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Impact of Clinic and Ambulatory Pulse Pressure on Heart Failure

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Impact of Clinic and Ambulatory Pulse Pressure on Heart Failure Risk in Elderly Treated Hypertensive Patients

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ABSTRACT

Background and Aim: The influence of clinic and ambulatory pulse pressure (PP) on heart failure (HF) is not yet clear. The aim of this study was to evaluate the impact of clinic, daytime, nighttime and 24-hour PP on HF risk in the elderly.

Methods: In this retrospective study, we evaluated 745 treated hypertensive subjects older than 65 years who underwent clinic blood pressure (BP) recording and ambulatory BP monitoring to assess clinic, daytime, nighttime and 24-hour PP. The association of PP parameters with future HF was investigated by univariate and multivariate Cox regression analyses. Receiver operating characteristic curve analysis was also used to assess the risk discrimination of the models including clinic or daytime or nighttime PP.

Results: During the follow-up (8.4 ± 4.8 years), 82 HF events occurred. After adjustment for covariates, including mean arterial pressure, the adjusted hazard ratio (95% confidence interval) of HF for each SD increase in clinic, daytime, nighttime and 24-hour PP was 1.06 (0.83-1.36), 1.31 (1.04-1.65), 1.42 (1.13-1.79) and 1.37 (1.10-1.70), respectively. The area under the curve (95% confidence interval) for the models including clinic, daytime or nighttime PP was 0.66 (0.60-0.73), 0.73 (0.68-0.79) and 0.74 (0.69-0.79), respectively. The models including daytime or nighttime PP differed significantly from that including clinic PP ($P=0.0001$), but did not differ between them.

Conclusions: In elderly treated hypertensive patients, daytime, nighttime and 24-hour PP are superior to clinic PP in predicting the occurrence of HF. Daytime and nighttime PP tend to be similar in discriminating the risk of future HF.

Key words: ambulatory; clinic; heart failure; hypertension; pulse pressure.

Pulse pressure (PP), that is, the pulsatile component of blood pressure (BP), has been widely studied beyond the other BP parameters in the past years. PP is calculated as the difference between systolic and diastolic BP describing changes of both BP measures, is representative of the response of the arterial system to left ventricular (LV) ejection and is affected by cardiac factors, vascular resistance, arterial wall properties and pulse wave reflection [1,2]. PP becomes wider after 50-60 years of age [3-5] and tends to be higher in women than in men [6].

Various studies evaluated the prognostic value of clinic PP recorded in the physician's office [4,5,7-15]. Most of them assessed the impact of PP on total cardiovascular events or coronary events or cerebrovascular events or mortality [4,5,7-15] and suggested that cardiovascular prognosis gets worse with higher clinic PP, though some differences regarding specific endpoints have also been reported. Only a few studies evaluated the association between clinic PP and heart failure (HF) [16-18].

Clinic PP may be affected by the alerting reaction induced by the clinic visit [19]. Thus, clinic PP could not be representative of the usual patients' PP. In this context, some studies attempted to evaluate whether out-of-office PP, such as ambulatory PP, could be superior to clinic PP in predicting cardiovascular risk in hypertensive patients [20-29]. The abovementioned studies investigated future risk of coronary events and/or cerebrovascular events and/or mortality and reported that ambulatory PP was a better predictor of adverse outcomes than clinic PP [20-29]. Globally, a few studies in the literature evaluated the impact of ambulatory BP on HF [30-34], and specifically only a single study assessed the influence of ambulatory PP on the occurrence of HF [35].

HF is a relevant public health burden characterized by high morbidity, mortality, hospitalization rates, and costs [36,37]. Its prevalence increases with age becoming higher than 10% in those aged 70 years or over [37]. Hypertension is one of the most frequent causes of HF onset [38] and its population-attributable risk has been reported to be as high as that of coronary artery disease [39].

