

ORIGINAL ARTICLE

Relationship between Clinic and Ambulatory Blood-Pressure Measurements and Mortality

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ABSTRACT

BACKGROUND

Evidence for the influence of ambulatory blood pressure on prognosis derives mainly from population-based studies and a few relatively small clinical investigations. This study examined the associations of blood pressure measured in the clinic (clinic blood pressure) and 24-hour ambulatory blood pressure with all-cause and cardiovascular mortality in a large cohort of patients in primary care.

METHODS

We analyzed data from a registry-based, multicenter, national cohort that included 63,910 adults recruited from 2004 through 2014 in Spain. Clinic and 24-hour ambulatory blood-pressure data were examined in the following categories: sustained hypertension (elevated clinic and elevated 24-hour ambulatory blood pressure), “white-coat” hypertension (elevated clinic and normal 24-hour ambulatory blood pressure), masked hypertension (normal clinic and elevated 24-hour ambulatory blood pressure), and normotension (normal clinic and normal 24-hour ambulatory blood pressure). Analyses were conducted with Cox regression models, adjusted for clinic and 24-hour ambulatory blood pressures and for confounders.

RESULTS

During a median follow-up of 4.7 years, 3808 patients died from any cause, and 1295 of these patients died from cardiovascular causes. In a model that included both 24-hour and clinic measurements, 24-hour systolic pressure was more strongly associated with all-cause mortality (hazard ratio, 1.58 per 1-SD increase in pressure; 95% confidence interval [CI], 1.56 to 1.60, after adjustment for clinic blood pressure) than the clinic systolic pressure (hazard ratio, 1.02; 95% CI, 1.00 to 1.04, after adjustment for 24-hour blood pressure). Corresponding hazard ratios per 1-SD increase in pressure were 1.55 (95% CI, 1.53 to 1.57, after adjustment for clinic and daytime blood pressures) for nighttime ambulatory systolic pressure and 1.54 (95% CI, 1.52 to 1.56, after adjustment for clinic and nighttime blood pressures) for daytime ambulatory systolic pressure. These relationships were consistent across subgroups of age, sex, and status with respect to obesity, diabetes, cardiovascular disease, and antihypertensive treatment. Masked hypertension was more strongly associated with all-cause mortality (hazard ratio, 2.83; 95% CI, 2.12 to 3.79) than sustained hypertension (hazard ratio, 1.80; 95% CI, 1.41 to 2.31) or white-coat hypertension (hazard ratio, 1.79; 95% CI, 1.38 to 2.32). Results for cardiovascular mortality were similar to those for all-cause mortality.

CONCLUSIONS

Ambulatory blood-pressure measurements were a stronger predictor of all-cause and cardiovascular mortality than clinic blood-pressure measurements. White-coat hypertension was not benign, and masked hypertension was associated with a greater risk of death than sustained hypertension. (Funded by the Spanish Society of Hypertension and others.)

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AMBULATORY BLOOD-PRESSURE DATA provide a more comprehensive assessment of blood pressure over the course of a day and have been reported to better predict health outcomes than blood pressure measured in the clinic (clinic blood pressure) or at home.¹⁻³ Evidence for the influence of ambulatory blood pressure on prognosis is derived mainly from population-based studies⁴⁻⁷ and a few relatively small clinical investigations.⁸⁻¹¹ However, in these studies, the number of clinical outcomes was limited, which reduced the ability to assess the predictive value of clinic blood-pressure data as compared with ambulatory data. In addition, whether the average ambulatory blood pressure over the nighttime, the daytime, or the full 24 hours is the strongest predictor of mortality remains uncertain.^{3-8,10,12,13} Moreover, the implications of hypertension phenotypes, such as “white-coat” hypertension and masked hypertension, with regard to mortality have remained ill-defined, mainly because of the small number of events reported in previous studies.¹⁴⁻²³

We report the prognostic value of clinic and ambulatory blood pressures, as well as of hypertension phenotypes, on total and cardiovascular mortality. We used data from the Spanish Ambulatory Blood Pressure Registry, which includes a large cohort of patients in primary care practice.

METHODS

STUDY OVERSIGHT

This study was supported by the Spanish Society of Hypertension, Lacer Laboratories, and European government agencies. The funding sources had no role in the design of the study, the collection and analysis of the data, the interpretation of results, the writing of the report, or the decision to submit the report for publication.

The study protocol and analyses were approved by the institutional review board for all participating centers. The authors vouch for the accuracy and completeness of the data. The full list of investigators is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.

PATIENT POPULATION

Data for this study were obtained from the ongoing Spanish Ambulatory Blood Pressure Registry, a national study of patients selected by

their physicians at 223 primary care centers within the Spanish National Health System in all the 17 regions of Spain.^{24,25} Patients were required to be 18 years of age or older and to meet guideline-recommended indications for ambulatory blood-pressure monitoring,²⁴⁻²⁸ which included suspected white-coat hypertension, refractory or resistant hypertension, high-risk hypertension, and labile or borderline hypertension, as well as assessment of drug-treatment efficacy and study of the circadian blood-pressure pattern (details are provided in the Supplementary Appendix). All patients included in the registry provided written informed consent.

The current study is an analysis of mortality among 66,636 persons 18 years of age or older who were enrolled in the registry between March 1, 2004, and December 31, 2014. Of these, 2726 were excluded because of incomplete information on demographic or clinical characteristics; thus, 63,910 patients were included in the analysis.

