

# Statins, antihypertensive treatment, and blood pressure control in clinic and over 24 hours: evidence from PHYLLIS randomised double blind trial

Giuseppe Mancia,<sup>1,2</sup> Gianfranco Parati,<sup>1,3</sup> Miriam Revera,<sup>1,3</sup> Grzegorz Bilo,<sup>1,3</sup> Andrea Giuliano,<sup>3</sup> Fabrizio Veglia,<sup>4</sup> Gaetano Crepaldi,<sup>5</sup> Alberto Zanchetti<sup>6,7</sup>

<sup>1</sup>Department of Clinical Medicine and Prevention, University of Milano-Bicocca, Milan, Italy

<sup>2</sup>Clinica Medica, Ospedale S. Gerardo, 20052 Monza, Italy

<sup>3</sup>Department of Cardiology, Istituto Auxologico Italiano, IRCCS, 20149 Milan

<sup>4</sup>Biostatistics Unit, Centro Cardiologico Monzino, IRCCS, 20138 Milan

<sup>5</sup>Clinica Medica I, University of Padova, 35128 Padova, Italy

<sup>6</sup>Centre of Clinical Physiology and Hypertension, University of Milan, Milan

<sup>7</sup>Istituto Auxologico Italiano, IRCCS, 20145 Milan

Correspondence to: G Mancia [giuseppe.mancia@unimib.it](mailto:giuseppe.mancia@unimib.it)

Cite this as: *BMJ* 2010;340:c1197 doi:10.1136/bmj.c1197

## ABSTRACT

**Objective** To investigate the possibility that statins reduce blood pressure as well as cholesterol concentrations through clinic and 24 hour ambulatory blood pressure monitoring.

**Design** Randomised placebo controlled double blind trial.  
**Setting** 13 hospitals in Italy

**Participants** 508 patients with mild hypertension and hypercholesterolaemia, aged 45 to 70 years.

**Intervention** Participants were randomised to antihypertensive treatment (hydrochlorothiazide 25 mg once daily or fosinopril 20 mg once daily) with or without the addition of a statin (pravastatin 40 mg once daily).

**Main outcome measures** Clinic and ambulatory blood pressure measured every year throughout an average 2.6 year treatment period.

**Results** Both the group receiving antihypertensive treatment without pravastatin (n=254) (with little change in total cholesterol) and the group receiving antihypertensive treatment with pravastatin (n=253) (with marked and sustained reduction in total cholesterol and low density lipoprotein cholesterol) had a clear cut sustained reduction in clinic measured systolic and diastolic blood pressure as well as in 24 hour, and day and night, systolic and diastolic blood pressure. Pravastatin performed slightly worse than placebo, and between group differences did not exceed 1.9 (95% confidence interval -0.6 to 4.3, P=0.13) mm Hg throughout the treatment period. This was also the case when participants who remained on monotherapy with hydrochlorothiazide or fosinopril throughout the study were considered separately.

**Conclusions** Administration of a statin in hypertensive patients in whom blood pressure is effectively reduced by concomitant antihypertensive treatment does not have an additional blood pressure lowering effect.

**Trial registration** BRISQUI\_\*IV\_2004\_001 (registered at Osservatorio Nazionale sulla Sperimentazione Clinica dei Medicinali—National Monitoring Centre on Clinical Research with Medicines).

## INTRODUCTION

Two main mechanisms have been proposed for the protection offered by statins against cardiovascular

disease. Firstly, statins reduce the incidence of morbid and fatal cardiovascular events by lowering total serum cholesterol and, more generally, by reducing the components of blood lipids that importantly contribute to cardiovascular risk.<sup>1,2</sup> Secondly, in addition to causing changes in the lipid profile, statins may have pleiotropic (for example, anti-inflammatory and anti-proliferative) effects that directly protect tissues and organs from cardiovascular risk factors.<sup>3-9</sup>

In the past few years a third mechanism for the cardiovascular protective effects of statins has been proposed—that statins may also lower blood pressure and thus act through a reduction in the blood pressure related risk. However, many of studies on which this hypothesis is based have important limitations,<sup>10-17</sup> as has their meta-analysis.<sup>18</sup> These include the uncontrolled nature of the experimental design, retrospective analysis of the data, the small number of participants included, and the short follow-up. Furthermore, available data are largely limited to blood pressure measured in the clinic without providing information on ambulatory blood pressure, which is of greater prognostic importance.<sup>19-21</sup> This limitation applies also to a large scale, long term, placebo controlled study in which addition of a statin to two effective antihypertensive treatment regimens was accompanied a very small (about 1 mm Hg) further blood pressure lowering effect.<sup>22</sup>

In the PHYLLIS (Plaque Hypertension Lipid-Lowering Italian Study) multicentre (13 centres) trial,<sup>23</sup> more than 500 patients with mild hypertension and hypercholesterolaemia were randomised to administration of hydrochlorothiazide or fosinopril, each of them with and without the addition of pravastatin, in a placebo controlled, double blind, double dummy factorial design, to determine which therapeutic approach could more effectively prevent carotid artery atherosclerosis. The results, reported in detail previously,<sup>23</sup> showed that progression of carotid intima-media thickness was slowed by fosinopril compared with hydrochlorothiazide or by the addition of pravastatin compared with placebo to the hydrochlorothiazide treatment regimen. However, the PHYLLIS

protocol also considered a pre-specified secondary analysis of a comparison of the effects on blood pressure of the antihypertensive agents compared, in combination with either pravastatin or placebo, because the treatment induced effects on blood pressure were important for the interpretation of the changes in carotid intima-media thickness. This analysis was based on the 24 hour ambulatory blood pressure data obtained in all patients at yearly intervals throughout the approximate three year duration of the trial. Ambulatory blood pressure values were particularly suited for this purpose because, compared with blood pressure measurements made in the clinic, they have a superior reproducibility and thus a greater ability to detect small differences in blood pressure between groups.<sup>19-21</sup> We report here the results of this analysis.

## METHODS

The design and methods of PHYLLIS have been described in detail elsewhere.<sup>23</sup> Briefly, men and postmenopausal women aged 45-70 years were recruited in 13 Italian hospitals if they had no history of cardiovascular events together with untreated or uncontrolled hypertension, hypercholesterolaemia, and asymptomatic carotid artery atherosclerosis, identified ultrasonographically.

