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ORIGINAL ARTICLE

Genetic risk factors influence nighttime blood pressure and related cardiovascular complications in patients with coronary heart disease

Marcin Wirtwein[1], Olle Melander[2], Marketa Sjőgren[2], Michal Hoffmann[3], Krzysztof Narkiewicz[3], Marcin Gruchala[4] and Wojciech Sobiczewski[4]

Genetic predisposition of elevated nighttime blood pressure (BP) in patients with coronary heart disease is unknown. We evaluated genetic predisposition and the relationship between elevated nighttime BP and cardiovascular complications over a median of 8.6 years of observation of hypertensive subjects with coronary atherosclerosis confirmed by coronary angiography. Genetic Risk Score (GRS19) was constructed to evaluate the additive effect of single-nucleotide polymorphisms for daytime and nighttime BP. The Receiver Operating Characteristic was used for determination of cutoff points for daytime BP (systolic BP (SBP) 133 mm Hg and diastolic BP (DBP) 77 mm Hg) and nighttime BP (SBP 122 mm Hg and DBP 73 mm Hg). The curves of cumulative incidence revealed an increased risk of major advanced cardiovascular events in subjects with elevated nighttime BP compared with those without elevated nighttime BP during the follow-up period. Subjects with normal daytime and elevated nighttime BP exhibited increased GRS19 compared with those with normal daytime and nighttime BPs (8.6 ± 3.0 *vs.* 7.9 ± 3.0, $P < 0.01$). After adjustment for cardiovascular risk factors, GRS19 determined nighttime SBP (β 0.4, 95% confidence interval (CI) 0.3–0.5, $P < 0.01$). Our study confirmed that elevated nighttime SBP was genetically determined and related to an increased risk of major adverse coronary events in patients with confirmed coronary atherosclerosis.
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Keywords: coronary atherosclerosis; coronary artery disease; dipping; DNA polymorphism; nighttime hypertension

INTRODUCTION

Several studies in different populations have confirmed that nighttime blood pressure (BP) is a stronger predictor of cardiovascular events than daytime BP.[1–4] Previous studies have suggested that nighttime BP is elevated in prediabetic and diabetic patients, patients with chronic kidney disease and those with lupus.[5–8] However, nighttime hypertension should be distinguished from a blunted nighttime BP decrease (referred to as 'non-dipping status'), but nighttime hypertension is more common in non-dippers.[9] From a pathophysiological point of view, there is a myriad of nighttime BP control mechanisms, for example, arterial baroreceptors and chemoreceptors, autonomic and central nervous systems, the renin–angiotensin–aldosterone system and pressure natriuresis.[10] Recently, Obayashi *et al.*[11] confirmed that renal function is an essential parameter related to elevated nighttime BP in patients with prediabetes. Our recently published study confirmed that non-dipping status is genetically determined in patients with coronary artery disease (CAD).[12] A previously published meta-analysis concluded that nighttime BP is superior to daytime BP in predicting cardiovascular events and total mortality.[13] However, little information is known about the genetic determinants of elevated nighttime BP in this group of patients. Therefore, we aim to investigate the relationship between genetic risk factors and elevated nighttime BP.

METHODS

Subjects

The present study recruited 1345 individuals (between August 2003 and August 2006) with signs of myocardial ischemia identified by ECG stress test, dobutamine stress echocardiography or myocardial perfusion scintigraphy stress test. Subjects with supraventricular and ventricular arrhythmias, NYHA class III or IV congestive heart failure, significant valvular heart disease (or valvular heart disease qualifying the patient for cardiosurgery), renal insufficiency with a creatinine level $\geqslant 2.0$ mg dl^{-1}, changes in pharmacotherapy of hypertension within 6 months before 24-h ambulatory BP monitoring and other chronic diseases leading to limited life expectancy were excluded.[12]

BP measurements

To avoid the influence on BP of either hospital conditions or the need for reduced physical activity, 24-h ambulatory BP monitoring was obtained over a period of 2–4 weeks after coronary angiography (SpaceLabs 90210, SpaceLabs, Redmond, WA, USA) with BP readings set at 20-min intervals (0600–

[1]Department of Pharmacology, Medical University of Gdansk, Gdansk, Poland; [2]Department of Clinical Sciences, Lund University, Malmö, Sweden; [3]Department of Hypertension and Diabetology, Medical University of Gdansk, Gdansk, Poland and [4]I Department of Cardiology, Medical University of Gdansk, Gdansk, Poland
Correspondence: Dr M Wirtwein, Department of Pharmacology, Medical University of Gdansk, Debowa 23, Gdansk 80-211, Poland.
E-mail: marwirt@interia.pl
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Table 1 Selected SNPs related to significant coronary artery disease

	Region	*Candidate gene(s)*	*Risk allele*	*Risk allele frequency*	*Other allele*
rs1746048	10q11	CXCL12	C	0.25	T
rs9349379	6p24	PHACTR1	G	0.68	A
rs17465637	1q41	MIA3	C	0.46	A
rs3798220	6q26	LPA	C	0.07	T
rs9818870	3q22	MRAS	C	0.27	T
rs17114036	1p32.2	PPAP2B	A	0.13	G
rs12413409	10q24.32	CNNM2	G	0.17	A
rs6725887	2q33	WDR12	C	0.24	T
rs9982601	21q22	KCNE2	T	0.28	C
rs12190287	6q23	TCF21	C	0.54	G
rs17609940	6p21.31	ANKS1A	C	0.32	G
rs3825807	15q25.1	ADAMTS7	C	0.66	T
rs4977574	9p.21	Chr9p21	G	0.73	A
rs1122608	19p13.2	LDLR	G	0.38	G
rs11206510	1p32.3	PCSK9	T	0.30	C
rs216172	17p13.3	SMG6	C	0.88	G
rs12936587	17p11.2	RALI	G	0.63	A
rs11556924	7q32.2	ZC3HC1	C	0.62	T
rs2259816	12q24.31	HNF1a	A	0.57	C

Abbreviation: SNP, single-nucleotide polymorphism.

1800 hours) and at 30-min intervals (1800–0600 hours). The non-dominant arm was used for measurement with cuff size adjusted to arm circumference (adult cuff 27–34 cm or large adult cuff 35–44 cm). All BP recordings were obtained on working days. Patients were instructed to maintain their usual activities but to refrain from strenuous exercise and emotional burden. Patients were instructed to hold their arm still by their side during BP measurement and to return to the hospital 24 h later. Participants had no access to their ambulatory BP values. BP measurements recorded between 0800 and 2200 hours were considered daytime BP values, and BP measurements recorded between 0000 and 0600 hours were considered as nighttime BP values. The percentage decrease in mean systolic BP (SBP) during the nighttime period was calculated as $100\times$(daytime SBP mean–nighttime SBP mean)/daytime SBP mean. Similarly, the percentage decrease in mean diastolic BP (DBP) during the nighttime period was calculated as $100\times$(daytime DBP mean–nighttime DBP mean)/daytime DBP mean. Using this percentage ratio, subjects were classified as dippers or non-dippers (nighttime relative SBP or DBP decline $\geqslant$ and $<10\%$, respectively).[14] This classification was performed for SBP and DBP for each included patient.