BLOOD PRESSURE AND OTHER STUDY VARIABLES

Blood pressure was measured in the clinic according to standardized procedures, with the use of validated oscillometric devices (in 85% of patients) or calibrated mercury sphygmomanometers (in 15%), after the patient had been resting in a seated position for 5 minutes.²⁶⁻²⁸ We used the mean of two clinic blood-pressure readings. Thereafter, ambulatory blood-pressure monitoring was performed with validated, automated, oscillometric devices (Spacelabs model 90207, Spacelabs Healthcare) that were programmed to record blood pressure at 20-minute intervals during the day and at 30-minute intervals during the night. An appropriate cuff size (one of two sizes) was used for each patient. We used the mean of all valid readings for the analysis. Valid measurements had to fulfill prespecified quality criteria, including the successful recording of at least 70% of systolic and diastolic blood-pressure readings during the 24-hour recording period. Day and night periods were defined according to sleeping and waking times reported by the patient.

Patient data were obtained from interviews and physical examinations during the visits and from clinical records. The clinical characteristics of the patients were assessed in accordance with international guidelines.²⁶⁻²⁸ Additional details are provided in the Supplementary Appendix.

MORTALITY DATA

The date and cause of death were ascertained from a computerized search of the vital registry of the Spanish National Institute of Statistics; evidence of the completeness, accuracy, and reliability of this vital-status information has been made available by the Institute.²⁹ Persons were designated as having died if the deaths were recorded in the vital registry. The cause of death was determined from the death certificate by a nosologist and was coded according to the *International Statistical Classification of Diseases, 10th Revision*. We included all deaths that were classified as being of cardiovascular origin (codes I00 to I99) and further subcategorized cardiovascular-related deaths as having been caused by ischemic heart disease (codes I21–I25), stroke (codes I60–I69), or heart failure (code I50). For each study participant, follow-up was from the date of the recruitment visit for the blood-pressure registry to the date of death or December 31, 2014, whichever occurred first.

STATISTICAL ANALYSIS

Hypertension phenotypes in untreated patients were defined as white-coat hypertension (clinic systolic blood pressure ≥ 140 mm Hg or diastolic ≥ 90 mm Hg and 24-hour systolic pressure < 130 mm Hg and diastolic < 80 mm Hg), masked hypertension (clinic systolic pressure < 140 mm Hg and diastolic < 90 mm Hg and 24-hour systolic pressure ≥ 130 mm Hg or diastolic ≥ 80 mm Hg), sustained hypertension (clinic systolic pressure ≥ 140 mm Hg or diastolic ≥ 90 mm Hg and ambulatory 24-hour systolic pressure ≥ 130 mm Hg or diastolic ≥ 80 mm Hg), or normotension (clinic systolic pressure < 140 mm Hg and diastolic < 90 mm Hg and 24-hour systolic pressure < 130 mm Hg and diastolic < 80 mm Hg).^{26–28} An explanation of the blood-pressure thresholds we used is provided in the Supplementary Appendix. In treated patients, the corresponding terms were white-coat uncontrolled hypertension, masked uncontrolled hypertension, sustained uncontrolled hypertension, and controlled hypertension, respectively.

Associations between blood pressure and mortality were summarized with hazard ratios and 95% confidence intervals, estimated with Cox models. Hazard ratios were calculated per 1-SD increment in blood pressure, and for hypertension phenotypes the reference group was untreated

normotension. Two Cox models were constructed. Model 1 was adjusted for age, sex, smoking status, body-mass index (the weight in kilograms divided by the square of the height in meters), and status with respect to diabetes, dyslipidemia, previous cardiovascular disease, and number of antihypertensive medications used. To assess whether the associations were independent of other blood-pressure measurements, additional adjustments were performed (model 2): the hazard ratio for clinic blood pressure was adjusted for 24-hour blood pressure; 24-hour pressure was adjusted for clinic pressure; daytime pressure was adjusted for clinic and nighttime pressure; nighttime pressure was adjusted for clinic and daytime pressure; and the hazard ratios for each hypertension phenotype were adjusted for clinic pressure.

We assessed consistency in the results according to age (< 60 vs. ≥ 60 years), sex, body-mass index (< 30 vs. ≥ 30), presence of diabetes (yes vs. no), previous cardiovascular disease (yes vs. no), and antihypertensive medication use (yes vs. no). We also calculated the discriminative performance (expressed as the C statistic [area under the receiver-operating-characteristic curve]) and predictive performance (Akaike and Bayesian information criteria) of models containing blood-pressure components.³⁰

In addition, we calculated rate advancement periods³¹ to estimate the number of additional years of chronologic age that would be required to yield the equivalent mortality rate per 1-SD increase in blood pressure or for each hypertension phenotype as compared with normotension. Population attributable fractions³² were calculated to estimate the fraction of mortality in the population that could be attributed to each hypertension phenotype (formulas are provided in the Supplementary Appendix).

Sensitivity analyses were performed in which persons who died in the first 2 years of follow-up were excluded, to minimize the influence of reverse causation. We also checked the robustness of results by defining hypertension phenotypes on the basis of all ambulatory periods (24-hour, daytime, and nighttime) (see the Supplementary Appendix).^{26–28,33,34} Finally, we tested the reproducibility of the main results among the 2811 participants who had two ambulatory blood-pressure measurement sessions, separated by a median time of 6.5 months.

