Cardiovascular Prognosis of "Masked Hypertension" Detected by Blood Pressure Self-measurement in Elderly Treated Hypertensive Patients

Guillaume Bobrie, MD
Gilles Chatellier, MD
Nathalie Genes, MD
Pierre Clerson, MD
Laurent Vaur, MD
Bernard Vaisse, MD
Joël Menard, MD
Jean-Michel Mallion, MD

Context Blood pressure (BP) measurement in clinicians' offices with a mercury sphygmomanometer has numerous drawbacks. In contrast, the use of home BP measurement improves measurement precision and reproducibility. However, data about its prognostic value are lacking.

Objective To assess the prognostic value of home vs office BP measurement by general practitioners in a European population of elderly patients being treated for hypertension.

Design, Setting, and Participants Office and home BP and cardiac risk factors were measured at baseline in a cohort of 4939 treated hypertensive patients (mean age, 70 [SD, 6.5] years; 48.9% men) who were recruited and followed up by their usual general practitioners without specific recommendations about their management. The cohort was then followed up for a mean of 3.2 (SD, 0.5) years. The thresholds defining uncontrolled hypertension were at least 140/90 mm Hg for office BP and 135/85 mm Hg for home BP.

Main Outcome Measures The primary end point was cardiovascular mortality. Secondary end points were total mortality and the combination of cardiovascular mortality, nonfatal myocardial infarction, nonfatal stroke, transient ischemic attack, hospitalization for angina or heart failure, percutaneous transluminal coronary angioplasty, or coronary artery bypass graft surgery.

Results At the end of follow-up, clinical status was known for 99.9% of patients. At least 1 cardiovascular event had occurred in 324 (incidence, 22.2/1000 patient-years). For BP self-measurement at home, each 10-mm Hg increase in systolic BP increased the risk of a cardiovascular event by 17.2% (95% confidence interval [CI], 11.0%-23.8%) and each 5-mm Hg increase in diastolic BP increased that risk by 11.7% (95% CI, 5.7%-18.1%). Conversely, for the same increase in BP observed using office measurement, there was no significant increase in the risk of a cardiovascular event. In a multivariable model with patients having controlled hypertension (normal home and office BP) as the referent, the hazard ratio of cardiovascular events was 1.96 (95% CI, 1.27-3.02) in patients with uncontrolled hypertension (high BP with both measurement methods), 2.06 (95% CI, 1.22-3.47) in patients with normal office BP and elevated home BP, and 1.18 (95% CI, 0.67-2.10) in patients with elevated office BP and normal home BP.

Conclusions Our findings suggest that home BP measurement has a better prognostic accuracy than office BP measurement. Blood pressure should systematically be measured at home in patients receiving treatment for hypertension.

JAMA. 2004;291:1342-1349 www.jama.com

THE REFERENCE METHOD FOR blood pressure (BP) measurement during clinical consultations is the auscultatory method with a mercury sphygmomanometer. This method has been used to demonstrate the relationship between BP and cardiovascular risk. A meta-analysis of individual data from almost 1 million adults participating in 61 prospective studies precisely established the prognostic value of this method of measurement: for each increase of 10 mm Hg in systolic BP (SBP) or 5 mm Hg in diastolic BP (DBP), the average risk of cerebrovascular mortality increases by 40% and the risk of mortality from ischemic heart disease by 30%.[1] The mercury sphygmomanometer, used during clinical consultations, is also the tool that has demonstrated the benefit of antihypertensive treatment. In the first meta-analysis of randomized controlled trials using the sphygmomanometer, a decrease in DBP of 5 mm Hg to 6 mm Hg was associated with a 42% reduction in the risk of stroke syndrome and a 14% reduction in the risk of coronary events.[2]

Author Affiliations: Service d'Hypertension Artérielle (Dr Bobrie) and Service de Santé Publique et d'Informatique Médicale (Drs Chatellier and Menard), Hôpital Européen Georges Pompidou, and Laboratoire Aventis (Drs Genes and Vaur), Paris, France; Interphase-Orgamétrie, Wattrelos, France (Dr Clerson); Service de Médecine Interne, Hôpital de la Timone, Marseille, France (Dr Vaisse); and Service de Cardiologie et Hypertension Artérielle, Centre Hospitalier Universitaire, Grenoble, France (Dr Mallion). **Corresponding Author:** Guillaume Bobrie, MD, Service d'Hypertension, Hôpital Européen Georges Pompidou, 20 rue Leblanc, 75908 Paris, Cedex 15, France (guillaume.bobrie@hop.egp.ap-hop-paris.fr).

There are, however, numerous criticisms of clinical BP measurement. Major interobserver and intraobserver variability exists, related to the difficulty of standardizing the measurement conditions and the insufficiency of the number of measurements. There is considerable variability among individual examiners; subjectivity can be related to hearing, sight, a preference for rounding digits during measurement, etc.[3] It fails to recognize "white-coat hypertension," also known as "office hypertension."[4] Finally, the mercury sphygmomanometer should probably be abandoned for ecological reasons (ie, the toxicity of mercury). Replacement of office BP measurement with physician-independent methods (ambulatory BP monitoring and home BP self-measurement) is advocated by many guidelines.

