ARTICLE

Prognostic value of home blood pressure monitoring in patients under antihypertensive treatment

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The prognostic value of home blood pressure monitoring (HBPM) has been investigated in several studies in the general population, demonstrating its independent association with cardiovascular events. However, in the case of treated hypertensive subjects, evidence is controversial. Our purpose was to evaluate the prognostic value of HBPM in this population. Medicated hypertensive patients who performed a 4-day HBPM (Omron® HEM-705CP-II) between 2008 and 2015 were followed up for a median of 5.9 years, registering the occurrence of a composite primary outcome of fatal and non-fatal cardiovascular events. Cox regression models were used to analyze the prognostic value of HBPM, considering 4-day measurements, discarding the first day, and analyzing morning, afternoon and evening periods separately. We included 1582 patients in the analysis (33.4% men, median age 70.8 years, on an average of 2.1 antihypertensive drugs). During follow-up, 273 events occurred. HBPM was significantly associated with cardiovascular events in all five scenarios in the unadjusted models. When adjusting for office BP and other cardiovascular risk factors, the association remained marginally significant for the 4-day period, discarding first-day measurements HBPM (HR 1.04 [95% CI 1–1.1] and 1.04 [95% CI 1–1.1], respectively) and statistically significant for all separate periods of measurement: HR 1.32 (95% CI 1.01–1.72); 1.33 (95% CI 1.02–1.72); and 1.30 (95% CI 1.01–1.67), for morning, afternoon and evening, respectively. When analyzing separately fatal and non-fatal events, statistical significance was held for the former only. In conclusion, HBPM is an independent predictor of cardiovascular events in hypertensives under treatment.

Journal of Human Hypertension; https://doi.org/10.1038/s41371-022-00758-x

INTRODUCTION

Out-of-office blood pressure (BP) measurement is currently considered crucial in the management of hypertensive patients [1, 2]. Among the two recommended techniques—ambulatory blood pressure monitoring (ABPM) and home blood pressure monitoring (HBPM)—the latter has been repositioned as an invaluable tool in the context of COVID-19 pandemic since it is similar (and better tolerated) than ABPM in clinical practice and can be entirely performed in the patient's home [3].

The prognostic value of HBPM has been investigated in several studies conducted in the general population which demonstrated the independent association of baseline HBPM with cardiovascular events [4–6]. However, in the case of hypertensive subjects who are already under treatment, evidence is less overwhelming, since not only is it scanter but there are also methodological issues that preclude the generalization of the findings. For instance, some studies evaluated only a kind of antihypertensive treatment, i.e., angiotensin receptor blockers [7, 8]; other studies failed to find significant results for the primary endpoint for which they were designed [9], and others did not make an adjustment for office blood pressure [9, 10]. In fact, recent hypertension guidelines state that there is a gap in the evidence regarding the incremental benefit for cardiovascular risk prediction of the addition of out-of-office BP to office BP measurement [2]. Therefore, we aimed at evaluating the prognostic value of HBPM, in terms of cardiovascular events, in hypertensive patients under treatment.

MATERIALS AND METHODS

Study population

This was a cohort study that included hypertensive patients, according to established criteria in national and international guidelines [1, 2, 11], who were 18 years or older and under stable antihypertensive treatment for at least 4 weeks. Participants performed a baseline HBPM, prescribed by their treating physician, between September, 1, 2008 and December, 31, 2015, in the Hypertension Section of Hospital Italiano de Buenos Aires. Duplicate HBPMs as well as HBPMs with less than 16 readings were excluded from the analysis.

The design of the study complied with the Code of Ethics of the World Medical Association (Declaration of Helsinki, 1964 and Declaration of Tokyo, 1975, as revised in 2008). The study protocol was approved by the local ethics committee. The patients duly authorized the use of the information in their medical records under the protection of their confidentiality through informed consent.

Home blood pressure monitoring

We used an automatic oscillometric device, Omron 705 CP (Omron® HEM-705CP-II, Omron®,Tokyo, Japan), previously validated [12] against a mercury sphygmomanometer according to the revised protocol of the

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Received: 29 May 2022 Revised: 24 August 2022 Accepted: 12 September 2022
Published online: 26 September 2022