Table 1. Characteristics of the Study Cohort.*

Characteristic	All Patients (N = 63,910)	Patients Alive at the End of the Study (N = 60,102)	Patients Who Died during Follow-up (N = 3808)	P Value†
Male sex — no. (%)	37,050 (58.0)	34,975 (58.2)	2075 (54.5)	<0.001
Age — yr	58.4±14.2	57.9±14.0	67.3±13.4	<0.001
Risk factors				
Body-mass index‡				
Mean	29.3±5.7	29.3±5.7	29.7±6.3	<0.001
≥30 — no. (%)	25,866 (40.5)	24,234 (40.3)	1632 (42.9)	<0.001
Current smoker — no. (%)	10,141 (15.9)	9,588 (16.0)	553 (14.5)	0.02
Diabetes — no. (%)§	12,510 (19.6)	11,271 (18.8)	1239 (32.5)	<0.001
Dyslipidemia — no. (%)¶	26,896 (42.1)	25,124 (41.8)	1772 (46.5)	<0.001
Previous cardiovascular disease — no. (%)				
Ischemic heart disease	3,262 (5.1)	2907 (4.8)	355 (9.3)	<0.001
Stroke	2,392 (3.7)	2104 (3.5)	288 (7.6)	<0.001
Heart failure	1,231 (1.9)	1038 (1.7)	193 (5.1)	<0.001
Any cardiovascular disease	7,192 (11.3)	6335 (10.5)	857 (22.5)	<0.001
Blood pressure — mm Hg				
Clinic systolic	147.9±18.8	147.3±18.4	156.3±22.0	<0.001
Clinic diastolic	86.7±11.6	86.8±11.4	85.1±13.2	<0.001
24-Hour systolic	129.2±13.7	128.6±13.1	138.4±18.7	<0.001
24-Hour diastolic	76.5±10.1	76.6±10.0	75.7±12.0	<0.001
Daytime systolic	132.3±14.0	131.8±13.5	140.7±18.8	<0.001
Daytime diastolic	79.4±10.7	79.5±10.6	78.0±12.5	<0.001
Nighttime systolic	120.2±15.8	119.4±15.0	132.0±21.4	<0.001
Nighttime diastolic	68.4±10.2	68.3±10.0	69.4±12.0	<0.001
Hypertension phenotypes — no. (%)**				
Normotension	4,221 (6.6)	4,145 (6.9)	76 (2.0)	<0.001
Controlled hypertension	6,692 (10.5)	6,490 (10.8)	202 (5.3)	<0.001
White-coat hypertension	6,628 (10.4)	6,319 (10.5)	309 (8.1)	<0.001
White-coat uncontrolled hypertension	11,042 (17.3)	10,373 (17.3)	669 (17.6)	0.97
Masked hypertension	2,278 (3.6)	2,165 (3.6)	113 (3.0)	0.07
Masked uncontrolled hypertension	3,092 (4.8)	2,855 (4.8)	237 (6.2)	<0.001
Sustained hypertension	12,555 (19.6)	11,960 (19.9)	595 (15.6)	<0.001
Sustained uncontrolled hypertension	17,402 (27.2)	15,795 (26.3)	1607 (42.2)	<0.001
No. of blood-pressure medications — no. (%)				
0	25,682 (40.2)	24,589 (40.9)	1093 (28.7)	<0.001
1	13,791 (21.6)	13,081 (21.8)	710 (18.6)	
≥2	24,437 (38.2)	22,432 (37.3)	2005 (52.7)	

* Plus-minus values are means ±SD.

† P values are for the comparison of patients who were alive at the end of the study with those who died during follow-up.

‡ Body-mass index is the weight in kilograms divided by the square of the height in meters. A body-mass index of 30 or more indicates obesity.

§ Participants were considered to have diabetes mellitus if they had a plasma fasting glucose level of 7 mmol or more per liter (130 mg per deciliter) or received antidiabetic drugs.

¶ Dyslipidemia was defined as a total cholesterol level greater than 4.9 mmol per liter (190 mg per deciliter), low-density lipoprotein cholesterol level greater than 3 mmol per liter (120 mg per deciliter), or high-density lipoprotein cholesterol level less than 1.0 mmol per liter (40 mg per deciliter) in men or less than 1.2 mmol per liter (46 mg per deciliter) in women; fasting triglycerides level greater than 1.7 mmol per liter (150 mg per deciliter); or the use of lipid-lowering drugs.

|| The specific cardiovascular diseases that were considered were ischemic heart disease, stroke, and heart failure, as documented in the clinical record.

** Hypertension phenotypes were defined in untreated patients as follows: normotension was normal clinic blood pressure (systolic <140 mm Hg and diastolic <90 mm Hg) and normal 24-hour pressure (systolic <130 mm Hg and diastolic <80 mm Hg); white-coat hypertension was defined as elevated clinic blood pressure (systolic ≥140 mm Hg or diastolic ≥90 mm Hg) and normal 24-hour pressure; masked hypertension was defined as normal clinic blood pressure and elevated 24-hour pressure (systolic ≥130 mm Hg or diastolic ≥80 mm Hg); and sustained hypertension was defined as elevated clinic and 24-hour blood pressures. In treated patients, the corresponding terms were controlled hypertension, white-coat uncontrolled hypertension, masked uncontrolled hypertension, and sustained uncontrolled hypertension, respectively, and were defined with the same blood-pressure cutoff points as those used for untreated patients.