Office BP measurements were performed immediately before ambulatory BP measurements using a validated oscillometric device (OMRON 705 IT, OMRON, Greenspoint Parkway, IL, USA) with the cuff fitted to arm circumference. BP was measured on the non-dominant arm.[12]

Laboratory tests

On admission day before a coronary angiography, fasting blood samples were collected to measure creatinine level, fasting glucose level, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglyceride levels. Additionally, blood samples were collected to analyze DNA separation.

Single-nucleotide polymorphism (SNP) selection and genotyping

SNPs were selected from genome-wide association studies in which genome-wide association exceeded the threshold of $P<5\times10^{-8}$. Selected SNPs were reported to be associated with CAD risk and are presented in Table 1.[15–20] DNA was obtained from whole blood. SNPs were genotyped using an IPLEX reaction on a MassARRAY platform (Sequenom, San Diego, CA, USA) according to the manufacturer's standard protocols at Lund University. Only SNPs with a genotyping success rate $>90\%$ and minor allele frequency $>5\%$ were analyzed. Regarding quality control, we re-genotyped a random sample of 20% of the successfully genotyped samples for all genotypes, and the concordance was 99.9%.

Genetic Risk Score

Genetic Risk Score (GRS19) was constructed to evaluate the additive effect of 19 SNPs for elevated nighttime BP. This multilocus score was created by summing the number of risk alleles (0/1/2) for each of the 19 SNPs (1 and 2 for heterozygous and homozygous risk allele, respectively, and 0 for homozygous non-risk allele). GRS19 was assessed for each participant.

Assessment of coronary atherosclerosis

Coronary angiography was performed in the Department of Invasive Cardiology, and angiograms were evaluated independently by two experienced invasive cardiologists. Coronary angiography was used to confirm CAD.

Follow-up period

Subjects were observed from the date of coronary angiography until 31 December 2013. Follow-up was performed during visits to the clinic. If patients were unable to attend, they were contacted by phone. Stroke diagnosis was performed according to European Stroke Organization guidelines, and acute coronary syndromes were diagnosed according to European Society of Cardiology guidelines. Cardiovascular mortality involved events due to acute coronary syndrome (myocardial infarction or unstable angina), heart failure and stroke. Major adverse coronary events included cardiovascular and total mortality and cardiovascular events (stroke, acute coronary syndromes and new onset of heart failure).

Statistical analysis

The main goal of the analysis was to create a relationship between SNPs and elevated nighttime BP in coronary heart disease patients. A multiple regression model was used for this purpose. An analysis of the Receiver Operating Characteristic was used for predicting daytime and nighttime SBP and DBP. To determine the ability of daytime and nighttime BPs, cutoff points used to correctly identify subjects with or without major adverse coronary events' sensitivity and specificity across sites were compared. BP cutoff points were determined by interpolation from the point of intersection between the lines of specificity and sensitivity (where sensitivity equaled specificity). The point of intersection between the lines of specificity and sensitivity identified the highest numbers of subjects with and without major adverse coronary events. We also calculated positive and negative predictive values of BP cutoff points for major adverse coronary events. To compare continuous variables, Student's *t*-test or Mann–Whitney *U*-test was used as appropriate. For categorical variables an χ^2 test was used. Log-rank tests were used for comparison of the probability of major adverse coronary events in the studied groups. Continuous variables were reported as the mean $\pm$ s.d., and categorical variables were reported as percentages. $P<0.05$ was considered as the level of statistical significance. Statistical analyses were performed using STATISTICA version 10 (STATISTICA, Tulsa, OK, USA) version 3.0.1.

The study protocol was approved by the Ethics Committee of the Medical University of Gdansk.

RESULTS

After considering the inclusion and exclusion criteria, 1345 subjects were included in the study. Daytime BP cutoff points that correctly identified the greatest number of patients with major adverse coronary events were 133 mm Hg for SBP and 77 mm Hg for DBP. Nighttime BP cutoff points that correctly identified the greatest number of patients with major adverse coronary events were 122 mm Hg for SBP and 73 mm Hg for DBP. According to daytime and nighttime BP cutoff points, patients were divided into four subgroups (Table 2).

The baseline characteristics of the study group are summarized in Table 2. In patients with diabetes, we revealed a significant relationship between glycated hemoglobin and both nighttime SBP ($r=0.16$,

