Ambulatory blood pressure monitoring predicts cardiovascular events in treated hypertensive patients – an Anglo-Scandinavian cardiac outcomes trial substudy

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Background **Results of the Anglo-Scandinavian cardiac outcomes trial-blood pressure lowering arm (ASCOT-BPLA) showed significantly lower rates of coronary and stroke events in individuals allocated an amlodipine–perindopril combination drug regimen than in those allocated an atenolol–thiazide combination drug regimen. The aims of the ambulatory blood pressure (ABP) substudy of ASCOT were to examine the impact of the two blood pressure (BP)-lowering regimens on ambulatory pressures, test to what extent the between-treatment differences in cardiovascular outcome could be attributed to differences in ABP and assess whether ABP provides predictive information additional to that of clinic blood pressure (CBP) in treated hypertensive patients.**

Methods and results **One thousand, nine hundred and five patients from four ASCOT centres had repeated ABPs performed over a median follow-up period of 5.5 years. As in the whole ASCOT population, CBP values were lower in amlodipine–perindopril-treated patients compared with those treated with atenolol–thiazide [between-regimen difference {95% confidence intervals (CIs)}]: [−1.5 (−2.4 to −0.5)/−1.2 (−1.8 to +0.5) mmHg]. Daytime BP during follow-up was higher in patients treated with amlodipine–perindopril therapy [+1.1 (0.1–2.1)/+1.6 (0.8–2.3) mmHg]; night-time systolic, but not diastolic BP, was lower in patients treated with amlodipine–perindopril therapy [−2.2 (−3.4 to +0.9)/+0.8 (0.0–1.6) mmHg]. The relative risk of a cardiovascular event associated with a 1 SD increment in accumulated mean BP was 1.35 (1.18–1.53) for clinic systolic BP, 1.30 (1.14–1.49) for daytime systolic BP and 1.42 (1.24–1.62) for night-time systolic BP. With adjustment for baseline variables, treatment regimen and clinic systolic BP, the hazard ratios were 1.17 (1.00–1.36) and 1.25 (1.08–1.47) for daytime and night-time systolic BP, respectively. The between-regimen adjusted hazard ratio for cardiovascular events (amlodipine–perindopril therapy versus atenolol–thiazide therapy) was 0.74 (0.55–1.01) and increased to 0.81 (0.60–1.10) after further adjustment for clinic systolic BP. Further, adjustment for night-time systolic BP increased the hazard ratio to 0.85 (0.62–1.16).**

Conclusion **The amlodipine–perindopril and atenolol–thiazide regimens had different effects on daytime and night-time ABP, which may have contributed to the lower rates of events in patients treated with amlodipine–perindopril therapy. Both CBP and ABP were significantly associated with rates of cardiovascular events. ABP nocturnal pressures provided complimentary and incremental utility over CBP in the prediction of cardiovascular risk in treated hypertensive patients. These data support the use of ABP to assess the effect of antihypertensive treatment in clinical practice. *J Hypertens* 27:876–885 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Keywords: ambulatory blood pressure measurement, Anglo-Scandinavian cardiac outcomes trial, cardiovascular risk, clinic blood pressure measurement, hypertension, mortality

Abbreviations: ABP, ambulatory blood pressure; ASCOT BPLA, Anglo-Scandinavian Cardiac Outcomes Trial – Blood Pressure Lowering Arm; ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; CBP, clinic blood pressure; DBP, diastolic blood pressure; HR, hazard ratio; SBP, systolic blood pressure

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Introduction

In Anglo-Scandinavian cardiac outcomes trial blood pressure-lowering arm (ASCOT-BPLA), an antihypertensive treatment regimen of amlodipine, adding perindopril as required to reach blood pressure (BP) targets (amlodipine–perindopril regimen), was associated with beneficial effects on almost all cardiovascular outcomes compared with a regimen of atenolol adding bendroflumethiazide

* A full list of ASCOT investigators may be found in Reference [1].

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and potassium chloride as required (atenolol–thiazide regimen) [1]. Multivariate adjustment for postrandomization differences in cardiovascular risk factors only explained about half of the between-treatment differences in event rates – the better lowering of clinic BP achieved by the amlodipine–perindopril regimen was the biggest single contributor to protection from stroke events, whereas differences in high-density lipoprotein (HDL) cholesterol were more important for coronary events [2].

Cross-sectional and prospective cohort studies have shown that ambulatory blood pressures (ABPs) have associations with hypertensive target organ damage stronger than clinic blood pressure (CBP), and baseline ABP is a superior predictor of cardiovascular outcome [3]. The ABP substudy of the Heart Outcomes Prevention Evaluation study showed that although CBP differences were insignificant on treatment, differences in ABP were of sufficient magnitude to account for the greater event-free survival of patients randomized to ramipril rather than to placebo [4].

The objectives of the ABP substudy of ASCOT were to examine the impact of the two BP-lowering regimens on ABP, test to what extent the benefits of the amlodipine–perindopril-based regimen might relate to differences in achieved ABP, and finally to evaluate whether repeated ABP could provide additional predictive information over repeated CBP in treated hypertensive patients.

