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Ambulatory blood pressure and risk of new-onset atrial fibrillation in treated hypertensive patients

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Abstract

The aim of this study was to evaluate the influence of clinic and ambulatory blood pressure (BP) on the occurrence of new-onset atrial fibrillation (AF) in treated hypertensive patients. We studied 2135 sequential treated hypertensive patients aged >40 years. During the follow-up (mean 9.7 years, range 0.4–20 years), 116 events (new-onset AF) occurred. In univariate analysis, clinic, daytime, nighttime, and 24-h systolic BP were all significantly associated with increased risk of new-onset AF, that is, hazard ratio (95% confidence interval) per 10 mm Hg increment 1.22 (1.11–1.35), 1.36 (1.21–1.53), 1.42 (1.29–1.57), and 1.42 (1.26–1.60), respectively. After adjustment for various covariates in multivariate analysis, clinic systolic BP was no longer associated with increased risk of new-onset AF, whereas daytime, nighttime, and 24-h systolic BP remained significantly associated with outcome, that is, hazard ratio (95% confidence interval) per 10 mm Hg increment 1.09 (0.97–1.23), 1.23 (1.10–1.39), 1.16 (1.03–1.31), and 1.22 (1.06–1.40), respectively. Daytime, nighttime, and 24-h systolic BP are superior to clinic systolic BP in predicting new-onset AF in treated hypertensive patients. Future studies are needed to evaluate whether a better control of ambulatory BP might be helpful in reducing the occurrence of new-onset AF.

1 | INTRODUCTION

Hypertension is a potent predictor of cardiovascular morbidity and mortality around the world.[1,2] Atrial fibrillation (AF) is the most common cardiac arrhythmia and it also predisposes to higher cardiovascular risk.[3,4] These conditions often coexist and their incidences increase with aging.[1-4]

Various studies have reported that hypertension is a relevant risk factor for the development of AF.[5-8] Some mechanisms have been

suggested to link hypertension and AF, comprising those involved in the pathophysiology of hypertension and those associated with cardiac organ damage.[9,10]

Clinic blood pressure (BP) measurement is traditionally used for diagnosis and management of hypertension. However, it has been largely shown that ambulatory BP is superior to clinic BP in predicting cardiovascular outcome.[11-16]

In this context, some studies have also tried to assess whether ambulatory BP is superior to clinic BP in predicting new-onset AF.[17-21]

It has been reported that 24-h BP,[17–21] daytime BP,[20,21] and nighttime BP[19–21] are independent predictors of new-onset AF and that these ambulatory BP measures are superior to clinic BP[20,21] in predicting future AF. However, given that there is little information in the literature on this topic,[22] further data could help to understand the relationship between new-onset AF and clinic and ambulatory BP.

The aim of this study was to evaluate the influence of clinic and ambulatory BP on the occurrence of new-onset AF in treated hypertensive patients.

2 | METHODS

2.1 | Subjects

We studied 2135 sequential treated hypertensive patients aged >40 years prospectively recruited from December 1992 to December 2012 who were referred to our hospital outpatient clinic for evaluation of BP control. From the original database of 2264 patients, 129 individuals aged ≤40 years were excluded. Other 103 patients had been lost during follow-up. Subjects with secondary hypertension were excluded. Individuals with AF at baseline were also excluded. All the patients underwent clinical evaluation, electrocardiogram, routine laboratory tests, echocardiographic examination, and non-invasive ambulatory BP monitoring. Study population came from the same geographical area (Chieti and Pescara, Abruzzo, Italy). The study was in accordance with the Second Declaration of Helsinki and was approved by the institutional review committee. Subjects gave informed consent.

2.2 | Office BP measurements

Clinic systolic and diastolic BP were recorded by a physician using a mercury sphygmomanometer and appropriate-sized cuffs. Measurements were performed in triplicate, 2 min apart, and the mean value was used as the BP for the visit. Clinic BP was defined as normal when it was <140/90 mm Hg.