Table 2 Baseline characteristics of the study group

	Total group, n = *1345*	*Daytime BP< 133/77 mm Hg, nighttime BP< 122-/73 mm Hg,* n = *565*	*Daytime BP⩾ 133/77 mm Hg, nighttime BP< 122-/73 mm Hg,* n = *221*	*Daytime BP< 133/77 mm Hg, nighttime BP⩾ 122-/73 mm Hg,* n = *103*	*Daytime BP⩾ 133/77 mm Hg, nighttime BP⩾ 122-/73 mm Hg,* n = *456*
Age, years	63.4 ± 10.9	63.5 ± 9.3#	59.9 ± 8.8	66.6 ± 8.9#	63.8 ± 9.2#
Male, % (*n*)	61.0 (820)	53.1 (300)	61.1 (135)	65.0 (67)*	68.6 (313)*
Waist circumference, cm	97.3 ± 10.9	95.2 ± 10.7	97.6 ± 10.8*	97.3 ± 11.8*	99.5 ± 10.5*
BMI, kg m^{-2}	28.2 ± 4.2	27.6 ± 4.2	27.8 ± 3.6	27.4 ± 4.2	28.9 ± 4.3
Glucose, mg dl^{-1}	117.3 ± 42.6	112.8 ± 39.1	113.2 ± 32.9	116.8 ± 37.8	125.2 ± 50.4*,#
Diabetes, % (*n*)	21.8 (294)	16.2 (91)	17.2 (38)	29.1 (30)*,#	29.8 (136)*,‡
HbA1c, %	6.4 ± 1.1	6.1 ± 1.0	6.1 ± 0.9	6.8 ± 1.4*,#	7.4 ± 1.1*,#
Peripheral artery disease, % (*n*)	3.7 (50)	3.5 (20)	2.3 (5)	2.0 (2)	5.0 (23)
Current smokers, % (*n*)	12.5 (168)	11.5 (65)	16.7 (37)	15.5 (16)	18.8 (86)*
Family history of HA, % (*n*)	43.0 (578)	38.6 (218)	47.5 (105)*	37.8 (39)#	47.4 (216)*,#
Total cholesterol, mg dl^{-1}	205.2 ± 52.8	206.8 ± 54.1	209.8 ± 50.1	192.2 ± 44.5#	204.3 ± 54.1
LDL cholesterol, mg dl^{-1}	120.1 ± 43.0	121.0 ± 45.4	125.3 ± 43.5	111.8 ± 36.4	120.0 ± 41.1
HDL cholesterol, mg dl^{-1}	55.3 ± 13.6	56.7 ± 13.3#	55.7 ± 11.9	52.6 ± 11.9	54.0 ± 14.9
Triglycerides, mg dl^{-1}	147.3 ± 99.6	142.9 ± 96.8	159.7 ± 123.4	137.9 ± 88.5	149.7 ± 92.4
Creatinine, mg dl^{-1}	1.1 ± 0.2	1.0 ± 0.2	1.0 ± 0.2	1.1 ± 0.2	1.1 ± 0.2
GRS 19	8.4 ± 2.6	7.9 ± 3.0	8.3 ± 2.9	8.6 ± 3.0*	8.9 ± 2.9*,#
All-cause deaths, *n* (%)	18.2 (245)	9.5 (54)	14.9 (33)	23.3 (24)	29.4 (134)*,#
CV deaths, *n* (%)	8.5 (114)	2.5 (14)	11.3 (25)†,#	17.4 (18)	12.5 (57)*,#
MACE, *n* (%)	32.7 (441)	27.1 (153)	27.6 (61)	34.9 (36)	41.9 (191)*,#

Abbreviations: BMI, body mass index; BP, blood pressure; CV, cardiovascular; GRS, Genetic Risk Score; HA, heart attack; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MACE, major adverse cardiovascular event.
*P<0.01 *vs.* daytime BP<133/77 mm Hg and nighttime BP<122/73 mm Hg; #P<0.01 *vs.* daytime BP⩾133/77 mm Hg and nighttime BP<122/73 mm Hg; †P<0.05 *vs.* daytime BP⩾133/77 mm Hg and nighttime BP<122/73 mm Hg; ‡P<0.01 *vs.* daytime BP<133/77 mm Hg and nighttime BP⩾122/73 mm Hg; §P<0.01 *vs.* daytime BP⩾133/77 mm Hg and nighttime BP⩾122/73 mm Hg.

$P<0.01$) and nighttime DBP ($r=0.10$, $P<0.01$). However, there was no relationship between glycated hemoglobin and daytime SBP and daytime DBP. The BP values and daytime–nighttime BP variability are presented in Table 3. Analysis of BP dipping revealed the following nighttime SBP drop in groups: daytime BP<133 and <77 mm Hg and nighttime BP<122 and <73 mm Hg (7.0 ± 5.8%), and daytime BP⩾133 and ⩾77 mm Hg and nighttime BP<122 and <73 mm Hg (13.0 ± 4.8%), daytime BP<133 and <77 mm Hg and nighttime BP⩾122 and ⩾73 mm Hg (3.0 ± 5.3%), daytime BP⩾133 and ⩾77 mm Hg and nighttime BP⩾122 and ⩾73 mm Hg (4.1 ± 6.6%). Analysis of BP dipping revealed the following nighttime DBP drop in groups: daytime BP<133 and <77 mm Hg and nighttime BP<122 and <73 mm Hg (11.3 ± 6.5%), daytime BP⩾133 and ⩾77 mm Hg and nighttime BP<122 and <73 mm Hg (17.5 ± 5.5%), daytime BP<133 and <77 mm Hg and nighttime BP⩾122 and ⩾73 mm Hg (2.0 ± 5.6%), and daytime BP⩾133 and ⩾77 mm Hg and nighttime BP⩾122 and ⩾73 mm Hg (8.1 ± 6.6%). The relationships between daytime and nighttime BPs and GRS19 are presented in Table 4. The median follow-up period was 8.6 years. During 11 567 person-years of follow-up, 245 participants died (2.1 per 1000 person-years), including 114 of participants from cardiovascular causes (0.98 per 1000 person-years). After taking into consideration cardiovascular events during the follow-up period, 441 (32.7%) subjects experienced major adverse coronary events.

Patients with elevated nighttime and normal daytime BP exhibited an increased risk of major adverse coronary events compared with those with normal nighttime and elevated daytime BP. The probability of major adverse coronary events in the studied subgroups of patients is presented in Figure 1. Significant differences were noted between the probability of major adverse coronary events in patients with daytime BP⩾133 and ⩾77 mm Hg and nighttime BP⩾122 and ⩾73 mm Hg and patients with daytime BP⩾133 and ⩾77 mm Hg and nighttime BP<122 and <73 mm Hg ($P<0.03$). We also observed significant differences between the probability of major adverse coronary events in patients with daytime BP⩾133 and ⩾77 mm Hg and nighttime BP⩾122 and ⩾73 mm Hg and patients with daytime BP<133 and <77 mm Hg and nighttime BP<122 and <73 mm Hg ($P<0.02$). Significant differences were noted between probability of major adverse coronary events in patients with daytime BP<133 and <77 mm Hg and nighttime BP⩾122 and ⩾73 mm Hg and patients with daytime BP⩾133 and ⩾77 mm Hg and nighttime BP<122 and <73 mm Hg ($P<0.05$). We also observed significant differences between the probability of major adverse coronary events in patients with daytime BP<133 and <77 mm Hg and nighttime BP⩾122 and ⩾73 mm Hg and patients with daytime BP<133 and <77 mm Hg and nighttime BP<122 and <73 mm Hg ($P<0.04$).

DISCUSSION

The main finding of our study is the confirmation that elevated nighttime BP is genetically determined and nighttime DBP is related to GRS19 in CAD patients. We also found that elevated nighttime BP is associated with risk of major adverse coronary events in CAD patients.