Perloff et al[5] and Verdecchia et al[6] demonstrated the better prognostic value of ambulatory BP monitoring than office measurement in a general untreated population, and Clement et al[7] did so in patients being treated for hypertension. Home BP has a high degree of measurement quality and is cheaper and better accepted by patients than ambulatory BP monitoring.[8] To date, there has been only 1 prognostic study of cardiovascular morbidity and mortality suggesting that this method is superior to office BP measurement. This study involved a normotensive Asian population living in a rural area and used a self-measurement protocol different from that in usual practice.[9] We therefore instituted a cohort study to evaluate the prognostic value of home BP measurement and that of office BP measurement by general practitioners in a European population of patients being treated for hypertension.

METHODS

Study Design

The SHEAF (Self-Measurement of Blood Pressure at Home in the Elderly: Assessment and Follow-up) study was a 3-year prospective cohort study designed to assess in general practice whether the prognostic value of home BP is greater than that of office BP. The study comprised 2 successive phases. The first phase consisted of a period of evaluation with 2 separate visits at an interval of 2 weeks. Office and home BP and heart rate (the mean of heart rate values measured at home) were recorded, as well as presence of antihypertensive treatment and demographic and medical history characteristics; ie, sex, age, obesity (body mass index ≥30), smoking status (current, former, or never), presence of diabetes mellitus, presence of treated hypercholesterolemia (fibrates or statins), history of cardiovascular events, and creatinine clearance (using the formula of Cockroft and Gault[10]). The second phase was a 3-year follow-up of patients. This was an observational study, and, therefore, there was no specific recommendation with regard to management of hypertension, including frequency of visits, type of drug treatment or BP goal, and no data were recorded concerning BP level or antihypertensive drug use during the follow-up.

The practitioners were instructed to carefully report and document all outcome events that occurred during the follow-up and were asked each year about the morbidity and mortality status of the patients. In case of no response, practitioners and then patients were telephoned by a study physician. If no contact could be established, a query was sent to the city hall (registry of births and deaths) of the town in which the patient was born to determine deaths. Study end points were identified by an end-point committee.

Approval, Support, and Conduct of the Study

The protocol was approved by the French National Data Protection Committee (Commission Nationale Informatique et Liberté) and conducted in accordance with the Declaration of Helsinki. All participants were informed about the study and gave oral consent.

Setting and Patient Recruitment

Patients of both sexes were recruited by general practitioners and were included in the study if they fulfilled the following criteria: age at least 60 years; primary permanent hypertension defined by the receipt of antihypertensive treatment or, in the absence of treatment, by office BP values greater than 140/90 mm Hg measured at 2 separate times during the year preceding inclusion; arm size allowing the use of a standard cuff; ability to perform an appropriate number of BP measurements at home with the study device; and absence of any threatening disease or recent acute cardiovascular event (eg, myocardial infarction, stroke). We did not ask general practitioners to record information about patients who fulfilled criteria inclusion but were not included in the study.

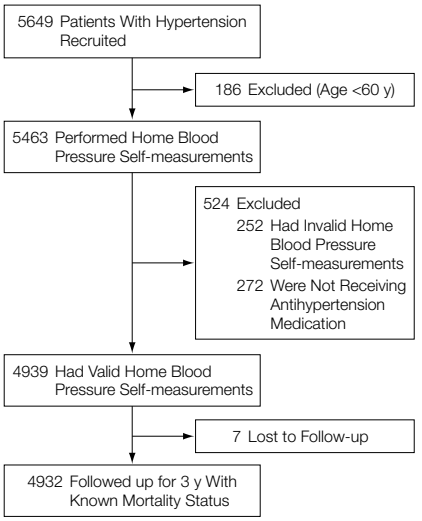
End Points

The primary end point was cardiovascular mortality. Secondary end points were total mortality and the combination of cardiovascular mortality, nonfatal myocardial infarction, nonfatal stroke, transient ischemic attack, hospitalization for angina or heart failure, percutaneous transluminal coronary angioplasty, and coronary artery bypass graft surgery.

The end-point committee, comprising a cardiologist, an internist, and a neurologist, identified all major end points by reviewing the patient discharge summaries and source documents. Complementary documentation was requested if necessary by this committee. The committee was blinded with respect to all BP data. Cardiovascular events were validated according to the principles used in randomized trials. The following definitions were used:

- Stroke was defined as a neurologic deficit with symptoms continuing for more than 24 hours or leading to death with no apparent cause other than vascular. Transient ischemic attack was defined as a neurologic deficit lasting less than 24 hours.
- Acute myocardial infarction was defined by the presence of 2 or more of the following: typical chest pain, electrocardiographic changes, and increased cardiac enzyme concentrations. The definition of myocardial infarction did not include silent myocardial infarction.

Figure. Flow of Study Participants



- Congestive heart failure required hospitalization and the presence of 2 or more of the following: symptoms, clinical signs, radiographic abnormalities, and abnormal noninvasive test (echocardiography, angiography) results.
- Sudden death was defined as any death of unknown cause occurring immediately or within 24 hours after onset of acute symptoms or any unwitnessed death for which no likely cause could be established on the basis of medical history.
- Angina pectoris was diagnosed if there was hospitalization and chest pain and documented electrocardiographic signs of coronary ischemia or if there was a need for coronary revascularization in the absence of acute myocardial infarction.
- An event was considered validated when all 3 members of the end-point committee agreed on the diagnosis.

BP Measurements

Office BP Measurement. During the first phase, triplicate BP measurements were taken at both visits by the physicians, using a mercury sphygmomanometer with the patient in the sitting position after a 5-minute rest, without specific training. No recommendation about time of measurement was made to the physicians. Systolic BP was measured at phase 1 of Korotkoff sounds and diastolic BP at phase 5 of Korotkoff sounds. The mean of the 6 readings was taken as the office baseline BP for each patient.