2.3 | Ambulatory BP monitoring

Ambulatory BP monitoring was performed with a portable non-invasive recorder (SpaceLabs 90207, Redmond, WA) on a day of typical activity, within 1 week from clinic BP measurement. Each time a reading was taken, subjects were instructed to remain motionless and to record their activity on a diary sheet. Technical aspects have been previously reported.[23] Ambulatory BP readings were obtained at 15-min intervals from 6 AM to midnight, and at 30-min intervals from midnight to 6 AM. The following ambulatory BP parameters were evaluated: daytime (awake period as reported in the diary), nighttime (asleep period as reported in the diary), and 24-h systolic and diastolic BP. Recordings were automatically edited (that is, excluded) if systolic

BP was >260 or <70 mm Hg or if diastolic BP was >150 or <40 mm Hg and pulse pressure was >150 or <20 mm Hg. Subjects had recordings of good technical quality (at least 70% of valid readings during the 24-h period, at least 20 valid readings while awake with at least 2 valid readings per hour and at least 7 valid readings while asleep with at least 1 valid reading per hour), in line with minimum requirement suggested by the European Society of Hypertension.[24]

2.4 | Echocardiography

Left atrial (LA) and left ventricular (LV) measurements and calculation of LV mass were made according to standardized methods.[25] LA diameter (cm) was indexed by body surface area (m^2), and LA enlargement was defined as LA diameter/body surface area ≥2.4 cm/m^2.[25] LV mass was indexed by height$^{2.7}$ and LV hypertrophy was defined as LV mass/height$^{2.7}$ >50 g/m$^{2.7}$ in men and >47 g/m$^{2.7}$ in women.[26] LV ejection fraction was calculated using the Teichholz formula or the Simpson rule and defined as low when it was <50%.[25]

2.5 | Follow-up

Subjects were followed-up in our hospital outpatient clinic or by their family doctors. The occurrence of the event, that is AF, was recorded during follow-up visits or by telephone interview of the family doctor or the patient or a family member, followed by a visit if the patient was alive. Later, medical records were obtained to confirm AF. Data were collected by the authors of this study. Those reviewing the endpoint were blinded to other patients' data. In this report, we evaluated the occurrence of new-onset AF, either paroxysmal or permanent, in patients with baseline sinus rhythm. AF was documented by ECG performed at the time of hospitalization or at follow-up visits or by family doctor. Each ECG was evaluated by two independent cardiologists. The incidence date of AF was defined as the date of the first ECG showing AF wherever it was performed.

2.6 | Statistical analysis

Standard descriptive statistics were used. Groups were compared by using unpaired t test and chi-square or Fisher's exact test, where appropriate. Event rates are expressed as the number of events per 100 patient-years based on the ratio of the observed number of events to the total number of patient-years of exposure up to the terminating event or censor. Cox regression analysis was used to evaluate univariate and multivariate association of factors with outcome. First, we evaluated univariate association between new-onset AF and various covariates, including clinic and ambulatory BP, that is, daytime, nighttime, and 24-h BP. Then, multiple regression analysis was performed reporting in the final model variables that were significantly ($p < .05$) associated with outcome in univariate analysis. The forced entry model was used. Goodness of fit of

different models was assessed by the −2 loglikelihood ratio test. Statistical significance was defined as p < .05. Analyses were made with the SPSS 21 software package (SPSS Inc). Graphs were made with GraphPad Prism 5 (GraphPad software Inc).

3 | RESULTS

Characteristics of patients with an without new-onset AF are reported in Table 1. Patients with new-onset AF were older, had

TABLE 1 Characteristics of patients with and without new-onset atrial fibrillation

Parameter	No AF (n = 2019)	New-onset AF (n = 116)	p
Age, years	61 ± 10	67 ± 9	.0001
Men, n (%)	930 (46)	45 (39)	.13
BMI, kg/m^2	27.9 ± 4.2	28.7 ± 4.8	.07
Smokers, n (%)	355 (18)	15 (13)	.20
FHCVD, n (%)	258 (13)	16 (14)	.75
Previous events, n (%)	133 (7)	7 (6)	.81
Diabetes, n (%)	171 (8)	28 (24)	.0001
eGFR, ml/min/1.73 m^2	73 ± 20	66 ± 18	.0001
LDL cholesterol, mg/dl	129 ± 30	126 ± 29	.29
LV hypertrophy, n (%)	569 (28)	44 (38)	.02
LA enlargement, n (%)	298 (15)	66 (57)	.0001
ALVSD, n (%)	55 (3)	8 (7)	.01

Note: Previous events included cerebral or cardiac events or peripheral revascularization. Diabetes was defined as fasting glucose >125 mg/dl or use of oral hypoglycemic agents or insulin.