Table 3 Blood pressure values in the studied group

	Total group n = *1345*	*Daytime BP< 133-/77 mm Hg, nighttime BP< 122/73 mm Hg,* n = *565*	*Daytime BP⩾ 133-/77 mm Hg, nighttime BP< 122/73 mm Hg,* n = *221*	*Daytime BP< 133-/77 mm Hg, nighttime BP⩾ 122/73 mm Hg,* n = *103*	*Daytime BP⩾ 133-/77 mm Hg, nighttime BP⩾ 122/73 mm Hg,* n = *456*
Office SBP, mm Hg	137.7 ± 20.1	127.4 ± 15.8	131.1 ± 17.0	138.7 ± 15.5*,#	150.4 ± 19.8*,#
Office DBP, mm Hg	78.3 ± 11.3	73.3 ± 8.4	72.3 ± 10.2	81.6 ± 8.7*,#	83.6 ± 12.4*,#
Office HR	70.5 ± 12.1	68.6 ± 11.2	68.2 ± 10.2	71.7 ± 12.2	72.7 ± 13.0
24 h SBP, mm Hg	124.1 ± 13.8	112.8 ± 7.2	124.5 ± 4.3*	123.8 ± 6.7*	138.1 ± 10.8*,#,‡
24 h DBP, mm Hg	71.4 ± 8.3	65.7 ± 4.9	69.3 ± 5.2	73.5 ± 5.5*,†	77.8 ± 8.4*,#
24 h HR, b.p.m.	66.7 ± 9.6	64.9 ± 8.3	65.1 ± 9.2	68.6 ± 10.0*,#	68.4 ± 10.4*,#
Daytime SBP, mm Hg	127.1 ± 14.0	115.8 ± 7.7	123.1 ± 4.7*	130.2 ± 7.8*,#	140.3 ± 11.3*,#,‡
Daytime DBP, mm Hg	74.3 ± 8.7	68.7 ± 5.4	69.8 ± 5.0	78.7 ± 6.1*,#	80.2 ± 8.7*,#
Daytime HR, b.p.m.	69.6 ± 10.5	67.6 ± 9.2	67.2 ± 9.7	72.2 ± 10.9*,#	71.3 ± 11.5*,#
Nighttime SBP, mm Hg	119.0 ± 15.4	107.6 ± 8.3	113.1 ± 6.8	126.7 ± 6.3*,#	134.3 ± 12.5*,#,‡
Nighttime DBP, mm Hg	66.4 ± 8.9	60.8 ± 5.4	64.8 ± 5.8	68.4 ± 6.3*	73.6 ± 8.9*,#,‡
Nighttime HR, b.p.m.	61.9 ± 8.9	60.3 ± 7.7	61.1 ± 8.5	62.7 ± 9.7	63.6 ± 9.5*
Dippers SBP and DBP, % (*n*)	29.7 (398)	28.3 (160)	71.9 (159)*	0 (0)	17.3 (79)#
Non-dippers SBP or DBP, % (*n*)	25.8 (349)	32.0 (181)	22.2 (49)	7.8 (8)*,‡	24.3 (111)
Non-dippers SBP and DBP, % (*n*)	44.5 (598)	39.7 (224)	5.9 (13)	92.2 (95)*,#	58.4 (266)*,#,‡

Abbreviations: b.p.m., beats per minute; DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure.
*P<0.01 *vs.* daytime BP<133/77 mm Hg and nighttime BP<122/73 mm Hg; #P<0.01 *vs.* daytime BP⩾133/77 mm Hg and nighttime BP<122/73 mm Hg; †P<0.05 *vs.* daytime BP⩾133/77 mm Hg and nighttime BP<122/73 mm Hg; ‡P<0.01 *vs.* daytime BP<133/77 mm Hg and nighttime BP⩾122/73 mm Hg.

Table 4 Multiple regression model of daytime and nighttime BP

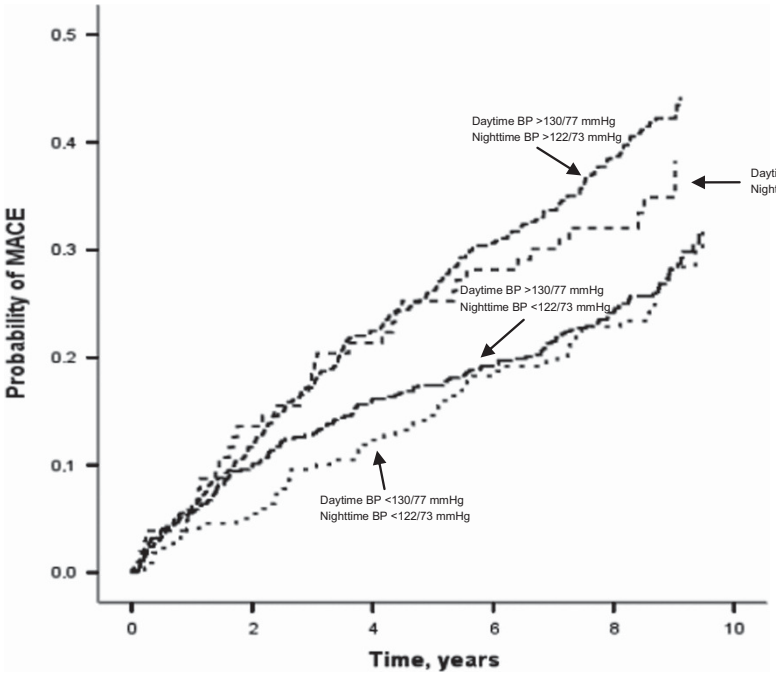
Variable	β *coefficient*	*S.e.*	*95% CI*	*Wald* χ^2	P-*value*
Daytime SBP[a]					
Diabetes	6.7	1.2	4.4 to 9.0	5.7	<0.01
Smoking	3.6	1.3	1.0 to 6.3	2.7	<0.01
BMI	0.5	0.1	0.2 to 0.7	4.0	<0.01
GRS19	0.04	0.2	−0.3 to 0.3	0.3	0.78
Daytime DBP[b]					
Diabetes	0.2	0.7	−1.1 to 1.6	0.3	0.74
Smoking	1.5	0.8	−0.1 to 3.1	1.8	0.06
BMI	0.1	0.1	−0.1 to 0.2	1.5	0.13
GRS19	0.1	0.1	−0.2 to 0.2	0.2	0.80
Nighttime SBP[c]					
Diabetes	8.3	1.3	5.8 to 10.9	6.4	<0.01
Smoking	4.8	1.5	1.9 to 7.7	3.2	<0.01
BMI	0.4	0.1	0.2 to 0.7	3.2	<0.01
GRS19	0.4	0.1	0.3 to 0.5	6.5	<0.01
Nighttime DBP[d]					
Diabetes	4.4	0.7	−0.1 to 2.9	1.9	0.06
Smoking	1.3	0.8	−0.3 to 3.0	1.6	0.11
BMI	0.1	0.1	−0.1 to 2.2	1.0	0.31
GRS19	0.1	0.1	−0.1 to 0.3	1.0	0.29

Abbreviations: BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; GRS, Genetic Risk Score; SBP, systolic blood pressure.
[a]Adjusted for daytime DBP, nighttime SBP, nighttime DBP, sex, age, dipping profile and LDL cholesterol.
[b]Adjusted for daytime SBP, nighttime SBP, nighttime DBP, sex, age, dipping profile and LDL cholesterol.
[c]Adjusted for daytime SBP, daytime DBP, nighttime DBP, sex, age, dipping profile and LDL cholesterol.
[d]Adjusted for daytime SBP, daytime DBP, nighttime SBP, sex, age, dipping profile and LDL cholesterol.

