Relationship between clinic and ambulatory blood pressure and mortality: an observational cohort study in 59 124 patients

Natalie Staplin, Alejandro de la Sierra*, Luis M Ruilope, Jonathan R Emberson, Ernest Vinyoles, Manuel Gorostidi, Gema Ruiz-Hurtado, Julián Segura, Colin Baigent, Bryan Williams*

Summary

Background Ambulatory blood pressure provides a more comprehensive assessment than clinic blood pressure, and has been reported to better predict health outcomes than clinic or home pressure. We aimed to examine associations of clinic and 24-h ambulatory blood pressure with all-cause and cardiovascular mortality in a large cohort of primary care patients referred for assessment of hypertension.

Methods We did an observational cohort study using clinic and ambulatory blood pressure data obtained from March 1, 2004, to Dec 31, 2014, from the Spanish Ambulatory Blood Pressure Registry. This registry included patients from 223 primary care centres from the Spanish National Health System in all 17 regions of Spain. Mortality data (date and cause) were ascertained by a computerised search of the vital registry of the Spanish National Institute of Statistics. Complete data were available for age, sex, all blood pressure measures, and BMI. For each study participant, follow-up was from the date of their recruitment to the date of death or Dec 31, 2019, whichever occurred first. Cox models were used to estimate associations between usual clinic or ambulatory blood pressure and mortality, adjusted for confounders and additionally for alternative measures of blood pressure. For each measure of blood pressure, we created five groups (ie, fifths) defined by quintiles of that measure among those who subsequently died.

Findings During a median follow-up of 9·7 years, 7174 (12·1%) of 59 124 patients died, including 2361 (4·0%) from cardiovascular causes. J-shaped associations were observed for several blood pressure measures. Among the top four baseline-defined fifths, 24-h systolic blood pressure was more strongly associated with all-cause death (hazard ratio [HR] 1·41 per 1 – SD increment [95% CI 1·36–1·47]) than clinic systolic blood pressure (1·18 [1·13–1·23]). After adjustment for clinic blood pressure, 24-h blood pressure remained strongly associated with all-cause deaths (HR 1·43 [95% CI 1·37–1·49]), but the association between clinic blood pressure and all-cause death was attenuated when adjusted for 24-h blood pressure (1·04 [1·00–1·09]). Compared with the informativeness of clinic systolic blood pressure (100%), night-time systolic blood pressure was most informative about risk of all-cause death (591%) and cardiovascular death (604%). Relative to blood pressure within the normal range, elevated all-cause mortality risks were observed for masked hypertension (HR 1·24 [95% CI 1·12–1·37]) and sustained hypertension (1·24 [1·15–1·32]), but not white-coat hypertension, and elevated cardiovascular mortality risks were observed for masked hypertension (1·37 [1·15–1·63]) and sustained hypertension (1·38 [1·22–1·55]), but not white-coat hypertension.

Interpretation Ambulatory blood pressure, particularly night-time blood pressure, was more informative about the risk of all-cause death and cardiovascular death than clinic blood pressure.

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*Joint first authors

Medical Research Council Population Health Research Unit, Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK (N Staplin PhD, Prof J R Emberson PhD, Prof C Baigent FMedSci); **Department of Internal Medicine, Hospital Mutua Terrassa, University of Barcelona, Barcelona, Spain** (Prof A de la Sierra MD); **Hypertension Unit and Cardiorenal Translational Research Laboratory, Institute of Research i+12, Hospital Universitario 12 de Octubre and CIBER of Cardiovascular Disease (CIBERCV), Madrid, Spain** (L M Ruilope, G Ruiz-Hurtado PhD, J Segura MD); **School of Doctoral Studies and Research, Universidad Europea de Madrid, Madrid, Spain** (L M Ruilope); **Primary Care Centre La Mina, Barcelona, Spain** (E Vinyoles MD); **Department of Nephrology, Hospital Universitario Central de Asturias, RedinRen, Oviedo, Spain** (M Gorostidi MD); **University College London (UCL) Institute of Cardiovascular Science and National Institute for Health Research, UCL Hospitals Biomedical Research Centre, London, UK** (Prof B Williams FMedSci)

Introduction

Ambulatory blood pressure provides a more comprehensive assessment of blood pressure over the course of a 24-h period than clinic blood pressure, and has been reported to better predict health outcomes than clinic or home pressure.[1–4] Evidence for the influence of ambulatory blood pressure on prognosis comes mainly from population-based studies,[4–8] and a few relatively small clinical investigations.[9–12] However, in most of these previous studies, the number of participants studied or clinical outcomes were often limited (even in studies that included information about non-fatal outcomes),[5,6,8–12] reducing the ability to discriminate the predictive value of the clinic versus ambulatory blood pressure. Moreover, studies including a larger number of participants were mainly obtained by pooling databases from previous small studies.[4,8] Furthermore, uncertainty exists about whether the average ambulatory blood pressure over the

Correspondence to:
Prof Bryan Williams, University College London (UCL) Institute of Cardiovascular Science and National Institute for Health Research, UCL Hospitals Biomedical Research Centre, London W1T 7DN, UK
bryan.williams@ucl.ac.uk

Research in context

Evidence before this study

The link between elevated clinic blood pressure and reduced life expectancy has been recognised for decades. Several studies have reported that ambulatory blood pressure measured over 24 h is more strongly associated with health outcomes than conventional clinic blood pressure measurement. These studies have varied in size and statistical power, particularly with respect to all-cause mortality, or have only achieved scale by pooling databases from previous smaller studies. Some studies have also assessed clinic, 24-h, daytime, or night-time average blood pressures to evaluate which are most strongly associated with death. The majority, but not all, suggest that night-time blood pressure is most predictive of cardiovascular morbidity or death. Specific blood pressure phenotypes that are distinct from sustained hypertension exist—notably, masked hypertension (clinic blood pressure normal, ambulatory blood pressure elevated) or white-coat hypertension (clinic blood pressure elevated, ambulatory blood pressure normal). The relationship between these phenotypes and death has remained ill-defined because of the small number of deaths in previous studies in which these phenotypes have been characterised.

