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ORIGINAL ARTICLE

24-Hour Ambulatory Blood Pressure Monitoring Predicts Outcomes of Hypertensive Patients in Primary Care: A Cohort Study

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Abstract

Background: Arterial hypertension is an important risk factor for cardiovascular outcomes. However, in most Primary Health Care centers, blood pressure remains at inadequate control levels. Ambulatory Blood Pressure Monitoring (ABPM) is a useful tool in predicting cardiovascular morbidity and mortality. The implementation of 24-hour ABPM and evaluation of cardiovascular outcomes in Primary Health Care may be effective in improving strategies for monitoring hypertensive patients in this setting.

Objective: To evaluate uncontrolled arterial hypertension detected by 24-hour ABPM as a predictor of cardiovascular outcomes in hypertensive patients from Primary Health Care in a low-resource environment.

Methods: Cohort study based on primary health care centers. The study was carried out with 143 hypertensive patients, who underwent 24-hour ABPM at baseline. Therapeutic targets were based on the Eighth Joint National Committee, the Brazilian Hypertension Guideline, and the European Hypertension Guideline. Medical records of emergency care, hospital admissions, and death certificates were reviewed.

Results: The sample consisted of 143 patients who met the inclusion criteria. After 4 years of follow-up, there were 17 deaths, 12 new cases of atrial fibrillation and 37 hospital admissions related to cardiovascular outcomes. During the follow-up period, the 24-hour ABPM showed a predictive result for new cases of atrial fibrillation ($p = 0.015$) and a combination of cardiovascular outcomes, mortality, and hospital admissions ($p = 0.012$).

Conclusion: The 24-hour ABPM was an important predictor of cardiovascular outcomes in a hypertensive population that seeks assistance in Primary Health Care centers. (Int J Cardiovasc Sci. 2017;30(4):285-292)

Keywords: Blood Pressure Monitoring, Ambulatory; Hypertension / complications; Public Health; Cardiovascular Diseases.

Introduction

Arterial hypertension is a major risk factor for cardiovascular disease.[1] Epidemiological studies have provided unequivocal evidence for the association between arterial hypertension and mortality from ischemic heart disease, cerebrovascular accident (CVA), and vascular diseases.[2] Additionally, there is a strong association between blood pressure (BP) reduction and prevention of coronary artery disease (CAD) and CVA.[3]

The number of individuals with uncontrolled hypertension (systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg) increased from 605 to 978 million, among other causes, influenced by population aging.[4] The absolute increase of the hypertensive population should lead to an increase in the use of health services, which increases the need to identify and treat hypertension to prevent having to manage the costs of complications associated with the disease.[5]

The 24-hour ambulatory blood pressure monitoring (ABPM) is the most accurate tool to assess BP as a predictor of cardiovascular events, when compared to other methods, such as home and conventional BP measurements.[6] However, in the primary health care

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(PHC) setting the availability and use of ABPM are below their indications, and general practitioners play a critical role in controlling hypertension.[7]

Several prospective studies have evaluated the predictive value of ABPM in relation to conventional BP measurement, such as the Dublin Outcome Study[8] and the International Database of Ambulatory Blood Pressure in relation to Cardiovascular Outcome (IDACO)[9], both with a significant follow-up time (8.4 and 9.5 years, respectively). Additionally, the CARDIORISC study,[10] with a sample size of 2,115 treated hypertensive patients, and a follow-up of 4 years, which included patients from the PHC setting, and national guidelines such as NICE[11] and CHEP,[12] recommend the ABPM method as a diagnostic tool for hypertension.

However, the diagnostic accuracy of hypertension based on conventional BP measurements is low,[13] and there is a scarcity in prospective studies evaluating the impact of 24-hour ABPM on hypertension control in PHC. In most PHC settings, 24-hour ABPM is still a scarcely used tool, and additional studies are needed to increase its implementation. The aim of the present study was to evaluate uncontrolled hypertension detected by 24-hour ABPM as a predictor of cardiovascular outcomes in hypertensive PHC patients in a low-resource setting.

Methods

Participants

This cohort study was based on PHC centers, including hypertensive patients from Antônio Prado (RS), a municipality in the Southern Region of Brazil, with a population of 12,883 inhabitants.[14] The samples were representative of the hypertensive patients who sought care at PHC centers in the municipality, being selected from a total of 646 patients registered in the system.

The inclusion criteria of the study were hypertensive patients, registered at the public health system participating in the hypertensive patient program and receiving regular pharmacological treatment in one of the two PHC centers of the municipality for at least 6 months.