As previously reported, to the best of our knowledge, there are a few studies evaluating the influence of clinic PP on HF [16-18] and only a single study evaluating the effect of ambulatory PP on future HF [35]. Thus, other studies are needed to add further insight into this topic.

The aim of this study was to evaluate the impact of clinic, daytime, nighttime and 24-hour PP on the risk of HF in elderly treated hypertensive patients.

METHODS

Patients

This study is a retrospective examination of our prospectively collected data in treated hypertension. In this specific report we evaluated 745 treated hypertensive patients older than 65 years, the most frequent age presently used to define the transition to the elderly status in Western nations, from a cohort of 2264 sequential treated individuals with complete follow-up. All these patients had been referred to our hospital outpatient clinic for the evaluation of BP control. Among the initial population of 781 subjects older than 65 years, 36 were lost during the follow-up. For this specific study, the inclusion criteria were: (1) age older than 65 years; (2) hypertensive patient; (3) use of antihypertensive drugs. Subjects with secondary hypertension were excluded, as well as those with a recent cardiovascular event (6 months), an acute illness, dementia, cancer and a disability. All the subjects underwent clinical evaluation, an electrocardiogram, routine laboratory tests, an echocardiographic examination and non-invasive ambulatory BP monitoring at baseline. The study population came from the same geographical area (Chieti and Pescara, Abruzzo, Italy). Our prospective observational study was approved by the Institutional Review Committee in 1992. Subjects gave written informed consent to be included in the study and for anonymous data processing.

Clinic BP Measurement

Clinic BP was recorded by a physician using a mercury sphygmomanometer and appropriate-sized cuffs. Measurements were performed three times in a quiet

room, 2 minutes apart, after at least 5 min of rest, and the mean value was used as the BP for the visit. Clinic systolic BP < 140 mmHg and clinic diastolic BP < 90 mmHg were defined as controlled hypertension. Clinic PP was defined as the difference between systolic and diastolic BP, and clinic mean arterial pressure (MAP) as diastolic BP + PP/3.

Ambulatory BP Monitoring

Ambulatory BP monitoring was performed with a noninvasive recorder (SpaceLabs 90207, Redmond, WA, USA) within 1 week of the clinical evaluation. Technical aspects have been previously reported [40]. We evaluated the following ambulatory BP parameters from the examination carried out at baseline: daytime (while awake, as reported in the diary), nighttime (while asleep, as reported in the diary) and 24-hour systolic and diastolic BP. We calculated daytime, nighttime and 24-hour PP as the difference between systolic and diastolic BP, and daytime, nighttime and 24-hour MAP as diastolic BP + PP/3. The recordings of all the subjects were of good quality (at least 70% of valid readings during the 24-hour period, at least 20 valid readings while awake, with at least two valid readings per hour, and at least 7 valid readings while asleep, with at least one valid reading per hour), in line with the European Society of Hypertension requirements [41].

Echocardiography

A complete echocardiographic examination, including two-dimensional, M mode, doppler and color doppler assessment, was performed. The measurements of the left atrial (LA) and left ventricular (LV) dimensions and the calculation of the LV

mass were made according to standardized methods [42]. The LA diameter (cm) was indexed by body surface area (m^2), and LA enlargement was defined as LA diameter/body surface area $\geq 2.4 \text{ cm}/\text{m}^2$ [42]. The LV mass value was indexed by $\text{height}^{2.7}$, and LV hypertrophy was defined as LV mass/ $\text{height}^{2.7} > 50 \text{ g}/\text{m}^{2.7}$ in men and $> 47 \text{ g}/\text{m}^{2.7}$ in women [43]. The LV ejection fraction (EF) was computed using the Teichholz formula or the Simpson rule [42] and was defined as low when it was $< 50\%$.