British Hypertension Society [13], and appropriate cuff sizes according to each individual's arm circumference. Patients received appropriate training to measure home BP after a 5-min rest, keeping their legs uncrossed, their back supported, and not talking. They registered duplicate sitting BP readings (1 min apart) in the non-dominant arm, during fixed hours in the morning (8–12 a.m.), afternoon (14–18 p.m.) and evening (20–24 p.m.), for four days. The reliability and reproducibility of this protocol of measurements has previously been addressed [14]. Briefly, in the cited study we assessed the reproducibility and reliability of a 4-day HBPM protocol with and without first-day measurements, analyzing a cohort of 353 subjects who required an HBPM for diagnostic purposes or evaluation of treatment efficacy. Reproducibility was quantified by test-re-test correlations and standard deviation of differences (SDD) between BP measurements obtained during the entire 4 days, with and without exclusion of the first day. The reliability criterion was the stabilization of the mean and standard deviation (SD). On the one hand, we found a strong test-re-test correlation between days 1 and 4 (0.80–0.91), which improved when we excluded the first day ($p < 0.001$). On the other, we found a reduction of the mean BP when we increased the number of days and a reduction of standard deviation of differences when we excluded day 1.

In the present study, morning readings were taken before breakfast and drug intake. The average of BP readings stored in the devices' memory (not self–reported measurements) was used for analysis. According to current recommendations, first-day measurements were discarded [15, 16].

For the analysis, we considered a 4-day average of systolic and diastolic home BP, the average discarding first day measurements, and at each measurement period (morning, afternoon, and evening) separately. We also categorized home BP into adequate control when the average was <135/85 mmHg, and inadequate control if systolic BP was ≥135 and/or diastolic BP was ≥85 mmHg, for each of the five scenarios.

Outcomes

Our primary outcome was a composite of fatal and non-fatal cardiovascular events, including cardiovascular death, myocardial infarction, unstable angina, surgical and percutaneous coronary revascularization, congestive heart failure, atrial fibrillation, stroke (ischemic, hemorrhagic, or undetermined) and transient ischemic attack, occurring during follow-up. We also analyzed total mortality, cardiovascular mortality, and non-fatal cardiac and cerebrovascular events as secondary outcomes. Data regarding outcomes were obtained through the exhaustive manual review of each electronic health record, in all its modules: Ambulatory, Hospitalization, Emergency Room, and Home Hospitalization. The World Health Organization International Classification of Diseases (ICD-10), Volume 1, was used to codify the causes of death. Since patients who perform an HBPM in our hospital are affiliated to a prepaid medicine plan, they constitute a "captive" population, receiving healthcare only at the institution. This allows access to all follow-up data (without loss), except in the rare occasions when the prepaid plan cancellation occurs.

In all outcome analyses, we only considered the first event per participant within each category.

Other variables included

Medical records of all patients were reviewed to extract data regarding office BP level prior to HBPM, the type of antihypertensive drugs used at baseline, the presence of risk factors (diabetes, smoking status), and the history of cardiovascular disease (coronary heart disease and cerebrovascular disease). Laboratory data from 6 months prior to HBPM were also collected from medical records.

Regarding office BP, one to three measurements were taken after at least 5-min sitting rest using a standard validated aneroid sphygmomanometer (Riester®, Jungingen, Germany or Wellch-Allyn®, Amsterdam, The Netherlands) or a validated automated upper arm-cuff devices (Omron® HEM-705CP-II or Omron® 7 200, Omron®,Tokyo, Japan) and appropriate cuff sizes according to each individual's arm circumference. The average BP of available readings was used in the analysis.

Statistical considerations

Sample size calculation. The sample size was estimated assuming an annual cardiovascular event rate of 2.5%. This figure was extracted from other cohorts that also evaluated hypertensive patients under treatment [9, 10]. For a mean follow-up of 6 years in our cohort, we expected to have 15 events per each 100 included subjects. According to Peduzzi et al., in order to ensure the accuracy and precision of estimated coefficients though Cox regression models, the number of events for each included independent variable must be at least 10 [17]. Given that we planned to include 13 co-variables, plus our main variable of interest -home BP- we needed to observe at least 140 events (14*10). Therefore, we had to include at least 934 patients (100*140/15).

Statistical analysis. Quantitative data are expressed as mean and standard deviation or median and interquartile range, according to data distribution. Qualitative data are expressed as absolute and relative frequency.

The prognostic value of home BP in terms of cardiovascular events was analyzed through Cox regression models (proportional hazards analysis), which accommodate censored data, estimating unadjusted and adjusted hazard ratios along with their 95% confidence interval. In the adjusted models, hazard ratios were adjusted for office systolic and diastolic BP, sex, age, body mass index, number of antihypertensive drugs, smoking habits, diabetes, history of cardiac and cerebrovascular disease, fasting plasma glucose, total cholesterol and creatinine level. Home BP was analyzed as a continuous and as a dichotomous variable (uncontrolled vs. controlled BP). We used the Akaike information criteria (AIC) to compare different modeling strategies. AIC are model selection criteria, i.e., statistical tools that help identify the best-fitted candidate model among a set of candidates. The best model is the one that obtains the lowest score, which measures how much the evaluated model deviates from a theoretical model that shows a perfect fit. To compare models, the AIC of each model is calculated. If a model is more than 2 AIC units lower than another, then it is considered significantly better than that model [18].