From January 2009 to December 2010, the random sample of hypertensive patients was selected from the total set of hypertensive patients enrolled in two Basic Health Units, through the generation of random numbers using the program Microsoft Excel 2008.

Between January 2013 and October 2014, patients were invited to participate in the second phase of the study by telephone and/or by letter. Before being enrolled in this study phase, patients were reassessed by their PHC physicians. Patients who were not able to answer the questionnaire, pregnant women, those with electrocardiograms showing non-sinus rhythm, those who lived outside the coverage area of the PHC centers, those who moved to another city or were not contacted, and/or did not tolerate the use of ABPM, or had technical difficulty during the method application were excluded from the study.[13]

All patients who agreed to participate in the study signed the Free and Informed Consent form. The results obtained from the biochemical analyses and ABPM assessment during the study were delivered to the patients. The study was approved by the Research Ethics Committee of Instituto de Cardiologia do Rio Grande do Sul (protocol n. 4278.08).

Measurements

BP measurements were performed by the physicians of the PHC units. Three BP measurements were performed using a mercury sphygmomanometer – the use of the mercury sphygmomanometer is allowed in the State of Rio Grande do Sul, which follows the guidelines of the Collegiate Board Resolution n. 63-2011, Art. 23 – after being instructed to use appropriate-size cuffs.

Patients were in the sitting position, with their feet flat on the floor, and measurements were taken after at least 5 minutes of rest. PHC physicians were instructed to perform BP measurements on both arms, using as reference the highest BP value obtained after an interval of approximately 3 minutes. The first measurement was discarded, and the mean of the two subsequent measurements was considered and recorded in the patient's medical record.[7]

After this procedure, the patients were referred to the care of a nurse trained for the study for the 24-hour ABPM device placement, questionnaire application and anthropometric measurements. The collected data also included analysis of patients' medical records, request for biochemical exams, and assessment of ABPM data by the first author of the study, who was blinded to the BP assessment performed by the PHC physicians. The ABPM was performed during the patient's normal workday, with weekends and holidays being excluded from the analysis.

The ABPM monitors used in the study were adequately validated and calibrated according to international recommendations.[15] The ABPM recorder used was the DMS Brasil, TM 2430 model and the mercury sphygmomanometer used in the study was the MDF 800 model. The ABPM recordings were programmed to perform a BP measurement every 15 minutes during the waking period and every 30 minutes during sleep. The sleep and waking periods were individualized according to each patient's habits.

Data were considered adequate when at least 60 recordings were performed during the 24-hour period, with at least two recordings every hour during sleep. The parameters assessed by ABPM were the mean systolic and diastolic BP of the 24-hour period, during the waking and sleep periods. Uncontrolled hypertension, consistent with conventional sphygmomanometer criteria was defined, according to the main hypertension guidelines, as BP values ≥ 140 / 90 mmHg.[7]

For uncontrolled hypertension, ABPM criteria were used according to the European Hypertension Guideline and the Brazilian Society of Cardiology Guideline.[5,16] Thus, hypertensive patients with a mean 24-hour BP ≥ 130/80 mmHg, ≥ 135/85 mmHg in the waking period, and ≥ 120/70 for the mean nocturnal BP measurement for the first criterion were considered uncontrolled. [5] When the Brazilian Hypertension Guidelines were considered,[16] the BP values used in the study were the borderline values considered normal as cutoff values for the 24-hour means: > 125/75 mmHg, > 130/85 mmHg for the waking period and > 110/70 mmHg for the mean BP during sleep.

The absence of nocturnal dipping was defined as the decrease in BP by ABPM ≤ 10% in relation to the diurnal mean BP value.[16] The guidelines of the Eighth Joint National Committee[17] were also adapted for the group of patients aged 60 years and older.

In addition to the conventional BP measurement and 24-hour ABPM assessment, the patients' biochemical profile was also evaluated considering the following items: total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, creatinine, Glycated Hemoglobin A1c (HbA1c), microalbuminuria in a sample and fasting glycemia. Microalbuminuria measurement in a sample was expressed by the albumin/creatinine ratio. Anthropometric data, such as muscle mass, weight, waist-to-hip ratio, and body mass index, were also evaluated. The assessment also included validated tools to estimate smoking/nicotine dependence (Fagerström Test), Alcohol Use Disorder Identification Test (AUDIT) and the self-reported scale, indicating adherence to the proposed treatment (Morisky).[13] All tests performed, both ABPM and biochemical exams were made available to patients and their PHC physicians.