Added value of this study

This study is by far the largest, single population-based study of the relationship of both clinic and ambulatory blood pressures with death, undertaken in primary care, involving almost 60 000 patients, over a long follow-up duration (median 9·7 years), during which 7174 deaths were reported, including 2361 from cardiovascular disease. The study shows that ambulatory blood pressure was more informative about the risk of all-cause death and cardiovascular death than conventional clinic blood pressure. Indeed, after adjustment for clinic blood pressure, 24-h blood pressure remained strongly associated with death (hazard ratio 1·43 per 1 – SD increment [95% CI 1·37–1·49]), whereas most of the association between clinic blood pressure and death was lost after adjustment for 24-h blood pressure (1·04 [1·00–1·09]). Night-time ambulatory systolic blood pressure was six times more informative for death than clinic systolic blood pressure and nearly twice as informative as daytime ambulatory systolic blood pressure. These findings were similar whether patients were treated for hypertension at baseline (35 128 [59%] of 59 124) or not, (23 996 [41%]) and were consistent for all ages and both sexes. Finally, relative to those with normal blood pressure, masked hypertension was associated with an increased risk of death whereas white-coat hypertension was not.

Implications of all the available evidence

The findings of this study reinforce and substantially extend the information from previous studies linking methods of blood pressure measurement to patient outcomes. This very large study unequivocally demonstrates the dominance of ambulatory blood pressure over clinic blood pressure in the association between blood pressure and all-cause death and cardiovascular death, whether treated for hypertension or not. The dominance of the association of night-time blood pressure with death confirms some previous reports and is striking, highlighting a need to both evaluate and control night-time blood pressure, particularly in higher risk patients. The risk of death associated with masked hypertension is concerning as these patients usually remain undetected with screening using clinic blood pressure alone. The absence of an association between white-coat hypertension and increased risk of death appears reassuring; however, many of these patients will progress to sustained hypertension.

night-time, daytime, or the full 24 h is the strongest predictor of death.[3–9,11,13,14] Some[4,6,9,11] but not all studies[5,10] have suggested that night-time blood pressure is the strongest predictor of death. Moreover, the implications of hypertension phenotypes such as white-coat hypertension and masked hypertension with regard to mortality have remained ill-defined—namely, because of the small number of deaths in previous studies.[15–24]

In this largest study to date, we aimed to report the associations between long-term usual levels of clinic and ambulatory blood pressure indices, and of hypertension phenotypes, with total and cardiovascular death in patients in primary care practice recruited into the Spanish Ambulatory Blood Pressure Monitoring Mortality Study.

Methods

Study design and patient population

We did an observational cohort study using clinic and ambulatory blood pressure data obtained from March 1, 2004, to Dec 31, 2014, from the Spanish Ambulatory Blood Pressure Registry, a national study of patients selected by their physicians at 223 primary care centres from the Spanish National Health System in all 17 regions of Spain.[25,26] Eligible participants were 18 years or older and had to meet guideline-recommended indications for ambulatory blood pressure monitoring,[27–29] which included suspected white-coat hypertension, refractory or resistant hypertension, assessment of drug treatment efficacy, high-risk hypertension, labile or borderline hypertension, and the study of circadian blood pressure pattern. All patients included into the registry provided written informed consent. The protocols for the registry analyses were approved by the Institutional Review Boards of the participating centres.

Blood pressure indices and study variables

Clinic blood pressure was measured with validated oscillometric devices or calibrated mercury sphygmomanometers after a 5-min rest while seated, using standardised procedures.[27,30] We used the mean of two clinic pressure readings. Thereafter, ambulatory blood

pressure monitoring was done using validated, oscillometric devices (Spacelabs 90207; Snoqualmie, WA, USA), programmed to record blood pressure at 20-min intervals for the day and at 30-min intervals for the night. Appropriate cuff sizes were used. We used the mean of all valid readings (based on predefined quality criteria for a valid 24 h blood pressure average, including successful recording of ≥70% of systolic and diastolic pressure readings during 24 h, and at least one valid measurement per h). 66% of patients achieved valid readings of more than 75%, 42% achieved valid readings of 80%, 25% achieved valid readings of 85%, 16% achieved valid readings of 90%, and 10% achieved valid readings of 95%.

Day and night periods were defined according to the patient's self-reported data for sleeping and waking times. Other variables were obtained at entry from personal interview and physical examination at study visits or from clinical records. The case report form included a question about previous cardiovascular disease with a box for investigators to tick to indicate presence of previous disease. However, if the box was not checked, distinguishing whether this omission was because the participant had no history of previous disease or the question was not answered was not possible; as such, some cases of previous cardiovascular disease might have been missed. For a subset of patients, clinic and ambulatory blood pressure was measured at two different timepoints (an average of 18 months apart).

Mortality data

The date and cause of death were ascertained by a computerised search of the vital registry of the Spanish National Institute of Statistics (contract 20534 between the University of Barcelona and the National Institute of Statistics), which has been shown to be accurate and reliable with complete coverage.[31] Individuals were designated as having died if they were recorded in the vital registry. Cause of death was determined from the death certificate, and was coded according to the International Classification of Diseases (10th Revision). Deaths with codes in the range I00–I99 were classified as of cardiovascular origin. Cardiovascular deaths were also further subdivided into deaths from coronary heart disease (I21–I25), stroke (I60–I69), or heart failure (I50). For each study participant, follow-up was from the date of their recruitment to the date of death or Dec 31, 2019, whichever occurred first.

