11.8 to –8.2], and –10.4 mm Hg [–12.5 to –8.4]; DBP, –8.7 [–10.0 to –7.5], –11.8 [–12.9 to –10.6], –5.9 [–7.1 to –4.6], and –5.8 mm Hg [–7.1 to –4.5]).

Patterns of Diurnal Blood Pressure Variation: Dippers and Nondippers

Twenty-four–hour profiles are summarized by dipping pattern in **Figure 3**. Daytime and nighttime SBP reductions are summarized in **Figure 4**.

In the patients classified as dippers in all of the treatment groups, BP reductions from baseline were statistically significant in both the daytime and the nighttime periods (all, $P < 0.001$), and daytime BP reductions were significantly greater compared with nighttime reductions (OLM/AZL 10/8 mg, OLM/AZL 20/16 mg, and AZL, $P < 0.001$; OLM, $P = 0.021$).

In the patients classified as nondippers in all of the treatment groups, daytime and nighttime BP reductions were statistically significant (all, $P < 0.001$), as were nighttime versus daytime BP reductions (OLM/AZL 10/8 mg and OLM, $P < 0.001$; OLM/AZL 20/16 mg, $P = 0.011$; and AZL, $P = 0.013$).

In dippers, daytime and nighttime BP reductions were significantly greater in the OLM/AZL 10/8-mg and OLM/AZL 20/16-mg groups compared with those in the monotherapy groups, with the exception of nighttime reduction with OLM/AZL 10/8 mg versus OLM (daytime: vs OLM, $P = 0.002$ and $P < 0.001$, respectively; vs AZL, $P = 0.002$ and $P < 0.001$; nighttime: vs OLM, P = NS and $P < 0.001$; vs AZL, both, $P < 0.001$). These comparisons were also significant in nondippers (daytime: OLM, both, $P < 0.001$; vs AZL, $P = 0.003$ and $P < 0.001$, respectively; vs OLM, both, $P < 0.001$; nighttime: all, $P < 0.001$).

Relationships Between Baseline Blood Pressure and Reduction in Nighttime Blood Pressure

A specific profile of BP reduction was observed with OLM and AZL in the nighttime period (**Figure 3**), and the relationships between baseline BP and reductions in nighttime SBP are shown in **Figure 5**, and the scatterplots were visually analyzed. Although there was a deviation in the distribution of points in the scatterplots between dippers and nondippers on visual inspection, the regression lines were similar. Therefore, dippers and nondippers in each group were treated as a uniform population in the following analyses. The proportions of patients who achieved the target nighttime SBP in the OLM/AZL 10/8-mg and OLM/AZL 20/16-mg groups were numerically greater (48/213 [22.5%] and 64/211 [30.3%] patients, respectively) than those in the monotherapy groups (OLM, 39/206 [18.9%]; AZL, 19/209 [9.1%]). The residual SD values of the regression lines for AZL-containing regimens were similar (11.7, 12.3, and 11.7 with OLM/AZL 10/8 mg, OLM/AZL 20/16 mg, and AZL, respectively) and numerically less than the value of 14.0 seen with OLM. The numbers of patients whose SBP reached 100 mm Hg were between 1 and 4 in each group; SBP did not decrease to <95 mm Hg in any of the patients. In contrast, the numbers of patients who had any increase in BP were 12/213 (5.6%) with OLM/AZL 10/8 mg, 13/211 (6.2%) with OLM/AZL 20/16 mg, 35/206 (17.0%) with OLM, and 36/209 (17.2%) with AZL.

DISCUSSION

As previously reported, combination therapy with OLM/AZL was found to be associated with a statistically significantly greater reduction in office sitting BP and in 24-hour mean ambulatory BP compared with each monotherapy.[18] In the present report, the full data from ABPM were analyzed. Combination therapy with OLM/AZL was associated with an additive and sustained antihypertensive effect during the daytime, nighttime, and early morning. A reduction in PR was observed during those time periods, especially from 6 AM to <11 AM in the groups treated with an AZL-containing regimen.

For the treatment of dippers, the Guidelines for Diagnosis and Treatment of Cardiovascular Disease (1998–1999 Yearly Report of the Research Group), Usage Guidelines for 24-hour Blood Pressure Monitoring Devices[21] mention that antihypertensive agents induce a larger BP reduction in the daytime than in the nighttime. CCBs have been associated with no further