Methods

Participants

The results of the ASCOT-BPLA study have been published [1]. Briefly, patients with hypertension who were aged 40–79 years and had at least three other cardiovascular risk factors, but no previous history of coronary heart disease, were randomized using a prospective, randomized, open, blinded end-point design to receive one of the two antihypertensive regimens. These two treatment regimens involved either amlodipine with perindopril as required or atenolol with bendroflumethiazide and potassium as required to achieve a clinic BP target of 140/90 mmHg or less for patients without diabetes and 130/80 mmHg or less for patients with diabetes. Other stipulated BP-lowering drugs were added to each regimen for further BP control. ASCOT participants at four trial centres in the United Kingdom and Ireland were eligible for recruitment into the ABP substudy [5]. The study protocol was approved by relevant institutional review boards and the appropriate local research ethics committees. All patients gave written informed consent.

Blood pressure measurements

CBP was performed at 6-monthly intervals throughout the trial, using a validated, semi-automated oscillometric device (Omron HEM-705CP; OMRON Healthcare, Inc., Bannockburn, Illinois, USA) [6]. Patients were seated and rested for 5 min in a quiet room, after which time BP was measured oscillometrically three times at 5-min intervals. The mean of the last two measurements was recorded as the CBP. ABP measurements were performed annually from the time of recruitment (in some patients this was at randomization – in most patients, the first ABP was measured as closely to the time of recruitment as possible). ABP was measured every half-an-hour throughout the 24-h period according to the European Society of Hypertension guidelines [7] using validated SpaceLabs 90207 monitors (SpaceLabs Inc.; Wokingham, Berkshire, UK) [8]. No editing criteria were applied to individual readings. Mean time-weighted daytime (0900–2100 h), night-time (0100–0600 h) and 24-h systolic, diastolic and pulse pressures and also heart rates were calculated from each ABP [8].

Outcome events

Three posthoc-defined composite endpoints were used in the analyses: total cardiovascular events and revascularization procedures, total coronary events (fatal coronary heart disease and nonfatal myocardial infarction) and coronary revascularization procedures and fatal and nonfatal stroke [2]. Total cardiovascular events and revascularization procedures were selected as the primary endpoint, as this composite occurred at significantly different rates in the two treatment groups and involved sufficient events to allow meaningful analyses.

Statistical analysis

Statistical analyses were performed using SAS software, version 9.2 (SAS Institute Inc.; Cary, North Carolina, USA). Only CBP and ABP performed at least 6 months after randomization and prior to any of the above-defined study endpoints or to the date of censoring were included in the analyses. Data were analysed according to treatment randomization without regard to compliance with study medication (intention-to-treat analysis). Between BP-lowering regimen differences in accumulated mean levels of CBP and ABP (time-weighted means) were compared by summarizing the BP load as the mean area under the curve to allow comparison of the two treatment effects. The association between each CBP and ABP variable and outcome event was tested using updated Cox proportional hazards regression models that allowed assessment of the association between accumulated mean levels of variables and subsequent events. In further models, adjustments were made for the following baseline variables: sex, age, BMI, presence of diabetes mellitus, total serum cholesterol, smoking status and treatment group. To allow a degree of comparability among the variables tested, the hazard ratios associated with 1 SD of each variable and calculated pseudo-r^2 values for each Cox model were assessed [9].

The extent to which ABP has incremental predictive utility over established cardiovascular risk factors

(including CBP) in the prediction of cardiovascular outcome was addressed by adjusting for all baseline variables, treatment regimen and CBP in multivariable Cox proportional hazards regression models.

In order to evaluate whether any between-treatment differences in cardiovascular outcome were attributable to differences in BP, updated Cox regression models were used to assess the effects of adjustment for differences in the accumulated mean levels of BP on the differential event rates of the two treatment groups. Only CBP and ABP variables that differed significantly between treatment groups after randomization and were significantly associated with outcome were tested in these models. Kaplan–Meier plots were created for each treatment group and according to BP range.

Results

The baseline clinical characteristics of 1905 patients recruited into the ABP substudy are shown in Table 1, along with the baseline characteristics for the 19 257 patients recruited into ASCOT-BPLA. There were on average 22 daytime readings and 10 night-time measurements for ABP recordings.

As in the whole ASCOT population, the ABP substudy participants were mainly white men with a mean age of 63 years. Most patients recruited into both ASCOT-BPLA and the ABP substudy had previously been treated for hypertension. There were few smokers, and alcohol consumption was slightly higher for patients recruited into the substudy. CBP at baseline was slightly lower than that of the total ASCOT-BPLA population. These small differences reflect differing regional demographics between patients recruited from the United Kingdom and Ireland for the ABP substudy and those recruited from the United Kingdom, Ireland and the Nordic countries for the main ASCOT-BPLA study. Importantly, as in the total ASCOT-BPLA population, the ABP substudy participants in the two treatment arms were well matched.

During the follow-up period (median 5.5 years), ABP substudy participants had on average 10 CBPs and 3.5 ABPs. The BP values of the two treatment groups for both CBP and ABP systolic and diastolic BP are illustrated in Fig. 1. Similar to the total ASCOT-BPLA population, CBP was slightly lower in the ABP substudy patients treated with amlodipine–perindopril therapy compared with those treated with atenolol–thiazide therapy [between-regimen difference (95% CIs); −1.4 (−2.4 to −0.53)/−1.1 (−1.8 to −0.5 mmHg)]. By contrast, daytime BP during follow-up was higher in patients on amlodipine–perindopril treatment [1.1 (0.1–2.1)/1.6 (0.8–2.3) mmHg], whereas night-time systolic, but not diastolic, BP was lower in patients in the amlodipine–perindopril arm [−2.2 (−3.4 to −0.9)/0.8 (0.0–1.6) mmHg] (Fig. 1).