Follow-Up

Patients were followed up in our outpatient clinic or by their general practitioner. The occurrence of events was recorded at hospitalization or during follow-up visits or by telephone interview of the general practitioner or the patient or a family member, followed by a visit if the patient was alive. Medical records were obtained to confirm the events. In the present study, we focused on HF requiring hospitalization. Diagnosis of HF was based on symptoms and signs of HF, B-type natriuretic peptide or N-terminal pro-B-type natriuretic peptide levels when available, chest X-ray and echocardiographic examination. HF subtypes were reclassified according to recent European Society of Cardiology guidelines for HF [37], that is, HF with reduced EF ($< 40\%$), mild reduced EF ($40\text{--}49\%$) and preserved EF ($\geq 50\%$). We established a priori to analyze the different HF subtypes as a single group of HF to maintain adequate statistical power.

Statistical Analysis

The data are described as mean $\pm$ standard deviation or number and percentage. The event rate is 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. Univariate Cox regression analysis was used to evaluate the association of various factors, with the outcome, calculating unadjusted hazard ratio (HR) and 95% confidence interval (CI). Then, multivariate Cox regression analysis was performed to evaluate the independent association of clinic, daytime, nighttime and 24-hour PP with outcome calculating adjusted HR and 95% CI. The forced entry model was used in multivariate analysis. A receiver operating characteristic (ROC) curve analysis, the area under the curve (AUC), was used to assess the risk discrimination of the models including clinic PP or ambulatory PP parameters. Statistical significance was defined as $p < 0.05$. Analyses were made with the SPSS 21 software package (SPSS Inc., Chicago, IL, USA). Graphs were made by using GraphPad Prism 5 (GraphPad Software Inc., San Diego, CA, USA) and SPSS 21 (SPSS Inc., Chicago, IL, USA).

RESULTS

The characteristics of the study population are reported in **Table 1**. The mean age was 72 years and 41% were men. Only a minority of patients had a previous event (10%).

Table 1. Baseline characteristics of study population

Parameter	
n.	745
Age, years	72 ± 5
Men, n (%)	304 (41)
BMI, kg/m ²	27 ± 4
Smokers, n (%)	73 (9.8)
Previous Events, n (%)	75 (10)
Diabetes, n (%)	114 (15)
eGFR < 60 ml/min, n (%)	336 (45)
LDL cholesterol, mg/dl	127 ± 29
LVH, n (%)	245 (33)
LA enlargement, n (%)	168 (23)
ALVSD, n (%)	36 (5)

ALVSD, asymptomatic left ventricular systolic dysfunction (ejection fraction < 50%); BMI, body mass index; eGFR, estimated glomerular filtration rate; LA, left atrial; LDL, low-density lipoprotein; LVH, left ventricular hypertrophy.

The clinic and ambulatory BP data are reported in **Table 2**.

Table 2. Blood pressure values of study population

Parameter	
Clinic SBP, mmHg	152 ± 18
Clinic DBP, mmHg	86 ± 10
Clinic PP, mmHg	66 ± 15.5
Clinic MAP, mmHg	108 ± 11.5
Daytime SBP, mmHg	136 ± 15
Daytime DBP, mmHg	77 ± 9
Daytime PP, mmHg	59 ± 13
Daytime MAP, mmHg	97 ± 9
Nighttime SBP, mmHg	125 ± 16
Nighttime DBP, mmHg	67 ± 9
Nighttime PP, mmHg	58 ± 13
Nighttime MAP, mmHg	86 ± 10
24-hour SBP, mmHg	133 ± 14
24-hour DBP, mmHg	74 ± 8
24-hour PP, mmHg	59 ± 12.5
24-hour MAP, mmHg	93 ± 9

DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; SBP, systolic blood pressure.

The antihypertensive therapy of the study population is reported in **Table 3**.

Diuretics and angiotensin-converting enzyme inhibitors were the most frequently used drug classes. Double therapy was the most frequent strategy.