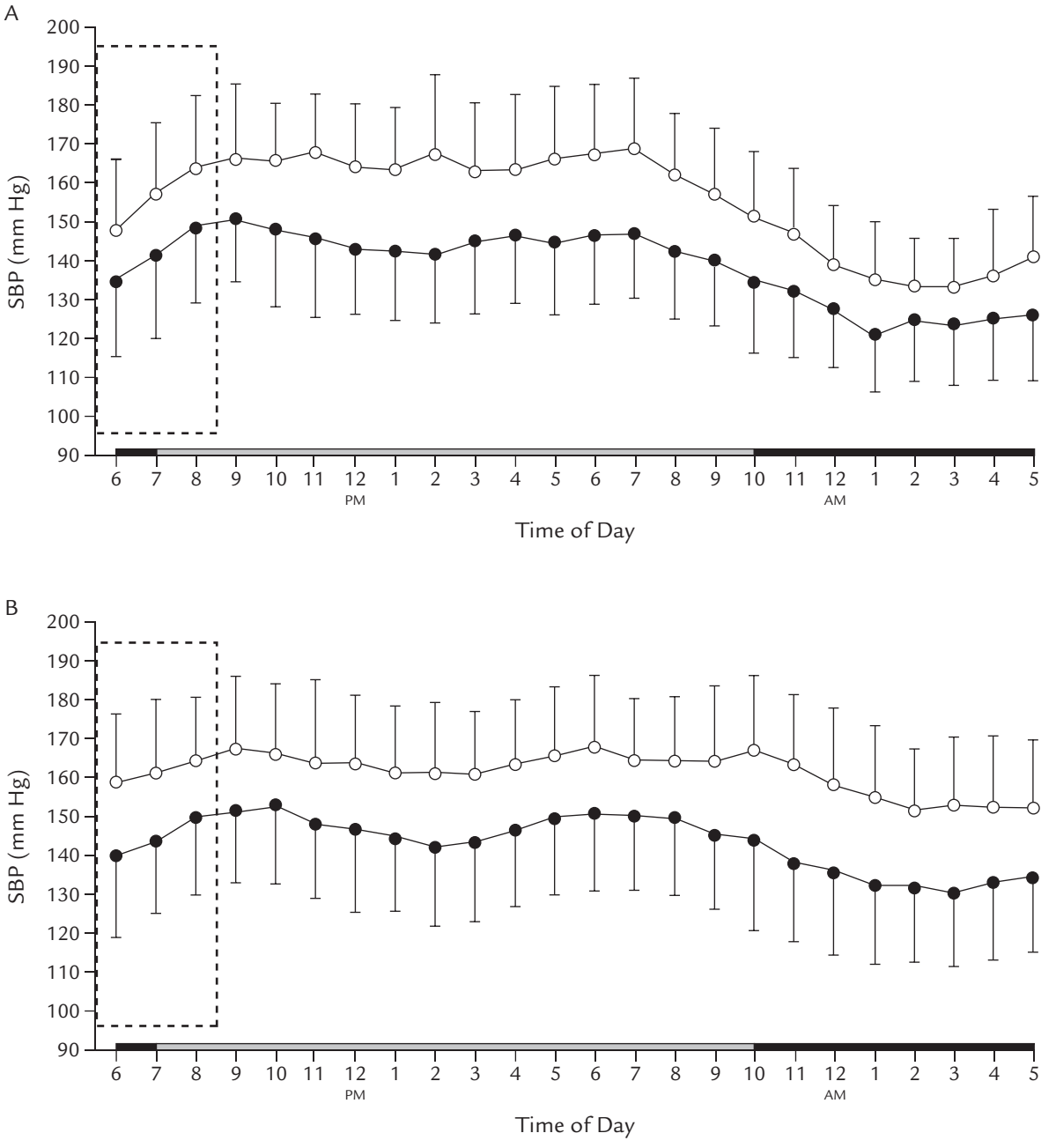

Figure 3. Twenty-four–hour profiles of arithmetic mean (SD) systolic blood pressure (SBP) in dippers ([Daytime BP – Nighttime BP]/Daytime BP ≥10%) (A; n = 80 dippers/213 total) or nondippers ([Daytime BP – Nighttime BP]/Daytime BP <10%) (B; n = 133 nondippers/213 total) before (open symbols) and after (solid symbols) 12-week treatment with combination olmesartan medoxomil/azelnidipine (OLM/AZL) 10/8 mg for essential hypertension in Japanese patients. The grey and black areas of the horizontal scales represent daytime (7 AM–<10 PM) and nighttime (10 PM–<7 AM), respectively. The early-morning period (6 AM–<9 AM) is indicated by the dashed lines.