Patients who gave an informed written consent had a six week washout with triple placebo, during which they were given the American Heart Association low lipid diet.<sup>24</sup> Patients who still had high clinic measured blood pressure (systolic 150-210 mm Hg; diastolic 95-115 mm Hg), high serum concentration of low density lipoprotein cholesterol (4.14-5.17 mmol/l (160-200 mg/dl)), and a serum triglyceride concentration of 3.39 mmol/l or lower ( $\leq 300$  mg/dl) were randomised to four types of double blind, double dummy treatment according to a factorial design: hydrochlorothiazide 25 mg once daily plus fosinopril placebo and pravastatin placebo; fosinopril 20 mg once daily plus hydrochlorothiazide placebo and pravastatin placebo; hydrochlorothiazide 25 mg once daily plus fosinopril placebo and pravastatin 40 mg; and fosinopril 20 mg once daily plus hydrochlorothiazide placebo and pravastatin 40 mg once daily. Each study treatment was placed in a numbered container according to a computer generated randomisation procedure with a block size of four. If after three months clinic diastolic blood pressure was not less than 90 mm Hg or less than 95 mm Hg with a fall of at least 10 mm Hg, open label nifedipine GITS (gastrointestinal therapeutic system) 30 mg once daily was added, to be eventually increased to 60 mg once daily after six months if necessary. Nifedipine GITS was selected because calcium antagonists are lipid neutral. The low lipid diet and drug treatment were maintained throughout the follow-up period (mean of 2.6 years). Patients and study personnel (local investigators, core laboratory readers of carotid ultrasound or ambulatory blood pressure monitoring data) were blinded to treatment allocation.

## Measurements

Measurements consisted of carotid artery wall thickness by ultrasonography, lipid profile (serum total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol, and triglycerides), fasting blood glucose and other blood chemistry values, clinic blood pressure, and ambulatory blood pressure. The lipid profile was assessed at baseline, three months after the start of treatment, and at yearly intervals thereafter. For each patient, trained personnel measured blood pressure in the clinic before randomisation to treatment and at visits after three months and at yearly intervals during treatment. On each occasion, three measurements were made over five minutes with a mercury sphygmomanometer after the patient had been seated comfortably for at least five minutes. We used the average of the three systolic and diastolic blood pressure values for data analyses. We calculated pulse pressure as the difference between systolic blood pressure and diastolic blood pressure. We calculated heart rate from the radial pulse during 30 seconds. A 24 hour ambulatory blood pressure recording was obtained immediately before randomisation to treatment and at yearly intervals during treatment. The recordings were not spaced by more than a week from the corresponding clinic blood pressure measurements. Each ambulatory blood pressure recording began in the morning, after the study drugs were taken, using validated devices,<sup>25,26</sup> and after a check had been made to show that the patient's readings did not differ by more than 5 mm Hg from simultaneously obtained auscultatory readings. The devices were programmed to provide automatic readings every 15 minutes during the day (from 6 am to midnight) and every 20 minutes during the night (from midnight to 6 am). Patients were instructed to continue their usual activities during the recording period but to avoid strenuous exercise and to keep the arm extended and still during the automatic cuff inflations. The ambulatory blood pressure data were sent to a core laboratory (Istituto Auxologico Italiano, Milan, Italy) for analysis, which was done only if valid ambulatory blood pressure readings, identified according to pre-defined criteria,<sup>27</sup> formed at least 70% of the expected number of readings and at least one reading per hour for at least 21 hours was available. We calculated 24 hour, daytime, and night-time average systolic, diastolic, and pulse pressures; day-night differences in systolic, diastolic, and pulse pressures; and standard deviation of 24 hour systolic blood pressure, which we took as an index of blood pressure variability.<sup>28</sup> We also calculated clinic and ambulatory values for heart rate. Ultrasonographers and personnel who read ambulatory blood pressure were kept blinded to lipid concentrations throughout the study.

## Statistical analysis

The main end point of this analysis (and a secondary end point of the main study) was the comparison between the reduction in 24 hour ambulatory blood pressure in the groups with and without administration

of pravastatin. To this end, we averaged each participant's systolic blood pressure values over 24 hours in the baseline condition and three times during treatment—that is, after 12 months, after 24 months, and at the end of the study. We also did this for diastolic blood pressure, pulse pressure, and heart rate. We also calculated daytime average, night-time average, and clinic measured values. We assessed differences between on-treatment and baseline values by averaging all on-treatment data and by separately considering values obtained at the three different times during treatment. We did a separate analysis on the subgroup of patients who remained on monotherapy for the whole duration of the study. We used a paired *t* test to compare averaged on-treatment and baseline blood pressure values and an unpaired *t* test for between group comparisons. We also did this for other (for example, metabolic) data. We used a repeated measures analysis of covariance model to test the time (within participant) effect and the pravastatin (between groups) effect. We adjusted the analysis for concomitant nifedipine treatment and for baseline values. We subsequently included an interaction term in the model, to test whether the pravastatin effect differed according to baseline values. We pooled data for the two groups taking antihypertensive treatment (hydrochlorothiazide or fosinopril) without pravastatin and compared them with the pooled data of the two groups taking antihypertensive treatment plus pravastatin.<sup>23</sup> We did the analyses on an intention to treat basis. We always took  $P < 0.05$  as the level of statistical significance. All significance tests were two sided. We present data as means and standard deviations or means and 95% confidence intervals.

The sample size for the PHYLLIS study was originally calculated on the basis of the hypothesis made for changes in carotid intima-media thickness—that is, the primary outcome.<sup>23</sup> For this pre-specified secondary analysis, we provide a post hoc power calculation. The two groups (with and without pravastatin) compared for blood pressure response were of a size (254 *v* 253 patients) sufficient to detect, with 90% power, a difference of 4.04 mm Hg in 24 hour average systolic blood pressure, with  $\alpha = 0.05$ , assuming a standard deviation of 14.0 mm Hg.

## RESULTS

Figure 1 shows the flow of participants in the study (considering only the randomisation to pravastatin or corresponding placebo). Recruitment started in April 1995 and was completed in May 1997, and the follow-up of the last participants was completed in November 1999. Throughout the study, 26 serious adverse events occurred (14 in the placebo group and 12 in the pravastatin group); the number of patients lost to follow-up was 23 in the placebo group and 30 in the pravastatin group. Table 1 shows that at baseline the patients in the two groups were matched for demographic characteristics, blood chemistry, and blood pressure values. Ambulatory blood pressure recordings were not analysed in 24 cases because they did not meet the study quality criteria.