The death certificates and medical records were reviewed to verify the cardiovascular diseases identified in patients who sought medical care in the PHC network during the study period. Data were also collected in the emergency service of the referral hospital of the municipality. A 12-lead electrocardiogram was performed to confirm new diagnoses of atrial fibrillation reported by the PHC physicians, as well as in patients who showed an irregular heart rhythm during the 24-hour ABPM assessment.

Data Analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS), version 21.0. Descriptive statistics were calculated using continuous and categorical variables. Considering the sample size, the Kolmogorov-Smirnov test was used to verify data normality. Continuous variables with normal distribution were shown as mean and standard deviation, and the categorical variables, as absolute numbers and percentages. Comparison between the subgroups was performed using the Chi-square test, Mann Whitney U-test (continuous variables with non-homogeneous variance) and t-test (variables with homogeneous variances). Student's t-test was used to compare two paired samples, the same subjects at two different times. Median and interquartile range values were used for continuous variables with non-normal distribution. Kaplan-Meier analysis was used for survival analysis calculation. The confidence interval was set at 95% with 80% power. The estimated sample size was 143 patients and the level of statistical significance was set at 5%.

Results

From January 2013 to October 2014, data from a sample of 143 hypertensive patients, with a mean follow-up period of 3 years and 8 months, were collected and evaluated from a previous cross-sectional study sample (standard deviation 0.27 = 3.77 ± 0.27)[13]. Of this sample, 16 patients were not located and nine dropped out of the

study protocol, although they did not report any clinical outcome before leaving the study during this period. There were 17 deaths and, thus, 101 hypertensive patients were included in the follow-up registry (flow chart).

The analyzed sample consisted predominantly of female patients (65.3%), Caucasians (77.2%), mean age of 61.7 years (standard deviation ± 13.43). The prevalence of type 2 diabetes mellitus was 19%, dyslipidemia was 41%, and 36% of the study sample had microalbuminuria. Table 1 summarizes the patients' demographic profile and lifestyle. All patients had used antihypertensive medication for at least 6 months, with diuretics (77.3%) and angiotensin-converting enzyme inhibitors (60.4%) being the most often prescribed medications.

Table 1 – Demographic analysis and lifestyle

Variables	Cohort*
Female gender, n (%)	66 (65.3%)
Age, years	61.72 ± 13.43 (25-89)
Caucasian ethnicity	78 (77.2%)
Body mass index	28.52 ± 4.58 (20-44)
Fasting glucose, mg/dL	98.97 ± 25.64 (65-211)
Glycated hemoglobin A1c	5.95 ± 0.67 (5-8.6)
Total cholesterol, mg/dL	196.65 ± 39.19 (88 -354)
HDL, mg/dL	53.06 ± 11.47 (30-84)
LDL, mg/dL	115.6 ± 31.75 (33-189)
Triglycerides, mg/dL	154.83 ± 119.54 (36-1015)
Creatinine, mg/dL	0.91 ± 0.34 (0.42-3.09)
Smoking	6.9%
Alcohol (> 2 u/day)	27.7%
Microalbuminuria, > 30 mg/dL	36%
Physical activity, > 150 minutes/week)	56%

** Standard deviation, percentage, and maximum and minimum values.*

After 3 years of follow-up, 56 cardiovascular outcomes were identified (14 deaths, 11 new cases of atrial fibrillation and 31 hospital admissions secondary to cardiovascular causes, such as heart failure and acute myocardial infarction). After 4 years of follow-up, three deaths, one new case of atrial fibrillation and six hospital admissions were identified and added to the outcomes observed in the study. Thus, there were a total of 17 deaths (two from heart failure, four from CVA, seven from CAD, one from sepsis, one from bronchopulmonary carcinoma, one of multiple organ failure and one from pneumonia), 12 new cases of atrial fibrillation and 37 hospital admissions secondary to cardiovascular causes.

In the endpoints identified after 3 years of follow-up, uncontrolled BP evaluated by 24-hour ABPM was an independent predictor for new cases of atrial fibrillation (p = 0.029) (Table 2). After 4 years of follow-up, 24-hour ABPM was a risk predictor for new cases of atrial fibrillation (p = 0.015) and combined cardiovascular outcomes (p = 0.012) (Table 3). Thus, at the end of the third year of follow-up, there were 77.8% (p = 0.092) of the total outcomes considering the BP group not controlled by ABPM and 79.7% (p = 0.012) at the end of the fourth year of follow-up (Table 4). In the survival analysis, the mean time until the event was 32.5 months (95% Confidence Interval - 95% CI: 30.4 - 34.7).