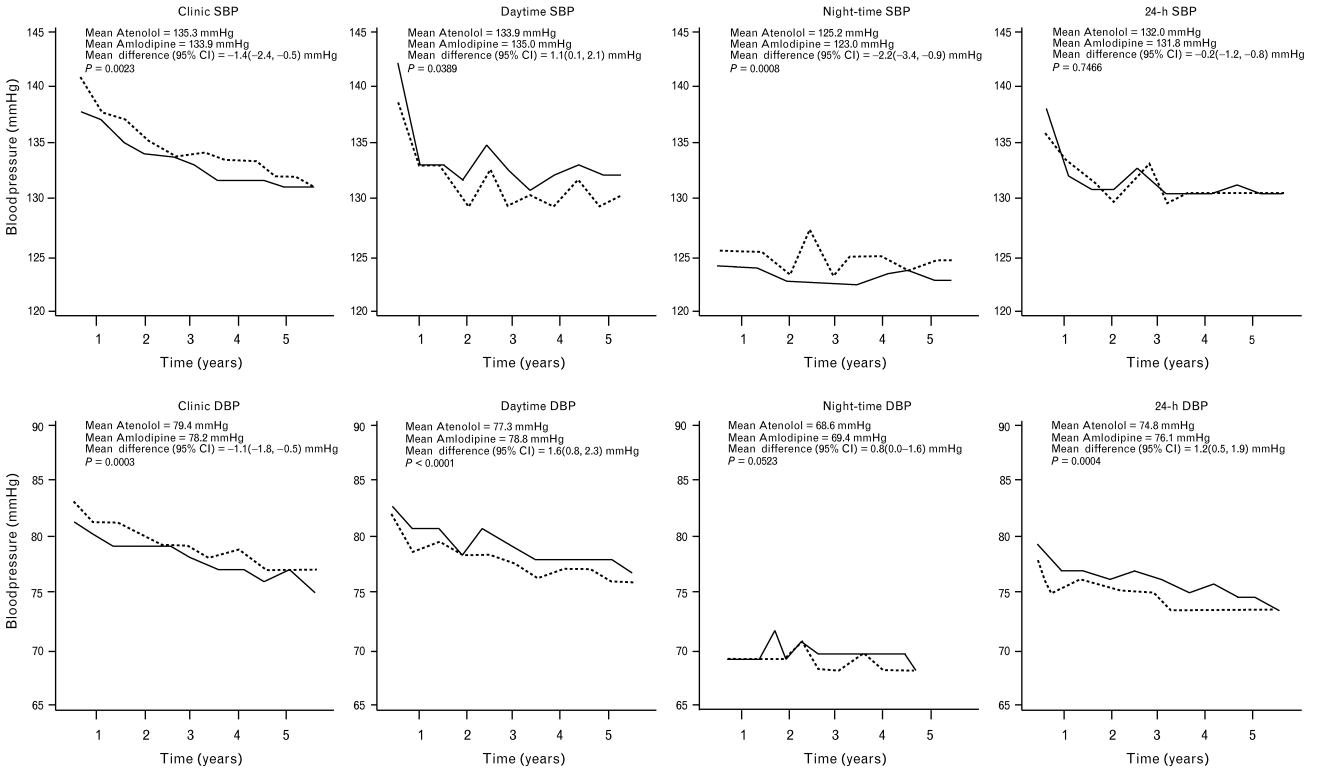
In total, 239 cardiovascular events and procedures, including 34 deaths, occurred in the 1905 participants. Of these, 143 were coronary events, and 46 were strokes. As Fig. 2 illustrates, both CBP and ABP were significantly associated with rates of cardiovascular outcome – the relative risk of a cardiovascular, coronary or stroke event, associated with a 1 SD increment in accumulated mean

Table 1 Demographic and clinical characteristics of participants in the Anglo-Scandinavian Cardiac Outcomes Trial ambulatory blood pressure substudy and the whole Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm population