Statistical analysis

Complete data were available for age, sex, all blood pressure measures, and BMI. Missing data for current smoking, diabetes, and dyslipidaemia status was less than 1%, so patients with missing data were assumed not to have the condition. Univariable group comparisons of continuous variables were done using ANOVA tests, and categorical variables were done using χ^2 tests. Pearson correlation coefficients were used to estimate correlation between blood pressure indices. For each measure of blood pressure, we created five groups (ie, fifths) defined by quintiles of that measure among those who subsequently died, to ensure similar number of deaths in each group. We used Cox regression to estimate mortality hazard ratios (HRs) for each of the top four-fifths of each blood pressure measure relative to the lowest one-fifth. Assessment of the proportional hazards assumption found some evidence against proportionality for some of the blood pressure measures. However, even in the presence of non-proportionality, the Cox HR still provides a useful summary statistic to describe the average association of the blood pressure index to risk over the follow-up period. These HR estimates were adjusted for age, sex, smoking status (current *vs* not), BMI, diabetes status (previous record of diabetes *vs* no record), dyslipidaemia status (previous record of dyslipidaemia *vs* no record), previous cardiovascular disease (previous record of ischaemic heart disease, stroke, or heart failure *vs* no record), and number of antihypertensive drugs (zero or untreated *vs* one *vs* two or more). The association of each blood pressure measure independently of other measures was then assessed by inclusion of those other measures into the model. Data from 2928 patients with repeated measurements of clinic and ambulatory blood pressure were used to calculate regression dilution ratios using Rosner's method.[32] Log HRs and their associated standard errors were then divided by these regression dilution ratios to correct for regression dilution bias (ie, the underestimation of the association of long-term usual blood pressure with risk caused by measurement error and within-person variability in blood pressure).

In the figures, each HR (including the reference group with an HR of 1·0) is shown with a group-specific confidence interval that reflects the amount of information only in that single category.[33] Means of the repeated blood pressure measurements were calculated for each baseline-derived fifth and the HRs were plotted at these values to show associations between usual blood pressure values and mortality. On the basis of non-linear associations, a post-hoc decision was made to estimate the mortality HR per 1 – SD increment in usual blood pressure across the top four-fifths of each distribution (analyses using all fifths were also done). The informativeness of the different blood pressure measures (compared with clinic systolic blood pressure) for prediction of all-cause and cardiovascular death was calculated with the following formula:[34]

$$\text{Informativeness} = 100 \times \left(\frac{\chi^2 \text{ for given measure}}{\chi^2 \text{ for clinic systolic pressure}} \right)$$

Wald tests were used to calculate the χ^2 statistic for each blood pressure measure, which provides an assessment of the goodness-of-fit of the confounder-adjusted Cox

models. Separate associations in subgroups defined by age (<60, ≥60 years), sex, obesity (BMI <30, ≥30 kg/m²), diabetes, and antihypertensive drug use were estimated by including an appropriate interaction term into a regression model. Additionally, to guard against potential estimation problems arising from collinearity in the mutually adjusted regression models, additional sensitivity analyses were done using the residuals of each blood pressure measure adjusted for other blood pressure measures (rather than models in which the correlated blood pressure measures were entered into the same regression model). Subsequently, hypertension phenotypes were defined as blood pressure in the normal range (clinic systolic blood pressure <140 mm Hg and clinic diastolic blood pressure <90 mm Hg; and 24-h systolic <130 mm Hg and 24-h diastolic <80 mm Hg); white-coat hypertension (clinic systolic ≥140 mm Hg or clinic diastolic ≥90 mm Hg, but 24-h systolic <130 mm Hg and 24-h diastolic <80 mm Hg); masked hypertension (clinic systolic <140 mm Hg and clinic diastolic <90 mm Hg, but 24-h systolic ≥130 mm Hg or 24-h diastolic ≥80 mm Hg); and sustained hypertension (clinic systolic ≥140 mm Hg or clinic diastolic ≥90 mm Hg, and 24-h systolic ≥130 mm Hg or 24-h diastolic ≥80 mm Hg).[27–29] HRs for white-coat, masked, and sustained hypertension (all compared with blood pressure in the normal range) were estimated using Cox regression

	Men (n=31 337)	Women (n=27 787)	All patients (n=59 124)
Age (year)	56·9 (14·0)	60·7 (14·1)	58·7 (14·1)
Risk factors			
BMI			
Mean	29 (4)	29 (5)	29 (5)
≥30 kg/m²	12 365 (39·5%)	11 391 (41·0%)	23 756 (40·2%)
Current smoker	6057 (19·3%)	3237 (11·6%)	9294 (15·7%)
Diabetes*	6490 (20·7%)	4901 (17·6%)	11 391 (19·3%)
Dyslipidaemia†	13 084 (41·8%)	11 610 (41·8%)	24 694 (41·8%)
Previous cardiovascular disease			
Ischaemic heart disease	1740 (5·6%)	939 (3·4%)	2679 (4·5%)
Stroke	1232 (3·9%)	951 (3·4%)	2183 (3·7%)
Heart failure	589 (1·9%)	544 (2·0%)	1133 (1·9%)
Any cardiovascular disease	3335 (10·6%)	2269 (8·2%)	5604 (9·5%)
Blood pressure (mm Hg)‡			
Clinic systolic	148·0 (18·0)	148·0 (19·7)	148·0 (18·8)
Clinic diastolic	87·4 (11·4)	85·5 (11·6)	86·5 (11·5)
24-h systolic	130·0 (13·1)	127·4 (14·1)	128·8 (13·7)
24-h diastolic	78·4 (9·8)	73·8 (9·9)	76·2 (10·1)
Daytime systolic	133·2 (13·5)	130·4 (14·4)	131·9 (14·0)
Daytime diastolic	81·3 (10·4)	76·7 (10·5)	79·1 (10·7)
Night-time systolic	120·8 (15·1)	119·0 (16·3)	120·0 (15·7)
Night-time diastolic	70·2 (10·0)	66·0 (9·9)	68·2 (10·2)
Hypertension phenotypes§			
Blood pressure in normal range	4593 (14·7%)	5413 (19·5%)	10 006 (16·9%)
White-coat hypertension	7991 (25·5%)	9190 (33·1%)	17 181 (29·1%)
Masked hypertension	2979 (9·5%)	2020 (7·3%)	4999 (8·5%)
Sustained hypertension	15 774 (50·3%)	11 164 (40·2%)	26 938 (45·6%)
Number of blood pressure medications			
0	12 960 (41·4%)	11 036 (39·7%)	23 996 (40·6%)
1	6641 (21·2%)	5902 (21·2%)	12 543 (21·2%)
≥2	11 736 (37·5%)	10 849 (39·0%)	22 585 (38·2%)