All hypothesis tests were two-tailed, and a p value <0.05 was considered statistically significant.

RESULTS

Between September 2008 and December 2015, a total of 2732 HBPMs were performed. After discarding untreated subjects, duplicate HBPMs and those with <16 readings, 1582 patients remained for the analysis (Fig. 1). Baseline patient characteristics and antihypertensive treatment profile are depicted in Table 1. BP profile is depicted in Table 2. Briefly, 33.4% of participants were men, median age was 70.8 years, 11.4% had diabetes and 14.3% had a history of ischemic cardiopathy or cerebrovascular disease. Patients were treated with an average of 2.1 antihypertensive drugs, and had a mean office and home BP of 137.6/77.8 and 132.9/73.6 mmHg, respectively.

Follow-up ended on April, 30 2 020, with a median of 5.9 years (IQR 4.9–8.7), during which 164 deaths (37 of cardiovascular cause) were registered. On that date, vital status was known for 81.2% of

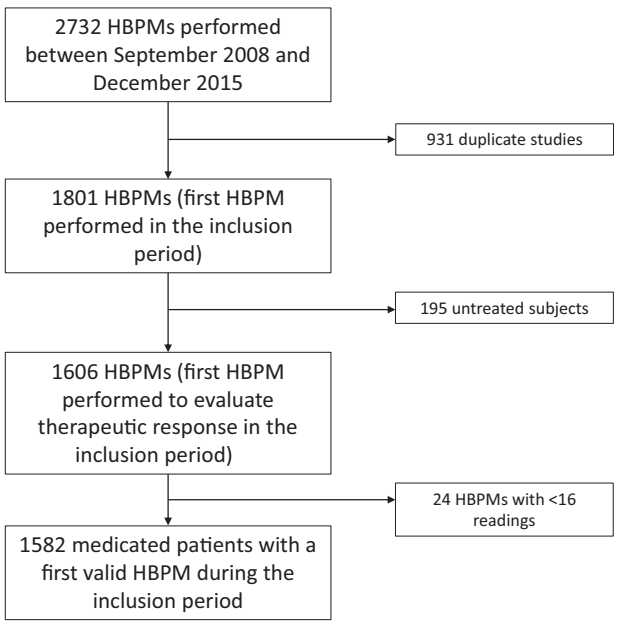

Fig. 1 Study population flowchart.

Table 1. Baseline characteristics of patients and antihypertensive treatment profile.

***n* = 1582**	
Age, years, median (IQR)	70.8 (61.7–78.5)
Male sex, % (*n*)	33.4 (528)
Diabetes, % (n)	11.4 (180)
Current smokers, % (*n*)	13.5 (214)
Former smokers, % (*n*)	20.5 (325)
History of ischemic heart disease[a], % (*n*)	7.3 (115)
History of cerebrovascular disease[b], % (*n*)	7 (111)
Body mass index, kg/m^2, mean (SD)	28.4 (4.9)
Fasting glucose, mg/dl, mean (SD)	99.8 (16.3)
Serum creatinine, mg/dl, mean (SD)	0.92 (0.38)
Total cholesterol, mg/dl, mean (SD)	188.5 (40.7)
Number of antihypertensive drugs, mean (SD)	2.1 (0.9)
Diuretics, % (*n*)	29.9 (473)
Beta-blockers, % (*n*)	39.3 (622)
ACEI, % (*n*)	35.3 (558)
ARB, % (*n*)	43.2 (683)
CCB, % (*n*)	52.5 (830)
Alpha-blockers, % (*n*)	2.5 (40)
Other, % (*n*)	4 (63)

ACEI angiotensin-converting enzyme inhibitors, *ARB* angiotensin receptor blockers, *CCB* calcium channel blockers, *IQR* interquartile range, *SD*, standard deviation.
[a]Including acute myocardial infarction, unstable angina, chronic stable angina, coronary bypass surgery.
[b]Including stroke (ischemic, hemorrhagic or undetermined) and transient ischemic attack.

Table 2. Blood pressure profile.