	ASCOT ABP substudy		ASCOT-BPLA population	
	Atenolol	Amlodipine	Atenolol	Amlodipine
n	966	939	9639	9618
Male (%)	77.8	77.4	76.5	76.6
Age (years)	62.6 (8.3)	62.6 (8.4)	63.0 (8.5)	63.0 (8.5)
Current smoker (%)	23.4	23.0	32.3	32.9
Alcohol (units/week)	11	11	8	7.9
BMI (kg/m^2)	29.0 (4.4)	29.2 (4.6)	28.7 (4.5)	28.7 (4.6)
Weight (kg)	83.5 (15.0)	83.7 (15.6)	84.6 (15.1)	84.6 (15.7)
Total cholesterol (mmol/l)	5.9 (1.1)	5.9 (1.1)	5.9 (1.1)	5.9 (1.1)
LDL cholesterol (mmol/l)	3.7 (0.9)	3.7 (0.9)	3.8 (1.0)	3.8 (1.0)
HDL cholesterol (mmol/l)	1.3 (0.4)	1.3 (0.4)	1.3 (0.4)	1.3 (0.4)
Triglycerides (mmol/l)	1.8 (0.1)	1.8 (0.1)	1.8 (0.1)	1.9 (0.1)
Creatinine (μmol/l)	99.4 (16.3)	98.2 (16.8)	98.7 (16.6)	98.7 (17.0)
Glucose (mmol/l)	6.2 (2.3)	6.2 (2.3)	6.2 (2.1)	6.2 (2.1)
Clinic SBP (mmHg)	158.6 (16.6)	159.0 (18.4)	163.9 (18.0)	164.1 (18.1)
Clinic DBP (mmHg)	92.0 (9.6)	92.2 (9.8)	94.5 (10.4)	94.8 (10.4)
Clinic HR (bpm)	71.8 (12.3)	72.2 (12.4)	71.8 (12.6)	71.9 (12.7)
History of stroke/TIA (%)	9.2	9.9	11.1	10.9
Diabetes (%)	24.2	23.4	26.8	26.6
LVH (%)	20.4	19.9	21.6	21.7
Other ECG abnormalities (%)	17.6	18.4	23.4	22.9
Peripheral vascular disease (%)	5.9	5.8	6.4	6.1

ASCOT ABP, Anglo-Scandinavian Cardiac Outcomes Trial ambulatory blood pressure; ASCOT-BPLA, Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm; BMI, body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; HR, heart rate; LDL, low-density lipoprotein; LVH, left ventricular hypertrophy; SBP, systolic blood pressure.

Fig. 1



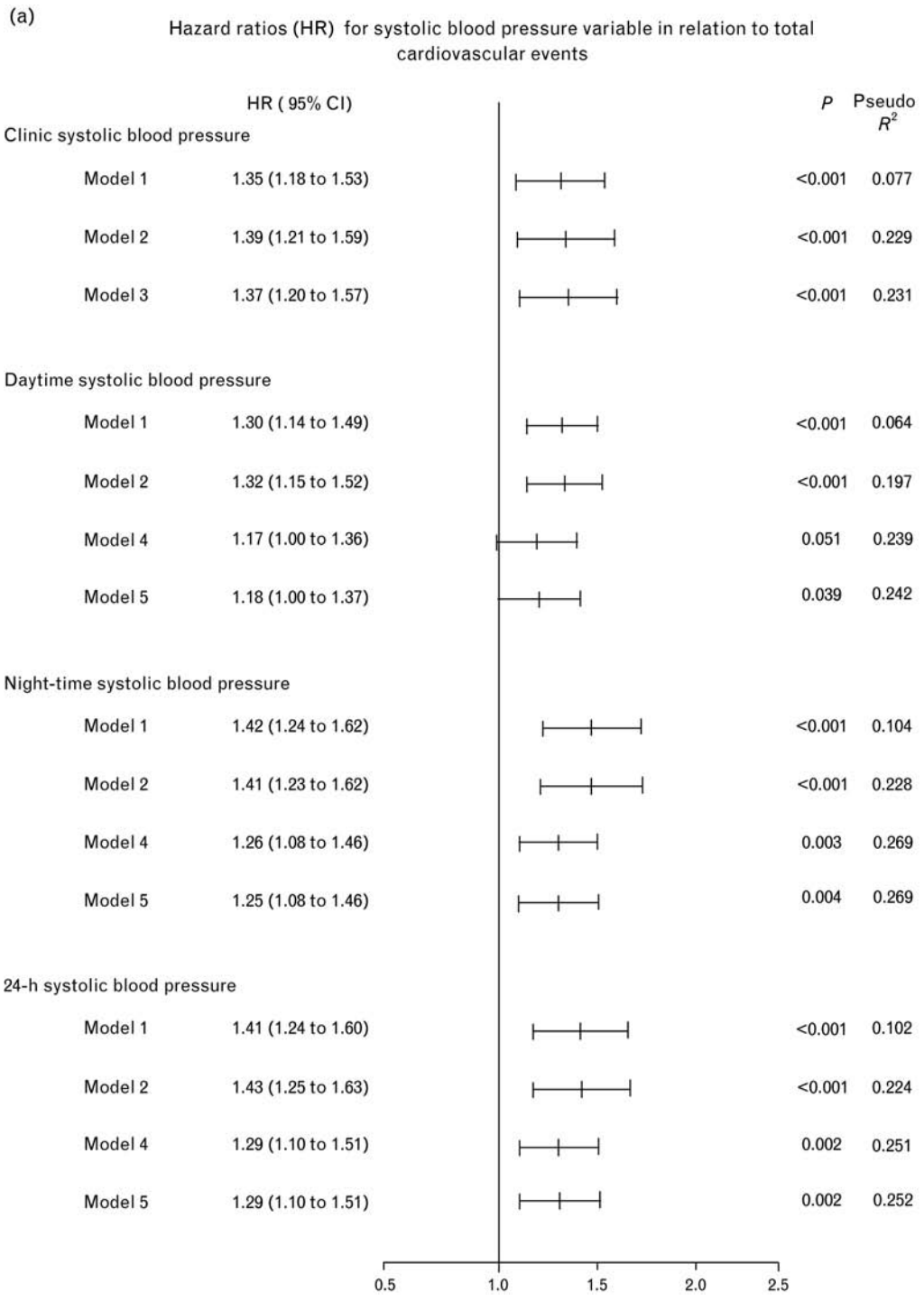
Blood pressure differences between treatment groups. Mean clinic and ambulatory (daytime, night-time and mean 24-h), systolic and diastolic BP, for patients randomized to receive atenolol–thiazide (hashed line) or amlodipine–perindopril therapy (solid line). Mean pressures, mean between-treatment regimen differences (95% CIs) and *P* values for between differences are provided. Time represents the duration from randomization. BP, blood pressure; CIs, confidence intervals; DBP, diastolic blood pressure; SBP, systolic blood pressure.