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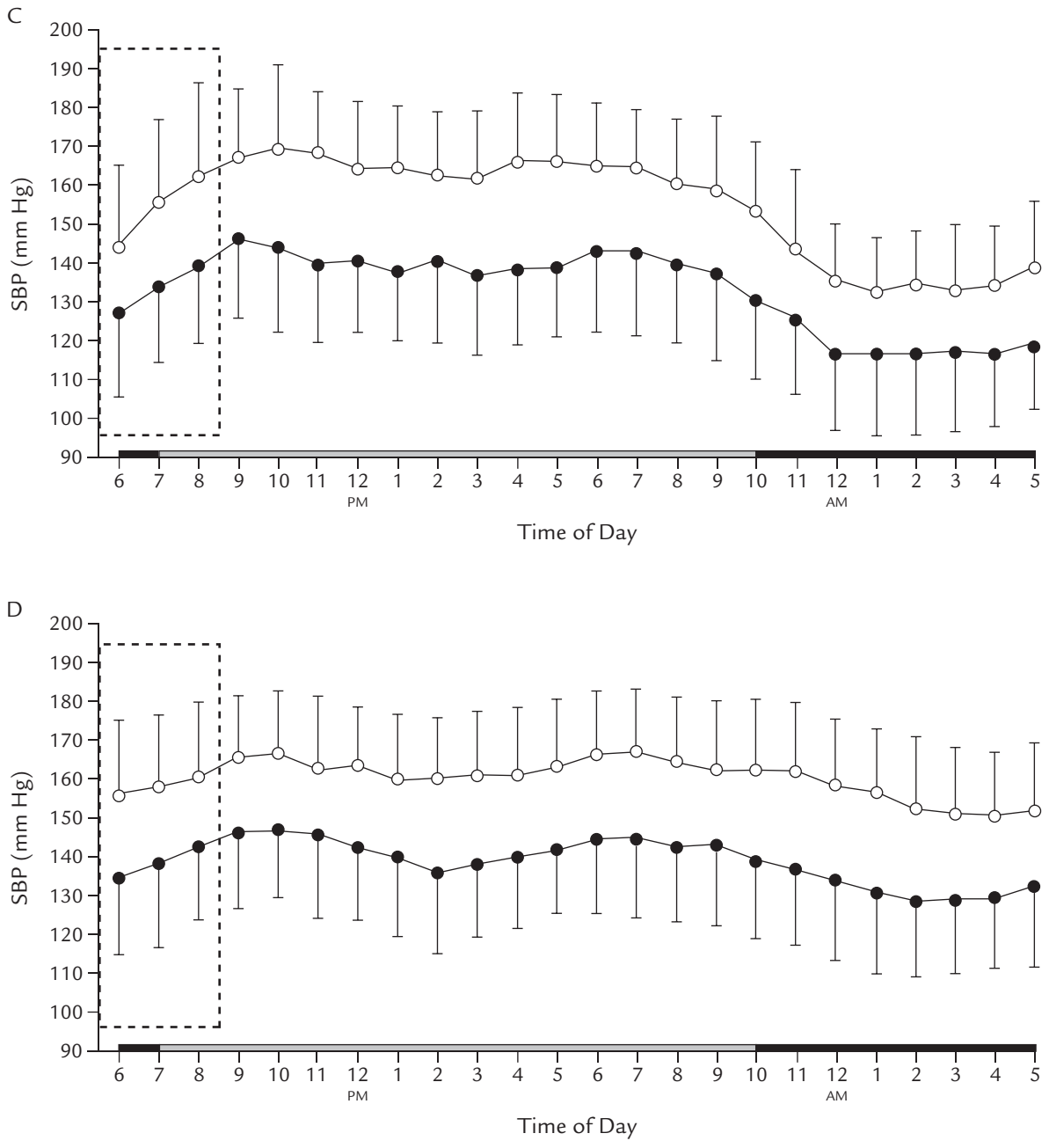

Figure 3 (continued). Twenty-four–hour profiles of arithmetic mean (SD) SBP in dippers (C; n = 77 dippers/211 total) or nondippers (D; n = 134 nondippers/211 total) before (open symbols) and after (solid symbols) 12-week treatment with combination OLM/AZL 20/16 mg for essential hypertension in Japanese patients. The grey and black areas of the horizontal scales represent daytime (7 AM–<10 PM) and nighttime (10 PM–<7 AM), respectively. The early-morning period (6 AM–<9 AM) is indicated by the dashed lines.