Office BP	
Number of office BP readings	
1 reading, % (*n*)	100 (1582)
2 readings, % (*n*)	19.2 (303)
3 readings, % (*n*)	2.1 (34)
Systolic BP, mmHg (SD)	137.6 (18.2)
Diastolic BP, mmHg (SD)	77.8 (10.5)
HBPM	
Number of readings (SD)	23.6 (2.1)
4-day systolic BP, mmHg (SD)	132.9 (14.5)
4-day diastolic BP, mmHg (SD)	73.6 (8.8)
Inadequate BP control considering 4-day measurements[a], % (*n*)	43.3 (685)
Systolic BP discarding first day measurements, mmHg (SD)	132.2 (14.4)
Diastolic BP discarding first day measurements, mmHg (SD)	73.3 (8.8)
Inadequate BP control discarding first day measurements[a], % (*n*)	41.4 (653)
Morning systolic BP, mmHg (SD)	134.4 (16.7)
Morning diastolic BP, mmHg (SD)	75.5 (9.6)
Inadequate BP control considering morning measurements only[a], % (*n*)	47.4 (749)
Afternoon systolic BP, mmHg (SD)	129 (14.9)
Afternoon diastolic BP, mmHg (SD)	71.2 (9.4)
Inadequate BP control considering afternoon measurements only[a], % (*n*)	32.7 (500)
Evening systolic BP, mmHg (SD)	133.3 (16.2)
Evening diastolic BP, mmHg (SD)	73.4 (9.4)
Inadequate BP control considering evening measurements only[a], % (*n*)	44.3 (700)
Heart rate during HBPM, bpm (SD)	69.7 (10)

BP blood pressure, *bpm* beats per minute, *HBPM* home blood pressure monitoring, *SD* standard deviation.
[a]Systolic blood pressure ≥135 and/or diastolic blood pressure ≥85 mmHg.

the sample. Our primary outcome (composite of fatal and non-fatal cardiovascular events) was observed in 273 patients. Table 3 describes in detail the cardiac and cerebrovascular events that occurred.

For our primary outcome (fatal and non-fatal cardiovascular events), we found a significant higher risk for uncontrolled vs. controlled home BP. This was true for the five scenarios, i.e., considering 4-day BP average, discarding first day measurements and analyzing morning, afternoon and evening separately. Figures 2 and 3 depict Nelson–Aalen cumulative hazard estimates for the primary outcome along these scenarios.

Table 4 shows the hazard ratios and their 95% CI for the unadjusted and adjusted models. Home BP was significantly associated with cardiovascular events in the unadjusted models for 4-day average home BP, discarding first-day measurements and for morning, afternoon, and evening home BP. Regarding the adjusted models, 4-day average and the average discarding first-day measurements were only marginally significant for systolic BP. In a sensitivity analysis excluding patients with previous cardiovascular disease, our results remained unchanged (Supplementary Table 1). Similar results were also obtained when analyzing major adverse cardiovascular events (cardiovascular mortality, myocardial infarction or stroke) as the outcome, and when adjusting for office systolic and office diastolic BP in separate models (Supplementary Tables 2 and 3). Of note, the association between home BP and cardiovascular events remained statistically significant in the adjusted models when analyzing morning, afternoon, and evening periods separately. When comparing models for these three periods of measurement through the AIC, the model with the lower score, i.e., the best predictor among the three models, was the one that included afternoon home BP readings: 3472 for afternoon home BP vs. 3622 for morning home BP vs. 3623 for evening home BP.

Multicollinearity between office and home BP was tested through a correlation matrix of the coefficients in the Cox models. The cut-off value used to consider the presence of multicollinearity through the correlation coefficient was 0.5, that is, absolute values of the coefficient greater than 0.5 were considered positive for the presence of multicollinearity. In these analyses, we found that, in all cases, the correlation coefficients were <0.5, which supports the absence of multicollinearity, and allows us to introduce both variables in the same model.

Considering our secondary outcomes, home BP was significantly associated with total mortality and cardiovascular mortality in the adjusted models, considering 4-day measurements, discarding first-day measurements, and analyzing morning, afternoon, and evening separately. Regarding non-fatal cardio and cerebrovascular events, no significant associations were found in any of the adjusted model scenarios (Table 5).

DISCUSSION

In our study, we found that increased baseline home BP is associated with an increased risk of fatal and non-fatal

Table 3. Cardiac and cerebrovascular events during follow-up.

Event	Number of events
Fatal and non-fatal cardiac and cerebrovascular events[a]	273
Fatal cardiac and cerebrovascular events[b]	37
Non-fatal cardiac events	
Myocardial infarction	14
Unstable angina	49
PTCA	34
CABG	14
Congestive HF	80
Atrial fibrillation	82
Non-fatal cerebrovascular events	
Stroke[c]	53
TIA	14

CABG coronary artery bypass graft surgery, *HF* heart failure, *PTCA* percutaneous transluminal coronary angioplasty, *TIA* transient ischemic attack.
[a]Primary outcome.
[b]Fatal stroke, myocardial infarction, heart failure, cardiac sudden death, valvulopathy or peripheral arterial disease.
[c]Including ischemic, hemorrhagic and cryptogenic stroke.