We used SPSS software, version 19.0 (IBM), and R software, version 3.0.2 (R Foundation for Statistical Computing), for statistical analysis. Two-tailed P values of less than 0.05 were considered to indicate statistical significance; no correction for multiple testing was performed.

RESULTS

COHORT CHARACTERISTICS

The mean (\pm SD) age of the study participants was 58.4 \pm 14.2 years, 58% were men, the mean clinic blood pressure was 147.9/86.7 mm Hg, and the mean 24-hour ambulatory blood pressure was 129.2/76.5 mm Hg (Table 1, and Fig. S1 in the Supplementary Appendix, which shows the full distribution of all blood-pressure components). During follow-up (median, 4.7 years), 3808 deaths occurred, of which 1295 were from cardiovascu-

lar causes, including 440 from ischemic heart disease, 291 from stroke, and 123 from heart failure.

RELATIONSHIP OF CONTINUOUS BLOOD-PRESSURE VARIABLES WITH MORTALITY

Clinic and ambulatory blood-pressure measurements were moderately concordant, with an intra-class correlation coefficient of 0.57 for systolic pressure ($P<0.001$) and 0.70 for diastolic pressure ($P<0.001$) (Fig. S2 in the Supplementary Appendix). Clinic and ambulatory blood-pressure measurements adjusted for cardiovascular risk factors were significantly associated with both all-cause and cardiovascular mortality, and the magnitude of the associations, in the case of both clinic and ambulatory blood pressure (especially for the systolic components), was generally similar (model 1 in Table 2). However, after

Table 2. Association of Clinic and Ambulatory Blood Pressure with All-Cause and Cardiovascular Mortality in Cox Regression Models.*

Mortality and Blood-Pressure Component	Model 1†		Model 2‡	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
All-cause mortality				
Clinic systolic blood pressure	1.54 (1.52–1.56)	<0.001	1.02 (1.00–1.04)	0.04
Clinic diastolic blood pressure	1.02 (1.00–1.04)	<0.001	0.89 (0.87–0.92)	0.01
24-Hour systolic blood pressure	1.58 (1.56–1.60)	<0.001	1.58 (1.56–1.60)	<0.001
24-Hour diastolic blood pressure	1.56 (1.54–1.58)	<0.001	1.56 (1.54–1.59)	<0.001
Daytime systolic blood pressure	1.57 (1.55–1.60)	<0.001	1.54 (1.52–1.56)	<0.001
Daytime diastolic blood pressure	1.55 (1.53–1.58)	<0.001	1.01 (0.99–1.04)	0.32
Nighttime systolic blood pressure	1.57 (1.55–1.59)	<0.001	1.55 (1.53–1.57)	<0.001
Nighttime diastolic blood pressure	1.56 (1.54–1.59)	<0.001	1.56 (1.54–1.59)	<0.001
Cardiovascular mortality				
Clinic systolic blood pressure	1.54 (1.52–1.56)	<0.001	1.02 (1.00–1.04)	0.08
Clinic diastolic blood pressure	1.02 (0.99–1.04)	0.14	0.89 (0.86–1.00)	0.06
24-Hour systolic blood pressure	1.58 (1.55–1.60)	<0.001	1.58 (1.55–1.60)	<0.001
24-Hour diastolic blood pressure	1.55 (1.53–1.58)	<0.001	1.56 (1.53–1.59)	<0.001
Daytime systolic blood pressure	1.57 (1.55–1.60)	<0.001	1.54 (1.52–1.57)	<0.001
Daytime diastolic blood pressure	1.55 (1.52–1.58)	<0.001	1.01 (0.98–1.04)	0.73
Nighttime systolic blood pressure	1.57 (1.54–1.59)	<0.001	1.55 (1.53–1.57)	<0.001
Nighttime diastolic blood pressure	1.56 (1.53–1.59)	<0.001	1.56 (1.53–1.59)	<0.001

* Of the 63,910 patients included in the analysis, 3808 died from any cause, and 1295 of those died from cardiovascular causes. Hazard ratios were estimated per 1-SD increase of each systolic and diastolic blood-pressure component, equivalent to approximately 19/12 mm Hg for clinic blood pressure or 14/10 mm Hg for ambulatory blood pressure. Rounding may have obscured small differences in hazard ratios. CI denotes confidence interval.

† Model 1 was adjusted for age, sex, smoking status, body-mass index, and status with respect to diabetes, dyslipidemia, previous cardiovascular disease, and number of antihypertensive drugs used.

‡ Model 2 was additionally adjusted as follows: clinic blood pressure was adjusted for 24-hour pressure, 24-hour blood pressure was adjusted for clinic pressure, daytime blood pressure was adjusted for clinic and nighttime pressures, and nighttime blood pressure was adjusted for clinic and daytime pressures.

additional adjustment for 24-hour systolic pressure, clinic systolic pressure lost much of its predictive power (hazard ratio for all-cause mortality, 1.54 before adjustment and 1.02 after adjustment); conversely, the hazard ratio for 24-hour ambulatory systolic pressure did not change markedly after adjustment for clinic blood pressure (hazard ratio for all-cause mortality, 1.58 before adjustment and 1.58 after adjustment) (model 2 in Table 2).