As shown in figure 2, in both groups antihypertensive treatment with fosinopril or hydrochlorothiazide was associated with a sustained reduction in 24 hour, day, night, and clinic systolic and diastolic blood pressure values, which was statistically significant at all times compared with baseline values. On-treatment blood pressures were never significantly different between groups with and without pravastatin.

Table 2 shows the data obtained by comparing the averaged on-treatment values with those at baseline. The reduction in 24 hour systolic blood pressure (pool of all on-treatment values) from baseline values tended to be smaller in patients receiving antihypertensive treatment plus pravastatin than in those receiving antihypertensive treatment and placebo, although the difference was not statistically significant. This was also the case for daytime, night-time, and clinic measured systolic blood pressure, as well as for diastolic pressure and pulse pressure. Neither treatment significantly affected heart rate values.

Repeated measures analysis of covariance yielded very similar results, with a strong effect of time ( $P < 0.001$  for all blood pressure measures) and a non-significant effect of pravastatin (except for a borderline effect ( $P = 0.06$ ) on 24 hour systolic blood pressure, indicating a slightly smaller blood pressure reduction in the pravastatin group). When we considered only on-treatment measures, we found no significant time effect, indicating a fairly stable blood pressure reduction in both groups. Moreover, in the pravastatin group all interactions with baseline values were non-significant (systolic blood pressure,  $P = 0.16$ ; diastolic blood pressure,  $P = 0.99$ ; pulse pressure,  $P = 0.08$ ). The

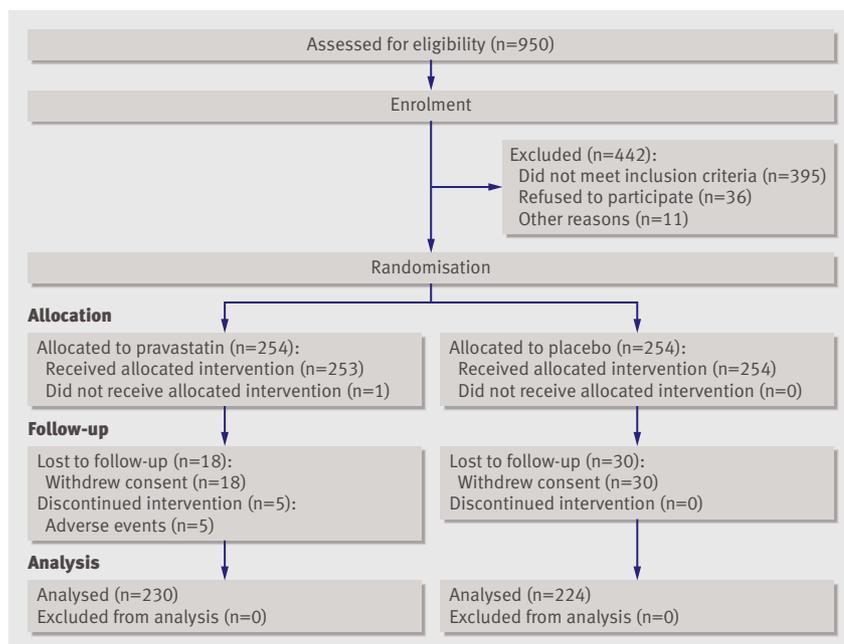


Fig 1 | Flow of participants in study (for purposes of analysis reported here, only randomisation to pravastatin or corresponding placebo is considered)

**Table 1** Baseline characteristics of hypertensive patients randomised to pravastatin or placebo. Values are mean (SD) unless stated otherwise

Characteristics	Placebo (n=254)	Pravastatin (n=253)	P value
No (%) male	155 (61)	148 (59)	0.56
Age (years)	58.3 (6.5)	58.5 (6.8)	0.81
Weight (kg)	69.3 (10.9)	70.4 (11.2)	0.28
No (%) current smokers	45 (18)	41 (16)	0.65
Total cholesterol (mmol/l)	6.78 (0.66)	6.79 (0.68)	0.88
LDL cholesterol (mmol/l)	4.68 (0.53)	4.70 (0.50)	0.59
HDL cholesterol (mmol/l)	1.38 (0.33)	1.35 (0.35)	0.48
Triglycerides (mmol/l)	1.59 (0.57)	1.60 (0.62)	0.92
Glucose (mmol/l)	5.21 (0.65)	5.22 (0.78)	0.82
Creatinine (µmol/l)	83.0 (16.0)	83.0 (16.0)	0.91
Clinic measurements:			
Systolic blood pressure (mm Hg)	160.0 (9.1)	159.6 (8.9)	0.66
Diastolic blood pressure (mm Hg)	98.3 (4.4)	98.3 (4.1)	0.93
Pulse pressure (mm Hg)	61.7 (8.5)	61.4 (8.1)	0.67
Heart rate (beats/min)	73.1 (7.4)	72.4 (7.3)	0.34
24 hour ambulatory measurements:			
Systolic blood pressure (mm Hg)	136.4 (14.1)	136.2 (14.0)	0.87
Diastolic blood pressure (mm Hg)	84.5 (10.7)	83.5 (9.3)	0.28
Pulse pressure (mm Hg)	51.9 (9.2)	52.7 (9.7)	0.37
Heart rate (beats/min)	73.2 (8.4)	72.6 (7.5)	0.37
Daytime measurements:			
Systolic blood pressure (mm Hg)	139.3 (14.6)	139.1 (14.4)	0.86
Diastolic blood pressure (mm Hg)	87.2 (11.1)	86.1 (9.7)	0.27
Pulse pressure (mm Hg)	52.2 (9.3)	53.0 (9.8)	0.35
Heart rate (beats/min)	75.6 (8.6)	75.0 (7.8)	0.44
Night time measurements:			
Systolic blood pressure (mm Hg)	124.8 (15.0)	125.0 (14.7)	0.88
Diastolic blood pressure (mm Hg)	74.1 (10.7)	73.6 (9.5)	0.60
Pulse pressure (mm Hg)	50.7 (9.6)	51.4 (10.0)	0.45
Heart rate (beats/min)	64.2 (8.6)	63.2 (7.9)	0.22

HDL=high density lipoprotein; LDL=low density lipoprotein.  
P values are for differences between groups; 24 hour, daytime, and night-time values are means for each period.

24 hour systolic blood pressure standard deviations also did not differ significantly between the groups with pravastatin or placebo. Heart rate values were also never significantly modified by treatment either with or without pravastatin.