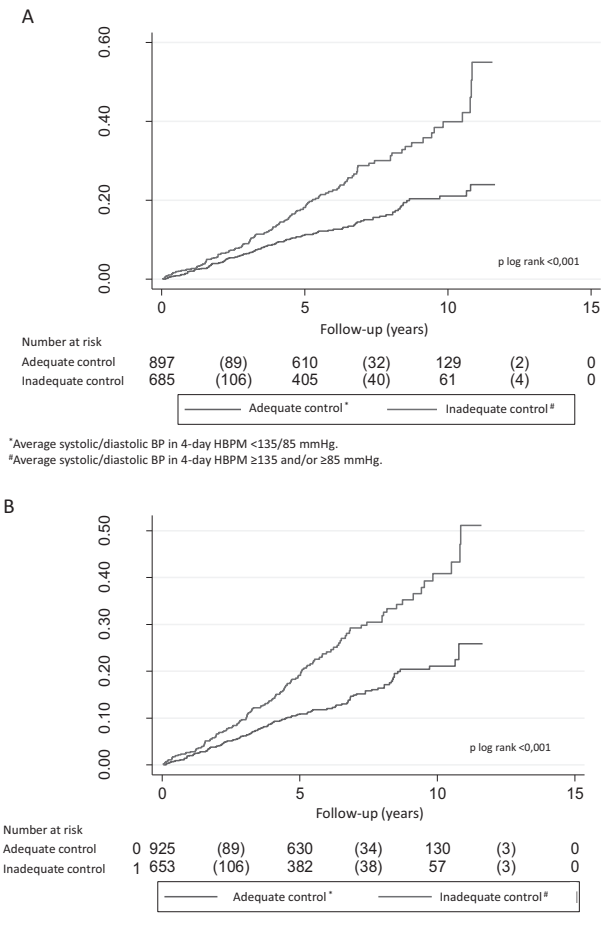

Fig. 2 Nelson–Aalen cumulative hazard estimates for the primary outcome. Considering 4-day HBPM average (**A**) and discarding first day measurements (**B**).

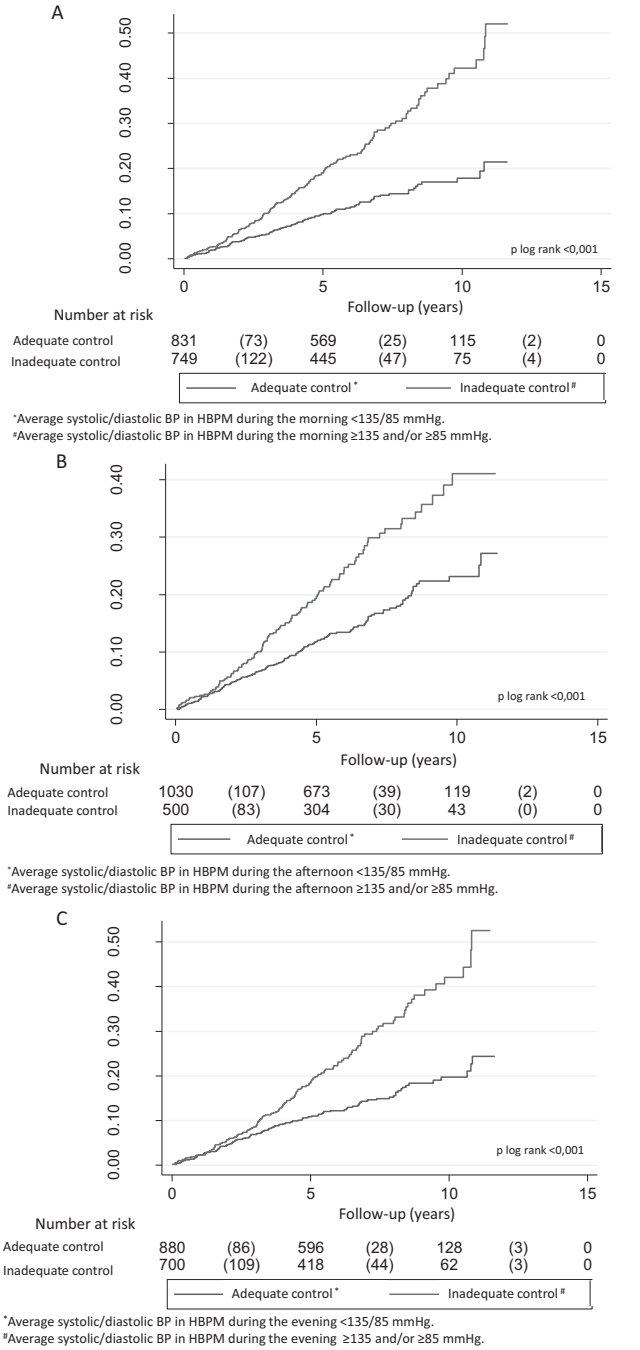

Fig. 3 Nelson–Aalen cumulative hazard estimates for the primary outcome considering measurement periods separately. Morning (**A**), afternoon (**B**), and evening (**C**).