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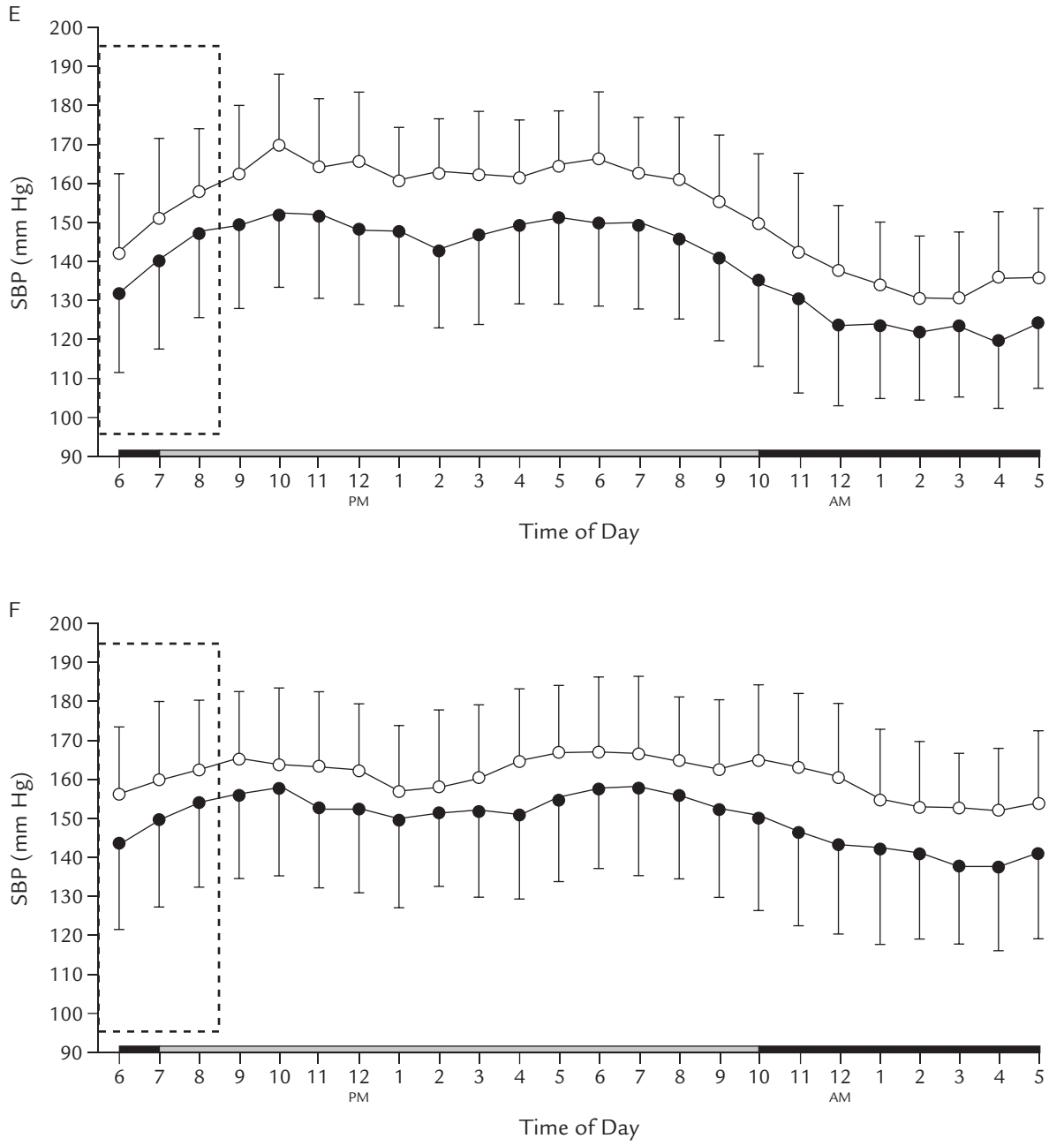

Figure 3 (continued). Twenty-four–hour profiles of arithmetic mean (SD) SBP in dippers (E; n = 83 dippers/206 total) or nondippers (F; n = 123 nondippers/206 total) before (open symbols) and after (solid symbols) 12-week treatment with monotherapy with