The large majority of patients remained on antihypertensive monotherapy with either hydrochlorothiazide or fosinopril both in the placebo group (88%) and in the pravastatin group (87%). As shown in table 3, when we limited the analysis to the participants who remained on monotherapy, the reduction from baseline in ambulatory and clinic blood pressure did not differ significantly between groups receiving pravastatin or placebo. This was also the case when we adjusted the data for the small difference in the proportion of patients on antihypertensive monotherapy between the two groups. Moreover, in a time to event Kaplan-Meier analysis, we found no significant difference between the two groups in the number of patients who needed open label nifedipine (log-rank test  $\chi^2=0.93$ ,  $P=0.33$ ). Finally, when we compared clinic

blood pressure values at three months (when all patients were on the initial antihypertensive monotherapy), we also found no difference in systolic and diastolic blood pressure between the placebo and pravastatin groups (systolic 144.8 and 144.8 mm Hg; diastolic 88.1 and 87.8 mm Hg) (fig 2).

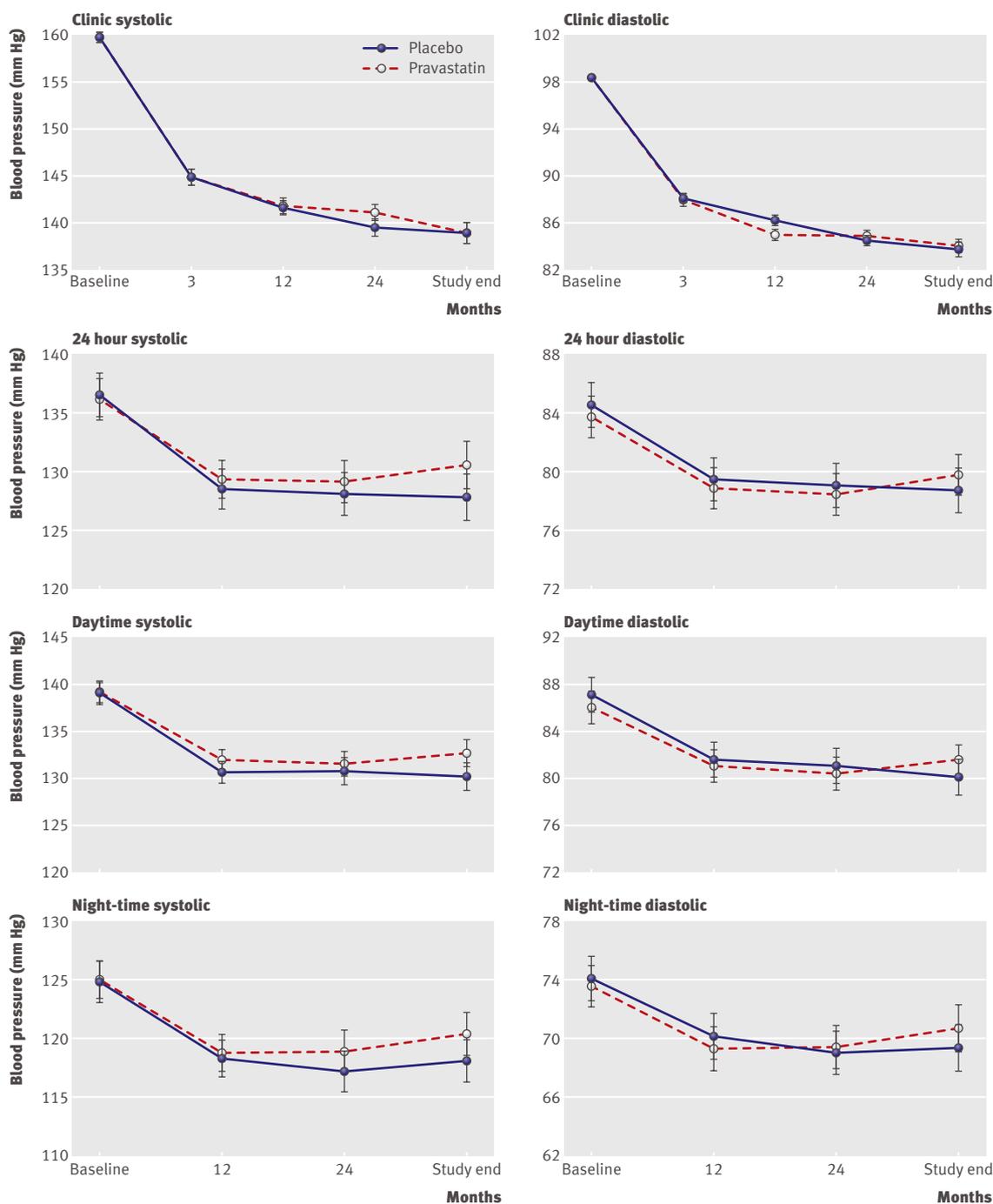
Figure 3 shows the lipid concentrations throughout the study. In the groups taking hydrochlorothiazide or fosinopril plus placebo, serum total cholesterol and low density lipoprotein cholesterol showed only minor changes, whereas in the groups in which one or other antihypertensive treatment was combined with the administration of pravastatin, both showed a sustained significant decrease. Differences between the groups with and without pravastatin (about 1 mmol/l) were highly significant throughout the treatment period ( $P<0.001$ ).

## DISCUSSION

In patients with mild hypertension and hypercholesterolaemia, antihypertensive treatment with a thiazide diuretic or an angiotensin converting enzyme inhibitor effectively lowered clinic measured and ambulatory blood pressure over a time interval of approximately three years. Compared with administration of placebo, addition of pravastatin to the antihypertensive treatment caused a marked and sustained reduction in serum total cholesterol and low density lipoprotein cholesterol. This addition, however, did not cause any further reduction in systolic or diastolic blood pressure values, either when they were measured at regular intervals in the physician's office or when they were repeatedly assessed on an ambulatory basis over 24 hours. This provides evidence against any substantial blood pressure lowering effect of statins in patients with high blood pressure, suggesting that the protective effects of these drugs on the cardiovascular system do not depend on a reduction in the blood pressure related risk of cardiovascular disease.