AF, atrial fibrillation; ALVSD, asymptomatic left ventricular systolic dysfunction (ejection fraction <50%); BMI, body mass index calculated as weight in kilograms divided by height in meters squared; eGFR, estimated glomerular filtration rate calculated by the MDRD equation; FHCVD, family history of premature cardiovascular disease defined as an event occurred in men aged <55 years and in women aged <65 years; LA, left atrial; LDL, low density lipoprotein calculated by the Friedewald's formula; LV, left ventricular.

TABLE 2 Blood pressure of patients with and without new-onset atrial fibrillation

Parameter	No AF (n = 2019)	New-onset AF (n = 116)	p
Clinic SBP, mm Hg	148 ± 17	152 ± 17	.02
Clinic DBP, mm Hg	89 ± 10	88 ± 11	.07
Daytime SBP, mm Hg	134 ± 14	140 ± 15	.0001
Daytime DBP, mm Hg	81 ± 9	80 ± 10	.30
Nighttime SBP, mm Hg	120 ± 15	129 ± 17	.0001
Nighttime DBP, mm Hg	69 ± 9	70 ± 10	.32
24-h SBP, mm Hg	130 ± 13	136 ± 15	.0001
24-h DBP, mm Hg	78 ± 9	77 ± 10	.51

Abbreviations: AF, atrial fibrillation; DBP, diastolic blood pressure; SBP, systolic blood pressure.

higher prevalence of diabetes, LV hypertrophy, LA enlargement, and asymptomatic LV systolic dysfunction and had lower estimated glomerular filtration rate.

BP values are reported in Table 2. Clinic, daytime, nighttime, and 24-h systolic BP were significantly higher in patients with new-onset AF.

Antihypertensive therapy is reported in Table 3. Use of various antihypertensive drug classes was not different between the groups. Triple therapy was higher in patients with new-onset AF. Use of aspirin was higher, and that of statin tended to be higher, in patients with new-onset AF.

During the follow-up (mean 9.7 years, range 0.4–20 years), 116 cases of new-onset AF occurred. The event rate was 0.56 per 100 patient/years.

Results of univariate analysis are reported in Table 4. Age, body mass index, family history of cardiovascular disease, diabetes, estimated glomerular filtration rate, LV hypertrophy, LA enlargement, asymptomatic LV systolic dysfunction and clinic, daytime, nighttime, and 24-h systolic BP were significantly associated with new-onset AF. No significant association was found between parameters of diastolic BP and new-onset AF.

Results of multivariate analysis are reported in Figure 1. After adjustment for age, body mass index, family history of cardiovascular disease, diabetes, estimated glomerular filtration rate, LV hypertrophy, LA enlargement, and asymptomatic LV systolic dysfunction as covariates associated with outcome in univariate analysis, and number of antihypertensive drugs forced into the model, clinic systolic BP was no longer associated with increased risk of new-onset AF, whereas daytime, nighttime, and 24-h systolic BP were significantly associated with outcome.

None of the excluded patients aged <40 years developed AF during the follow-up and if these patients were included in the analysis, the results remained the same.

TABLE 3 Therapy of patients with and without new-onset atrial fibrillation

Parameter	No AF (n = 2019)	New-onset AF (n = 116)	p
Diuretic, n (%)	1100 (54)	68 (59)	.38
Beta-blocker, n (%)	667 (33)	39 (34)	.90
Calcium antagonist, n (%)	666 (33)	42 (36)	.47
ACE-inhibitor, n (%)	968 (48)	59 (51)	.54
AR-blocker, n (%)	474 (23)	24 (21)	.49
Alpha-blocker, n (%)	268 (13)	16 (14)	.87
Single therapy, n (%)	505 (25)	29 (25)	.99
Double therapy, n (%)	1023 (51)	49 (42)	.08
Triple therapy, n (%)	491 (24)	38 (33)	.04
Aspirin, n (%)	321 (16)	32 (28)	.001
Statin, n (%)	175 (9)	16 (14)	.06

Abbreviations: AF, atrial fibrillation; ACE, angiotensin converting enzyme; AR, angiotensin receptor.