systolic BP was 1.35 (1.18–1.53), 1.41 (1.19–1.66) and 1.14 (0.84–1.55), respectively, for clinic systolic BP (1 SD = 10 mmHg); 1.30 (1.14–1.49), 1.267 (1.06–1.51) and 1.36 (1.03–1.81) for daytime systolic BP (1 SD = 11 mmHg); 1.42 (1.24–1.62), 1.33 (1.11–1.59) and 1.57 (1.19–2.08) for night-time systolic BP (1 SD = 14 mmHg); and 1.41 (1.24–1.60), 1.34 (1.13–1.59) and 1.534 (1.19–1.99) for 24-h systolic BP (1 SD = 11 mmHg). Sequential adjustment for baseline cardiovascular risk factors, and for BP-lowering treatment regimen, did not materially alter these associations (Fig. 2, models 2 and 3). Further, adjustment for CBP reduced the hazard ratios for systolic ABP for coronary outcomes such that these were no longer statistically significant (Fig. 2b, model 4). By contrast, with adjustment for CBP and treatment regimen, the hazard ratios for cardiovascular events and stroke and night-time and 24-h systolic BP remained statistically significant (Fig. 2a and c, models 4 and 5). Similar, although weaker, associations were observed between CBP and diastolic ABP with cardiovascular outcome. The magnitude of hazard ratios and pseudo-r^2 values, associated with the pressure variables and the Cox regression models, respectively, suggests that CBP was more predictive of coronary outcomes, whereas ABP indices, particularly nocturnal BP, were more predictive of stroke outcomes (Fig. 2).

As in the total ASCOT cohort, after adjustment for baseline variables, there were lower rates of total cardiovascular events in patients in the amlodipine–perindopril arm compared with patients in the atenolol–thiazide arm [adjusted hazard ratio (95% CIs); 0.74 (0.55–1.01)]. Further, adjustment for accumulated mean CBP resulted in a rise in the hazard ratio to 0.81 (0.60–1.10). Adjustment for either mean accumulated daytime or night-time systolic ABP resulted in similar rises in the hazard ratio. Inclusion of both clinic and night-time systolic BP in the same multivariate model caused a further increase in the hazard ratio [0.85 (0.62–1.16)].

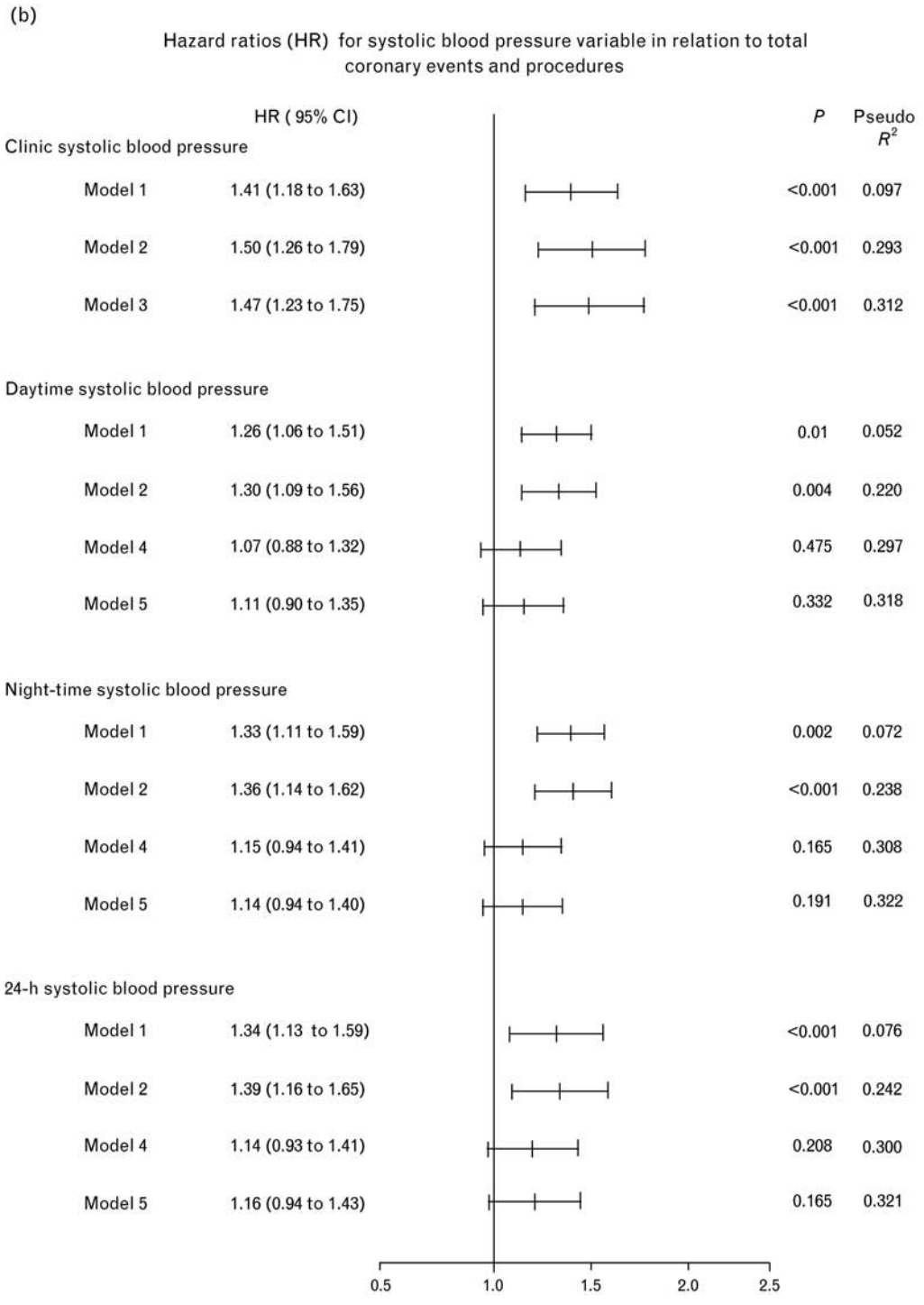
Figure 3 illustrates the effects of treatment regimen, clinic and nocturnal pressures on cardiovascular risk. Following stratification of patients to both treatment arms, on the basis of CBP outcome, is dependent on the level of night-time systolic BP. It is apparent that in patients in both treatment groups with low CBP who appear to be well controlled are at much higher risk if night-time systolic BP is elevated. Also, patients