Home BP Measurement. Home BP measurement was performed during the initial phase of the study. Home BP measurements were planned over a 4-day period chosen at the patient's convenience. Every day, a series of 3 consecutive measurements was requested in the morning (8 AM) and repeated in the evening (8 PM). Measurements were performed in the sitting position after a 5-minute rest. The Omron-705 CP device (Omron Corp, Tokyo, Japan), which is a printer-equipped, semiautomatic, digitized device based on the oscillometric method, was used by all participants. This device had been previously validated against a mercury sphygmomanometer according to the revised protocol of the British Hypertension Society.[11] Because it has been shown that the degree of reliability of hypertensive patients' reporting of self-measured BP values is both variable and unpredictable,[12] each patient was asked to write their measurement results in a booklet designed for the study and to keep all printouts and staple them in the booklet.

Home BP Data Management

For each patient, aberrant values were deleted according to the following predefined rules: DBP less than 40 mm Hg or more than 150 mm Hg; SBP less than 60 mm Hg or more than 250 mm Hg; and pulse pressure less than 10 mm Hg. Measurements performed outside of the predefined morning and evening time frames (4-12 AM range or 4-12 PM range) were also discarded.

Patients were included in the study only if they had at least 15 valid measurements, with at least 6 measurements in the morning and 6 measurements in the evening. For each included patient, the mean of all the available home measurements was taken as the home BP value and used for comparison with office measurements.[13]

Data and Statistical Analyses

Sample Size and Patient Recruitment. The calculation of the sample size of the cohort was based on an assumed cardiovascular death rate of 0.5% to 1.0% per year in elderly patients with hypertension in France, giving an estimated total 3-year number of 15 to 30 deaths per 1000 included patients. On the basis of a ratio of 1 nonfatal event to 1 death, we anticipated 30 to 60 events per 1000 included patients. According to Peduzzi et al,[14] the accuracy and precision of the coefficients estimated by the proportional hazards method are low when the number of events per variable is less than 10. Since we anticipated a model comprising 10 to 15 variables, at least 150 events should be observed. We therefore decided to include 5000 patients to observe a total 3-year number of 150 to 300 events.

From February 1998 to March 1999, 1429 general practitioners recruited 5649 patients. Among these patients, 186 were excluded for age younger than 60 years and 252 for nonvalid home BP measurements. Thus, 5211 patients (2565 men and 2646 women) with a mean age of 70 years (SD, 7 years) and valid home BP measurements were included. A total of 4939 (95%) were being treated with at least 1 antihypertensive drug. Characteristics of treated and untreated patients were comparable.[13] For homogeneity purposes, further analyses were performed only in the 4939 treated patients (FIGURE).

BP Thresholds. We formed subgroups of patients with hypertension according to the following rules: For the office BP measurement, the internationally accepted limit of 140/90 mm Hg was adopted[4] and for the home BP measurement, the internationally accepted limit of 135/85 mm Hg was adopted.[15] Patients were classified into 4 subgroups: those with "controlled" hypertension (ie, BP below the limit for each of the methods); those with "uncontrolled" hypertension (ie, BP greater than or equal to the limit for each of the methods); those with BP below the limit of normality of the home BP measurement and greater than or equal to the limit of normality

of the office BP measurement; and those with BP below the limit of normality of the office BP measurement and greater than or equal to the limit of normality of the home BP measurement.

Prognostic Value of Home BP. The prognostic value of home BP was analyzed at the time of the first composite end point occurring during follow-up. Hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated using the Cox proportional hazards model after adjustment for sex, age, heart rate (mean of values measured during the series of home BP measurements), smoking status (current vs former or never), history of cardiovascular events, presence of diabetes mellitus, presence of obesity, and presence of treatment of hypercholesterolemia. Separate models were used for office and home BP and for SBP and DBP, after verification of the hypothesis of the proportional risk. For the analysis of the prognoses of the 4 subgroups individualized according to BP thresholds, the HRs were calculated in a multivariable (Cox) model with the group of patients with controlled hypertension as the referent.

Quantitative data are summarized as mean (SD) and qualitative data as percentages. Unpaired *t* tests were used for normally distributed data and comparisons of 2 groups, and analysis of variance for comparisons of more than 2 groups. The χ^2 test was used for categorical data.

The analyses were performed using SAS software, version 8.2 (SAS Institute Inc, Cary, NC). For all analyses, $P<.05$ was considered statistically significant.

RESULTS

General characteristics of the 4939 patients treated for hypertension are shown in TABLE 1. Inclusion was limited to those with valid measurements to avoid bias due to a variable number of measurements that could influence precision of home BP estimates. As required in the protocol, the mean of 6 measurements defined office BP, and the mean number of measurements used to define home BP was 27 (SD, 5). At baseline, only 13.9% appeared to have their hypertension controlled by both measurement methods, 13.3% had elevated BP in the office but not at home, 9.4% had elevated BP at home but not in the office, and 63.4% had uncontrolled hypertension by both measurement methods.

The follow-up of the study ended in early 2002. The vital status was known for 4932 patients (99.9%) at the end of a mean follow-up of 3.2 (SD, 0.5) years (93.1% had a follow-up >2.5 years). In terms of cardiovascular morbidity and mortality, the status was known for 4928 patients (99.78%) at the end of a mean follow-up of 3.0 (SD, 0.6) years (88.8% had a follow-up >2.5 years).