OLM 20 mg for essential hypertension in Japanese patients. The grey and black areas of the horizontal scales represent daytime (7 AM–<10 PM) and nighttime (10 PM–<7 AM), respectively. The early-morning period (6 AM–<9 AM) is indicated by the dashed lines.

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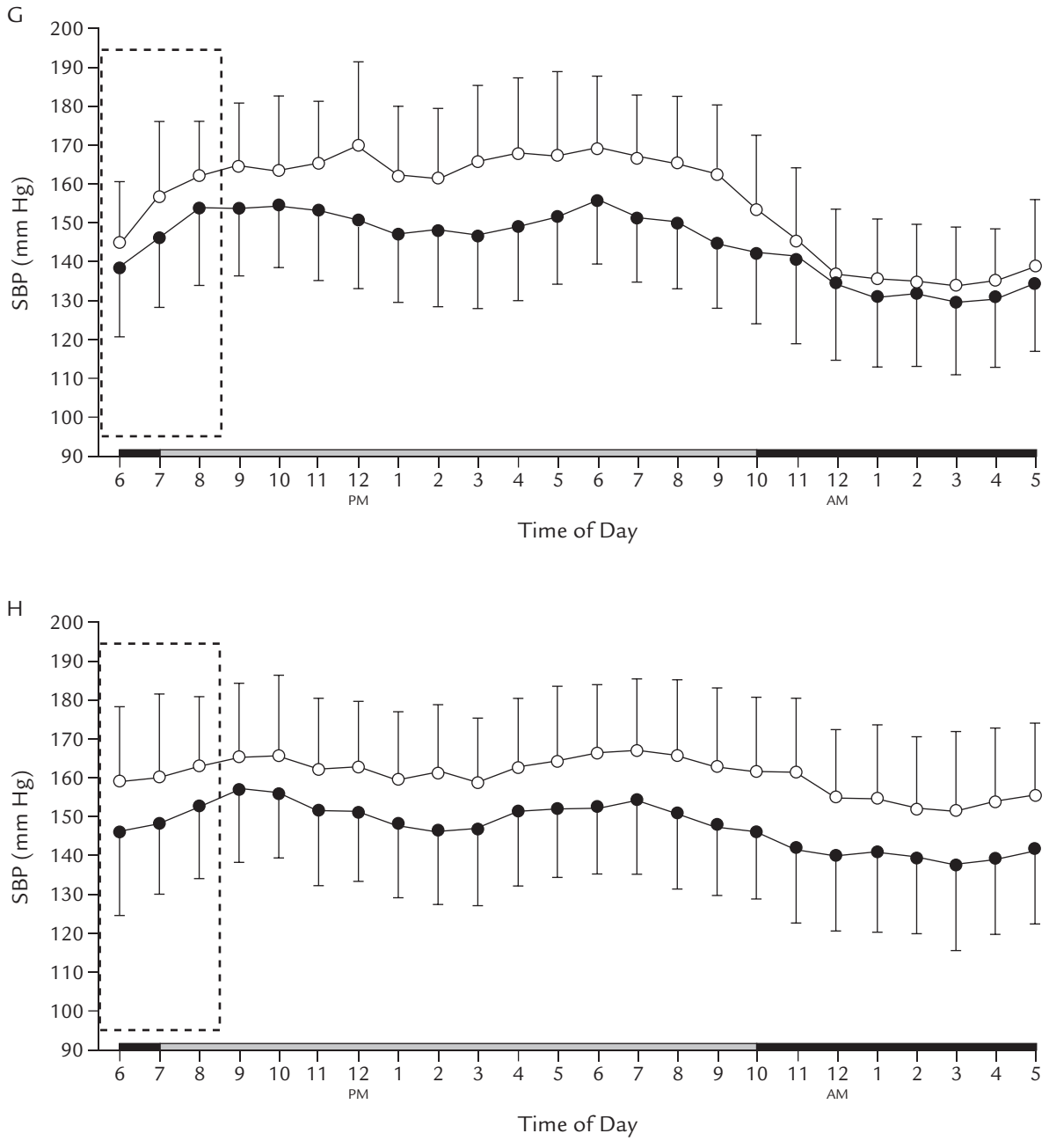