Discussion

The main outcome of this contemporary cohort study evaluating hypertensive patients coming from the PHC setting is that 24-hour ABPM is a predictor for cardiovascular outcomes at this level of health care. Moreover, many of these patients were considered as having uncontrolled BP when they were reclassified according to the BP means using the 24 hour-ABPM after a mean period of 3 years and 8 months of follow-up.[8] These findings allow some interpretations when considering the control of cardiovascular risk factors and the most appropriate use of diagnostic tools in the hypertensive population treated at the PHC level. There is evidence that 24-hour ABPM can be considered a useful tool in the PHC scenario, being used to improve cardiovascular risk stratification in hypertensive patients at the PHC level.[18]

Ohkubo et al.[19] observed a correlation between BP levels obtained from ABPM and mortality. Large and significant prospective studies have demonstrated that ABPM is a better predictor of future cardiovascular events when compared to conventional BP measurements obtained in the medical office.[8,9,20] The 24-hour ABPM is a tool capable of predicting cardiovascular outcomes in the long-term with odds ratios ranging from 1.28 to 1.4,[15] being the only BP measurement strategy with such capacity.[6] Therefore, based on the prognostic evidence, ABPM was selected as the reference standard for BP measurements and to assess the diagnostic accuracy of conventional BP measurements.[15]

Table 2 – Cardiovascular outcomes after 3 years of follow-up through 24-hour ambulatory blood pressure monitoring (ABPM)

Outcome	Controlled BP (%)	Uncontrolled BP (%)	*p* value*
Death	7.7	19.1	0.216
AF	0	17.7	0.029
Combined outcomes†	46.2	67.7	0.92

** Chi-square; †death, atrial fibrillation, and hospital admission; BP: blood pressure; AF: atrial fibrillation.*

Table 3 – Cardiovascular outcomes after 4 years of follow-up through 24-hour ambulatory blood pressure monitoring (ABPM)

Outcome	Controlled BP (%)	Uncontrolled BP (%)	*p* value*
Death	7.7	22.6	0.134
AF	0	19.4	0.015
Combined outcomes†	46.2	75.8	0.012

** Chi-square; †death, atrial fibrillation, and hospital admission; BP: blood pressure; AF: atrial fibrillation.*

Table 4 – Combined cardiovascular outcomes (death, atrial fibrillation and hospital admission) after 4 years of follow-up assessed by conventional blood pressure (BP) measurement and 24-hour ambulatory BP monitoring (ABPM)

Uncontrolled BP	Outcome		*p* value
	Present (%)	Absent (%)	
Uncontrolled BP at ABPM	79,7	24,2	0,012
Uncontrolled BP at conventional BP measurement	54,5	45,5	0,064

In the present cohort study, we expected to find a population of hypertensive patients with low to intermediate cardiovascular risk, as the entire sample consisted of patients from PHC. However, most of the patients were classified as intermediate to high risk for cardiovascular outcomes, due to the findings of type 2 diabetes, dyslipidemia, and microalbuminuria in the assessed sample. Such findings are probably due to the fact that the municipality where the study was carried out does not have a tertiary care center and, thus, most patients are treated in these PHC centers, regardless of their basal pathological condition. This aspect, in the care of the hypertensive patient, could justify the significant number of cardiovascular outcomes including mortality, new cases of atrial fibrillation and hospital admissions, being the same predicted by the uncontrolled BP assessment by 24 hour-ABPM. Conversely, when compared with conventional BP measures, a reverse causality of outcomes was observed. Thus, ABPM was a better predictor of cardiovascular outcomes in hypertensive patients, when compared to conventional BP measurements. These findings agree with previous studies that analyzed the relative risk of cardiovascular outcomes associated with the mean nocturnal and 24-hour BP measurements. [21]

The innovative aspect of the present study is the fact that the sample was obtained from a population originated exclusively from PHC, where most arterial hypertension diagnoses and treatment are performed.[22] The patients had a high mortality rate (17 deaths in a total of 143 patients in 3.5 years of follow-up) compared to other studies, such as the TASMINH 3 Trial,[23] of high-risk UK patients in PHC, randomized to BP self-measurement or control, in which two deaths were observed in a sample of 555 patients with a follow-up period of approximately two years. Moreover, no death was reported in the TASMINH Trial 2[24], which had a similar sample size to the previously mentioned one, with a 1-year follow-up. The differences in mortality rates could reflect the impact of several care strategies used with hypertensive patients, as well as differences in cardiovascular risk in the assessed populations. Thus, the broad use of health technologies, such as ABPM in this context, could be used as an auditing tool for the public health system quality assessment.