There were 205 deaths (incidence, 13.6/1000 patient-years), of which 85 were of cardiovascular origin (inci-

Table 1. Participant Characteristics (n = 4939)

Characteristics	No. (%) of Patients*
Men	2413 (48.9)
Age, mean (SD) [range], y	70.0 (6.5) [60-97]
Blood pressure, mean (SD), mm Hg	
Office	
Systolic	152 (17)
Diastolic	85 (9)
Pulse	67 (13)
Home	
Systolic	146 (19)
Diastolic	82 (10)
Pulse	64 (15)
Obesity (body mass index ≥30)	935 (19.0)
Current smokers	379 (7.7)
Diabetes	726 (14.7)
Treatment for hypercholesterolemia	2150 (43.7)
Previous coronary event	616 (12.5)
Previous episode of heart failure	254 (5.1)
Previous stroke/transient ischemic attack	232 (4.7)
No. of classes of antihypertensive drugs prescribed	
1	2224 (45.0)
2	1696 (34.3)
3	741 (15.0)
>3	278 (5.6)

*Data are expressed as No. (%) unless otherwise noted.

Table 2. Causes of Death*

Causes	No.	% of Population	% of Deaths	% of Cardiovascular Deaths
All deaths	205	4.16	100	NA
Deaths of cardiovascular origin	85	1.72	41.46	100
Myocardial infarction	13	0.26	6.34	15.29
Heart failure	11	0.22	5.37	12.94
Stroke	18	0.36	8.78	21.18
Sudden death	25	0.51	12.20	29.41
Other†	18	0.36	8.78	21.18
Deaths of noncardiovascular origin	95	1.93	46.34	NA
Cancer	63	1.28	30.73	NA
Injury	7	0.14	3.41	NA
Other	25	0.51	12.20	NA
Deaths of unknown origin	25	0.51	12.20	NA

Abbreviation: NA, not applicable.
*Vital status was known for 4932 participants (99.86%) at the end of follow-up.
†Cardiovascular deaths of other origin included aortic dissection and aortic aneurysm.

dence, 5.6/1000 patient-years). The causes of death and their respective frequencies are listed in TABLE 2.

In the cohort, 324 patients had at least 1 cardiovascular event, used for the analysis of morbidity and mortality (incidence, 22.2/1000 patient-years). The origins of the cardiovascular events and their respective frequencies are listed in TABLE 3.

The conventional cardiovascular risk factors (age, male sex, smoking, diabetes, history of heart failure, previous coronary disease, and renal failure [creatinine clearance ≤60 mL/min]) appear to be predictive of the occurrence of cardiovascular death and cardiovascular events (TABLE 4). The same applies to global mortality.

After adjustment for age, sex, previous cardiovascular history, smoking status, etc, using a Cox proportional hazards model, home BP was predictive of the occurrence of cardiovascular events (TABLE 5). The magnitude of adjusted HRs was comparable for both sexes. Neither office SBP (for men, HR, 1.01; 95% CI, 1.00-1.02; for women, HR, 1.00; 95% CI, 0.99-1.01) nor office DBP (for men, HR, 1.00, 95% CI, 0.98-1.02; for women, HR, 1.01; 95% CI, 0.99-1.03) were linked to prognosis. Home SBP was linked to prognosis in both sexes (for men, HR, 1.02; 95% CI, 1.01-1.03; for women, HR, 1.01, 95% CI, 1.01-1.02). Home DBP was linked to prognosis in men and the significance level was borderline among women (for men, HR, 1.02, 95% CI, 1.01-1.04; for women, HR, 1.02, 95% CI, 1.00-1.04).

We also used a model with the same predictors but with increments of 5 mm Hg and 10 mm Hg (rather than 1 mm Hg) for DBP and SBP, respectively. Using this model for home BP self-measurement, for each increase in SBP of 10 mm Hg, the risk of a cardiovascular event increased by 17.2% (95% CI, 11.0%-23.8%) and for each increase in DBP of 5 mm Hg, the risk of a cardiovascular event increased by 11.7% (95% CI, 5.7%-18.1%). Conversely, after adjustment for the same predictors, for the same increases in BP observed using office measurement, there was no significant increase in the risk of an event (5.8% increase; 95% CI, –0.8% to 12.5% and 1.4% increase; 95% CI, –4.8% to 7.9%, respectively). Irrespective of the measurement method, BP was not significantly related to either cardiovascular mortality or total mortality.

The incidence of cardiovascular events in patients with elevated BP in the office but not at home was the same as that of patients considered to have their hy-

Table 3. First Cardiovascular Events Occurring During Follow-up*

Events	No.	% of Population	% of Cardiovascular Events
Total No. with ≥1 cardiovascular event	324	6.57	100
Death of cardiovascular origin	62	1.26	19.14
Nonfatal myocardial infarction	33	0.67	10.19
Hospitalization for angina	66	1.34	20.37
Percutaneous transluminal coronary angioplasty	17	0.34	5.25
Coronary artery bypass graft surgery	9	0.18	2.78
Hospitalization for heart failure	44	0.89	13.58
Nonfatal stroke	58	1.18	17.90
Transient ischemic attack	35	0.71	10.80

*Status was known for 4928 participants (99.78%) at the end of follow-up.