### Strengths and limitations of study

PHYLLIS has several characteristics that make its results robust. Firstly, the study had a prospective randomised double blind design, which guarantees against errors due to inappropriate matching of patients and selection bias of patients or physicians. Secondly, the study had a relatively long duration, which allowed us to determine both the early effect and the possible delayed effect of statins on blood pressure. Thirdly, the effects of administration of statin on blood pressure were regularly assessed by ambulatory blood pressure monitoring—that is, by a method characterised by greater reproducibility than clinic blood pressure measurements,<sup>19,20</sup> and thus by a greater ability (because of a reduction of background erratic blood pressure changes) to detect small blood pressure differences between treatment groups.<sup>21</sup> Fourthly, the absence of any effect of statins on blood pressure was also shown on additional blood pressure variables, which have been shown to have an independent



**Fig 2** | Clinic, 24 hour, daytime, and night-time systolic and diastolic blood pressure, showing mean values at baseline, throughout treatment period, and at study end in patients taking pravastatin or corresponding placebo. All values during treatment were always significantly different from those at baseline ( $P < 0.001$ ). Baseline and on-treatment values were not significantly different between treatment groups

prognostic significance, such as night-time blood pressure and blood pressure variability.<sup>27-30</sup>

Our study has also some limitations. One limitation is that the design of PHYLLIS allowed the initial antihypertensive treatment to be complemented by the administration of open label nifedipine GITS at increasing doses in the absence of blood pressure control or of a satisfactory blood pressure response. This

could have introduced a confounding factor, as the absence of a blood pressure lowering effect of pravastatin in patients on placebo might have been compensated by more common addition of a second antihypertensive drug. However, in PHYLLIS the vast majority of the patients (almost 90%) remained on antihypertensive monotherapy throughout the study, presumably because their mild hypertensive

**Table 2** | Blood pressure reductions by antihypertensive treatment in hypertensive patients randomised to either placebo or pravastatin (intention to treat population). Values are mean (95% confidence interval)

	Antihypertensive treatment v baseline		Difference pravastatin v placebo	P value
	Placebo	Pravastatin		
<b>Clinic measurements</b>				
Systolic blood pressure (mm Hg)	-19.2 (-20.6 to -17.8)	-18.1 (-19.5 to -16.7)	1.0 (-0.9 to 3.0)	0.31
Diastolic blood pressure (mm Hg)	-12.4 (-13.2 to -11.7)	-12.8 (-13.5 to -12.0)	-0.3 (-1.4 to 0.7)	0.54
Pulse pressure (mm Hg)	-6.7 (-7.9 to -5.6)	-5.3 (-6.6 to -4.1)	1.4 (-0.3 to 3.0)	0.10
Heart rate (beats/min)	-0.4 (-1.3 to 0.4)	-0.3 (-1.2 to 0.6)	0.1 (-1.1 to 1.4)	0.82
<b>24 hour ambulatory measurements</b>				
Systolic blood pressure (mm Hg)	-8.7 (-10.3 to -7.0)	-7.0 (-8.5 to -5.6)	1.6 (-0.6 to 3.8)	0.15
Diastolic blood pressure (mm Hg)	-6.2 (-7.2 to -5.1)	-5.0 (-6.0 to -4.1)	1.2 (-0.2 to 2.6)	0.11
Pulse pressure (mm Hg)	-2.5 (-3.4 to -1.6)	-2.0 (-2.8 to -1.2)	0.4 (-0.7 to 1.6)	0.46
Heart rate (beats/min)	-0.9 (-1.7 to -0.1)	-0.4 (-1.2 to 0.4)	0.5 (-0.7 to 1.7)	0.41
<b>Daytime measurements</b>				
Systolic blood pressure (mm Hg)	-8.8 (-10.5 to -7.2)	-7.3 (-8.8 to -5.8)	1.5 (-0.7 to 3.8)	0.18
Diastolic blood pressure (mm Hg)	-6.4 (-7.5 to -5.3)	-5.2 (-6.2 to -4.2)	1.2 (-0.3 to 2.7)	0.12
Pulse pressure (mm Hg)	-2.5 (-3.4 to -1.5)	-2.1 (-2.9 to -1.3)	0.3 (-0.9 to 1.6)	0.58
Heart rate (beats/min)	-0.7 (-1.6 to 0.1)	-0.2 (-1.1 to 0.7)	0.5 (-0.7 to 1.8)	0.42
<b>Night-time measurements</b>				
Systolic blood pressure (mm Hg)	-7.4 (-9.3 to -5.6)	-5.6 (-7.2 to -3.9)	1.9 (-0.6 to 4.3)	0.13
Diastolic blood pressure (mm Hg)	-5.1 (-6.3 to -3.9)	-4.0 (-5.0 to -2.9)	1.1 (-0.4 to 2.7)	0.15
Pulse pressure (mm Hg)	-2.3 (-3.3 to -1.4)	-1.6 (-2.5 to -0.7)	0.7 (-0.6 to 2.0)	0.27
Heart rate (beats/min)	-1.2 (-2.1 to -0.4)	-0.7 (-1.5 to 0.2)	0.6 (-0.6 to 1.7)	0.34

status favoured the effectiveness of a single drug. Furthermore, restricting the analysis to patients on monotherapy did not reveal any blood pressure lowering effect of pravastatin, even when we made adjustment for the small difference in the rate of nifedipine use between the placebo and the statin groups (12% v 13%). Finally, the time to event Kaplan-Meier analysis did not detect any significant between group difference in the number of patients who needed open label nifedipine, and the clinic blood pressure values measured three months after randomisation (that is, when the protocol required all patients to still be on initial monotherapy) were superimposable in the placebo and pravastatin groups. This limitation thus does not detract from the conclusion that pravastatin is devoid of a blood pressure lowering effect.

A second limitation is that participants in PHYLLIS were hypertensive and received antihypertensive drugs capable of causing a clear cut reduction in ambulatory and clinic measured blood pressure. This restricts our conclusion that statins do not exert any significant blood pressure lowering effect to patients with high blood pressure who receive effective antihypertensive treatment. In other words, the possibility remains that statins cause some reduction in blood pressure when given alone—that is, in the absence of

a possible confounding effect of the antihypertensive drug treatment. In this context, however, we should mention that in PHYLLIS on-treatment ambulatory and clinic blood pressure remained well above normal values,<sup>19,31</sup> leaving a large potential for a further reduction in blood pressure to occur. This makes the above possibility unlikely.

The third limitation relates to the suggestion from a recently published cross sectional analysis that the reduction in blood pressure by statins is mainly evident when the initial blood pressure is particularly high (that is, above the mild hypertension range explored in PHYLLIS).<sup>32</sup> This suggestion is not in line with the observation that in our patients no interaction occurred between baseline blood pressure and the effects of pravastatin on blood pressure. In this context, we also emphasise that our study has a randomised design, which, compared with cross sectional assessment of drug effects, produces results that are much less affected by many confounders that are never completely accounted for in statistical analysis.