Table 3. Antihypertensive therapy of study population

Parameter	
n.	745
Diuretic, n (%)	431 (58)
Beta blocker, n (%)	210 (28)
Calcium antagonist, n (%)	260 (35)
ACE-inhibitor, n (%)	396 (53)
ARB, n (%)	188 (25)
Alpha blocker, n (%)	104 (14)
Single therapy, n (%)	180 (24)
Double therapy, n (%)	344 (46)
Triple or more therapy, n (%)	221 (30)

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

During the follow-up (8.4 ± 4.8 years, range 0.4–20.5), 82 HF events requiring hospitalization occurred, including 34 HF with reduced EF, 2 with mild reduced EF, and 46 with preserved EF (as previously stated, HF subtypes were analyzed together). The event rate was 1.3 per 100 patient-years. None of the HF events were preceded by coronary events in this population.

The results of univariate Cox regression analysis are reported in **Table 4**. Age, diabetes, LV hypertrophy, asymptomatic LV systolic dysfunction, and clinic, daytime, nighttime and 24-hour PP, and clinic, daytime, nighttime and 24-hour MAP were significantly associated with outcome.

Table 4. Results of univariate Cox regression analysis

Parameter	HR (95% CI)
Age (5 years)	1.36 (1.09-1.71)
DM (yes vs no)	2.10 (1.14-3.86)
LVH (yes vs no)	2.87 (1.86-4.44)
ALVSD (yes vs no)	6.49 (3.57-11.78)
CPP (15.5 mmHg)	1.24 (1.00-1.54)
DPP (13 mmHg)	1.66 (1.35-2.04)
NPP (13 mmHg)	1.75 (1.43-2.14)
24hPP (12.5 mmHg)	1.71 (1.41-2.08)
CMAp (11.5) mmHg)	1.19 (0.95-1.49)
DMAp (9 mmHg)	1.53 (1.26-1.85)
NMAp (10 mmHg)	1.42 (1.17-1.73)
24hMAp (9 mmHg)	1.50 (1.24-1.81)

ALVSD, asymptomatic left ventricular systolic dysfunction (ejection fraction < 50%); CI, confidence interval; CMAp, clinic mean arterial pressure; CPP, clinic pulse pressure; DM, diabetes mellitus; DMAp, daytime mean arterial pressure; DPP, daytime pulse pressure; HR, hazard ratio; LVH, left ventricular hypertrophy; MAP, mean arterial pressure; NMAp, nighttime mean arterial pressure; NPP, nighttime pulse pressure; PP, pulse pressure. HRs for PP and MAP parameters are expressed for each SD increase.

Concerning multivariate Cox regression analysis, we built a model including age, diabetes, LV hypertrophy, asymptomatic LV systolic dysfunction, clinic or daytime or nighttime or 24-hour PP, clinic or daytime or nighttime or 24-hour MAP (to account for the steady component of BP beyond the pulsatile component represented by PP), and forced into the model previous events, estimated glomerular filtration rate, LA enlargement and antihypertensive drug

classes because of their previously reported impact on the occurrence of HF or potential influence on PP. Results are reported in **Figure 1**.