Table 4. Risk Factors at Baseline for Occurrence of CV Deaths, Total Deaths, and Fatal and Nonfatal CV Events

	CV Deaths			Total Deaths			Fatal and Nonfatal CV Events*		
Risk Factors	Yes (n = 85)	No (n = 4847)	*P* Value	Yes (n = 205)	No (n = 4727)	*P* Value	Yes (n = 324)	No (n = 4604)	*P* Value
Age, mean (SD), y	76.1 (8.4)	69.9 (6.4)	<.001	74.8 (8.5)	69.8 (6.3)	<.001	73.3 (7.5)	69.8 (6.4)	<.001
Men, No. (%)	54 (53.6)	2352 (48.52)	.006	123 (60.0)	2283 (48.3)	<.001	208 (64.2)	2197 (47.7)	<.001
Smoking, No. (%)									
Current smokers	10 (11.8)	369 (7.6)		22 (10.7)	357 (7.6)		30 (9.3)	349 (7.6)	
Nonsmokers	45 (52.9)	3306 (68.2)	.01	113 (55.1)	3238 (68.5)	<.001	180 (55.6)	3167 (68.8)	.27
Past smokers	30 (35.3)	1172 (24.2)		70 (34.2)	1132 (24.0)		114 (35.2)	1088 (23.6)	
Diabetes, No. (%)	21 (24.7)	705 (14.6)	.009	47 (22.9)	679 (14.4)	<.001	72 (22.2)	653 (14.2)	<.001
Previous episode of heart failure, No. (%)	25 (29.4)	229 (4.7)	<.001	41 (20.0)	213 (4.5)	<.001	54 (16.7)	200 (4.3)	<.001
Previous coronary event, No. (%)	33 (38.8)	581 (12.0)	<.001	49 (23.9)	565 (12.0)	<.001	110 (33.9)	503 (10.9)	<.001
Previous stroke, No. (%)	21 (24.7)	211 (4.7)	<.001	29 (14.2)	203 (4.3)	<.001	49 (15.1)	183 (4.0)	<.001
Creatinine clearance ≤60 mL/min, No. (%)†	47 (59.5)	1659 (37.4)	<.001	103 (55.1)	1603 (37.0)	<.001	145 (47.5)	1559 (37.0)	<.001
Office blood pressure, mean, mm Hg	151/83	152/85	.57/.03	151/83	152/85	.34/.006	154/84	152/85	.04/.08
Home blood pressure, mean, mm Hg	151/82	146/82	.008/.79	149/82	146/82	.006/.74	155/83	145/82	<.001/.01

Abbreviation: CV, cardiovascular.
*For patients with multiple end points, only the first that occurred was included.
†Creatinine clearance was calculated according to the Cockroft and Gault formula[10] (n = 413 with missing data).

pertension controlled: 11.1 and 12.1 cases per 1000 patient-years, respectively. Conversely, the incidence of cardiovascular events in patients with elevated BP at home but not in the office was high and similar to that of patients with uncontrolled hypertension (30.6 and 25.6 cases per 1000 patient-years, respectively) (TABLE 6). In a multivariable model using patients with controlled hypertension as the referent, the HR of cardiovascular events was double for patients with uncontrolled hypertension (HR, 1.96; 95% CI, 1.27-3.02) and for patients with elevated BP at home but not in the office (HR, 2.06; 95% CI, 1.22-3.47), whereas the HR of patients with elevated BP in the office but not at home did not differ (HR, 1.18; 95% CI, 0.67-2.10).

COMMENT

In this cohort study conducted among patients aged 60 years or older being treated for hypertension in general practitioners' offices, home BP self-measurement defines the prognosis in

Table 5. Adjusted HR of Occurrence of CV Events With a BP Increase of 1 mm Hg*

	CV Deaths (n = 85)		Total Deaths (n = 205)		Fatal or Nonfatal CV Events (n = 324)†	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Office SBP	1.00 (0.98-1.01)	.43	0.99 (0.99-1.00)	.13	1.01 (1.00-1.01)	.09
Home SBP	1.01 (0.99-1.02)	.39	1.00 (1.00-1.01)	.60	1.02 (1.01-1.02)	<.001
Office DBP	0.99 (0.97-1.02)	.51	0.99 (0.97-1.01)	.19	1.00 (0.99-1.02)	.67
Home DBP	1.02 (0.99-1.04)	.20	1.01 (0.99-1.02)	.50	1.02 (1.01-1.03)	<.001
Office PP	1.00 (0.98-1.01)	.56	0.99 (0.98-1.01)	.28	1.01 (1.00-1.02)	.05
Home PP	1.00 (0.99-1.02)	.75	1.00 (0.99-1.01)	.81	1.02 (1.01-1.03)	<.001

Abbreviations: CI, confidence interval; CV, cardiovascular; DBP, diastolic blood pressure; HR, hazard ratio; PP, pulse pressure; SBP, systolic blood pressure.
*Adjusted for sex, age, heart rate (mean of values recorded during the series of HBP measurements), smoking status (current vs former or never), history of cardiovascular events, presence of diabetes mellitus, and presence of treated hypercholesterolemia.
†For patients with multiple end points, only the first that occurred was included.