Most results were similar in analyses stratified according to age, sex, and status with respect to obesity, diabetes, cardiovascular disease, antihypertensive medication use, the number of antihypertensive drugs used, and the use of specific antihypertensive drug classes (Fig. S3 and Tables S1 and S2 in the Supplementary Appendix). Figure 1 shows that the risk of death increased as all clinic and ambulatory blood-pressure components increased. With regard to cause-specific cardiovascular mortality, 24-hour systolic pressure showed a stronger association with ischemic heart disease, stroke, and heart failure than clinic systolic pressure (Table S3 in the Supplementary Appendix).

MORTALITY DISCRIMINATION AND PREDICTIVE PERFORMANCE

In a model that included age, sex, and status with respect to cardiovascular risk factors (model 1), the addition of ambulatory systolic pressure resulted in a model with better mortality discrimination (C statistic for model, 0.94) than the addition of clinic systolic pressure (C statistic for model, 0.79). Predictive performance was also better for the model that included ambulatory pressure (lower values for the Akaike and Bayesian information criteria) (model 1 in Table S4 in the Supplementary Appendix). Also, when 24-hour blood pressure was added to the clinic blood-pressure models (model 2), the discriminative and predictive performance improved for the relationship between systolic pressure and all-cause mortality (C statistic for model 1, 0.79; C statistic for model 2, 0.94; $P=0.002$). However, with the converse adjustment (clinic blood pressure added to the 24-hour ambulatory blood-pressure model), there was only a minor change in discrimination (C statistic for model 1, 0.94; C statistic for model 2, 0.94; $P=0.93$). For diastolic blood pressure, and for overall cardiovascular mortality, there was less evidence of an

incremental improvement in discrimination with the addition of 24-hour ambulatory blood pressure to the clinic blood-pressure models.

RELATIONSHIP OF HYPERTENSION PHENOTYPES WITH MORTALITY

Of all the hypertension phenotypes evaluated, masked hypertension was associated with the highest risk and showed a stronger association with all-cause mortality (hazard ratio, 2.83) than sustained hypertension (hazard ratio, 1.80) or white-coat hypertension (hazard ratio, 1.79) when adjusted for clinic blood pressure (Table 3). Similar findings were noted for cardiovascular mortality. Results for treated patients were similar to those for untreated patients, except that the results for white-coat uncontrolled hypertension did not reach statistical significance (model 2 in Table 3). Cumulative mortality curves illustrate that, after full adjustment, masked hypertension was the strongest predictor of risk, followed by masked uncontrolled hypertension (Fig. S4 in the Supplementary Appendix). Most results were similar in analyses stratified according to age, sex, and status with respect to obesity, diabetes, and cardiovascular disease (Fig. S5 in the Supplementary Appendix). Finally, when the group with masked uncontrolled hypertension was compared with the group with controlled hypertension, fully adjusted hazard ratios were 2.61 (95% confidence interval [CI], 2.14 to 3.17) for all-cause mortality and 2.48 (95% CI, 1.83 to 3.37) for cardiovascular mortality.

ADDITIONAL ANALYSES

The rate advancement period for all-cause mortality was 1.4 years per 1-SD increase in clinic systolic blood pressure and increased to 8.5 to 10.2 years per 1-SD increase in ambulatory systolic blood pressures (Table 4). Of all the hypertension phenotypes, masked hypertension had the greatest rate advancement periods as compared with normotension. Rate advancement periods for treated patients were somewhat smaller. The values were generally similar for cardiovascular mortality.

Regarding population attributable fractions, sustained hypertension (observed in 15.6% of the patients who died) and masked hypertension (in 3.0% of the patients who died) accounted for 7.0% and 1.9%, respectively, of deaths from any cause that occurred in the whole cohort. Among