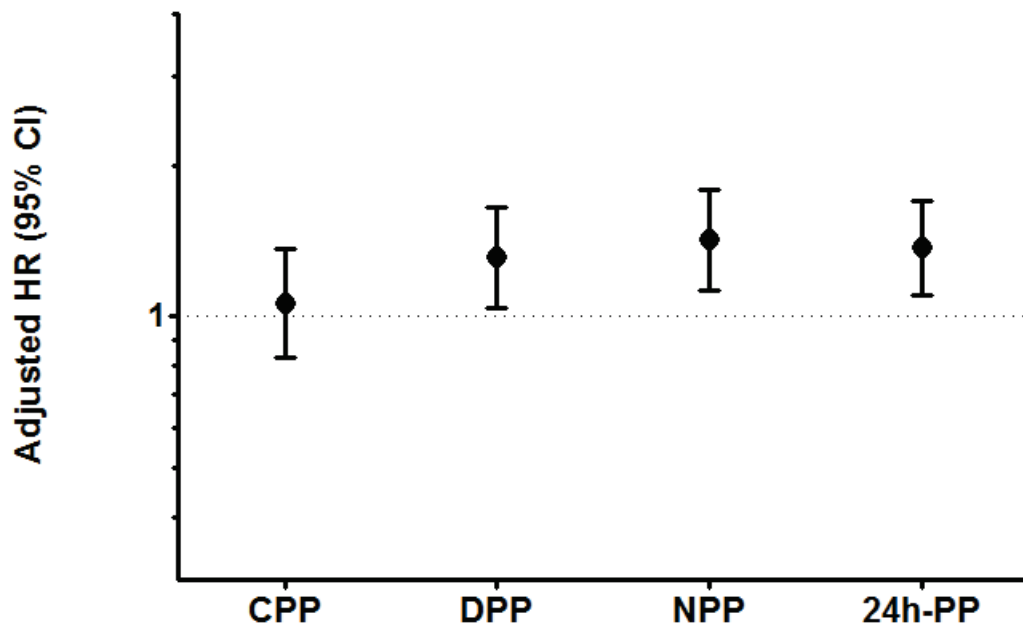


Figure 1. Adjusted hazard ratio (HR) and 95% confidence interval (CI) for heart failure hospitalization according to clinic pulse pressure (CPP), daytime pulse pressure (DPP), nighttime pulse pressure (NPP) and 24-hour pulse pressure (24h-PP). Adjustments included age, diabetes, left ventricular (LV) hypertrophy, asymptomatic LV systolic dysfunction, previous events, estimated glomerular filtration rate, left atrial enlargement, antihypertensive drug classes, clinic or daytime or nighttime or 24-hour mean arterial pressure. Adjusted HRs (95% CI) are 1.06 (0.83-1.36), 1.31 (1.04-1.65), 1.42 (1.13-1.79), and 1.37 (1.10-1.70), for CPP, DPP, NPP and 24h-PP, respectively.

Figure 2 shows ROC curves, based on the various covariates comprised in multivariate analyses and clinic or daytime or nighttime PP, in predicting HF.