Table 6. Population Baseline Characteristics and Follow-up Events Classified by Threshold of BP Normality by Measurement Method*

	Controlled Hypertension (n = 685)	Elevated BP in the Office but Not at Home (n = 656)	Elevated BP at Home but Not in the Office (n = 462)	Uncontrolled Hypertension (n = 3125)	*P* Value
Age, mean (SD), y	68.7 (6.3)	69.5 (6.2)	70.0 (6.5)	70.4 (6.6)	<.001
Duration of hypertension, y					
Mean (SD)	10.8 (7.4)	10.8 (7.7)	11.7 (7.3)	11.5 (8.6)	
Median (IQR)	9.4 (4.9-16.1)	9.5 (4.5-15.3)	10.4 (6.1-16.7)	10.2 (4.3-17.2)	.54
Men	264 (38.5)	242 (36.9)	269 (58.2)	1630 (52.1)	<.001
Obesity	112 (16.4)	102 (15.6)	92 (20.1)	629 (20.3)	.01
Diabetes	74 (10.8)	89 (13.6)	65 (14.1)	497 (15.9)	.005
Treated dyslipidemia	305 (44.5)	292 (44.5)	202 (43.7)	1349 (43.2)	.88
Ex-smoker	139 (20.3)	117 (17.8)	124 (26.8)	822 (26.3)	<.001
Current smoker	52 (7.6)	40 (6.1)	39 (8.4)	248 (7.9)	.39
≥1 Previous coronary event	89 (13.0)	56 (8.5)	61 (13.2)	407 (13.0)	.01
Heart failure	40 (5.8)	24 (3.7)	25 (5.4)	165 (5.3)	.28
Peripheral vascular disease	25 (3.7)	28 (4.3)	27 (5.8)	217 (6.9)	.001
Previous stroke syndrome	24 (3.5)	21 (3.2)	30 (6.5)	157 (5.0)	.02
BP, mean (SD), mm Hg					
Office					
Systolic	130.2 (6.8)	150.5 (10.3)	133.7 (5.0)	159.5 (14.1)	NA
Diastolic	77.0 (5.9)	84.8 (7.3)	78.3 (6.2)	87.3 (8.5)	NA
Home					
Systolic	123.0 (7.9)	126.6 (6.7)	143.8 (9.8)	155.4 (15.3)	NA
Diastolic	73.6 (6.3)	74.3 (6.1)	82.5 (7.3)	85.6 (9.4)	NA
Home heart rate, mean (SD), beats/min	69.4 (9.0)	68.3 (9.1)	68.0 (9.5)	68.8 (9.9)	.07
Cardiovascular events					
Incidence	23 (3.4)	24 (3.7)	41 (8.9)	236 (7.6)	NA
Incidence rate per 1000 patient-years (95% CI)	11.1 (6.5-15.6)	12.1 (7.3-16.9)	30.6 (21.2-39.9)	25.6 (22.4-28.9)	NA

Abbreviations: BP, blood presure; CI, confidence interval; IQR, interquartile range; NA, not applicable.
*Data are expressed as No. (%) unless otherwise noted.

terms of cardiovascular morbidity and mortality better than office measurement. In this study, home BP self-measurement identified a very specific subgroup of 9% of patients with poor control of their hypertension at home that appeared controlled in the physician's office. The initial profile (in terms of risk factors and previous cardiovascular history) of patients with elevated BP at home but not in the office is similar to that of patients considered to have uncontrolled hypertension by both measurement methods.[13] This study adds new information that their cardiovascular prognoses are comparable. In the cross-sectional part of this study, at the time of inclusion, the profile of the 13% of patients with elevated BP in the office but not at home was similar to that of patients considered to have controlled hypertension by both measurement methods.[13] This study also shows that their cardiovascular prognoses are comparable. Therefore, cross-sectional observation is confirmed by a prospective cohort study.

One of the strengths of the study is that these results were obtained in a large patient population by a prospective cohort study with exhaustive collection of information on morbidity and mortality status. In addition, all the events that occurred were validated in terms of precise criteria predefined by an independent validation committee blinded to the results of the office and home BP measurements. The general practitioner investigators were aware of the results of the home BP measurement performed at baseline but were not given any specific recommendations for management of hypertension, either in terms of utilization of the results, of BP target ranges, or of therapeutic procedures. It is therefore unlikely that, over a 3-year period, these results might have influenced the behavior of the general practitioners, but we cannot confirm this in the absence of collection of data relating to the changes in antihypertensive treatment during follow-up. The same limitation is present in the study by Clement et al,[7] who demonstrated that ambulatory BP monitoring had a better prognostic value than office measurement in patients treated for hypertension.

It is unlikely that a systematic relationship between timing of antihypertensive drug ingestion and that of BP measurement could explain the better values of home over office BP measurement, although we did not record data on these 2 parameters. Thus, home BP measurement is the mean of BP trough (morning) and peak (evening) values. Since office BP measurement was performed during the usual working hours of general practitioners, it is likely that every possible timing of measurement is represented in our large sample.

A large enough number of morbidity and mortality events enable the prognostic superiority of standardized home BP measurement to be demonstrated. Superiority is related to the reduced intrapatient variability compared with the office BP measurement,[16-18] itself due to the increased number of measurements; 27 measurements defined home BP while only 6 measurements defined office BP. This result is also due in part to poor performance of office BP measurement; for example, a marked preference to round measurement digits.[3] The lack of prognostic value of home BP measurement for cardiovascular mortality and total mortality is probably related to the lower incidence of cardiovascular mortality in this population of patients treated for hypertension, as expected, and/or to a shorter follow-up than that of many epidemiological studies. The lack of relationship between BP levels measured by the physician and the incidence of cardiovascular morbidity and mortality contrasts with the data from the largest meta-analysis, which includes 958 074 individuals with a larger range of BP and followed up for a longer time, giving it substantial statistical power.[1]

The Japanese study by Ohkubo et al[9] is the only other prospective study of home BP self-measurement. This study followed up 1789 patients for 6.6 years. As with the SHEAF study, the authors found no association between BP level measured in the physician's office and incidence of cardiovascular mortality. They demonstrated a relationship between the SBP level measured at home and incidence of total mortality on one hand (HR, 1.01; 95% CI, 1.00-1.03) and cardiovascular mortality on the other hand (HR, 1.02; 95% CI, 1.00-1.04). For each increase in SBP of 10 mm Hg, an increase of 23% was noted in the risk of cardiovascular mortality. Conversely, there was no relationship between DBP and global or cardiovascular mortality.