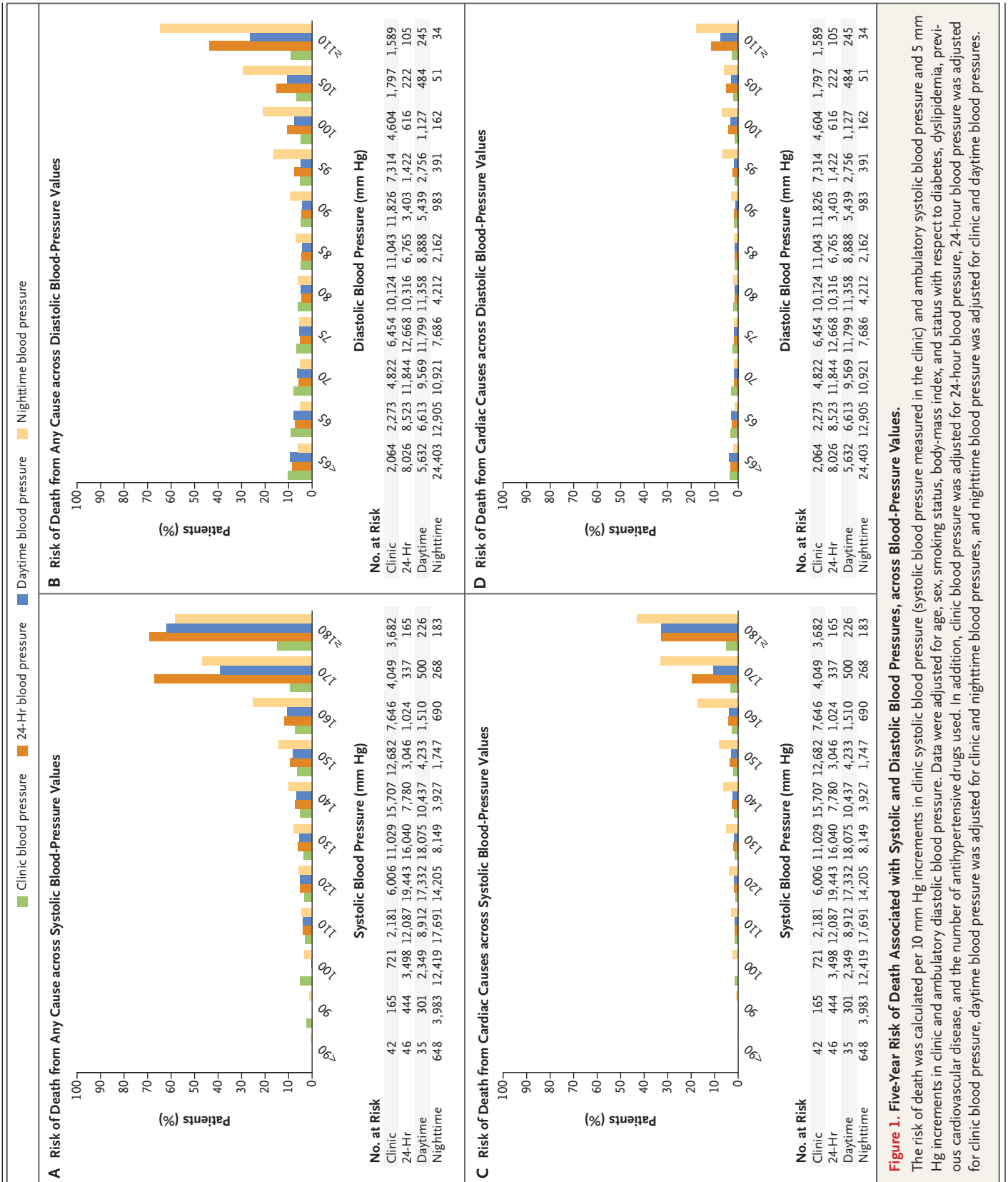


Figure 1. Five-Year Risk of Death Associated with Systolic and Diastolic Blood Pressures, across Blood-Pressure Values. The risk of death was calculated per 10 mm Hg increments in clinic systolic blood pressure (systolic blood pressure measured in the clinic) and ambulatory systolic blood pressure and 5 mm Hg increments in clinic and ambulatory diastolic blood pressure. Data were adjusted for age, sex, smoking status, body-mass index, and status with respect to diabetes, dyslipidemia, previous cardiovascular disease, and the number of antihypertensive drugs used. In addition, clinic blood pressure was adjusted for 24-hour blood pressure, 24-hour blood pressure was adjusted for clinic blood pressure, daytime blood pressure was adjusted for clinic and nighttime blood pressures, and nighttime blood pressure was adjusted for clinic and daytime blood pressures.

Table 3. Association of Hypertension Phenotypes with All-Cause and Cardiovascular Mortality in Cox Regression Models.*

Mortality and Blood-Pressure Phenotype			Model 1†		Model 2‡	
	All Patients	Deaths	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
All-cause mortality						
Normotension	4,221	76	Reference	—	Reference	—
Controlled hypertension	6,692	202	0.76 (0.57–0.99)	0.04	0.81 (0.62–1.07)	0.133
White-coat hypertension	6,628	309	2.24 (1.74–2.88)	<0.001	1.79 (1.38–2.32)	<0.001
White-coat uncontrolled hypertension	11,042	669	1.30 (1.01–1.66)	0.045	1.06 (0.82–1.37)	0.66
Masked hypertension	2,278	113	2.92 (2.18–3.90)	<0.001	2.83 (2.12–3.79)	<0.001
Masked uncontrolled hypertension	3,092	237	1.89 (1.44–2.47)	<0.001	1.96 (1.50–2.56)	<0.001
Sustained hypertension	12,555	595	2.36 (1.86–2.99)	<0.001	1.80 (1.41–2.31)	<0.001
Sustained uncontrolled hypertension	17,402	1607	1.90 (1.49–2.42)	<0.001	1.43 (1.11–1.85)	0.006
Cardiovascular mortality						
Normotension	4,221	22	Reference	—	Reference	—
Controlled hypertension	6,692	84	0.90 (0.55–1.46)	0.66	0.95 (0.59–1.55)	0.84
White-coat hypertension	6,628	94	2.36 (1.49–3.76)	<0.001	1.96 (1.22–3.15)	0.005
White-coat uncontrolled hypertension	11,042	223	1.23 (0.78–1.94)	0.37	1.04 (0.65–1.66)	0.86
Masked hypertension	2,278	32	2.92 (1.70–5.03)	<0.001	2.85 (1.66–4.90)	<0.001
Masked uncontrolled hypertension	3,092	95	2.20 (1.36–3.55)	0.001	2.27 (1.41–3.68)	0.001
Sustained hypertension	12,555	172	2.42 (1.55–3.78)	<0.001	1.94 (1.23–3.07)	0.005
Sustained uncontrolled hypertension	17,402	573	1.93 (1.23–3.01)	0.004	1.57 (1.00–2.47)	0.046