cardiovascular and cerebrovascular events in patients with hypertension under treatment. This association is independent from office BP and other vascular risk factors and is observed in all measurement periods (morning, afternoon, and evening). The association with an increased risk of events would appear to occur primarily at the expense of fatal events.

There are several reasons that might explain why home BP is a better predictor of cardiovascular events than office BP: on the one hand, HBPM allows a significantly higher number of BP measurements than the one to three measurements that are usually performed in the office, making the former more reproducible [15, 16]. On the other, given that office BP is

Table 4. Hazard ratios for the primary outcome in relation to baseline home blood pressure.

	Unadjusted HR (95% CI)	Fully adjusted HR[a] (95% CI)
Inadequate BP control considering 4-day measurements	1.79 (1.41–2.28)	1.11 (0.85–1.43)
4-day systolic BP[b]	1.14 (1.10–1.18)	1.04 (1–1.09)[#]
4-day diastolic BP[b]	0.93 (0.87–1)	1.06 (0.98–1.14)
Inadequate BP control discarding first-day measurements	1.86 (1.46–2.36)	1.20 (0.93–1.55)
Systolic BP discarding first-day measurements[b]	1.13 (1.09–1.18)	1.04 (1–1.09)[#]
Diastolic BP discarding first-day measurements [b]	0.93 (0.86–0.99)	1.05 (0.98–1.14)
Inadequate BP control considering morning measurements only	2.11 (1.65–2.70)	1.32 (1.01–1.72)[‡]
Morning systolic BP[b]	1.13 (1.10–1.17)	1.05 (1.01–1.09)[&]
Morning diastolic BP[b]	0.95 (0.9–1.02)	1.03 (0.97–1.10)
Inadequate BP control considering afternoon measurements only	1.69 (1.32–2.16)	1.33 (1.02–1.72)[¥]
Afternoon systolic BP[b]	1.09 (1.05–1.13)	1.03 (1–1.07)
Afternoon diastolic BP[b]	0.90 (0.85–0.97)	1.05 (0.97–1.13)
Inadequate BP control considering evening measurements only	1.89 (1.49–2.41)	1.30 (1.01–1.67)[¶]
Evening systolic BP[b]	1.11 (1.07–1.15)	1.03 (1–1.08)[£]
Evening diastolic BP[b]	0.96 (0.89–1.02)	1.07 (1–1.14)[#]
Office systolic BP[b]	1.05 (1.02–1.09)	1.02 (0.98–1.06)
Office diastolic BP[b]	0.93 (0.88–0.98)	0.99 (0.92–1.05)

BP blood pressure, *HR* hazard ratio, *95% CI* 95% confidence interval.
[#]$p = 0.06$; [‡]$p = 0.04$; [&]$p = 0.02$; [¥]$p = 0.03$; [¶]$p = 0.04$; [£]$p = 0.08$.
[a]Adjusted for office systolic and diastolic blood pressure, sex, age, body mass index, number of antihypertensives, smoking habits, diabetes, history of cardiovascular disease, fasting plasma glucose, total cholesterol, and creatinine level.
[b]For each 5-mmHg increase.

frequently assessed through the auscultatory method, it is subject to observer bias, manifested, for example, in rounding up the last digit of the reading preferably to 0 or 5. This is not an issue in HBPM, where the oscillometric method is used. Office BP readings are also particularly more susceptible to the alerting reaction, a frequent phenomenon, where the first reading is higher than the subsequent ones [19]. Finally, home BP measurements tend to drop 20% less with treatment than office BP measurements, allowing a more accurate warning of the presence of sub-optimal treatment [20].