Persuasive evidence suggests that nighttime BP is superior to daytime BP in predicting outcome.[21] Given the limited reproducibility of daytime BP levels due to the dependence of daily physical activity, cardiovascular risk assessment might be more accurate if based on nighttime BP. Therefore, it is essential to understand the potential mechanisms that underlie BP regulation at night.

The Georgia Cardiovascular Twin Study demonstrated that, apart from genes that also influence daytime BP, specific genetic determinants explained 44% and 67% of nighttime SBP and DBP heritabilities, respectively.[22] In addition to genes that influence both daytime and nighttime BP, a large portion of heritability is explained by genes that specifically influence BP at night.[23] In the present study, we detected and examined the relationship between nighttime BP and SNPs in patients with CAD for the first time. Although a single SNP determines cardiovascular risk to a very small extent, Ripatti *et al.*[24] revealed that a GRS based on the additive effects of SNPs is more associated with cardiovascular risk. Using the concept of the additive effect of SNPs, we constructed GRS based on 19 SNPs significantly associated with cardiovascular risk, and we revealed that GRS19 was related to nighttime DBP. Moreover, we confirmed that elevated nighttime BP was related to an increased risk of major adverse coronary events. Therefore, GRS19 may be taken into consideration in cardiovascular risk assessment for patients with inappropriate daytime–nighttime BP variability. Leu *et al.*[25] confirmed genetic association with diurnal BP changes among subjects with young-onset hypertension. In contrast to our study, Leu *et al.*[25] did not assess coronary atherosclerosis in coronary angiography.

Previously performed clinical trials confirmed that both elevated daytime BP and nighttime BP were related to cardiovascular risk in CAD patients.[26] Moreover, blunted nighttime BP dipping was associated with advanced CAD and cardiovascular complications that arise from this condition.[27] Similarly, in a small group of men, Mousa *et al.*[28] confirmed the association between blunted nighttime BP values and coronary atherosclerosis extent in coronary angiography. Brotman



MACE:						
<130/77 mmHg <122/73 mmHg	n=563	56 (10%)	91 (16%)	109 (19%)	135 (24%)	153 (27%)
>130/77 mmHg <122/73 mmHg	n=221	13 (6%)	28 (13%)	41 (18%)	51 (23%)	60 (27%)
<130/77 mmHg >122/73 mmHg	n=103	14 (14%)	22 (21%)	29 (28%)	33 (32%)	36 (35%)
>130/77 mmHg >122/73 mmHg	n=458	54 (12%)	103 (22%)	140 (31%)	176 (38%)	191 (42%)

Figure 1 Probability of MACE in the studied groups of patients.

et al.[29] demonstrated that non-dipping status was a risk factor for all-cause mortality. Similar to the study by Brotman *et al.*,[29] greater than half of the patients were non-dippers in our study. However, in the study by Brotman *et al.*,[29] non-dipping status was defined as a reduction in mean nocturnal SBP < 10% compared with mean daytime values. In our study, non-dipping status was defined as a reduction in mean SBP < 10% and/or a reduction in mean DBP < 10% compared with respective daytime values. Pierdomenico *et al.*[30] confirmed that circadian BP changes were independently associated with increased cardiovascular risk in elderly subjects. In contrast to our study, they did not take into consideration coexisting CAD confirmed by coronary angiography.

Of note, in our study, elevated nighttime BPs were observed more often in patients with diabetes, and glycemic control was worse in diabetics with elevated nighttime BPs. Diabetes mellitus is associated with markedly increased cardiovascular risk, and the predictive role of nighttime BP has already been established in patients with diabetes.[3,31] Previously performed clinical trials confirmed that nocturnal hypertension is more frequent in diabetics, partially due to autonomic dysfunction.[32,33] However, our study confirmed that elevated nighttime BP is more frequent in diabetics with less effectively controlled glycemia. Accordingly, diabetes, especially when uncontrolled, may predispose a patient to elevated nighttime BP that may subsequently be related to high cardiovascular risk. A modification as simple and inexpensive as switching the ingestion time of one or more hypertensive medications from morning to evening or bedtime may be the only action necessary to achieve proper control of nighttime BP. Recently published results from the MAPEC study confirmed that elevated asleep BP was associated with cardiovascular morbidity and mortality, and a bedtime antihypertensive treatment strategy significantly reduced cardiovascular risk.[34]

Our study confirmed that elevated nighttime BP was related to an increased probability of major adverse coronary events in patients with confirmed CAD. Moreover, the highest risk of major adverse coronary events was observed in patients with elevated nighttime and daytime BPs, but patients with elevated nighttime BP and normal daytime BP had increased risk of major adverse coronary events compared with subjects with normal nighttime BP and elevated daytime BP. To date, our studies have confirmed that nighttime BP contribute to increased cardiovascular risk in patients with coronary atherosclerosis confirmed by coronary angiography.[35] The systematic review by O'Flynn *et al.*[36] attempted to explain the reasons for high cardiovascular mortality related to isolated nighttime hypertension. However, analyzed data did not produce a clear answer concerning the relationship between elevated nighttime BP and target organ damage associated with cardiovascular mortality.[36] Haruhara *et al.*[37] suggested that isolated

nocturnal hypertension was related to renal interstitial fibrosis or tubular atrophy. Furthermore, in the RESIST-POL study, nighttime SBP was independently related to concentric heart hypertrophy.[38]

Sherwood *et al*.[39] confirmed that CAD and advanced age are accompanied by blunted nighttime BP dipping, which may increase the risk of adverse cardiovascular events.

Some limitations of our study are worth mentioning. Given that this study was retrospective, longitudinal assessment of hypertension control and changes in antihypertensive therapy were beyond the scope of the investigation. In addition, multiple assessments of ambulatory BP were not performed, thereby eliminating our ability to determine whether BP values were stable over time or impacted by antihypertensive treatment. Cutoff points of BP values were established on the basis of BP values measured over 24 h in patients with confirmed CAD.