Fig. 2



Hazard ratios (95% CIs) for total cardiovascular, coronary and stroke events, associated with 1 SD increments in accumulated mean levels of clinic, daytime, night-time and mean 24-h systolic BP. Hazard ratios represent the models as listed below. Model 1 = Unadjusted. Model 2 = Adjusted for baseline covariates (age, sex, history of diabetes, total cholesterol, smoking status and BMI). Model 3 = Adjusted for baseline covariates and treatment group. Model 4 = Adjusted for baseline covariates and systolic CBP. Model 5 = Adjusted for baseline covariates, CBP and treatment group. BMI, body mass index; CBP, clinic blood pressure; CI, confidence interval; HR, hazard ratio; *P*, *P* value; r^2, pseudo *r*-squared value.

Fig. 2. *(Continued).*

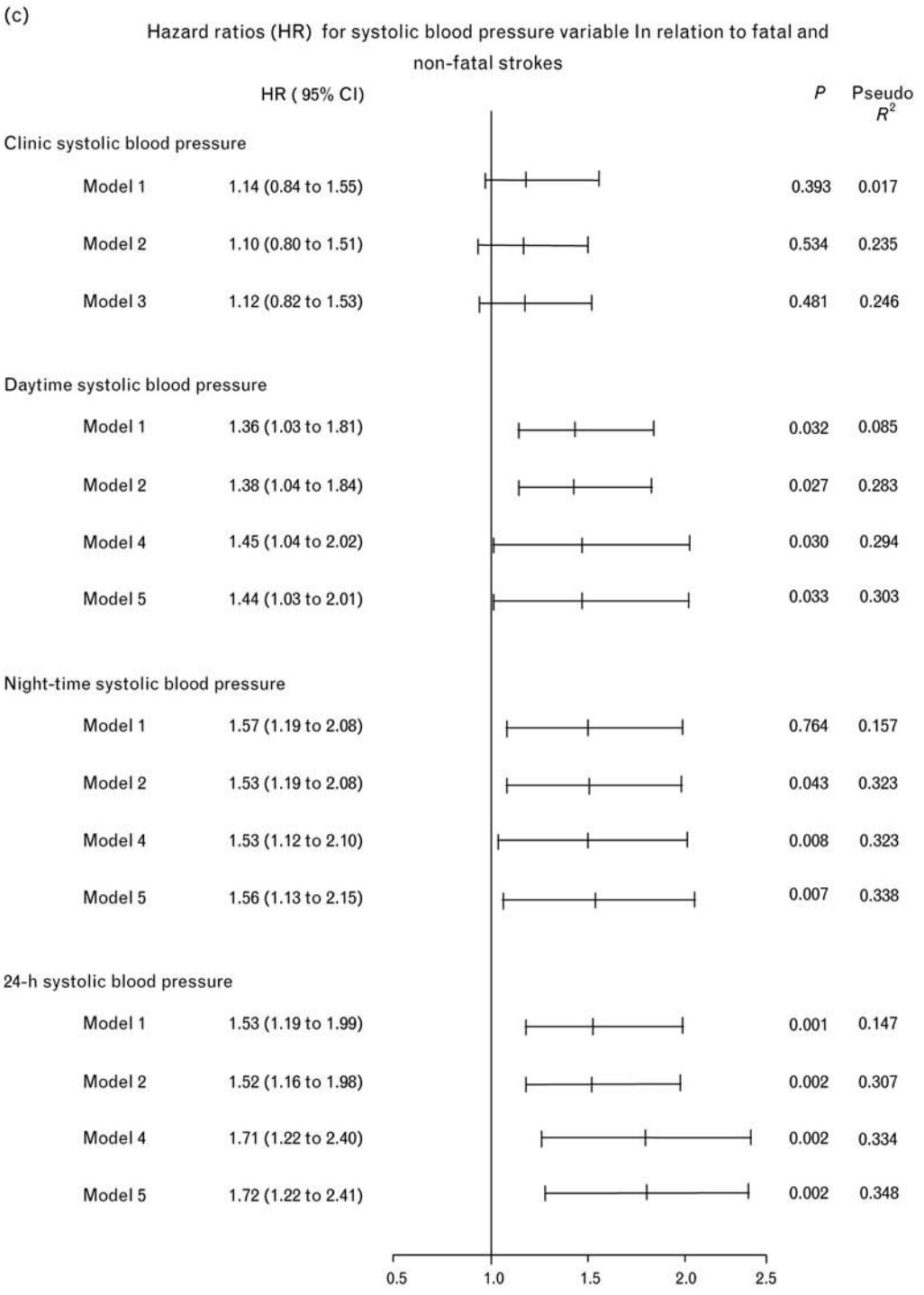


randomized to the atenolol–thiazide regimen, in whom clinic or night-time systolic BP or both, were greater than the median (134 and 122 mmHg, respectively) and more likely to suffer a major cardiovascular event than individuals whose pressures were similar, but who were randomized to the amlodipine–perindopril regimen.

Discussion

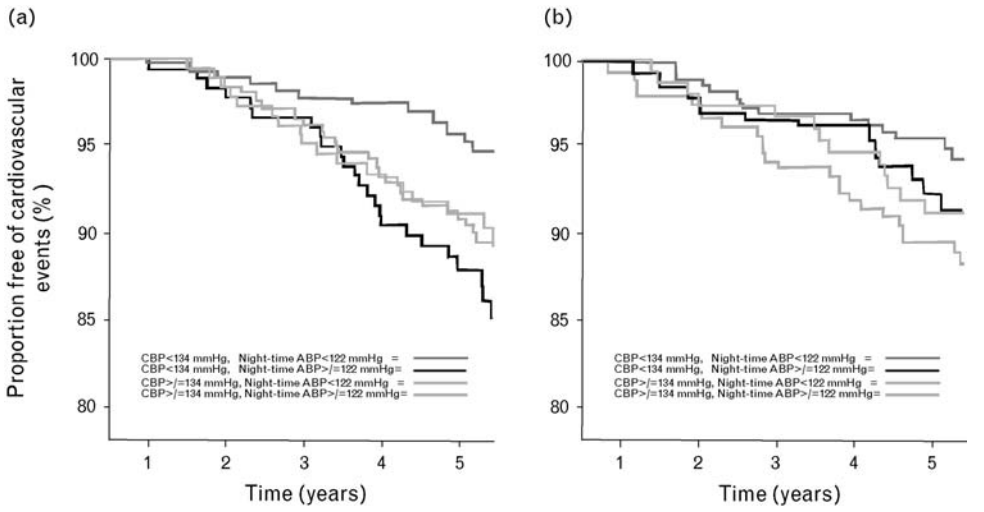
Hypertension remains a major risk factor for cardiovascular events such as stroke and coronary disease. Considerable resources are expended in its management that, irrespective of the method of measurement, remains a considerable challenge to clinicians. This study

Fig. 2. *(Continued).*



demonstrates that in hypertensive patients on treatment, additional prognostic information can be gained from repeated ABP measurements, especially in relation to the prediction of stroke. Examination of the average 24-h BP changes in each treatment group showed that patients in the amlodipine–perindopril arm had a lower night-time systolic BP when compared with those in the atenolol–thiazide arm, but during the day, systolic BP was higher in the former group. This may account for why there was no difference in systolic BP between groups for the 24-h period. Whether the differences in night-time pressures between the two treatment groups contributed

Fig. 3



Survival curves based on clinic and night-time systolic blood pressure. Kaplan–Meier curves of freedom from cardiovascular events amongst participants randomized to atenolol–thiazide therapy (a) and those randomized to amlodipine–perindopril therapy (b). Participants were further subgrouped according to achieved clinic systolic BP (low < median of 134 mmHg, high ≥ median) and achieved nocturnal systolic BP (low < median of 122 mmHg, high ≥ median). ABP, ambulatory blood pressure; BP, blood pressure; CBP, clinic blood pressure.

to the lower rate of coronary and stroke events in those treated with amlodipine-based therapy is important to consider.