When considering studies that evaluated hypertensive patients under treatment, our study is similar to the SHEAF study, conducted in older treated hypertensive patients in France [9]. The SHEAF was designed for the primary outcome "cardiovascular mortality", for which the authors did not find a significant association, although the follow-up period was 3.2 years vs. 5.9 years in our study. For their secondary outcome "fatal and non-fatal cardiovascular events", there was a significant association with home BP, but the model did not include office BP as an adjustment variable. Other relevant data come from the International Database of HOme blood pressure in relation to Cardiovascular Outcome (IDHOCO) [10], where 22.4% of the subjects were hypertensive patients under treatment. In this subgroup, an association between baseline home BP and cardiovascular events was found. Of note, no adjustment for office BP was made in the analysis. We therefore consider that our finding that home BP has added value to predict cardiovascular events beyond office BP and other factors in this particular population, is an original contribution.

An important issue in patients that are already under treatment is the moment of the day when home BP measurements are taken, given the influence that medication could have in the different periods evaluated. Few studies, mainly from Asian origin, have evaluated different periods during HBPM separately. In the J-HOP study, for example, patients with uncontrolled morning home BP had a higher risk of stroke in comparison with those with controlled morning BP [21]. Of note, the predictive ability of morning BP was attenuated when combining these measurements with evening BP ones. Other studies found similar results [22]. As a consequence, a recent consensus highlighted the importance of the moment at which home BP is measured in patients under treatment and stated that isolated morning hypertension could be a marker of an inadequate antihypertensive regimen, urging to screen patients for this situation [23]. In accordance with these results, we found that combining all the periods in a single average might not be an appropriate strategy (only marginally significance was reached regarding the adjusted models), perhaps being better to inform BP average for each period separately. In fact, the latter case maintained statistical significance for cardiovascular risk prediction. Interestingly, the measurement period found to be the best predictor was the afternoon. In a study conducted by Almeida et al., a measurement protocol that included afternoon readings had a higher association with prognostic biomarkers, such as microalbuminuria and left ventricular hypertrophy, than a protocol that only included morning and evening measurements [24]. Of note, we decided to use Akaike information criteria, a well-known estimator of relative quality of statistical models for a given set of data, to compare models that considered BP measurements at different times of the day. These findings might have been different had other comparison strategies been used.

Another finding of our research is that, when analyzing fatal and non-fatal events separately, HBPM constitutes a significant independent predictor of fatal events whereas statistical significance is lost for non-fatal events. Studies evaluating hypertensive patients under treatment have shown heterogeneous results on this subject: while the SHEAF study, for example, failed to find an association between HBPM and cardiovascular death [9], in the IDHOCO database, HBPM was an independent predictor of this event in the subgroup of medicated patients [10], although, once again, we emphasize that no adjustment was made for office BP in the models. Consequently, given that our study was designed based on the primary endpoint, the results emanating from the secondary endpoints, such as an eventual higher prognostic value

Table 5. Adjusted hazard ratios for the secondary outcomes: total mortality, cardiovascular mortality and non-fatal cardiac and cerebrovascular events in relation to baseline home blood pressure.

	Total mortality[a] HR (95% CI)	Cardiovascular mortality[a] HR (95% CI)	Non-fatal cardiac and cerebrovascular events[a] HR (95% CI)
4-day systolic BP[b]	1.08 (1.02–1.14)[#]	1.16 (1.04–1.3)[#]	1.03 (0.98–1.08)
4-day diastolic BP[b]	1.08 (0.98–1.18)	1.34 (1.12–1.60)[#]	1.02 (0.94–1.10)
Systolic BP discarding first day measurements[b]	1.07 (1.01–1.13)[#]	1.15 (1.03–1.28)[#]	1.03 (0.98–1.08)
Diastolic BP discarding first day measurements[b]	1.07 (0.97–1.18)	1.34 (1.10–1.57)[§]	1.02 (0.72–1.10)
Morning systolic BP[b]	1.06 (1.02–1.11)[#]	1.17 (1.07–1.29)[§]	1.03 (0.99–1.07)
Morning diastolic BP[b]	1.06 (0.97–1.15)	1.28 (1.09–1.49)[§]	1 (0.93–1.08)
Afternoon systolic BP[b]	1.07 (1.01–1.13)[&]	1.08 (0.97–1.21)	1.02 (0.97–1.06)
Afternoon diastolic BP[b]	1.09 (1–1.20)	1.28 (1.07–1.53)[§]	1.02 (0.94–1.10)
Evening systolic BP[b]	1.05 (1–1.10)	1.11 (1.01–1.22)[¶]	1.03 (0.99–1.07)
Evening diastolic BP[b]	1.09 (1–1.19)	1.36 (1.14–1.61)[§]	1.04 (0.97–1.11)
Office systolic BP[b]	0.95 (0.90–1.01)	0.93 (0.85–1.03)	1.03 (0.99–1.07)
Office diastolic BP[b]	1.08 (0.99–1.16)	1.09 (0.91–1.31)	0.97 (0.90–1.04)

BP blood pressure, *HR* hazard ratio, *95% CI* 95% confidence interval.
[#]$p = 0.01$; [&]$p = 0.02$; [§]$p < 0.01$; [¶]$p = 0.03$.
[a]Adjusted for office systolic and diastolic blood pressure, sex, age, body mass index, number of antihypertensives, smoking habits, diabetes, history of cardiovascular disease, fasting plasma glucose, total cholesterol and creatinine level.
[b]For each 5-mmHg increase.

of HBPM for fatal events, are currently simple hypothesis generators.