Figure 3 (continued). Twenty-four–hour profiles of arithmetic mean (SD) SBP in dippers (G; n = 91 dippers/209 total) or nondippers (H; n = 118 nondippers/209 total) before (open symbols) and after (solid symbols) 12-week treatment with monotherapy with AZL 16 mg for essential hypertension in Japanese patients. The grey and black areas of the horizontal scales represent daytime (7 AM–<10 PM) and nighttime (10 PM–<7 AM), respectively. The early-morning period (6 AM–<9 AM) is indicated by the dashed lines.

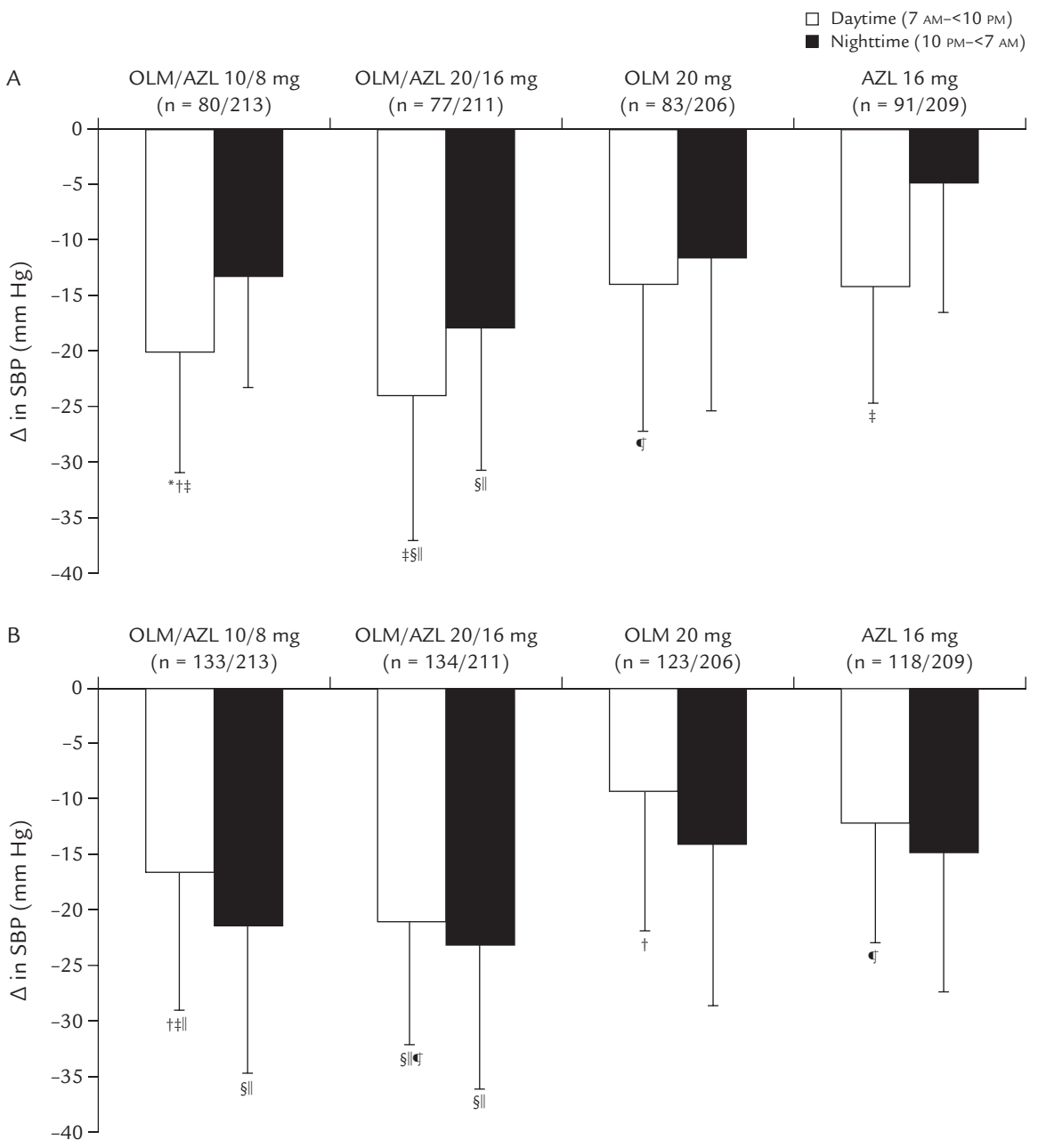

Figure 4. Arithmetic mean (SD) changes from baseline in daytime and nighttime systolic blood pressure (SBP) in (A) dippers ([Daytime BP – Nighttime BP]/Daytime BP ≥10%) or (B) nondippers ([Daytime BP – Nighttime BP]/Daytime BP <10%) after 12 weeks of treatment with combination olmesartan medoxomil/azelnidipine (OLM/AZL) 10/8 mg or 20/16 mg versus monotherapy with either agent for essential hypertension in Japanese patients. *$P < 0.01$ versus OLM; †$P < 0.01$ versus AZL; ‡$P < 0.001$ versus nighttime; §$P < 0.001$ versus AZL; ‖$P < 0.001$ versus OLM; ¶$P < 0.05$ versus nighttime (one-way ANOVA or paired *t* test).