*Previous diagnosis of diabetes if the patient had elevated concentrations of fasting serum glucose in at least two occasions (>125 mg/dL) or was treated with antidiabetic drugs. †Previous diagnosis of dyslipidaemia if the patients had elevated concentrations of total, LDL, or triglycerides, or low concentrations of HDL (values defined following the contemporary guidelines), or the use of lipid-lowering drugs. ‡Day and night periods were defined according to sleeping and waking times reported by the patient. §White-coat hypertension is defined as clinic systolic of 140 mm Hg or more or clinic diastolic of 90 mm Hg or more and 24-h systolic of less than 130 mm Hg and 24-h diastolic of less than 80 mm Hg. Masked hypertension is defined as clinic systolic of less than 140 mm Hg and clinic diastolic of less than 90 mm Hg and 24-h systolic of 130 mm Hg or more or 24-h diastolic of 80 mm Hg or more. Sustained hypertension is defined as clinic systolic of 140 mm Hg or more or clinic diastolic of 90 mm Hg or more and 24-h systolic of 130 mm Hg or more or 24-h diastolic of 80 mm Hg or more.

Table 1: **Characteristics of the study cohort**

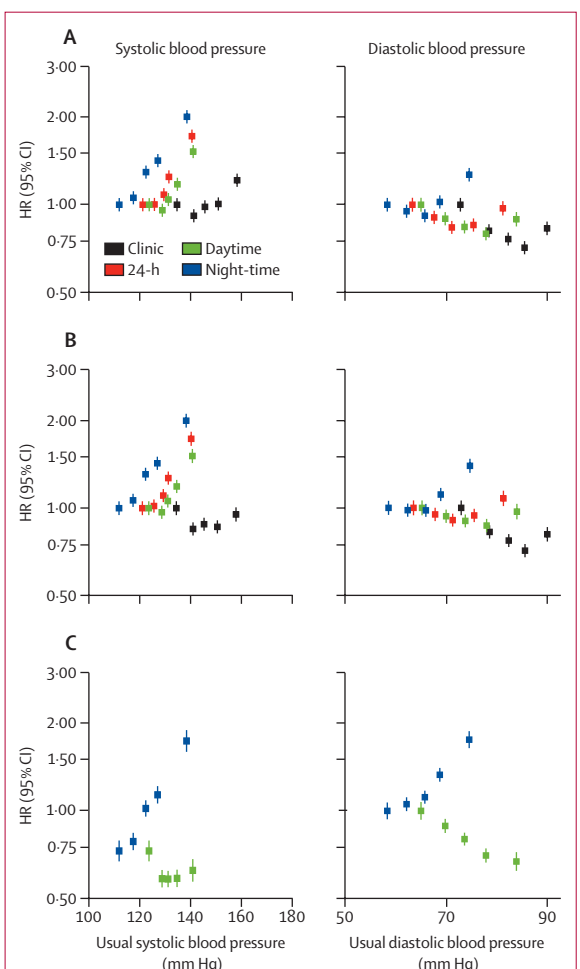

Figure 1: **Association of clinic and ambulatory blood pressure with all-cause death**

Error bars are 95% CIs. (A) Confounder-adjusted model is adjusted for age, sex, smoking status, BMI, diabetes status, dyslipidaemia status, previous cardiovascular disease, and number of antihypertensive drugs. (B) In the model with additional adjustment for clinic or 24-h blood pressure, clinic blood pressure is adjusted for 24-h blood pressure and ambulatory blood pressure measures are adjusted for clinic blood pressure. (C) In the model additionally adjusted for components of 24-h blood pressure, daytime blood pressure is adjusted for night-time blood pressure and night-time blood pressure is adjusted for daytime blood pressure. HR=hazard ratio.

adjusted for the same aforementioned confounders. Analyses excluding patients with clinic diastolic blood pressure of less than 70 mm Hg from the normal range category and estimating the associations separately in treated and untreated patients were also done.

Two-tailed p<0·05 were considered to indicate statistical significance; no correction for multiple testing was done. We did the analyses using SAS (version 9.4) and R (version 4.2.1).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

In total, 59746 individuals who were 18 years or older in the Spanish Ambulatory Blood Pressure Registry could be linked to the vital registry of the Spanish National Institute of Statistics. Of these individuals, 622 (1·0%) were excluded because of incomplete information about demographic or clinical characteristics; as a result, 59124 patients were included in this analysis. The mean age of the study participants at recruitment into the registry was 58·7 years (SD 14·1), the mean clinic systolic blood pressure was 148·0 mm Hg and diastolic blood pressure was 86·5 mm Hg, and the mean 24-h ambulatory systolic blood pressure was 128·8 mm Hg and diastolic blood pressure was 76·2 mm Hg. 31337 (53·0%) of 59124 were men and 27787 (47·0%) were women (table 1; appendix pp 4, 11–12). 35128 (59·4%) of 59124 were treated for hypertension. During a median follow-up of 9·7 years (IQR 7·7–11·3), 7174 (12·1%) participants died, including 2361 (4·0%) from a cardiovascular cause, which included 685 coronary heart disease deaths, 503 stroke deaths, and 302 heart failure deaths.