Finally, our conclusion obviously refers to data obtained with pravastatin, which means that a blood pressure lowering effect of other statins cannot be ruled out. However, virtually all cardiovascular effects attributable to statins have been documented for more than one drug and are therefore reported as common to the class,<sup>33</sup> and the studies that have reported a statin related blood pressure reduction have used pravastatin as well as of other statins with no evidence of a differential effect on blood pressure.<sup>10-17</sup> Furthermore, in PHYLLIS pravastatin was used at a dose (40 mg daily) similar to that used in the studies that have reported blood pressure lowering by statins. This dosage caused a marked lipid lowering effect (reduction in serum low density lipoprotein cholesterol greater than 1 mmol/l or 40 mg/dl), in line with what is commonly observed with effective doses of any statin.

#### Comparison with other studies

The data provided by PHYLLIS do not confirm the conclusion of previous studies that statins exert a blood pressure lowering effect.<sup>10-17</sup> However, the effect in these studies was relatively small, and in a recent meta-analysis that pooled most available data it amounted to no more than 2 mm Hg reduction in systolic blood pressure and 1 mm Hg reduction in diastolic blood pressure.<sup>18</sup> Also, the 11 studies included in the meta-analysis were all small—the total number of patients was only slightly greater (n=563) than the number included in PHYLLIS alone (n=508)—and the studies were of a short duration (mostly one to six months; only two studies extended the treatment period to one year) and had rather heterogeneous designs.

The results of PHYLLIS are also not in line with those of the California San Diego Statin Study,<sup>34</sup> which has recently reported that in about 1000 patients with hypercholesterolaemia administration of simvastatin (20 mg daily) or pravastatin (40 mg daily) caused a small (2-3 mm Hg) statistically significant reduction in

**Table 3** Blood pressure reductions in placebo and pravastatin groups in subset of patients who remained on antihypertensive monotherapy (hydrochlorothiazide 25 mg once daily or fosinopril 20 mg once daily) throughout study. Values are mean (95% confidence interval)

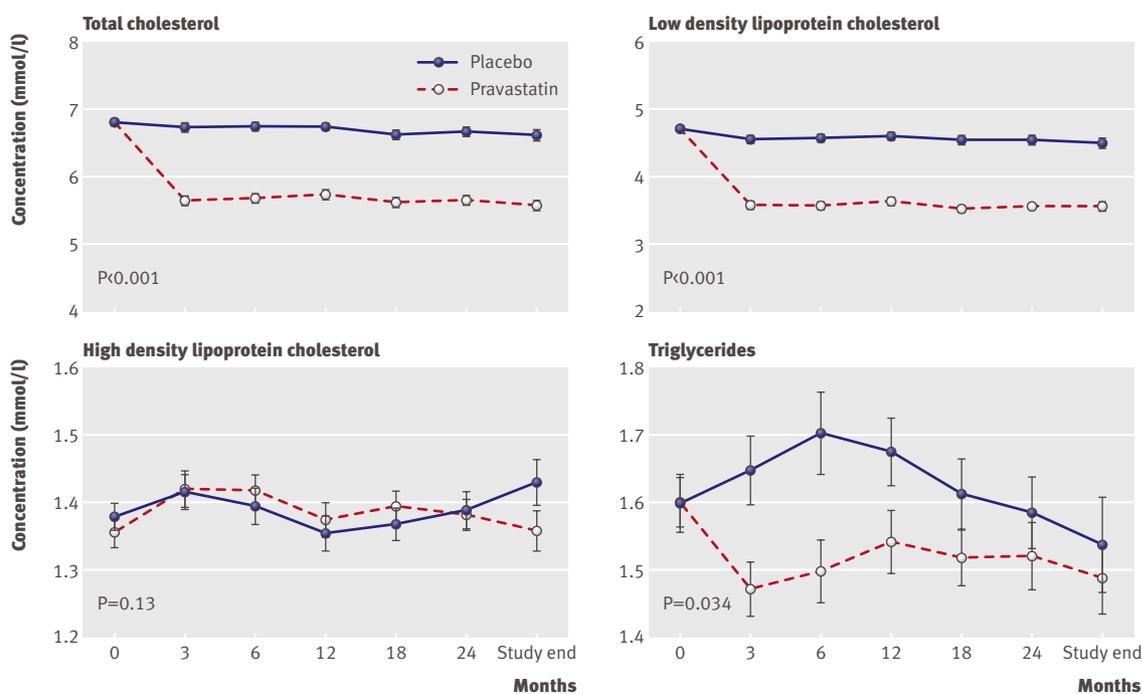
	Antihypertensive monotherapy v baseline		Difference pravastatin v placebo	Adjusted difference pravastatin v placebo*	P value
	Placebo (n=198)	Pravastatin (n=199)			
<b>Clinic measurements</b>					
Systolic blood pressure (mm Hg)	-19.6 (-21.2 to -18.0)	-18.8 (-20.2 to -17.3)	0.8 (-1.3 to 2.9)	1.1 (-3.1 to 3.1)	0.44
Diastolic blood pressure (mm Hg)	-12.7 (-13.6 to -11.9)	-12.9 (-13.7 to -12.0)	-0.1 (-1.3 to 1.0)	-0.3 (-0.8 to 0.8)	0.83
Pulse pressure (mm Hg)	-6.9 (-8.2 to -5.6)	-5.9 (-7.2 to -4.6)	1.0 (-0.9 to 2.8)	-0.3 (-0.8 to 0.8)	0.30
<b>24 hour ambulatory measurements</b>					
Systolic blood pressure (mm Hg)	-7.8 (-9.5 to -6.1)	-6.3 (-7.8 to -4.7)	1.6 (-0.7 to 3.9)	1.5 (-3.7 to 3.7)	0.18
Diastolic blood pressure (mm Hg)	-5.7 (-6.8 to -4.6)	-4.6 (-5.6 to -3.5)	1.2 (-0.3 to 2.7)	1.1 (-2.5 to 2.5)	0.12
Pulse pressure (mm Hg)	-2.1 (-3.2 to -1.0)	-1.7 (-2.6 to -0.8)	0.4 (-0.9 to 1.7)	0.4 (-1.6 to 1.6)	0.56

\*Adjusted for difference between groups in proportion of participants on monotherapy.

systolic blood pressure. Because this effect was seen in patients who were not receiving antihypertensive treatment (most patients were normotensive), these results are compatible with the above mentioned possibility that statins exert a small blood pressure lowering effect that can be detected only when they are given alone and the masking effect of the more powerful antihypertensive drugs is avoided. However, treatment was short lasting in this study (six months), only clinic measured blood pressure was available, and blood pressure measurements were rare and obtained with

an aneroid device, the accuracy of which is questionable.