TABLE 4 Risk of new-onset atrial fibrillation in univariate analysis

Parameter	HR (95% CI)	p
Age (10 year)	2.44 (2.00–2.96)	.0001
Body mass index (10 kg/m^2)	1.54 (1.02–2.32)	.03
FHCVD (yes vs. no)	1.99 (1.15–3.43)	.01
Diabetes (yes vs. no)	6.11 (3.93–9.51)	.0001
eGFR (10 ml/min/1.73 m^2)	0.73 (0.66–0.81)	.0001
LV hypertrophy (yes vs. no)	2.25 (1.54–3.29)	.0001
LA enlargement (yes vs. no)	6.09 (4.22–8.81)	.0001
ALVSD (yes vs. no)	3.31 (1.61–6.79)	.001
Clinic SBP (10 mm Hg)	1.22 (1.11–1.35)	.0001
Daytime SBP (10 mm Hg)	1.36 (1.21–1.53)	.0001
Nighttime SBP (10 mm Hg)	1.42 (1.29–1.57)	.0001
24-h SBP (10 mm Hg)	1.42 (1.26–1.60)	.0001

Abbreviations: ALVSD, asymptomatic left ventricular systolic dysfunction; CI, confidence interval; eGFR, estimated glomerular filtration rate; FHCVD, family history of cardiovascular disease; HR, hazard ratio; LA, left atrial; LV, left ventricular; SBP, systolic blood pressure.

When added to a model including covariates and clinic BP, daytime (p < .01), nighttime (p < .05), and 24-h BP (p < .01) significantly improved prediction of outcome as documented by the reduction of −2 loglikelihood ratio values. On the contrary, when added to a model including covariates and daytime or nighttime or 24-h BP, clinic BP (p > .2) did not improve prediction of incident AF.
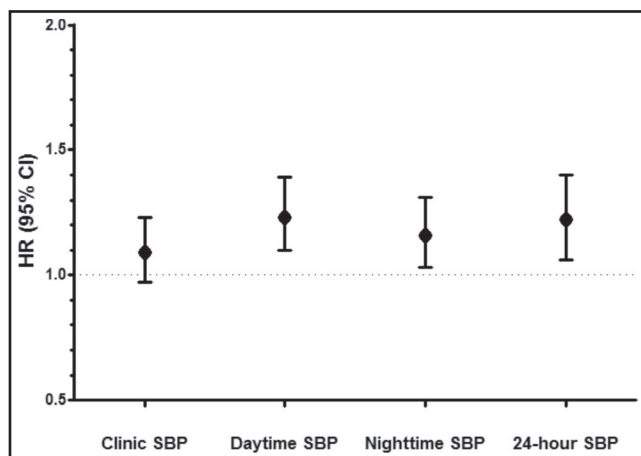

FIGURE 1 Risk of new-onset atrial fibrillation based on clinic, daytime, nighttime, and 24-h systolic blood pressure (SBP), per 10 mm Hg increment. Data are adjusted for age, body mass index, family history of cardiovascular disease, diabetes, estimated glomerular filtration rate, left ventricular hypertrophy, left atrial enlargement and asymptomatic left ventricular systolic dysfunction as covariates associated with outcome in univariate analysis, and number of antihypertensive drugs forced into the model. Hazard ratio (HR) and 95% confidence interval (CI) values are 1.09 (0.97–1.23), 1.23 (1.10–1.39), 1.16 (1.03–1.31), and 1.22 (1.06–1.40) for clinic, daytime, nighttime, and 24-h SBP, respectively

4 | DISCUSSION

This study shows that ambulatory systolic BP is superior to clinic systolic BP in predicting new-onset AF in treated hypertensive patients.

Various studies have reported that risk of cardiovascular events is more strongly associated with ambulatory than with clinic BP.[11–16] In this context, some studies have also tried to assess the influence of ambulatory BP on new-onset AF.[17–21]

Ciaroni et al[17] studied 597 subjects with clinic hypertension, aged >50 years, who were followed for a mean period of 7 years; 28 cases of AF occurred. After adjustment for age, gender, and body mass index, the hazard ratio (HR) and 95% confidence interval (CI)) for new-onset AF per 10 mm Hg increment of 24-h systolic BP was 1.16 (1.06–2.47). The effect of clinic BP was not reported.

We[18] previously assessed 1141 untreated subjects at baseline with clinic and ambulatory hypertension (sustained), aged >40 years, who were followed for a mean period of 6 years; 43 cases of AF were recorded. After adjustment for age, LA enlargement and nondipping, the HR (95% CI) for new-onset AF per 10 mm Hg increment of 24-h systolic BP was 1.32 (1.05–1.67). The impact of clinic BP was not described.