See Online for appendix

Clinic and ambulatory blood pressure measurements were modestly correlated (correlation coefficients of 0·43 for systolic blood pressure and 0·52 for diastolic blood pressure; appendix pp 5, 13). Daytime and night-time blood pressure measurements were more strongly correlated (correlation coefficients of 0·73 for systolic blood pressure and 0·74 for diastolic blood pressure; appendix p 5). Substantial variability was observed in clinic and ambulatory blood pressure monitoring measurements taken at two different visits (regression dilution ratios for measurements an average of 18 months apart were 0·46 for clinic systolic blood pressure and 0·48 for 24-h systolic blood pressure; appendix pp 14–15).

Associations between systolic blood pressure measures and all-cause death were J-shaped, particularly for clinic blood pressure, but the associations were log-linear when excluding the fifth with the lowest blood pressure values (figure 1; appendix p 6). In the confounder-adjusted model, 24-h systolic blood pressure was more strongly associated with all-cause death (HR 1·41 [95% CI

	All patients						Excluding patients in the fifth with the lowest blood pressure values					
	Confounder adjusted		Additionally adjusted for clinic or 24-h blood pressure		Additionally adjusted for components of 24-h blood pressure		Confounder adjusted		Additionally adjusted for clinic or 24-h blood pressure		Additionally adjusted for components of 24-h blood pressure	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
All-cause death												
Clinic systolic	1·08 (1·04–1·11)	<0·0001	0·95 (0·92–0·99)	0·01	..	..	1·18 (1·13–1·23)	<0·0001	1·04 (1·00–1·09)	0·06	..	..
24-h systolic	1·30 (1·26–1·34)	<0·0001	1·32 (1·28–1·37)	<0·0001	..	..	1·41 (1·36–1·47)	<0·0001	1·43 (1·37–1·49)	<0·0001	..	..
Daytime systolic	1·25 (1·21–1·29)	<0·0001	1·26 (1·22–1·31)	<0·0001	0·96 (0·92–1·01)	0·12	1·38 (1·33–1·44)	<0·0001	1·38 (1·32–1·45)	<0·0001	1·07 (1·01–1·14)	0·02
Night-time systolic	1·36 (1·32–1·40)	<0·0001	1·37 (1·33–1·41)	<0·0001	1·40 (1·35–1·47)	<0·0001	1·42 (1·37–1·47)	<0·0001	1·44 (1·38–1·49)	<0·0001	1·45 (1·38–1·52)	<0·0001
Cardiovascular death												
Clinic systolic	1·11 (1·05–1·17)	0·0002	0·94 (0·89–1·00)	0·06	..	..	1·22 (1·13–1·31)	<0·0001	1·04 (0·96–1·12)	0·37	..	..
24-h systolic	1·41 (1·34–1·49)	<0·0001	1·45 (1·37–1·53)	<0·0001	..	..	1·48 (1·38–1·58)	<0·0001	1·51 (1·41–1·62)	<0·0001	..	..
Daytime systolic	1·35 (1·28–1·43)	<0·0001	1·38 (1·30–1·46)	<0·0001	1·01 (0·93–1·10)	0·75	1·46 (1·36–1·56)	<0·0001	1·48 (1·37–1·59)	<0·0001	1·10 (0·99–1·21)	0·07
Night-time systolic	1·46 (1·39–1·53)	<0·0001	1·47 (1·40–1·55)	<0·0001	1·46 (1·36–1·57)	<0·0001	1·50 (1·41–1·59)	<0·0001	1·51 (1·42–1·61)	<0·0001	1·51 (1·39–1·63)	<0·0001

HR per 1 – SD increment in usual blood pressure, equivalent to 12·8 mm Hg for clinic systolic, 9·5 mm Hg for 24-h systolic, 9·4 mm Hg for daytime systolic, and 11·5 mm Hg for night-time systolic. Confounder-adjusted model is adjusted for age, sex, smoking status, BMI, diabetes status, dyslipidaemia status, previous cardiovascular disease, and number of antihypertensive drugs. In the model with additional adjustment for clinic or 24-h systolic blood pressure, clinic blood pressure is adjusted for 24-h blood pressure and ambulatory blood pressure indices are adjusted for clinic blood pressure. In the model additionally adjusted for components of 24-h blood pressure, daytime blood pressure is adjusted for night-time blood pressure and night-time blood pressure is adjusted for daytime blood pressure. HR=hazard ratio.

Table 2: **Association of clinic and ambulatory systolic blood pressure with all-cause death and cardiovascular death among all participants**

	All-cause death		Cardiovascular death	
	Confounder-adjusted χ^2 statistic	Informativeness*	Confounder-adjusted χ^2 statistic	Informativeness*
Clinic systolic	61·2	100%	29·1	100%
24-h systolic	293·1	479%	135·4	465%
Daytime systolic	233·0	381%	113·3	389%
Night-time systolic	361·7	591%	175·8	604%

*Informativeness of the given measure (as indicated by the confounder-adjusted χ^2 statistic relating it to mortality), as a percentage of the informativeness of clinic systolic blood pressure. Models adjusted for age, sex, smoking status, BMI, diabetes status, dyslipidaemia status, previous cardiovascular disease, and number of antihypertensive drugs.

Table 3: **Relative informativeness of different blood pressure indices for all-cause death and cardiovascular death**

1·36–1·47] per 1 – SD increment for the top four fifths) than was clinic systolic blood pressure (1·18 [1·13–1·23]; table 2). 24-h blood pressure was almost five-times more informative about the risk of all-cause death than clinic blood pressure (table 3). After adjustment for clinic systolic blood pressure, 24-h systolic blood pressure remained strongly associated with all-cause death (HR 1·43 [95% CI 1·37–1·49]), but the association between clinic systolic blood pressure and all-cause death was attenuated when adjusted for 24-h systolic blood pressure (1·04 [1·00–1·09]; table 2). The results were slightly attenuated, but still significant when all patients (including the lowest fifth) were analysed, with the exception of clinic systolic blood pressure, which was inversely associated with mortality after adjustment for 24-h blood pressure. Results were similar in sensitivity analyses using the residuals of each blood pressure measure adjusted for other blood pressure measures (appendix p 7). Similar results were observed for cardiovascular death (figure 2; table 2), including deaths from coronary heart disease and stroke but not heart failure (appendix p 8).