The SHEAF study confirms in patients treated for hypertension the prevalence and favorable prognosis of the "white coat effect" (elevated BP in the office but not at home) that has already been indicated by studies conducted initially with ambulatory BP measurement in untreated patients.[6,19,20] The new element relates to masked hypertension (elevated BP at home but not in the office), a term proposed by Pickering et al[21] in preference to the term of "reverse white-coat hypertension" or "isolated home hypertension." The reproducibility of this classification has not been evaluated and the mechanisms of this phenomenon are not known.[21,22] According to the available studies using either ambulatory measurement[23-25] or home self-measurement and ambulatory measurement,[26] and including either patients with hypertension or a general population, this phenomenon is observed in 7% to 45% of the participants studied. Pickering et al suggest that this frequency decreases with age,[21] which corroborates the fairly low frequency observed in our 70-year-old population. Pickering et al noted, like us, that patients with masked hypertension are more often women and have a high frequency of conventional cardiovascular risk factors (eg, age, obesity, hypercholesterolemia, hyperglycemia).[23] In particular, these patients have a greater frequency of damage to target organs (left ventricular mass index and presence of carotid plaques).[23] In a recent analysis of the data from the PAMELA study, from which individuals being treated for hypertension were excluded, 67% were normotensive, 12% were hypertensive, 12% had white-coat hypertension, and

9% had masked hypertension. Here again, the left ventricular mass index was higher in those with masked hypertension and hypertension than in normotensive individuals.[23] These data concerning surrogate end points suggested an adverse effect of masked hypertension.[21,22] A recent prospective study of 578 untreated elderly men confirms the adverse effect of masked hypertension determined by ambulatory BP monitoring. In a multivariable analysis that took into account serum cholesterol levels, smoking, and diabetes, both isolated ambulatory hypertension (HR, 2.77; 95% CI, 1.15-6.68) and sustained hypertension (HR, 2.94; 95% CI, 1.49-5.82) were independent predictors of cardiovascular morbidity.[27] These results are in keeping with those of the SHEAF study, which demonstrates the severity of elevated BP at home but not in the office in treated patients.

In conclusion, home BP self-measurement has a better prognostic value than office BP measurement. In this elderly population, office BP measurement failed to identify 13% of patients with elevated BP in the office but not at home with a good prognosis and 9% of those with elevated BP at home but not in the office with a poor prognosis. The frequency of this double error, which is both diagnostic (with respect to the control of hypertension) and prognostic (with respect to the incidence of cardiovascular events), suggests that the monitoring of patients being treated for hypertension must include home BP self-measurement, which is the method preferred by patients,[8] with an excellent feasibility.[28] It remains to be shown that the adaptation of treatment to the results of home BP self-measurement allows better cardiovascular prevention than adaptation of treatment to results of measurements in the physician's office. Treatment and follow-up of patients with elevated BP at home but not in the office need to be studied.

Author Contributions: Dr Bobrie had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Bobrie, Chatellier, Mallion, Vaisse, Vaur, Genès.
Acquisition of data: Vaur, Genès, Clerson.
Analysis and interpretation of data: Bobrie, Chatellier, Mallion, Vaisse, Vaur, Genès, Clerson.
Drafting of the manuscript: Bobrie, Chatellier, Ménard.
Critical revision of the manuscript for important intellectual content: Bobrie, Chatellier, Ménard, Mallion, Vaisse, Vaur, Genès.
Obtained funding: Vaur, Genès.
Statistical expertise: Clerson.
Administrative, technical, or material support: Vaur, Genès.
Study supervision: Bobrie, Chatellier, Mallion, Vaisse, Vaur, Genès.
SHEAF Study Organization: *Steering Committee*: G. Bobrie, G. Chatellier, J. M. Mallion, B. Vaisse; *Event Committee*: J. P. Rinaldi, A. Simon, F. Woimant; *Coordination*: P. Clerson, N. Genès, G. Gourtchiglouian, L. Vaur.
Funding/Support: The study was supported by funding from Laboratoire Aventis.
Role of the Sponsor: Laboratoire Aventis was involved, along with the steering committee, in the study concept and design, in the analysis and interpretation of the data, in the critical review and approval of the manuscript, and in the study supervision. Laboratoire Aventis was responsible for the recruitment of the health care practitioners, for the organization of the study as a whole, and for collection of all the data. Members of the steering and event committees have no financial relationship with Aventis. They received reimbursements for "study supervision" meetings (meeting and transportation). Dr Clerson, as an independent statistician directing a contract research organization (CRO), was responsible, in combination with the scientific board of the study, for the data management and statistical analysis. As an employee of a CRO, Dr Clerson was paid by Aventis but remained independent in conducting the statistical analyses.
Acknowledgment: We are grateful to the 1429 French investigators who participated in the study.