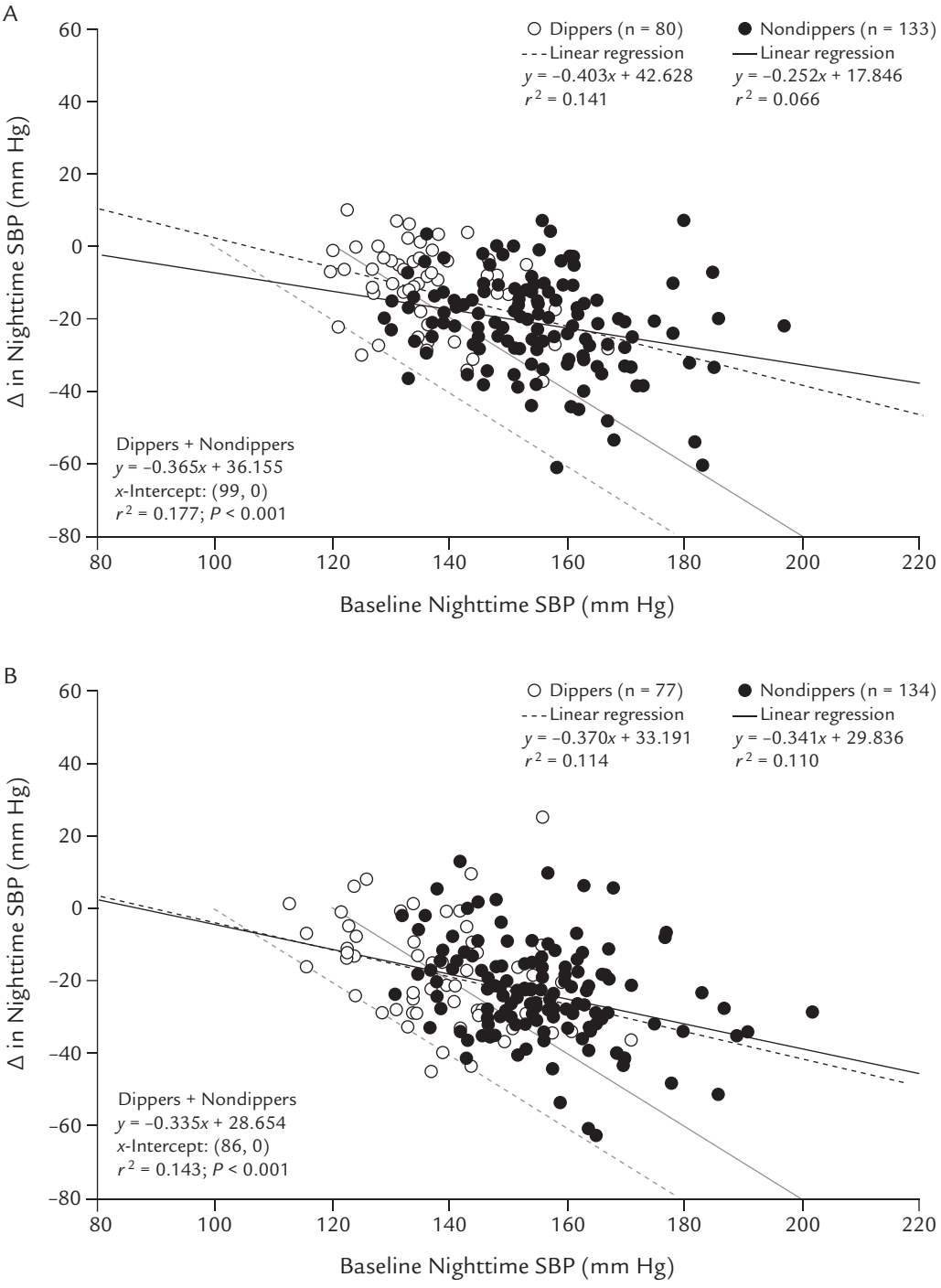

Figure 5. Relationships between arithmetic mean baseline nighttime systolic blood pressure (SBP) and changes from baseline in SBP with 12 weeks of treatment with combination olmesartan medoxomil/azelnidipine (OLM/AZL) 10/8 mg (A; n = 213) or 20/16 mg (B; n = 211) for essential hypertension in Japanese patients. The grey solid lines indicate SBP goals. The grey dashed lines indicate the BP change required to reach 100 mm Hg for reference.

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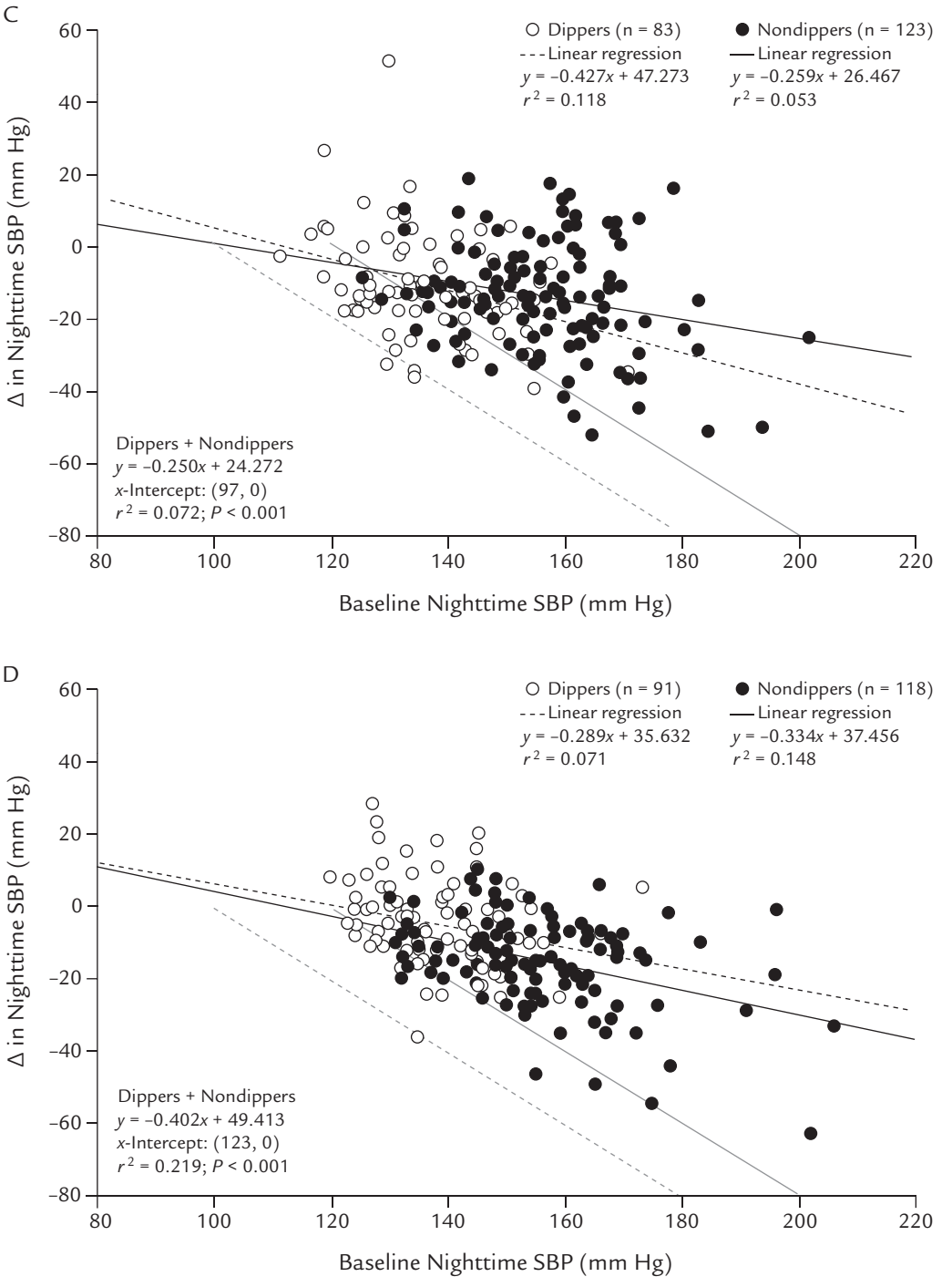