In a recent meta-analysis, it was observed that a large part of the cardiovascular risk obtained from the 24-hour BP assessment could be explained by the reduction in the nocturnal dipping, with a significant cardiovascular risk excess of 27% in relation to the normal nocturnal dipping pattern during sleep.[18] When considering only the nocturnal BP mean, 63.3% of the assessed patients did not have nocturnal dipping, which may have contributed to the observed outcomes. This prevalence is similar to that found in other studies, in which the absence of nocturnal dipping ranged from 60 to 67.5%.[25]

However, these studies were carried out in different health care settings, which did not incorporate PHC. Masked hypertension could be pointed out as another factor contributing to the high number of outcomes observed in the study. The prevalence of masked hypertension in the study ranged from 46.9 to 56.1%, considering the different thresholds for the ABPM targets used in the study. Additionally, there is an association between target-organ lesions in patients with masked hypertension and unfavorable cardiovascular prognosis.[26,27]

Arterial hypertension is a risk factor for new cases of atrial fibrillation due to left atrial overload and subsequent arrhythmia.[22] However, this study identified that the mean age of patients who developed atrial fibrillation was 63.6 years, consisting of another risk factor for new cases of atrial fibrillation.[28] Additionally, mortality due to CAD and CVA can show a 3-fold increase with each increase of 10 years in age, demonstrating the importance of adequate BP control in reducing cardiovascular risk over the years.[29]

The ABPM can provide prognostic information in terms of cardiovascular risk, contributing to treatment from the 24-hour BP assessment and antihypertensive treatment optimization.[30] These benefits are inherent to 24-hour BP and have been shown to be associated with a reduction in hospital admissions from cardiovascular disease and death in patients seeking medical care at PHC centers. Moreover, the routine use of ABPM in BP assessment may prevent the unnecessary treatment of hypertensive patients with white-coat effect and masked hypertension,[26] thus contributing to the cost-effectiveness of arterial hypertension management at the PHC level.[31]

In a relatively short period of time, a significant number of hospital admissions from cardiovascular causes was observed, and this was a relevant finding of this study. When considering the impact of patient reclassification according to the different thresholds of normality for ABPM and the conventional BP measurement, the diagnostic accuracy of the conventional BP assessment performed at the PHC centers was low, regardless of the method used. Therefore, the 24-hour ABPM resulted in the auditing of the care provided at the PHC centers, based on the incidence of cardiovascular outcomes observed, and the association with low BP control. These findings can contribute to the development of new hypertensive patient care strategies in the PHC setting.

Sample size may be considered a limitation of the present study. However, considering the high number of cardiovascular outcomes observed in the relative short period of time, the sample calculation based on a previous study with the same population base,[13] the absence of PHC service offered by the private network and the population size, the present study power was adequate for the study aim. The sample, consisting of patients with chronic pathological conditions and having PHC as the highest reference in detriment to the availability of secondary and tertiary health care, may have contributed to the important number of outcomes observed. Therefore, the use of ABPM as a predictive tool for cardiovascular outcomes in a sample obtained exclusively from PHC centers provides some perspectives for the development of preventive strategies for patients whose clinical profile is similar to that of the studied sample.

Conclusion

A large number of hospital admissions and cardiovascular events were identified in a cohort of hypertensive patients who sought medical assistance in Primary Health Care centers. The 24-hour ABPM showed adequate predictive capacity for cardiovascular outcomes when compared to conventional BP measurements. This study suggests the need for reassessment of preventive strategies in PHC centers, especially considering the care of the hypertensive patient. The 24-hour ABPM can be considered a good tool for assessing BP measurements and could be useful in the management of BP control in hypertensive patients and as a predictor of cardiovascular outcomes in the Primary Health Care setting.

Author contributions

Conception and design of the research: Grezzana GB, Stein AT, Pellanda LC. Acquisition of data: Grezzana GB. Analysis and interpretation of the data: Grezzana GB, Stein AT, Pellanda LC. Statistical analysis: Grezzana GB. Obtaining financing: Grezzana GB. Writing of the manuscript: Grezzana GB, Stein AT, Pellanda LC. Critical revision of the manuscript for intellectual content: Grezzana GB, Stein AT, Pellanda LC.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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