REFERENCES

1. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet.* 2002;360:1903-1913.
2. Collins R, Peto R, MacMahon S, et al. Blood pressure, stroke, and coronary heart disease, II: short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. *Lancet.* 1990;335:827-838.
3. Chatellier G, Dutrey-Dupagne C, Vaur L, et al. Home self blood pressure measurement in general practice: the SMART study: Self-measurement for the Assessment of the Response to Trandolapril. *Am J Hypertens.* 1996;9:644-652.
4. 1999 World Health Organization-International Society of Hypertension Guidelines for the Management of Hypertension. *J Hypertens.* 1999;17:151-183.
5. Perloff D, Sokolow M, Cowan RM, Juster RP. Prognostic value of ambulatory blood pressure measurements: further analyses. *J Hypertens Suppl.* 1989;7:S3-S10.
6. Verdecchia P, Porcellati C, Schillaci G, et al. Ambulatory blood pressure: an independent predictor of prognosis in essential hypertension. *Hypertension.* 1994;24:793-801.
7. Clement DL, De Buyzere ML, De Bacquer DA, et al. Prognostic value of ambulatory blood-pressure recordings in patients with treated hypertension. *N Engl J Med.* 2003;348:2407-2415.
8. Little P, Barnett J, Barnsley L, Marjoram J, Fitzgerald-Barron A, Mant D. Comparison of acceptability of and preferences for different methods of measuring blood pressure in primary care. *BMJ.* 2002;325:258-259.
9. Ohkubo T, Imai Y, Tsuji I, et al. Home blood pressure measurement has a stronger predictive power for mortality than does screening blood pressure measurement: a population- based observation in Ohasama, Japan. *J Hypertens.* 1998;16:971-975.
10. Cockroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron.* 1976;16:31-41.
11. O'Brien E, Mee F, Atkins N, Thomas M. Evaluation of three devices for self-measurement of blood pressure according to the revised British Hypertension Society Protocol: the Omron HEM-705CP, Philips HP5332, and Nissei DS-175. *Blood Press Monit.* 1996;1:55-61.
12. Mengden T, Hernandez Medina RM, Beltran B, Alvarez E, Kraft K, Vetter H. Reliability of reporting self-measured blood pressure values by hypertensive patients. *Am J Hypertens.* 1998;11:1413-1417.
13. Bobrie G, Genès N, Vaur L, et al. Is "isolated home" hypertension as opposed to "isolated office" hypertension a sign of greater cardiovascular risk? *Arch Intern Med.* 2001;161:2205-2211.
14. Peduzzi P, Concato J, Feinstein AR, Holford TR. Importance of events per independent variable in proportional hazards regression analysis, II: accuracy and precision of regression estimates. *J Clin Epidemiol.* 1995;48:1503-1510.
15. Thijs L, Staessen JA, Celis H, et al. Reference values for self-recorded blood pressure: a meta-analysis of summary data. *Arch Intern Med.* 1998;158:481-488.
16. Chatellier G, Day M, Bobrie G, Menard J. Feasibility study of N-of-1 trials with blood pressure self-monitoring in hypertension. *Hypertension.* 1995;25:294-301.
17. Denolle T. Comparison and reproducibility of 4 methods of indirect blood pressure measurement in moderate hypertension [in French]. *Arch Mal Coeur Vaiss.* 1995;88:1165-1170.
18. Stergiou GS, Efstathiou SP, Argyraki CK, Gantzarou AP, Roussias LG, Mountokalakis TD. Clinic, home and ambulatory pulse pressure: comparison and reproducibility. *J Hypertens.* 2002;20:1987-1993.
19. Khattar RS, Senior R, Lahiri A. Cardiovascular outcome in white-coat versus sustained mild hypertension: a 10-year follow-up study. *Circulation.* 1998;98:1892-1897.
20. Pickering TG, Coats A, Mallion JM, Mancia G, Verdecchia P. Blood pressure monitoring: Task Force V: white-coat hypertension. *Blood Press Monit.* 1999;4:333-341.
21. Pickering TG, Davidson K, Gerin W, Schwartz JE. Masked hypertension. *Hypertension.* 2002;40:795-796.
22. Mancia G. Reversed white-coat hypertension: definition, mechanisms and prognostic implications. *J Hypertens.* 2002;20:579-581.
23. Liu JE, Roman MJ, Pini R, Schwartz JE, Pickering TG, Devereux RB. Cardiac and arterial target organ damage in adults with elevated ambulatory and normal office blood pressure. *Ann Intern Med.* 1999;131:564-572.
24. Wing LM, Brown MA, Beilin LJ, Ryan P, Reid CM. "Reverse white-coat hypertension" in older hypertensives. *J Hypertens.* 2002;20:639-644.
25. Selenta C, Hogan BE, Linden W. How often do office blood pressure measurements fail to identify true hypertension? an exploration of white-coat normotension. *Arch Fam Med.* 2000;9:533-540.
26. Larkin TK, Schauss SL, Elnicki DM. Isolated clinic hypertension and normotension: false positives and false negatives in the assessment of hypertension. *Blood Press Monit.* 1998;3:247-254.
27. Bjorklund K, Lind L, Zethelius B, Andren B, Lithell H. Isolated ambulatory hypertension predicts cardiovascular morbidity in elderly men. *Circulation.* 2003;107:1297-1302.
28. Vaisse B, Genes N, Vaur L, et al. The feasibility of at-home self-monitoring blood pressure in elderly hypertensive patients [in French]. *Arch Mal Coeur Vaiss.* 2000;93:963-967.