In the confounder-adjusted model, daytime and night-time systolic blood pressure had broadly similar associations with both all-cause death (HR across top four-fifths was 1·38 [95% CI 1·33–1·44] per 1 – SD increment for daytime *vs* 1·42 [1·37–1·47] for night-time) and cardiovascular death (1·46 [1·36–1·56] for daytime *vs* 1·50 [1·41–1·59] for night-time). Adjustment for clinic systolic blood pressure did not materially change these associations (table 2). Night-time systolic blood pressure was the most informative measure for all-cause and cardiovascular death risk (its relative informativeness compared with clinic systolic blood pressure was 591% for all-cause death and 604% for cardiovascular death risk; table 3). After adjustment for daytime systolic blood pressure, night-time systolic blood pressure remained strongly associated with all-cause death (HR 1·45 [95% CI 1·38–1·52]) and cardiovascular death (1·51 [1·39–1·63]). By contrast, after adjustment for night-time systolic blood pressure, daytime systolic blood pressure was only weakly associated with all-cause death (HR 1·07 [95% CI 1·01–1·14]) and unrelated to cardiovascular death (1·10

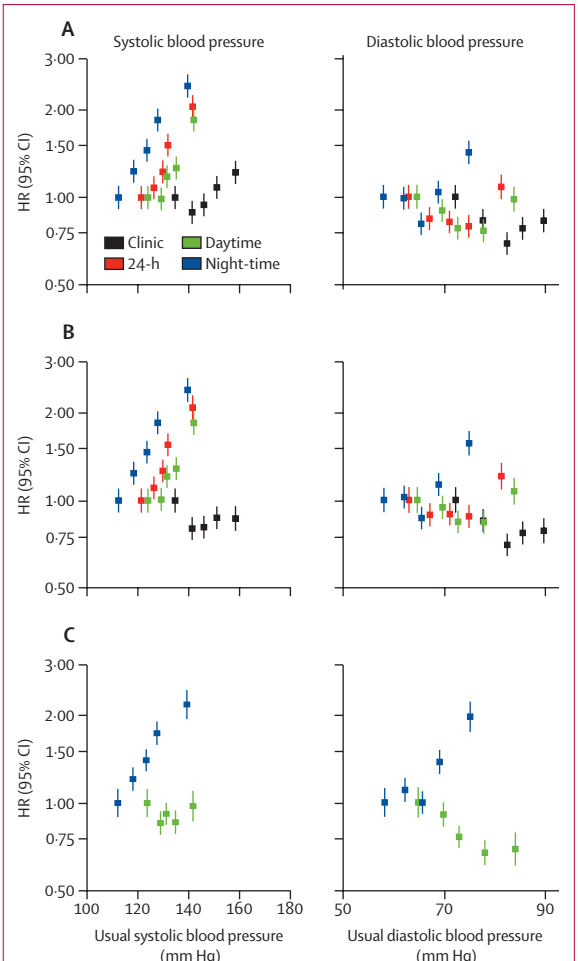

Figure 2: **Association of clinic and ambulatory blood pressure with cardiovascular death**

Error bars are 95% CIs. (A) Confounder-adjusted model is adjusted for age, sex, smoking status, BMI, diabetes status, dyslipidaemia status, previous cardiovascular disease, and number of antihypertensive drugs. (B) In the model with additional adjustment for clinic or 24-h blood pressure, clinic blood pressure is adjusted for 24-h blood pressure and ambulatory blood pressure measures are adjusted for clinic blood pressure. (C) In the model additionally adjusted for components of 24-h blood pressure, daytime blood pressure is adjusted for night-time blood pressure and night-time blood pressure is adjusted for daytime blood pressure. HR=hazard ratio.

[0·99–1·21]; figures 1, 2; table 2). Results were similar in sensitivity analyses using the residuals of each blood pressure measure adjusted for other blood pressure measures (appendix p 7). Associations were consistent across subgroups (appendix pp 16–17) and, except for night-time blood pressure, were attenuated when refitted across all fifths of each distribution (table 2). For cause-specific cardiovascular death, night-time systolic blood pressure was most strongly associated with risk of death, even after adjustment for daytime systolic blood pressure (appendix p 7).

Associations between measures of diastolic blood pressure and all-cause death and cardiovascular death were generally J-shaped or U-shaped (figures 1–2). This

finding was most evident for clinic diastolic blood pressure, in which the lowest fifth had the highest risk of all-cause death (HR 0·83 [95% CI 0·77–0·90] for highest *vs* lowest fifth; appendix p 9). Those in the highest fifth of night-time diastolic blood pressure were more likely to die than those in the lowest fifth (HR 1·27 [95% CI 1·17–1·37]), and this association was strengthened after adjustment for clinic diastolic blood pressure (1·40 [1·29–1·51]) and daytime diastolic blood pressure (1·57 [1·36–1·81]). Similar patterns were observed for cardiovascular death.