Perkiömäki et al[19] evaluated 903 subjects with normotension and clinic hypertension (49%), aged 40–59 years, who were followed for a mean period of 16 years; 91 cases of AF were observed. After adjustment for age, sex, body mass index, height, smoking, alanine aminotransferase, uric acid, and fasting plasma glucose, the HR (95% CI) for new-onset AF per 5 mm Hg increment of daytime, nighttime, and 24-h systolic BP was 1.05 (0.98–1.13), 1.07 (1.004–1.15), and 1.09 (1.01–1.17), respectively. The influence of clinic BP was not reported.

Tikhonoff et al[20] investigated 2776 subjects with normotension and clinic untreated or treated hypertension (about 30%), aged >18 years, who were followed for a mean period of 14 years; 111 cases of AF occurred. After adjustment for sex, age, body mass index, cholesterol, tobacco and alcohol use, history of cardiovascular disease and diabetes mellitus and antihypertensive drug treatment, the HR (95% CI) for new-onset AF per 12 mm Hg increment of daytime, nighttime and 24-h systolic BP was 1.22 (1.02–1.46), 1.20 (1.02–1.42), and 1.27 (1.07–1.51), respectively. Clinic BP had a borderline association with AF (p = .06).

Matsumoto et al[21] studied 769 elderly and mainly Hispanic subjects who were followed for a mean period of 9.5 years; 83 cases of AF were recorded. After adjustment for age, sex, race, and hypertension status at baseline, clinic BP was not associated with new-onset AF whereas daytime (HR 1.21; 95% CI, 1.04–1.40), nighttime (HR 1.22; 95% CI, 1.07–1.39) and 24-h systolic BP (HR 1.24; 95% CI, 1.07–1.44) were significantly associated with new-onset AF.

The present results confirm and extend previous findings. Compared with prior reports, our study included a larger and more homogeneous hypertensive population, reported a higher number of events and had the opportunity to adjust for markers of hypertension-mediated cardiac organ damage.

In accordance with the studies by Tikhonoff et al[20] and Matsumoto et al,[21] but at variance with that by Perkiömäki et al,[19]

we observed that both daytime and nighttime systolic BP were significantly associated with increased risk of new-onset AF. The difference with the study by Perkiömäki et al[19] may be related to the different characteristics of studied populations.

In our study, ambulatory BP remained significantly associated with increased risk of AF even after adjustment for cardiac organ damage which has the potential to influence the occurrence of AF.[9,10] Beyond various advantages of ambulatory BP over clinic BP, this aspect suggests that ambulatory BP is better than clinic BP in integrating the pathophysiological background that could be implicated in both hypertension and AF onset.[22]

Various studies have evaluated the impact of clinic BP control on the occurrence of new-onset AF but results are debated.[27–31] This feature could partly be explained by the partial ability of clinic BP to detect real BP control, at variance with ambulatory BP.[15,32] Given this aspect, future research to evaluate the impact of ambulatory BP control on the occurrence of new-onset AF is needed.

This study has some limitations. First, we studied only Caucasian subjects and our results cannot be applied to other ethnic groups. Second, we included clinical cases of permanent AF and symptomatic paroxysmal AF, thus we cannot rule out that clinical cases of asymptomatic paroxysmal AF may have been lost. Third, for the minority of patients who were followed by their family doctor, it cannot be totally excluded that some of them with potential asymptomatic/mildly symptomatic permanent AF did not request a visit to their family doctor or did not refer problems during our telephone interview at the last contact and have been lost leading to an underestimation of incident AF.

In conclusion, daytime, nighttime, and 24-h systolic BP are superior to clinic systolic BP in predicting new-onset AF in treated hypertensive patients. Future studies are needed to evaluate whether a better control of ambulatory BP might be helpful in reducing the occurrence of new-onset AF.

AUTHOR CONTRIBUTIONS

Francesca Coccina wrote the paper, revised the manuscript critically for important intellectual content and gave final approval of the version to be submitted and of the revised version. Anna M. Pierdomenico performed statistical analysis, revised the manuscript critically for important intellectual content and gave final approval of the version to be submitted and of the revised version. Umberto Ianni, Matteo De Rosa, Andrea De Luca, Davide Pirro, and Jacopo Pizzicannella collected the data, revised the manuscript critically for important intellectual content and gave final approval of the version to be submitted and of the revised version. Oriana Trubiani, Francesco Cipollone, and Giulia Renda designed the study, revised the manuscript critically for important intellectual content and gave final approval of the version to be submitted and of the revised version. Sante D. Pierdomenico collected the data, designed the study, contributed to the writing of the paper, revised the manuscript critically for important intellectual content and gave final approval of the version to be submitted and of the revised version.

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