CONCLUSION

In conclusion, our study confirmed an important role of nighttime BP in the development of cardiovascular complications in CAD patients. Subjects with elevated nighttime BP and normal daytime BP exhibit an increased risk of cardiovascular complications compared with those with normal nighttime and elevated daytime BP. Nighttime SBP is genetically determined and related to the additive effect of SNPs. Future studies should address the application of GRSs in clinical practice.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

1 Staessen JA, Thijs L, Fagard R, O'Brien ET, Clement D, de Leeuw PW, Mancia G, Nachev C, Palatini P, Parati G, Tuomilehto J, Webster J. Predicting cardiovascular risk using conventional *vs*. ambulatory blood pressure in older patients with systolic hypertension. Systolic Hypertension in Europe Trial Investigators. *JAMA* 1999; **282**: 539–546.

2 Dolan E, Stanton A, Thijs L, Hinedi K, Atkins N, McClory S, Den Hond E, McCormack P, Staessen JA, O'Brien E. Superiority of ambulatory over clinic blood pressure measurement in predicting mortality: the Dublin outcome study. *Hypertension* 2005; **46**: 156–161.

3 Hermida RC, Ayala DE, Mojon A, Fernandez JR. Sleep-time blood pressure as a therapeutic target for cardiovascular risk reduction in type 2 diabetes. *Am J Hypertens* 2012; **25**: 325–334.

4 Sega R, Facchetti R, Bombelli M, Cesana G, Corrao G, Grassi G, Mancia G. Prognostic value of ambulatory and home blood pressures compared with office blood pressure in the general population: follow-up results from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study. *Circulation* 2005; **111**: 1777–1783.

5 Rossen NB, Knudsen ST, Fleischer J, Hvas AM, Ebbehoj E, Poulsen PL, Hansen KW. Targeting nocturnal hypertension in type 2 diabetes mellitus. *Hypertension* 2014; **64**: 1080–1087.

6 Ruiz-Hurtado G, Ruilope LM, de la Sierra A, Sarafidis P, de la Cruz JJ, Gorostidi M, Segura J, Vinyoles E, Banegas JR. Association between high and very high albuminuria and nighttime blood pressure: influence of diabetes and chronic kidney disease. *Diabetes Care* 2016; **39**: 1729–1737.

7 Drawz PE, Alper AB, Anderson AH, Brecklin CS, Charleston J, Chen J, Deo R, Fischer MJ, He J, Hsu CY, Huan Y, Keane MG, Kusek JW, Makos GK, Miller 3rd ER, Soliman EZ, Steigerwalt SP, Taliercio JJ, Townsend RR, Weir MR, Wright Jr JT, Xie D, Rahman M. Masked hypertension and elevated nighttime blood pressure in CKD: prevalence and association with target organ damage. *Clin J Am Soc Nephrol* 2016; **11**: 642–652.

8 Sabio JM, Martinez-Bordonado J, Sanchez-Berna I, Vargas-Hitos JA, Mediavilla JD, Navarrete-Navarrete N, Zamora-Pasadas M, Ruiz ME, Jimenez-Alonso J. Nighttime blood pressure patterns and subclinical atherosclerosis in women with systemic lupus erythematosus. *J Rheumatol* 2015; **42**: 2310–2317.

9 Sobiczewski W, Wirtwein M, Gruchala M, Kocic I. Mortality in hypertensive patients with coronary heart disease depends on chronopharmacotherapy and dipping status. *Pharmacol Rep* 2014; **66**: 448–452.

10 Portaluppi F, Smolensky MH. Perspectives on the chronotherapy of hypertension based on the results of the MAPEC study. *Chronobiol Int* 2010; **27**: 1652–1667.

11 Obayashi K, Saeki K, Kurumatani N. Nighttime BP in elderly individuals with prediabetes/diabetes with and without CKD: The HEIJO-KYO Study. *Clin J Am Soc Nephrol* 2016; **11**: 867–874.

12 Wirtwein M, Melander O, Sjogren M, Hoffmann M, Narkiewicz K, Gruchala M, Sobiczewski W. The relationship between gene polymorphisms and dipping profile in patients with coronary heart disease. *Am J Hypertens* 2016; **29**: 1094–1102.

13 Hansen TW, Li Y, Boggia J, Thijs L, Richart T, Staessen JA. Predictive role of the nighttime blood pressure. *Hypertension* 2011; **57**: 3–10.

14 O'Brien E, Sheridan J, O'Malley K. Dippers and non-dippers. *Lancet* 1988; **2**: 397.

15 Kathiresan S, Voight BF, Purcell S, Musunuru K, Ardissino D, Mannucci PM, Anand S, Engert JC, Samani NJ, Schunkert H, Erdmann J, Reilly MP, Rader DJ, Morgan T, Spertus JA, Stoll M, Girelli D, McKeown PP, Patterson CC, Siscovick DS, O'Donnell CJ, Elosua R, Peltonen L, Salomaa V, Schwartz SM, Melander O, Altshuler D, Merlini PA, Berzuini C, Bernardinelli L, Peyvandi F, Tubaro M, Celli P, Ferrario M, Fetiveau R, Marziliano N, Casari G, Galli M, Ribichini F, Rossi M, Bernardi F, Zonzin P, Piazza A, Yee J, Friedlander Y, Marrugat J, Lucas G, Subirana I, Sala J, Ramos R, Meigs JB, Williams G, Nathan DM, MacRae CA, Havulinna AS, Berglund G, Hirschhorn JN, Asselta R, Duga S, Spreafico M, Daly MJ, Nemesh J, Korn JM, McCarroll SA, Surti A, Guiducci C, Gianniny L, Mirel D, Parkin M, Burtt N, Gabriel SB, Thompson JR, Braund PS, Wright BJ, Balmforth AJ, Ball SG, Hall A, Linsel-Nitschke P, Lieb W, Ziegler A, Konig I, Hengstenberg C, Fischer M, Stark K, Grosshennig A, Preuss M, Wichmann HE, Schreiber S, Ouwehand W, Deloukas P, Scholz M, Cambien F, Li M, Chen Z, Wilensky R, Matthai W, Qasim A, Hakonarson HH, Devaney J, Burnett MS, Pichard AD, Kent KM, Satler L, Lindsay JM, Waksman R, Knouff CW, Waterworth DM, Walker MC, Mooser V, Epstein SE, Scheffold T, Berger K, Huge A, Martinelli N, Olivieri O, Corrocher R, McKeown P, Erdmann E, Konig IR, Holm H, Thorleifsson G, Thorsteinsdottir U, Stefansson K, Do R, Xie C, Siscovick D. Genome-wide association of early-onset myocardial infarction with single nucleotide polymorphisms and copy number variants. *Nat Genet* 2009; **41**: 334–341.