In the confounder-adjusted model, all-cause death was greater in patients with masked hypertension (normal clinic but elevated 24-h blood pressure; HR 1·24 [95% CI 1·12–1·37]) and sustained hypertension (1·24 [1·15–1·32]) than those with normal blood pressure, and

	Number of patients	Deaths	Mean systolic blood pressures (mm Hg)				Mean diastolic blood pressures (mm Hg)				Confounder-adjusted model	
			Clinic	24 h	Daytime	Night-time	Clinic	24 h	Daytime	Night-time	HR (95% CI)	p value
All patients												
Confounder adjusted												
All-cause death												
Blood pressure in normal range	10 006	1074	126	116	119	109	76	70	72	62	1·00 (ref)	..
White-coat hypertension	17 181	1824	152	119	123	111	88	70	73	62	0·90 (0·84–0·97)	0·01
Masked hypertension	4999	605	129	133	136	125	79	81	83	72	1·24 (1·12–1·37)	<0·0001
Sustained hypertension	26 938	3671	157	139	142	129	91	82	85	73	1·24 (1·15–1·32)	<0·0001
Cardiovascular death												
Blood pressure in normal range	10 006	337	126	116	119	109	76	70	72	62	1·00 (ref)	..
White-coat hypertension	17 181	557	152	119	123	111	88	70	73	62	0·89 (0·77–1·01)	0·08
Masked hypertension	4999	206	129	133	136	125	79	81	83	72	1·37 (1·15–1·63)	0·0004
Sustained hypertension	26 938	1261	157	139	142	129	91	82	85	73	1·38 (1·22–1·55)	<0·0001
Excluding participants with clinic diastolic pressure <70 mmHg from the blood pressure in normal range category												
Confounder adjusted												
All-cause mortality												
Blood pressure in normal range*	8076	656	128	117	120	109	79	71	74	63	1·00 (ref)	..
White-coat hypertension	17 181	1824	152	119	123	111	88	70	73	62	1·04 (0·95–1·14)	0·34
Masked hypertension	4999	605	129	133	136	125	79	81	83	72	1·44 (1·29–1·60)	<0·0001
Sustained hypertension	26 938	3671	157	139	142	129	91	82	85	73	1·43 (1·31–1·55)	<0·0001
Cardiovascular mortality												
Blood pressure in normal range*	8076	200	128	117	120	109	79	71	74	63	1·00 (ref)	..
White-coat hypertension	17 181	557	152	119	123	111	88	70	73	62	1·02 (0·87–1·20)	0·77
Masked hypertension	4999	206	129	133	136	125	79	81	83	72	1·59 (1·31–1·93)	<0·0001
Sustained hypertension	26 938	1261	157	139	142	129	91	82	85	73	1·59 (1·37–1·85)	<0·0001

All analyses adjusted for age, sex, smoking status, BMI, diabetes status, dyslipidaemia status, and previous cardiovascular disease. White-coat hypertension is defined as clinic systolic of 140 mm Hg or more or clinic diastolic of 90 mm Hg or more and 24-h systolic of less than 130 mm Hg and 24-h diastolic of less than 80 mm Hg. Masked hypertension is defined as clinic systolic of less than 140 mm Hg and clinic diastolic of less than 90 mm Hg and 24-h systolic of 130 mm Hg or more or 24-h diastolic of 80 mm Hg or more. Sustained hypertension is defined as clinic systolic of 140 mm Hg or more or clinic diastolic of 90 mm Hg or more and 24-h systolic of 130 mm Hg or more or 24-h diastolic of 80 mm Hg or more. HR=hazard ratio. *Excluding participants with clinic diastolic pressure of less than 70 mm Hg.

Table 4: **Association of hypertension phenotypes with all-cause and cardiovascular death**

cardiovascular death was more likely in patients with masked hypertension (1·37 [1·15–1·63]) and sustained hypertension (1·38 [1·22–1·55]; table 4) than those with normal blood pressure. Patients with white-coat hypertension (elevated clinic but normal 24-h blood pressure) appeared to be at lower risk of all-cause death (HR 0·90 [95% CI 0·84–0·97]) and cardiovascular death (0·89 [0·77–1·01]) than those with normal blood pressure. Similar patterns were observed when treated and untreated patients were considered separately (appendix p 10).

For patients with blood pressure in the normal range, inverse associations between clinic diastolic blood pressure and both all-cause death and cardiovascular death were observed (appendix p 18), suggesting that the lowest clinic diastolic blood pressures might be a manifestation of pre-existing disease. In sensitivity analyses that excluded patients with a clinic diastolic blood pressure of less than 70 mm Hg from those with normal blood pressure, patients with white-coat hypertension had similar risks of all-cause death (HR 1·04 [95% CI 0·95–1·14]) and cardiovascular death (1·02 [0·87–1·20]; table 4) compared with those with normal blood pressure. In these sensitivity analyses, risks of all-cause death were greater in patients with masked hypertension (HR 1·44 [95% CI 1·29–1·60]) and sustained hypertension (1·43 [1·31–1·55]) than those with normal blood pressure, and risks of cardiovascular death were more highly elevated in patients with masked hypertension (1·59 [1·31–1·93]) and sustained hypertension (1·59 [1·37–1·85]; table 4) than those with normal blood pressure.

Discussion

In this large study of clinic and ambulatory blood pressure, blood pressure measures obtained through ambulatory blood pressure monitoring were more informative about the risk of all-cause death or cardiovascular death than conventional clinic blood pressures. Importantly, once 24-h blood pressure was known, most of the informativeness of clinic systolic blood pressure was lost, whereas associations for ambulatory blood pressure measures were largely unaffected by adjustment for clinic systolic blood pressure. The relative informativeness of 24-h ambulatory systolic blood pressure for risk of death was almost five-times greater than clinic systolic blood pressure. Furthermore, with respect to ambulatory blood pressure measures, night-time systolic blood pressure was about six-times more informative for death than clinic systolic blood pressure and nearly twice as informative as daytime systolic blood pressure. Although masked and sustained hypertension were associated with an increased risk of death compared with patients with 24-h blood pressure within normal range, white-coat hypertension was not.