Our findings are in line with some large scale studies that have explored the blood pressure lowering effect of statins over a longer follow-up period, although never by ambulatory blood pressure monitoring. In the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA) in more than 10 000 hypertensive patients with a serum total cholesterol of 6.5 mmol/l (250 mg/dl) or below, the addition of atorvastatin to an effective antihypertensive



**Fig 3** | Average serum lipid concentrations in patients taking pravastatin or corresponding placebo at baseline and throughout treatment period. Data are means and standard deviations; P values refer to overall treatment effect in analysis of covariance. In groups randomised to receive pravastatin in combination with either hydrochlorothiazide or fosinopril, total cholesterol and low density lipoprotein cholesterol during treatment were always significantly lower than at baseline (P<0.001)

**WHAT IS ALREADY KNOWN ON THIS TOPIC**

Statins provide cardiovascular protection through their lowering effect on serum cholesterol and probably also through specific (pleiotropic) protective effects

Several studies have reported that statins exert a blood pressure lowering effect, which might thus be listed as an additional protective mechanism

In several instances, however, these studies have methodological limitations that make this hypothesis unproved

**WHAT THIS STUDY ADDS**

PHYLLIS tested the possible blood pressure lowering effect of a statin in a long term prospective placebo controlled study, using ambulatory blood pressure monitoring

In patients with hypertension and hypercholesterolaemia on antihypertensive treatment, statins offered no additional blood pressure lowering effect over 24 hours

treatment regimen was accompanied by a clear cut reduction in total serum cholesterol without any substantial effect on clinic measured blood pressure.<sup>22</sup> Similarly, no blood pressure lowering effect of pravastatin at doses capable of effectively improving the lipid profile was reported by a recent analysis of the Cholesterol and Recurrent Events (CARE) trial.<sup>35</sup>

Finally, the results of PHYLLIS complement the evidence provided by a substudy of ASCOT, in which central blood pressure was derived from the peripheral blood pressure signal by using a Sphygmocor device, the Conduit Artery Function Evaluation—Lipid-Lowering Arm (CAFE-LLA) study. Central blood pressure was similar in patients taking atorvastatin or placebo, thus again providing no evidence of a blood pressure lowering effect.<sup>36</sup>

**Conclusions**

The results of PHYLLIS show that at doses which markedly lower serum total cholesterol and low density lipoprotein cholesterol, pravastatin does not exert a lowering effect on systolic and diastolic blood pressure measured in patients with hypertension and hypercholesterolaemia who are receiving anti-hypertensive treatment. It further shows that this is the case for both clinic measured and ambulatory blood pressure over short and long term (about three years) administration of the drug. The protective cardiovascular effects of pravastatin and, most likely, of all statins are thus unlikely to depend on an anti-hypertensive effect of these drugs.

**Contributors:** GM was involved in study conception and design, study supervision, data interpretation, and drafting and revision of the paper. GP was involved in study design, data interpretation, and drafting and revision of the paper. MR, GB, and AG were involved in data interpretation and analysis and drafting and revision of the paper. FV was the study statistician and was involved in study design, data analysis, and revision of the paper. GC was involved in study conception and design and in revision of the paper. AZ was involved in study conception and design, study supervision, data interpretation, and drafting and revision of the paper. All authors approved the final version of the paper. GM is the guarantor.

**Funding:** PHYLLIS was an investigator generated trial sponsored by Bristol-Myers Squibb Italy, Rome, and Menarini, Florence. All authors carried out this research project in full independence from funders.

**Competing interests:** GC, GM, AZ, and GP have received research grants or honorariums for lectures from the sponsors. FV has received research grants from Menarini and Bristol-Myers Squibb Italy.

**Ethical approval:** The protocol of the study was approved by the ethics committees of the institutions involved.  
Data sharing: No additional data available.