16 Clarke R, Peden JF, Hopewell JC, Kyriakou T, Goel A, Heath SC, Parish S, Barlera S, Franzosi MG, Rust S, Bennett D, Silveira A, Malarstig A, Green FR, Lathrop M, Gigante B, Leander K, de Faire U, Seedorf U, Hamsten A, Collins R, Watkins H, Farrall M. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. *N Engl J Med* 2009; **361**: 2518–2528.

17 Erdmann J, Grosshennig A, Braund PS, Konig IR, Hengstenberg C, Hall AS, Linsel-Nitschke P, Kathiresan S, Wright B, Tregouet DA, Cambien F, Bruse P, Aherrahrou Z, Wagner AK, Stark K, Schwartz SM, Salomaa V, Elosua R, Melander O, Voight BF, O'Donnell CJ, Peltonen L, Siscovick DS, Altshuler D, Merlini PA, Peyvandi F, Bernardinelli L, Ardissino D, Schillert A, Blankenberg S, Zeller T, Wild P, Schwarz DF, Tiret L, Perret C, Schreiber S, El Mokhtari NE, Schafer A, Marz W, Renner W, Bugert P, Kluter H, Schrezenmeir J, Rubin D, Ball SG, Balmforth AJ, Wichmann HE, Meitinger T, Fischer M, Meisinger C, Baumert J, Peters A, Ouwehand WH, Deloukas P, Thompson JR, Ziegler A, Samani NJ, Schunkert H. New susceptibility locus for coronary artery disease on chromosome 3q22.3. *Nat Genet* 2009; **41**: 280–282.

18 Schunkert H, Konig IR, Kathiresan S, Reilly MP, Assimes TL, Holm H, Preuss M, Stewart AF, Barbalic M, Gieger C, Absher D, Aherrahrou Z, Allayee H, Altshuler D, Anand SS, Andersen K, Anderson JL, Ardissino D, Ball SG, Balmforth AJ, Barnes TA, Becker DM, Becker LC, Berger K, Bis JC, Boekholdt SM, Boerwinkle E, Braund PS, Brown MJ, Burnett MS, Buysschaert I, Carlquist JF, Chen L, Cichon S, Codd V, Davies RW, Dedoussis G, Dehghan A, Demissie S, Devaney JM, Diemert P, Do R, Doering A, Eifert S, Mokhtari NE, Ellis SG, Elosua R, Engert JC, Epstein SE, de Faire U, Fischer M, Folsom AR, Freyer J, Gigante B, Girelli D, Gretarsdottir S, Gudnason V, Gulcher JR, Halperin E, Hammond N, Hazen SL, Hofman A, Horne BD, Illig T, Iribarren C, Jones GT, Jukema JW, Kaiser MA, Kaplan LM, Kastelein JJ, Khaw KT, Knowles JW, Kolovou G, Kong A, Laaksonen R, Lambrechts D, Leander K, Lettre G, Li M, Lieb W, Loley C, Lotery AJ, Mannucci PM, Maouche S, Martinelli N, McKeown PP, Meisinger C, Meitinger T, Melander O, Merlini PA, Mooser V, Morgan T, Muhleisen TW, Muhlestein JB, Munzel T, Musunuru K, Nahrstaedt J, Nelson CP, Nothen MM, Olivieri O, Patel RS, Patterson CC, Peters A, Peyvandi F, Qu L, Quyyumi AA, Rader DJ, Rallidis LS, Rice C, Rosendaal FR, Rubin D, Salomaa V, Sampietro ML, Sandhu MS, Schadt E, Schafer A, Schillert A, Schreiber S, Schrezenmeir J, Schwartz SM, Siscovick DS, Sivananthan M, Sivapalaratnam S, Smith A, Smith TB, Snoep JD, Soranzo N, Spertus JA, Stark K, Stirrups K, Stoll M, Tang WH, Tennstedt S, Thorgeirsson G, Thorleifsson G, Tomaszewski M, Uitterlinden AG, van Rij AM, Voight BF, Wareham NJ, Wells GA, Wichmann HE, Wild PS, Willenborg C, Witteman JC, Wright BJ, Ye S, Zeller T, Ziegler A, Cambien F, Goodall AH, Cupples LA, Quertermous T, Marz W, Hengstenberg C, Blankenberg S, Ouwehand WH, Hall AS, Deloukas P, Thompson JR, Stefansson K, Roberts R, Thorsteinsdottir U, O'Donnell CJ, McPherson R, Erdmann J, Samani NJ. Large-scale association analysis identifies 13 new susceptibility loci for coronary artery disease. *Nat Genet* 2011; **43**: 333–338.

19 Roberts R, Stewart AF. Genes and coronary artery disease: where are we? *J Am Coll Cardiol* 2012; **60**: 1715–1721.

20 Deloukas P, Kanoni S, Willenborg C, Farrall M, Assimes TL, Thompson JR, Ingelsson E, Saleheen D, Erdmann J, Goldstein BA, Stirrups K, Konig IR, Cazier JB, Johansson A, Hall AS, Lee JY, Willer CJ, Chambers JC, Esko T, Folkersen L, Goel A, Grundberg E, Havulinna AS, Ho WK, Hopewell JC, Eriksson N, Kleber ME, Kristiansson K, Lundmark P, Lyytikainen LP, Rafelt S, Shungin D, Strawbridge RJ, Thorleifsson G, Tikkanen E, Van Zuydam N, Voight BF, Waite LL, Zhang W, Ziegler A, Absher D, Altshuler D, Balmforth AJ, Barroso I, Braund PS, Burgdorf C, Claudi-Boehm S, Cox D, Dimitriou M, Do R, Doney AS, El Mokhtari N, Eriksson P, Fischer K, Fontanillas P, Franco-Cereceda A, Gigante B, Groop L, Gustafsson S, Hager J, Hallmans G, Han BG, Hunt SE, Kang HM, Illig T, Kessler T, Knowles JW, Kolovou G, Kuusisto J, Langenberg C, Langford C, Leander K, Lokki ML, Lundmark A, McCarthy MI, Meisinger C, Melander O, Mihailov E, Maouche S, Morris AD, Muller-Nurasyid M,