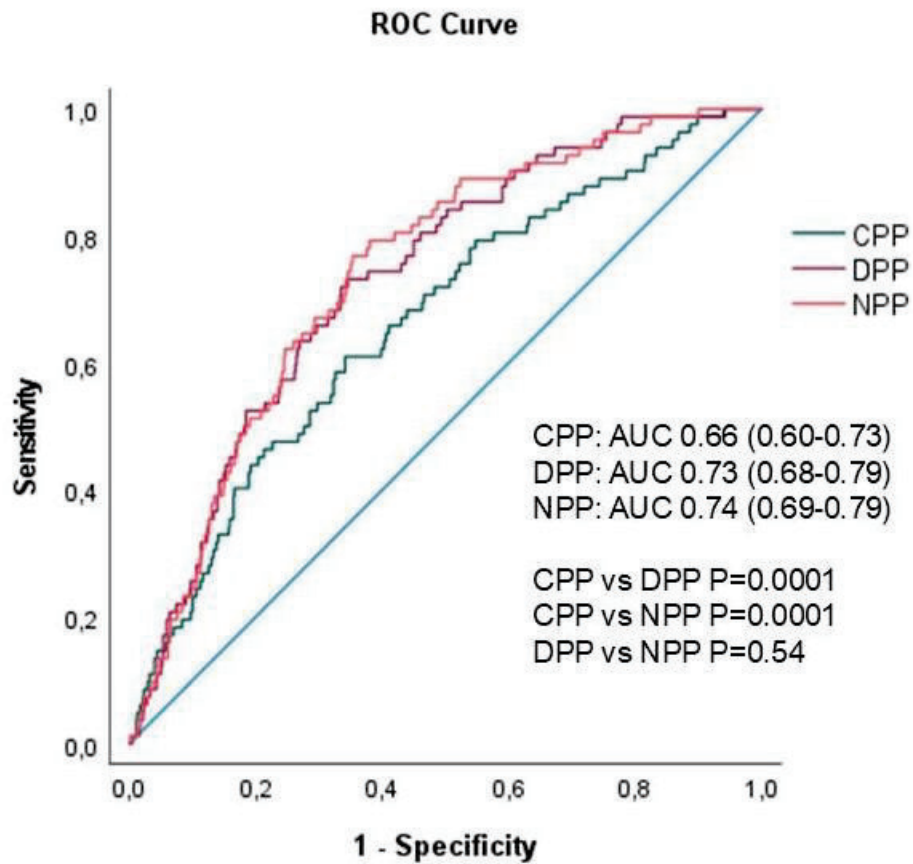


Figure 2. Receiver operating characteristic (ROC) curves, based on various covariates included in multivariate analyses (age, diabetes, LV hypertrophy, asymptomatic LV dysfunction, previous events, estimated glomerular filtration rate, LA enlargement, antihypertensive drug classes and clinic or daytime or nighttime or 24-hour mean arterial pressure) and clinic or daytime or nighttime PP, in predicting HF. AUC, area under the curve; CPP clinic pulse pressure; DPP, daytime pulse pressure; NPP nighttime pulse pressure.

As reported, the AUC was significantly different between models including clinic PP or daytime or nighttime PP, but there was no significant difference between models including daytime or nighttime PP. Beyond the superiority of ambulatory PP over clinic PP, the data indicate that daytime and nighttime PP tend to be similar in discriminating the risk of future HF.

DISCUSSION

The main findings of this study are as follows: 1) ambulatory PP is superior to clinic PP in predicting HF in elderly treated hypertensive patients; 2) daytime and nighttime PP tend to be similar in discriminating the risk of future HF.

Three previous studies [16-18] evaluated the influence of clinic PP on HF. Chae et al [16] investigated a community-based cohort of 1621 individuals (mean age 78 years) followed for approximately 4 years. After adjustment for age, sex, mean arterial pressure, history of coronary artery disease, diabetes, atrial fibrillation, valvular heart disease, and antihypertensive medication, clinic PP was an independent predictor of HF. Indeed, for each 10 mmHg increase in PP the HR (95% CI) was 1.14 (1.05-1.24). Vaccarino and coworkers [17] assessed a cohort of 2152 subjects aged ≥ 65 years derived from a general population that was followed for 10 years. After adjustment for various covariates, including major risk factors, a 10-mmHg increment in clinic PP was associated with a 14% increase in risk of HF (95% CI, 5%-24%). Haider and colleagues [18] studied a community-based cohort including 2040 participants (mean age 61 years) who were followed for approximately 17 years. After adjustment for age, sex, smoking, left ventricular hypertrophy (electrocardiogram), body mass index, diabetes, high-density lipoprotein cholesterol and heart rate, each SD (16 mm Hg) increment in PP conferred a 55% higher risk of HF (HR 1.55, 95% CI 1.37-1.75). In our study, clinic PP was not significantly associated with the outcome. The difference with other studies could be linked to various factors, including the characteristics of the populations, the inclusion of normotensive and hypertensive subjects in the other studies, the use of antihypertensive drugs only in part of the

individuals in the other studies and the adjustment for different covariates in the Cox models. Another explanation of our findings and of difference with other studies could be that clinic PP is influenced by the alerting reaction induced by the clinic visit [19]. It has been shown a bigger rise in systolic than in diastolic BP during the visit [19] which may overestimate the usual patient's PP. This aspect may be different in diverse populations, making clinic PP comparisons difficult.