* Hazard ratios were estimated for each blood-pressure phenotype, with normotension as reference. Hypertension phenotypes were defined in untreated patients as follows: normotension was normal clinic blood pressure (systolic <140 mm Hg and diastolic <90 mm Hg) and normal 24-hour pressure (systolic <130 mm Hg and diastolic <80 mm Hg); white-coat hypertension was defined as elevated clinic blood pressure (systolic \geq 140 mm Hg or diastolic \geq 90 mm Hg) and normal 24-hour pressure; masked hypertension was defined as normal clinic blood pressure and elevated 24-hour pressure (systolic \geq 130 mm Hg or diastolic \geq 80 mm Hg); and sustained hypertension was defined as elevated clinic and 24-hour blood pressures. In treated patients, the corresponding terms were controlled hypertension, white-coat uncontrolled hypertension, masked uncontrolled hypertension, and sustained uncontrolled hypertension, respectively, and were defined with the same blood-pressure cutoff points as those used for untreated patients.

† Model 1 was adjusted for age, sex, smoking status, body-mass index, and status with respect to diabetes, dyslipidemia, previous cardiovascular disease, and number of antihypertensive drugs used.

‡ Model 2 was additionally adjusted for clinic systolic and diastolic blood pressures.

treated patients (those with uncontrolled sustained or masked hypertension), the population attributable fractions nearly doubled. Population attributable fractions were similar for cardiovascular mortality. Among all treated patients with controlled clinic blood pressure (patients with controlled hypertension plus those with masked uncontrolled hypertension), those with masked uncontrolled hypertension (i.e., normal clinic blood pressure but elevated 24-hour blood pressure, observed in 54.0% of the patients in this subgroup who died) accounted for a population attributable fraction of 33.3% (Table 4).

Sensitivity and reproducibility analyses were consistent with the primary findings. These analyses are described in the Supplementary Appendix.

DISCUSSION

In this large cohort study, ambulatory systolic blood pressure was a stronger predictor of all-cause and cardiovascular mortality than clinic systolic pressure. We also found that masked hypertension had strong associations with all-cause and cardiovascular mortality, although the

Table 4. Rate Advancement Periods and Population Attributable Fractions for Blood-Pressure Components and Hypertension Phenotypes.*

Blood-Pressure Component and Hypertension Phenotype	Rate Advancement Period†		Population Attributable Fraction‡	
	All-Cause Mortality	Cardiovascular Mortality	All-Cause Mortality	Cardiovascular Mortality
	yr (95% CI)		% (95% CI)	
Blood-pressure component				
Clinic systolic	1.4 (0.6–2.2)	—	—	—
Clinic diastolic	0.9 (0.4–1.5)	—	—	—
24-Hour systolic	9.5 (4.2–14.8)	8.0 (3.5–12.5)	—	—
24-Hour diastolic	7.3 (3.2–11.5)	5.7 (2.5–8.9)	—	—
Daytime systolic	8.5 (3.7–13.3)	7.2 (3.2–11.3)	—	—
Daytime diastolic	—	—	—	—
Nighttime systolic	10.2 (4.4–15.9)	8.4 (3.7–13.1)	—	—
Nighttime diastolic	7.3 (3.2–11.4)	7.3 (3.2–11.5)	—	—
Hypertension phenotypes				
White-coat hypertension§	9.4 (4.3–14.4)	6.6 (2.3–10.9)	3.6 (2.2–4.6)	4.0 (1.5–5.5)
White-coat uncontrolled hypertension¶	—	—	—	—
Masked hypertension	22.6 (15.0–30.2)	20.5 (14.7–26.4)	1.9 (1.6–2.2)	1.6 (1.0–2.0)
Masked uncontrolled hypertension**	14.6 (6.9–22.3)	16.1 (10.1–22.1)	3.0 (2.1–3.8)	4.1 (2.1–5.3)
Masked uncontrolled hypertension among all patients with controlled clinic pressure††	13.2 (5.6–20.7)	11.4 (7.4–15.4)	33.3 (28.8–36.9)	31.7 (24.0–37.3)
Sustained hypertension‡‡	12.8 (5.9–19.7)	13.0 (7.4–18.6)	7.0 (4.5–8.9)	6.5 (2.5–9.0)
Sustained uncontrolled hypertension§§	12.1 (5.4–18.9)	10.2 (4.6–15.8)	12.7 (4.2–19.4)	16.1 (0.1–26.3)

* Cells with dashes indicate that the fully adjusted hazard ratios for the corresponding blood-pressure components or hypertension phenotypes were not statistically significant.

† Rate advancement periods estimate the number of additional years of chronologic age that would be required to yield the equivalent mortality rate per 1-SD increase in blood pressure or for each hypertension phenotype as compared with normotension (normal clinic and normal 24-hour blood pressure in untreated patients). The rate advancement periods were based on beta coefficients adjusted for age, sex, smoking status, body-mass index, and status with respect to diabetes, dyslipidemia, previous cardiovascular disease, and number of antihypertensive drugs used and were additionally adjusted as follows: clinic blood pressure was adjusted for 24-hour pressure, 24-hour blood pressure was adjusted for clinic pressure, daytime blood pressure was adjusted for clinic and nighttime pressures, nighttime blood pressure was adjusted for clinic and daytime pressures, and hypertension phenotypes were adjusted for clinic systolic and diastolic pressures.

‡ Population attributable fractions were calculated for hypertension phenotypes (with normotension as reference) with the use of hazard ratios adjusted for age, sex, smoking status, body-mass index, and status with respect to diabetes, dyslipidemia, previous cardiovascular disease, number of antihypertensive drugs used, and clinic systolic and diastolic blood pressure.