Nikus K, Peden JF, Rayner NW, Rasheed A, Rosinger S, Rubin D, Rumpf MP, Schafer A, Sivananthan M, Song C, Stewart AF, Tan ST, Thorgeirsson G, van der Schoot CE, Wagner PJ, Wells GA, Wild PS, Yang TP, Amouyel P, Arveiler D, Basart H, Boehnke M, Boerwinkle E, Brambilla P, Cambien F, Cupples AL, de Faire U, Dehghan A, Diemert P, Epstein SE, Evans A, Ferrario MM, Ferrieres J, Gauguier D, Go AS, Goodall AH, Gudnason V, Hazen SL, Holm H, Iribarren C, Jang Y, Kahonen M, Kee F, Kim HS, Klopp N, Koenig W, Kratzer W, Kuulasmaa K, Laakso M, Laaksonen R, Lind L, Ouwehand WH, Parish S, Park JE, Pedersen NL, Peters A, Quertermous T, Rader DJ, Salomaa V, Schadt E, Shah SH, Sinisalo J, Stark K, Stefansson K, Tregouet DA, Virtamo J, Wallentin L, Wareham N, Zimmermann ME, Nieminen MS, Hengstenberg C, Sandhu MS, Pastinen T, Syvanen AC, Hovingh GK, Dedoussis G, Franks PW, Lehtimaki T, Metspalu A, Zalloua PA, Siegbahn A, Schreiber S, Ripatti S, Blankenberg SS, Perola M, Clarke R, Boehm BO, O'Donnell C, Reilly MP, Marz W, Collins R, Kathiresan S, Hamsten A, Kooner JS, Thorsteinsdottir U, Danesh J, Palmer CN, Roberts R, Watkins H, Schunkert H, Samani NJ. Large-scale association analysis identifies new risk loci for coronary artery disease. *Nat Genet* 2013; **45**: 25–33.

21 Boggia J, Li Y, Thijs L, Hansen TW, Kikuya M, Bjorklund-Bodegard K, Richart T, Ohkubo T, Kuznetsova T, Torp-Pedersen C, Lind L, Ibsen H, Imai Y, Wang J, Sandoya E, O'Brien E, Staessen JA. Prognostic accuracy of day versus night ambulatory blood pressure: a cohort study. *Lancet* 2007; **370**: 1219–1229.

22 Wang X, Ding X, Su S, Yan W, Harshfield G, Treiber F, Snieder H. Genetic influences on daytime and night-time blood pressure: similarities and differences. *J Hypertens* 2009; **27**: 2358–2364.

23 Xu X, Su S, Treiber FA, Vlietinck R, Fagard R, Derom C, Gielen M, Loos RJ, Snieder H, Wang X. Specific genetic influences on nighttime blood pressure. *Am J Hypertens* 2015; **28**: 440–443.

24 Ripatti S, Tikkanen E, Orho-Melander M, Havulinna AS, Silander K, Sharma A, Guiducci C, Perola M, Jula A, Sinisalo J, Lokki ML, Nieminen MS, Melander O, Salomaa V, Peltonen L, Kathiresan S. A multilocus genetic risk score for coronary heart disease: case-control and prospective cohort analyses. *Lancet* 2010; **376**: 1393–1400.

25 Leu HB, Chung CM, Lin SJ, Chiang KM, Yang HC, Ho HY, Ting CT, Lin TH, Sheu SH, Tsai WC, Chen JH, Yin WH, Chiu TY, Chen CI, Fann CS, Chen YT, Pan WH, Chen JW. Association of circadian genes with diurnal blood pressure changes and non-dipper essential hypertension: a genetic association with young-onset hypertension. *Hypertens Res* 2015; **38**: 155–162.

26 Sobiczewski W, Wirtwein M, Gruchala M. Is daytime blood pressure adequate in cardiovascular risk assessment in patients with coronary atherosclerosis? *Blood Press* 2014; **23**: 96–101.

27 Wirtwein M, Gruchala M, Sobiczewski W. Diurnal blood pressure profile and coronary atherosclerosis extent are related to cardiovascular complications. *Blood Press* 2016; **26**: 1–6.

28 Mousa T, el-Sayed MA, Motawea AK, Salama MA, Elhendy A. Association of blunted nighttime blood pressure dipping with coronary artery stenosis in men. *Am J Hypertens* 2004; **17**: 977–980.

29 Brotman DJ, Davidson MB, Boumitri M, Vidt DG. Impaired diurnal blood pressure variation and all-cause mortality. *Am J Hypertens* 2008; **21**: 92–97.

30 Pierdomenico SD, Pierdomenico AM, Coccina F, Lapenna D, Porreca E. Circadian blood pressure changes and cardiovascular risk in elderly-treated hypertensive patients. *Hypertens Res* 2016; **39**: 805–811.

31 Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, Ingelsson E, Lawlor DA, Selvin E, Stampfer M, Stehouwer CD, Lewington S, Pennells L, Thompson A, Sattar N, White IR, Ray KK, Danesh J. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* 2010; **375**: 2215–2222.

32 Tofe Povedano S, Garcia, De La Villa B. 24-Hour and nighttime blood pressures in type 2 diabetic hypertensive patients following morning or evening administration of olmesartan. *J Clin Hypertens (Greenwich)* 2009; **11**: 426–431.

33 Hermida RC, Ayala DE, Mojon A, Fernandez JR. Influence of time of day of blood pressure-lowering treatment on cardiovascular risk in hypertensive patients with type 2 diabetes. *Diabetes Care* 2011; **34**: 1270–1276.

34 Hermida RC, Ayala DE, Smolensky MH, Fernandez JR, Mojon A, Portaluppi F. Chronotherapy with conventional blood pressure medications improves management of hypertension and reduces cardiovascular and stroke risks. *Hypertens Res* 2016; **39**: 277–292.

35 Sobiczewski W, Wirtwein M, Gruchala M. Is nighttime blood pressure important in cardiovascular risk assessment in coronary atherosclerosis? *J Hum Hypertens* 2014; **28**: 564–566.

36 O'Flynn AM, Madden JM, Russell AJ, Curtin RJ, Kearney PM. Isolated nocturnal hypertension and subclinical target organ damage: a systematic review of the literature. *Hypertens Res* 2015; **38**: 570–575.

37 Haruhara K, Tsuboi N, Koike K, Fukui A, Miyazaki Y, Kawamura T, Ogura M, Yokoo T. Renal histopathological findings in relation to ambulatory blood pressure in chronic kidney disease patients. *Hypertens Res* 2015; **38**: 116–122.

38 Dobrowolski P, Prejbisz A, Klisiewicz A, Florczak E, Rybicka J, Januszewicz A, Hoffman P. Determinants of concentric left ventricular hypertrophy in patients with resistant hypertension: RESIST-POL study. *Hypertens Res* 2015; **38**: 545–550.

39 Sherwood A, Bower JK, Routledge FS, Blumenthal JA, McFetridge-Durdle JA, Newby LK, Hinderliter AL. Nighttime blood pressure dipping in postmenopausal women with coronary heart disease. *Am J Hypertens* 2012; **25**: 1077–1082.