Figure 5 (continued). Relationships between arithmetic mean baseline nighttime SBP and changes from baseline in SBP with 12 weeks of treatment with monotherapy with OLM 20 mg (C; n = 206) or AZL 16 mg (D; n = 209) for essential hypertension in Japanese patients. The grey solid lines indicate SBP goals. The grey dashed lines indicate the BP change required to reach 100 mm Hg for reference.

antihypertensive effects when nighttime BP reaches almost normal levels in dippers or extreme dippers (patients with a nighttime reduction in SBP of ≥20%).[22–25] OLM, with a half-life of 12 to 18 hours,[26] was associated with a sustained antihypertensive effect, as previously reported.[27,28] This effect has been explained to be due to OLM's inverse-agonist activity and insurmountable binding to the angiotensin II type 1 receptor via the double-chain domain.[29–31] The OLM/AZL combination was associated with a further sustained antihypertensive effect throughout the daytime and the subsequent nighttime by adding a sustained nighttime BP reduction with OLM to the BP reduction from AZL. The OLM/AZL combination was associated with apparent control of nighttime BP in these dippers.

In nondippers, conversely, the extent of nighttime BP reduction by antihypertensive therapy has been reported to be greater than that in dippers and similar to the effect on daytime BP.[21,32] Among the nondippers in any group in the present study, a significantly larger BP reduction was observed in the nighttime than in the daytime. In addition, compared with each monotherapy, the OLM/AZL combination was associated with significantly greater antihypertensive effects during the daytime and nighttime and a sustained antihypertensive effect over a period of 24 hours. This combination treatment has been associated with apparent control of absolute BP values during the daytime and nighttime, with modest diurnal BP variation in these nondippers. These findings suggest that the OLM/AZL combination may be effective in reducing BP without disrupting the diurnal BP variation, regardless of whether patients are dippers or nondippers.

Concerning the relationship between baseline BP and BP reduction, CCBs have baseline-dependent effects; that is, the higher the baseline BP, the greater the BP reduction, but ARBs do not appear to show this relationship.[23–25,33] The present study found a steeper slope of the regression line with AZL treatment compared with all 3 other treatments. AZL was associated with a baseline-dependent antihypertensive effect as with other CCBs.[23–25] Conversely, regression lines with OLM had a more gradual slope than with AZL, suggesting a baseline-independent BP reduction. Compared with the monotherapies, the distributions and regression lines shifted vertically downward, and more patients achieved the BP goal with combination therapy on visual inspection in the scatterplots. From another perspective, a narrower variation in BP reduction (ie, numerically smaller residual SD) was found with combination therapy than with AZL and coincided with a significantly greater BP reduction than with either monotherapy ($P < 0.001$). Combination treatment was associated with an acceptable BP reduction, that is, neither too much nor too little, although the analysis was considered to have been influenced by regression to the mean.

Heart rate has been reported to be a CV risk factor,[34] and increased heart rate has been associated with CV-related morbidity and mortality as well as all-cause mortality.[35] Although amlodipine, the other dihydropyridine CCB, has been associated with significantly increased PR in patients with essential hypertension in the clinical trials using ABPM,[25,36] AZL has not.[25] This phenomenon with AZL has been explained as being due to the potent direct negative chronotropic action and gradual hypotensive effect.[37,38] Analysis of the 24-hour profiles of PR found a statistically significant decrease during the morning (6 AM–<11 AM) in the AZL or OLM/AZL group, although PR increases were observed in 34.0% to 48.5% of patients. In this morning period, BP reductions were significant with all 4 treatments. This morning PR reduction with AZL-containing regimens was probably due to the preservation of an inhibitory effect of AZL on sympathetic nerve activity in the morning.[25,33] The J-CORE study reported that central SBP and aortic pulse wave velocity were significantly decreased with OLM/AZL compared with OLM + hydrochlorothiazide, and that the effect of AZL on arterial stiffness might be explained partly as being due to sympathetic inhibition.[19] Further studies are needed to assess whether this PR reduction with AZL-containing regimens translates to a clinically meaningful reduction in the risk for CV events.

Study Limitations

Although ABPM was conducted once at each time point of assessment in this study, ≥2 measurements are considered necessary for an exact diagnosis of elevated nighttime BP.[39] The lack of repeated measurements was a major limitation of this study. This study did not assess weekly, monthly, or yearly periodicity of 24-hour BP. The time window for intake of the study drug was set from after breakfast until noon, and sleeping and awakening times were not specified. This study was not designed to measure BP reductions or PR changes with placebo adjustment.

CONCLUSION

In this study in these Japanese patients with essential hypertension, combination treatment with OLM/AZL

was associated with significantly greater reductions in daytime, nighttime, and early-morning BP, as assessed using 24-hour ABPM, compared with either monotherapy, regardless of dipping pattern at baseline.

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The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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