§ White-coat hypertension refers to elevated clinic and normal 24-hour blood pressure in untreated patients in the whole cohort.

¶ White-coat uncontrolled hypertension refers to elevated clinic and normal 24-hour blood pressure in treated patients in the whole cohort.

|| Masked hypertension refers to normal clinic and elevated 24-hour blood pressure in untreated patients in the whole cohort.

** Masked uncontrolled hypertension refers to normal clinic and elevated 24-hour blood pressure in treated patients in the whole cohort.

†† These data are for masked uncontrolled hypertension in the subpopulation of all treated patients with controlled clinic blood pressure (i.e., patients with controlled hypertension plus patients with masked uncontrolled hypertension).

‡‡ Sustained hypertension refers to elevated clinic and 24-hour blood pressure in untreated patients in the whole cohort.

§§ Sustained uncontrolled hypertension refers to elevated clinic and 24-hour blood pressure in treated patients in the whole cohort.

population attributable fraction was greater for sustained hypertension, which is more common than masked hypertension.

Previous population and clinical studies have shown that ambulatory blood pressure predicts cardiovascular events better than clinic blood

pressure.^{4,5,7-10} Our large study corroborated these findings. A model that included clinic blood pressure as well as age, sex, and status with respect to cardiovascular risk factors (model 1) was a reasonably good discriminator of cardiovascular mortality (C statistic for model, 0.91)

but was not as good a discriminator of all-cause mortality (C statistic for model, 0.79), probably because the C statistic measures the discrimination ability of all the variables in model 1, including the cardiovascular risk factors, which have greater influence on cardiovascular mortality than on all-cause mortality. Indeed, the improvement in discrimination with the addition of 24-hour systolic pressure (model 2) for all-cause but not for cardiovascular mortality is probably because the C statistic for model 1 was already quite high for cardiovascular mortality. The association of 24-hour systolic blood pressure with all-cause and cardiovascular mortality was similar to that seen for daytime systolic pressure and nighttime systolic pressure and remained significant in multivariate adjustment that included clinic blood pressure. These findings were consistent in subgroups defined according to age, sex, the presence or absence of obesity, and status with respect to diabetes, previous cardiovascular disease, and antihypertensive drug treatment.

In our study, unlike most previous studies,^{2,14-18,35} we observed consistently greater mortality associated with masked hypertension than with sustained hypertension, which might be due to the delayed detection of masked hypertension in patients, who consequently could have more organ damage and cardiovascular disease than patients with sustained hypertension. In previous research, white-coat hypertension showed a risk similar to that of normotension,^{14,16,18-22} or an intermediate risk between normotension and hypertension.^{15,36-39} In our study, white-coat hypertension was not benign, which may be due in part to the higher mean blood pressure over 24 hours in these patients (119.9/71.9 mm Hg, vs. 116.6/70.6 mm Hg in normotensive patients; $P < 0.001$) or to their metabolic phenotype.^{2,39} The somewhat weaker association with mortality of treated phenotypes than of untreated phenotypes is probably because treated patients were more likely to have frequent follow-up visits, repeated blood-pressure checks, medication adjustments, and treatment of concomitant conditions contributing to risk.

Masked uncontrolled hypertension was associated with high mortality in the subpopulation of patients with treated hypertension and controlled clinic blood pressure who died (population attributable fraction, 33.3%) but much lower mortality

in the whole cohort who died (population attributable fraction, 3.0%), mainly because the percentage of persons with masked uncontrolled hypertension was much higher in the first than in the second population (54.0% vs. 6.2%). Rate advancement periods can highlight the clinical implications of the data by showing, for example, that on average, a 50-year-old patient with masked uncontrolled hypertension, as compared with a normotensive person, had an all-cause mortality rate equivalent to being 14 years older.

This study has some limitations. First, clinic blood pressure represented the average of only two readings at each clinic visit; thus, the mean clinic pressure could be overestimated because it tends to become lower with repeated measurements. Nevertheless, this is a pragmatic study of real-world clinical practice where this approach to clinic blood-pressure measurement is more typical than that adopted in clinical trials. Likewise, in most patients, ambulatory blood-pressure monitoring was performed at a single time point, thus limiting its prognostic power. Nevertheless, hazard ratios in the reproducibility analyses (among participants who had two ambulatory blood-pressure measurement sessions) were generally similar for each blood-pressure component in the two ambulatory monitoring sessions in all participants. Second, we have no data on medication during the follow-up period except in patients who had two ambulatory blood-pressure monitoring sessions; in these patients, the main study associations did not vary according to the number of medications received (Table S8 in the Supplementary Appendix). Third, there may be some selection bias from inclusion criteria for ambulatory blood-pressure monitoring. However, the participants with hypertension in our registry have a cardiovascular risk profile similar to that of patients with hypertension in other studies that are representative of primary care.⁴⁰ Fourth, this is 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. Finally, we studied a white population, and the results may not apply to people of other races.

In conclusion, in this large study, 24-hour, daytime, and nighttime ambulatory systolic blood

pressures were all better predictors of all-cause and cardiovascular mortality than clinic blood pressure. Sustained hypertension, white-coat hypertension, and masked hypertension were all associated with an increased risk of death; the strongest association was found with masked hypertension.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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APPENDIX

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