In the ASCOT ABP substudy, a 1 SD increase in night-time or 24-h systolic BP increased the possibility of a cardiovascular event after adjustment for systolic CBP by 26 and 29%, respectively. In both these models, there was a sizable increase of the pseudo-r^2 value, indicating a true increase in risk prediction. Several studies have confirmed that ABP is superior to CBP in predicting outcome [10–18]. However, in most of these studies, the ABP data were recorded in initially untreated patients. There is a lack of data on the prognostic value for ABP in patients on treatment in whom both ABP and CBP have been recorded, as is the usual circumstance in clinical practice. In the Office versus Ambulatory study, both systolic and diastolic ABP predicted cardiovascular death in treated hypertensive patients after adjustment for CBP [16]. This finding was based on one ABP measurement taken at study commencement rather than on regular periodic measurements during treatment, as in the ASCOT ABP substudy. Similarly, Verdecchia *et al.* [17] showed that stratification of cardiovascular risk was greater with ABP than CBP in treated patients followed up for a period of 3.7 years.

The superiority of night-time over daytime ABP as a predictor of outcome has been demonstrated in the Dublin Outcome Study. In 5292 hypertensive patients, an elevated nocturnal ABP was a predictor of cardiovascular mortality risk, independent of baseline covariates, CBP and daytime ABP [10]. In this study, a 10 mmHg increase in mean night-time systolic BP was associated with a 21% increase in cardiovascular mortality after adjustment. This finding is confirmed in the ASCOT ABP substudy. Longitudinal studies are needed to determine which ABP profiles are associated with low and elevated cardiovascular risk, and how these profiles might be influenced by antihypertensive therapy to reduce risk.

A number of studies have demonstrated the superiority of ABP over CBP in predicting stroke [15,19–22]. The first prospective study to demonstrate that a diminished nocturnal decline in BP was a risk factor for cardiovascular mortality, independently of the overall BP load during a 24-h period, was the Ohasama study, which showed that, on average, each 5% shortfall in the decline in nocturnal BP was associated with an approximately 20% greater risk of cardiovascular mortality [15]. In the ASCOT ABP substudy, the pseudo-r^2 values indicate that night-time systolic BP is superior to systolic CBP in predicting stroke (unadjusted values: 0.157 versus 0.017, respectively).

As in the main ASCOT study, there was a treatment effect favouring the amlodipine group seen in this study. In comparable analysis to that undertaken in the main study [2], the addition of night-time systolic BP attenuated this treatment effect for total cardiovascular events. This was seen after adjustment for systolic CBP. This suggests that the differences in night-time ABP between the two drug regimens may have contributed to the lower rates of events in those treated with amlodipine–perindopril therapy.

Important prognostic information can be provided by the use of ABP as shown in Fig. 3. Following stratification of patients to both treatment arms, on the basis of CBP, outcome is dependent on the level of night-time systolic BP. It is apparent that in patients of both treatment groups with low CBP who appear to be well controlled are at much higher risk if night-time systolic BP is elevated. This risk is greater in patients in the atenolol–thiazide arm. This finding has important implications for the follow-up and management of high-risk cardiovascular patients. ABP, by providing night-time values, gives important prognostic information over and above CBP in treated hypertensive patients.

When contrasting the ambulatory profiles of both treatment regimens, it is of course necessary to consider their respective pharmacodynamic properties. Atenolol has a much shorter half-life than amlodipine, and thus, would be expected to have less of an effect during the night-time period. Overall, β-blockade has previously been described to have a lesser effect at night [19], whereas in the recent valsartan antihypertensive long-term use evaluation (VALUE) ambulatory substudy, amlodipine was shown to give superior night-time control compared with an angiotensin receptor blocker [20]. There are also data to suggest that amlodipine is effective in reducing the morning rise in BP [21,23]. It is also noteworthy that although having a higher clinic SBP, the atenolol group had a lower daytime mean, suggesting that we are measuring different phenomena and the timing of peak action.

Some limitations of this study must be addressed. The ASCOT ABP substudy had a considerably smaller sample size than that of the main ASCOT-BPLA study – 1905 versus 19 257, respectively. ABPs were not performed in all patients at randomization and were not always performed at annual intervals in all patients, thereby reducing the power of the study to detect ABP differences that might have been contributory to the lower rates of coronary, stroke and cardiovascular events in patients in the amlodipine–perindopril arm. If more frequent ABPs had been recorded, the predictive value of ABP relative to CBP might have been strengthened. In the ASCOT ABP substudy, CBP was measured at 6-monthly intervals according to a strictly standardized protocol using an automated device for the first time in a large, multicentre trial [24]. The frequency of CBP probably resulted in cumulative values close to those yielded by daytime ABP, supporting the importance of considering repeated clinic readings rather than single measurements in evaluating BP control. Repeated clinic readings or home BP monitoring may provide predictive information little different from that provided by daytime ABP [25]. In patients with higher clinic BP, night-time BP is relevant in the amlodipine, but not the atenolol group, which may reflect the fact that mean night-time BP was higher in the atenolol group. However, the findings from this study support the added value of night-time BP readings, which can only be obtained by ABP.

The findings of the ASCOT ABP substudy have clear clinical relevance. Despite the abundance of evidence for the superiority of ABP over clinic BP as a predictor of outcome, current guidelines generally recommend ABP only in selected circumstances. The importance of night-time BP control supports the use of ABP in the follow-up of treated patients. Only ABP allows adjustment of therapy to control night-time BP, which may be crucial in determining outcome.

Acknowledgements

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