A single study [35] evaluated the impact of clinic and ambulatory PP on the occurrence of HF. Ingelsson et al [35] evaluated a community-based cohort including 951 elderly men who were followed for a median period of 9 years. Normotensive and hypertensive patients (untreated and treated) were investigated. Seventy men developed HF during follow-up. In multivariable Cox proportional hazards models adjusted for myocardial infarction, diabetes, smoking, body mass index, serum cholesterol level and antihypertensive treatment, each SD increase in clinic PP (14 mmHg), daytime PP (12 mmHg), nighttime PP (14 mmHg), and 24-hour PP (12 mmHg) was associated with a HR (95% CI) for HF of 1.20 (0.95-1.52), 1.10 (0.88-1.37), 1.14 (0.93-1.41) and 1.14 (0.91-1.42), respectively. The abovementioned data indicate that neither clinic nor ambulatory PP were significantly and independently associated with HF. Our results are different, reporting no association with clinic PP but significant and independent association with daytime, nighttime, and 24-hour PP. This aspect could be explained by differences concerning characteristics of the studied populations (inclusion of normotensive subjects and untreated hypertensive patients) and methodological aspects (definition of daytime and nighttime using fixed clock times) in the Uppsala study [35].

Some plausible mechanisms could explain the association between PP and HF. A higher PP is considered an indicator (or a consequence) of aortic stiffening which raises systolic BP and lowers diastolic BP [44]. A higher afterload [45,46] and the premature return of reflected waves [47,48] increase end-systolic stress which is associated with increased myocardial oxygen demand [49], LV hypertrophy development [50,51], and impairment of LV diastolic [52] and systolic function [46]. Moreover, the reduction in diastolic coronary perfusion pressure, on which coronary flow is dependent, may result in subendocardial ischemia with or without coronary artery disease [53-55]. All these aspects, taken together, increase the vulnerability of the heart to HF.

As, with respect to clinic PP, ambulatory PP gives wider information on patient's real PP it should receive more attention as a potential target for preventive and therapeutic strategies. Given our data, it could be hypothesized that HF risk could be reduced by narrowing ambulatory PP, that is the pulsatile BP component, at any level of reduction of mean BP, that is the steady BP component. Concerning therapeutic approaches, it has been reported that drugs interfering with the renin-angiotensin-aldosterone system to a greater extent, and other antihypertensive drugs to a lesser extent, seem to improve distensibility and to reduce stiffness of large arteries [56-60]. Thus, a wise use of these drugs targeted to ambulatory PP could be of benefit. However, future studies are needed to clarify this matter and to establish which is the best therapeutic window, if any, in the natural history of arterial hypertension for a better prevention and treatment of arterial stiffness.

Study limitations and strengths

This study has some limitations. First, we evaluated only Caucasian patients, and our results cannot be applied to other ethnic groups. Second, we assessed only treated hypertensive patients older than 65 years and our data cannot be extrapolated to untreated or younger patients. Third, part of these patients was followed up in our outpatient clinic and part by their family doctors. Thus, BP control during time was not known in all the patients. Fourth, ambulatory BP data were obtained at baseline in all the patients, but only part of them underwent repeated ambulatory BP monitoring during follow-up; thus, potential temporal changes and their relevance could not be evaluated. Fifth, to maintain adequate statistical power, we did not analyze HF subtypes separately. Sixth, we did not specifically design a study to estimate the risk associated with PP, but this study is part of a prospective evaluation of the prognostic relevance of ambulatory BP parameters and other risk markers in our initially treated hypertensive patients. Our study also has some strengths including: 1) the use of ambulatory BP monitoring to evaluate out-of-office BP; 2) a fairly large sample size; 3) a large number of HF events; 4) adjustment of risk by means of relevant covariates.

Conclusions

This study shows that ambulatory PP is superior to clinic PP in predicting HF in elderly treated hypertensive patients, indicating that the alerting reaction during clinic BP recording weakens the relationship between PP and HF and that ambulatory PP gives a more accurate risk estimation. Moreover, daytime and nighttime PP tend to be similar in discriminating the risk of future HF. Our

findings could be helpful to plan a better therapeutic approach in hypertensive patients based on ambulatory PP to reduce the forthcoming burden of HF.

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