- Riche DM, McClendon KS. Role of statins for the primary prevention of cardiovascular disease in patients with type 2 diabetes mellitus. *Am J Health Syst Pharm* 2007;64:1603-10.
- Chan PS, Nallamothu BK, Gurm HS, Hayward RA, Vijan S. Incremental benefit and cost-effectiveness of high-dose statin therapy in high-risk patients with coronary artery disease. *Circulation* 2007;115:2398-409.
- Ray KK, Cannon CP. Lipid-independent pleiotropic effects of statins in the management of acute coronary syndromes. *Curr Treat Options Cardiovasc Med* 2007;9:46-51.
- Ichihara A, Hayashi M, Koura Y, Tada Y, Kaneshiro Y, Saruta T. Long-term effects of statins on arterial pressure and stiffness of hypertensives. *J Hum Hypertens* 2005;19:103-9.
- Patterson D, Dick JBC, Struthers AD. Intensive statin treatment improves baroreflex sensitivity: another cardioprotective mechanism for statins? *Heart* 2002;88:415-6.
- Leibovitz E, Hazanov N, Zimlichman R, Shargorodsky M, Gavish D. Treatment with atorvastatin improves small artery compliance in patients with severe hypercholesterolemia. *Am J Hypertens* 2001;14:1096-8.
- Ferrier KE, Muhlmann MH, Baguet JP, Cameron JD, Jennings GL, Dart AM, et al. Intensive cholesterol reduction lowers blood pressure and large artery stiffness in isolated systolic hypertension. *J Am Coll Cardiol* 2002;39:1020-5.
- Simons LA, Sullivan D, Simons J, Celermajer DS. Effects of atorvastatin monotherapy and simvastatin plus cholestyramine on arterial endothelial function in patients with severe primary hypercholesterolemia. *Atherosclerosis* 1998;137:197-203.
- Laufs U, Wassmann S, Hilgers S, Ribaud N, Bohm M, Nickening G. Rapid effects on vascular function after initiation and withdrawal of atorvastatin in healthy, normocholesterolemic men. *Am J Cardiol* 2001;88:1306-7.
- Borghesi C, Dormi A, Veronesi M, Sangiorgi Z, Gaddi A, on behalf of the Brisighella Heart Study Working Party. Association between different lipid-lowering treatment strategies and blood pressure control in the Brisighella Heart Study. *Am Heart J* 2004;148:285-92.
- Kanbay M, Yildirim A, Bozbas H, Ulus T, Bilgi M, Muderrisoglu H, et al. Statin therapy helps to control blood pressure levels in hypertensive dyslipidemic patients. *Ren Fail* 2005;27:297-303.
- Koh KK, Quon MJ, Han SH, Chung WJ, Ahn JY, Seo YH, et al. Additive beneficial effects of losartan combined with simvastatin in the treatment of hypercholesterolemic, hypertensive patients. *Circulation* 2004;110:3687-92.
- Straznicki NE, Howes LG, Lam W, Louis WJ. Effects of pravastatin on cardiovascular reactivity to norepinephrine and angiotensin II in patients with hypercholesterolemia and systemic hypertension. *Am J Cardiol* 1995;75:582-6.
- Glorioso N, Troffa C, Filigheddu F, Dettori F, Soro A, Parpaglia PP, et al. Effect of the HMG-CoA reductase inhibitors on blood pressure in patients with essential hypertension and primary hypercholesterolemia. *Hypertension* 1999;34:1281-6.
- Borghesi C, Prandin MG, Costa FV, Bacchelli S, Degli Esposti D, Ambrosioni E. Use of statins and blood pressure control in treated hypertensive patients with hypercholesterolemia. *J Cardiovasc Pharmacol* 2000;35:549-55.
- Prasad GV, Ahmed A, Nash MM, Zaltzman JS. Blood pressure reduction with HMG-CoA reductase inhibitors in renal transplant recipients. *Kidney Int* 2003;63:360-4.
- Dorval JF, Anderson T, Buithieu J, Chan S, Hutchison S, Huynh T, et al. Reaching recommended lipid and blood pressure targets with amlodipine/atorvastatin combination in patients with coronary heart disease. *Am J Cardiol* 2005;95:249-53.
- Strazzullo P, Kerry SM, Barbato A, Versiero M, D'Elia L, Cappuccio FP. Do statins reduce blood pressure? A meta-analysis of randomized, controlled trials. *Hypertension* 2007;49:792-8.
- O'Brien E, Asmar R, Beilin L, Imai Y, Mallion JM, Mancia G, et al. European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. *J Hypertens* 2003;21:821-48.
- Parati G, Bilo G, Mancia G. Prognostic and diagnostic value of ambulatory blood pressure monitoring. In: Oparil S, Weber MA (eds). *Hypertension: companion to Brenner & Rector's 'The kidney'*. Elsevier Saunders, 2005.

- 21 Mancia G, Parati G. Guiding antihypertensive treatment decisions using ambulatory blood pressure monitoring. *Curr Hypertens Rep* 2006;8:330-7.
- 22 Sever PS, Dahlöf B, Poulter NR, Wedel H, Beevers G, Caulfield M, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003;361:1149-58.
- 23 Zanchetti A, Crepaldi G, Bond MG, Gallus G, Veglia F, Mancia G, et al. Different effects of antihypertensive regimens based on fosinopril or hydrochlorothiazide with or without lipid lowering by pravastatin on progression of asymptomatic carotid atherosclerosis: principal results of PHYLLIS—a randomized double-blind trial. *Stroke* 2004;35:2807-12.
- 24 Krauss RM, Eckel RH, Howard B, Appel LJ, Daniels SR, Deckelbaum RJ, et al. AHA dietary guidelines—revision 2000: a statement for healthcare professionals from the Nutrition Committee of the American Heart Association. *Circulation* 2000;102:2284-99.
- 25 O'Brien E, Waeber B, Parati G, Staessen J, Myers MG. Blood pressure measuring devices: recommendations of the European Society of Hypertension. *BMJ* 2001;322:531-6.
- 26 O'Brien E, Pickering T, Asmar R, Myers M, Parati G, Staessen J, et al. Working Group on Blood Pressure Monitoring of the European Society of Hypertension International Protocol for validation of blood pressure measuring devices in adults. *Blood Press Monit* 2002;7:3-17.
- 27 Mancia G, Ferrari A, Gregorini L, Parati G, Pomidossi G, Bertinieri G, et al. Blood pressure and heart rate variability in normotensive and hypertensive human beings. *Circ Res* 1983;53:96-104.
- 28 Staessen JA, Thijs L, Fagard R, O'Brien E, Clement D, de Leeuw PW, et al. Predicting cardiovascular risk using conventional versus ambulatory blood pressure in older patients with hypertension. *JAMA* 1999;282:539-46.
- 29 Parati G, Pomidossi G, Albini F, Malaspina D, Mancia G. Relationship of 24-hour blood pressure mean and variability to severity of target-organ damage in hypertension. *J Hypertens* 1987;5:93-8.
- 30 Mancia G, Bombelli M, Facchetti R, Madotto F, Corrao G, Trevano FQ, et al. Long-term prognostic value of blood pressure variability in the general population: results of the Pressioni Arteriose Monitorate e Loro Associazioni Study. *Hypertension* 2007;49:1265-70.
- 31 Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, et al. 2007 guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2007;25:1105-87.
- 32 Bautista LE. Blood pressure-lowering effects of statins: who benefits? *J Hypertens* 2009;27:1478-84.
- 33 Zhou Z, Rahme E, Pilote L. Are statins created equal? Evidence from randomized trials of pravastatin, simvastatin, and atorvastatin for cardiovascular disease prevention. *Am Heart J* 2006;151:273-81.
- 34 Golomb BA, Dimsdale JE, White HL, Ritchie JB, Criqui MH. Reduction in blood pressure with statins: results from the UCSD Statin Study, a randomized trial. *Arch Intern Med* 2008;168:721-7.
- 35 Tonelli M, Sacks F, Pfeffer M, Lopez-Jimenez F, Jhangri GS, Curhan G. Effect of pravastatin on blood pressure in people with cardiovascular disease. *J Hum Hypertens* 2006;20:560-5.
- 36 Williams B, Lacy PS, Cruickshank JK, Collier D, Hughes AD, Stanton A, et al. Impact of statin therapy on central aortic pressures and hemodynamics: principal results of the Conduit Artery Function Evaluation—Lipid-Lowering Arm (CAFE-LLA) Study. *Circulation* 2009;119:53-61.

Accepted: 17 November 2009