Previous population and clinical studies have shown that ambulatory systolic blood pressure predicts death and cardiovascular outcomes better than clinic systolic blood pressure.[4–6,8–11] The present study extends these findings in a single population with more than 50 000 patients and also demonstrates the effect of commonly encountered blood pressure phenotypes on death. A recent study by Yang and colleagues also demonstrated the dominance of 24-h ambulatory systolic pressure and, in particular, night-time systolic pressure compared with clinic systolic pressure in predicting death.[4] However, unlike the present study, Yang and colleagues' study did not include data for hypertension phenotypes.

The superiority of night-time blood pressure over daytime blood pressure has been observed in other previous studies,[4,9,11,13,14,35,36] including a small group of high-risk patients from the Spanish Registry.[37] Although daytime blood pressure lost its predictive ability after adjustment for night-time blood pressure, night-time blood pressure maintained its predictive ability after adjusting for daytime blood pressure. Several mechanisms might be responsible for this nocturnal blood pressure superiority, the most likely being the more standardised conditions under which blood pressure is recorded during sleep, relative to much more variable activity during daytime, which is supported by the reproducibility data in the appendix (p 14), in which night-time systolic pressure had a higher regression dilution ratio than daytime or clinic systolic pressure. Studies have also reported that elevated night-time blood pressure is associated with target organ damage (eg, chronic kidney disease[38] and heart failure[36]), which might contribute to a higher risk of death.

Interesting relationships were also observed between clinic or ambulatory diastolic blood pressure and death, which were J-shaped or U-shaped. The strength of the association between increasing diastolic blood pressure and mortality appears weaker than for systolic blood pressure, as observed in previous studies,[4,5,7,8,11,13,35] although these studies did not explicitly assess the shape of the underlying associations. The increased risk of death at lower values of diastolic blood pressure is likely to reflect, at least in part, reverse causation due to the effects of arterial ageing, stiffening, and subclinical disease, all of which are associated with a widened pulse pressure and lower diastolic pressure.[39]

Our findings that masked and sustained hypertension are associated with increased risks of death are consistent with other studies.[2,12,15,17,19] Poorer outcomes in patients with masked hypertension most likely relates to a delayed recognition of hypertension and undertreatment in such individuals as, at the time of this study, guidelines generally recommended that the diagnosis of hypertension and its drug treatment be guided predominantly by clinic blood pressure. More recent guidelines[30,40] promote the wider use of so-called out-of-office blood pressure that will better facilitate the diagnosis and treatment of masked hypertension. The prognosis of white-coat hypertension has been a matter

of debate, with some studies showing a cardiovascular risk similar to that of normotensives,[15,17,19–21] whereas others found increased incidence of events.[41] Our study suggests that this phenotype is not associated with an increased risk of mortality compared with those with blood pressure in the normal range. Ambulatory blood pressure measurements were also taken for clinical reasons, and therefore, patients with normal blood pressures are not necessarily a healthy population, which might explain why a lower risk of death, relative to normotensive patients, was observed for patients with white-coat hypertension in this study. Supporting this idea, when patients with a diastolic blood pressure of less than 70 mm Hg were excluded from the analysis, white-coat hypertension became neither protective nor deleterious for all-cause death or cardiovascular death.

This study has some limitations. First, clinic blood pressure represented the average of only two readings at each clinic visit; thus, the mean clinic blood pressure could be overestimated. Moreover, variability existed in both clinic and ambulatory blood pressure monitoring where repeated measures were taken, although adjustment for regression dilution bias was used to account for this variability where possible. Second, data for medication, although available at baseline, were not available during the follow-up period. Third, some selection bias might have occurred from the inclusion criteria for ambulatory blood pressure monitoring, obtained on the basis of indications for this procedure contained in guidelines contemporary to the study design and follow-up. Fourth, we did an observational study on the prognostic value of blood pressure monitoring and, thus, no direct inference can be made regarding the benefit of basing treatment on ambulatory blood pressure measurements. Fifth, the present study does not consider the association of ambulatory blood pressure monitoring with non-fatal events, as only data for deaths were available. The introduction of revascularisation therapies after a cardiovascular event is known to influence the probability of death. Finally, the patients we studied were predominantly a White population, and the results might not apply to people of other races.

In conclusion, in this large study, systolic blood pressure obtained through ambulatory blood pressure monitoring, and particularly night-time systolic blood pressure, were more informative measures for the risk of all-cause death and cardiovascular death, compared with clinic systolic blood pressure. Masked and sustained hypertension were also associated with an increased risk of death compared with patients with 24-h blood pressure within normal range. Conversely, we found no evidence that white-coat hypertension was associated with increased risk of death.

Contributors

AdlS, LMR, and BW designed the study and contributed to data gathering. NS, JRE, and CB analysed the data. All authors drafted and revised the paper, and approved the final version of the manuscript.

Declaration of interests

NS reports institutional grant support from Boehringer Ingelheim, Lilly, and Novo Nordisk for investigator led/designed research unrelated to this project. AdlS reports lecture fees from Viatris, and support for travel to attend meetings from Menarini and Lacer. LMR reports consulting fees from Novartis, Bayer, Pfizer, Medtronic, ReCor, Sanofi, and Sandoz and lecture fees from Novartis, Bayer, Pfizer, Medtronic, ReCor, and Sanofi. CB reports institutional grant support from Boehringer Ingelheim for investigator designed/led research unrelated to this work. BW reports lecture fees from Daichi Sankyo, Servier, and Pfizer, and institutional grant support from Omron for investigator designed/led research unrelated to this work. All other authors declare no competing interests. The Clinical Trial Service Unit and Epidemiological Studies Unit has a staff policy of not accepting honoraria or other payments from the pharmaceutical industry, except for the reimbursement of costs to participate in scientific meetings. BW on behalf of University College London has received an investigator-led grant award from Omron, Japan and honoraria for lectures on blood pressure measurement, and is supported by the National Institute for Health and Care Research University College London Hospitals Biomedical Research Centre.

Data sharing

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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