When comparing HBPM with the other available technique for out-of-office BP assessment, i.e., ABPM, it is important to consider that the former is better tolerated by patients, more widely available and less expensive than ABPM, while it provides similar information for the usual clinical scenarios of everyday practice [25, 26]. Moreover, HBPM is currently the preferred method for long-term follow-up of patients that are already under treatment [27, 28]. This underscores the relevance of having found an independent predictive value of HBPM in this subgroup of patients.

Our study has some limitations that must be taken into consideration. First, this research was conducted in a single center, a community hospital in the city of Buenos Aires, representative of Argentine middle-class patients, mainly from European descent. As a consequence, our results may not be generalizable to other populations. Second, only about 20% of the patients in our study had their BP measured twice or thrice in the office: most subjects had one office BP reading only. Although this is in line with common clinical practice, it reduces the reproducibility of office BP, increasing its disadvantage compared to HBPM. Third, the time at which the patients took their antihypertensive medication was not controlled. This could have led to differences in BP in the different moments of the day considered. Additionally, Cox models, usually employed in this kind of analysis in all similar research, evaluate a basal measurement (in this case, home BP with the antihypertensive medication taken at that moment) and then estimate what occurs during follow-up, regarding events. As a result, possible changes in antihypertensive medication during follow-up are not taken into account in the analysis. Moreover, drug adherence was not formally tested in the present study. Fourth, LDL-cholesterol level is a more reliable predictor of cardiovascular events than the total cholesterol level used in our study. Finally, although the main advantage of using composites is increased statistical efficiency, this approach -used in our study- might also open the door to misdirection, especially when there is heterogeneity of response among components of composite outcomes. In some situations, the overall positive effect may be related to the less clinically relevant component(s) of the composite measure, leading to inadequate conclusions. In addition, the choice to combine of different types of events in one composite endpoint could also lead to different results. In this study, we followed the analytical strategies from previous similar studies against which we pretended to make comparisons.

On the other hand, our study also has some strengths: all patients used a validated oscillometric device (same brand and model) and followed the same HBPM protocol, the cuff was adapted to each patient´s arm circumference, and the readings stored in the devices' memory were used for analysis, avoiding a possible reporting bias [29]. Regarding the recording of events, our hospital has a long history in the use of patient-centered electronic medical records, being the first Argentine hospital certified as 100% computerized by the Healthcare Information and Management Systems Society (HIMSS). Therefore, the use of Systematized nomenclature of medicine clinical terms (SNOMED CT) enables the coding of all medical concepts and allows the multiple classifications to be related. This improves the quality of the registry, by storing both controlled codes and narrative text in the clinical data repository, resulting in a high-quality registry of the events in the present study.

In conclusion, home BP is a predictor of cardiovascular events in hypertensive patients under treatment, independent from office BP and other vascular risk factors. Such association is observed in all measurement periods (morning, afternoon, and evening) and would seem to occur primarily at the expense of fatal events.

SUMMARY

What is known about the topic

- Home blood pressure monitoring is recommended for out-of-office blood pressure assessment, especially in patients under treatment.
- It has prognostic value in the general population.
- Evidence in medicated hypertensive patients is controversial.

What this study adds

- Home blood pressure monitoring was an independent predictor of cardiovascular events in hypertensives under treatment.
- This held true for all measurement periods: morning, afternoon, and evening.

DATA AVAILABILITY

Additional data are available from the corresponding author on reasonable request.

CODE AVAILABILITY

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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ACKNOWLEDGEMENTS

We are grateful to Ms. Erika Barochiner for language editing.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation and data collection were performed by JBa, LA, and RM. Analysis of data was performed by JBa and JBo. The first draft of the manuscript was written by JBa and all authors commented on subsequent versions of the manuscript. All authors read and approved the final manuscript.

FUNDING

This study was partially funded by a grant from *Asociación Mutual de Profesionales del Hospital Italiano* (AMPHI).

COMPETING INTERESTS

The authors declare no competing interests.

ETHICAL APPROVAL

The study protocol was approved by the local ethics committee (Comité de Ética de Protocolos de Investigación [CEPI], approval #3319).

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41371-022-00758-x.

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