

Prognostic Effects of Short-term Blood Pressure Variability Among Patients With Heart Failure With Reduced Ejection Fraction

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Abstract

Objective: To assess the prognostic impact of short-term blood pressure variability among heart failure patients with reduced ejection fraction.

Methods: The pooled endpoint of cardiac death, stroke, myocardial infarction, and hospitalization were examined in 156 HF subjects with reduced EF. All subjects had their blood pressure measured ambulatorily. Mean average real variability (ARV) 24-hour systolic BP (n=78; n=78) was used to classify individuals as having the lowest (0.77 mmHg) or the highest (0.77 mmHg) ARV.

Results:

Throughout the follow-up period (7.6 ± 3.6 months), 107 events occurred, of which 29 (19%) were cardiac deaths, 18 (12%) myocardial infarction, 9 (6%) stroke, and 51(33%) hospitalizations. Patients with low 24-hour systolic ARV had significantly higher cardiac death and MI than those with high 24-hour systolic ARV. Risk of negative outcomes identified as an independent variable by logistic regression analysis; age (AOR 1.08, 95% CI: 1.01-1.15; $p = 0.01$), coronary artery disease (AOR 0.34, 95% CI: 0.12-0.98; $P = 0.04$), valvular cardiomyopathy (AOR 0.08, 95% CI: 0.09-0.82; $P = 0.03$), daytime systolic BP (AOR 1.25, 95% CI: 1.04-1.49; $p=0.01$) daytime diastolic BP (AOR 1.07, 95% CI: 1.00-1.14; $p = 0.04$) and 24-hour DBP (AOR 1.12, 95% CI: 1.02-1.22; $P=0.01$)

Conclusion:

Low ARV of 24-hour systolic BP is associated with greater cardiovascular risk indicators daytime systolic BP variability, night-time systolic BP variability, 24-h systolic BP variability, and 24-h diastolic BP variability with HF with reduced EF patients.

Keywords: Average real variability, Blood pressure variability, Heart failure, Prognostic effect, Reduced ejection fraction.

1. Introduction

The variability of BP is a complicated process that increases when blood pressure levels fluctuate over time. Various periods (Parati, Ochoa, Lombardi, & Bilo, 2013) highlight the physiological distinctions between the regulatory systems that activate different forms of BPV and offer the mean assessment of blood pressure (BP) level. Monitored blood pressure ambulatorily has recently been shown to be a stronger predictor of major cardiovascular events than clinic-based BP readings. Monitored blood pressure ambulatorily assists in lowering the number of probable erroneous readings while also providing insight into the dynamic fluctuation of blood pressure (Dadlani, Madan, & Sawhney, 2019)

Higher systolic BP is linked to a lower death rate in people with chronic heart failure. Paradoxically, in hypertensive subjects, high systolic BP is an unfavorable risk factor, but low systolic blood pressure is always linked with a more favorable prognosis in hypertensive patients (Raphael et al., 2009; Regnault et al., 2014). This result can be explained partly because, in chronic heart failure (CHF), a higher blood pressure corresponds to higher cardiac output (Güder et al., 2009). In a meta-analysis, Raphael et al. highlighted a paradox in the impact of increased systolic BP on mortality in CHF patients, finding a 13% reduction in premature death with an increased systolic BP over 10 mmHg (Raphael et al., 2009).

Over the past decades, the significant prognosis of each BP profiling determinant, such as systolic BP, diastolic BP, heart rate (HR), and BP variability (BPV), as well as standard deviation (SD), average real variability (ARV), has primarily been investigated in hypertensive patients (Clement et al., 2003; Coccina, Pierdomenico, Cuccurullo, & Pierdomenico, 2019), but few in chronic HF patients. A high 24-hour systolic BP ARV is linked to a greater risk of cardiovascular disease in a hypertensive population (Coccina et al., 2019).

Mena et al. (L. Mena et al., 2005) recommended using the average real variation (ARV) index to enhance the predictive potential of 24-hour BPV. This technique focuses on changes that occur in a short period, thus overcoming some of SD's constraints. It only illustrates the spread of blood pressure values around the mean. Thus, as a result, further studies may be devoted to understanding the prognostic effect of short-term BPV heart failure subjects with reduced ejection fraction. This research aimed to assess how short-term blood pressure fluctuation affected patients' prognosis in HF with reduced EF.

2. Methods

2.1 Subjects

Subjects were collected retrospectively from the cardiology department's database, which comprised admitted patients for systolic HF at the cardiology ward of Lanzhou University Second Hospital between 2014 and 2020. Nevertheless, a single reading was required to determine the average real variability (ARV). Clinical assessments, standard laboratory testing, echocardiographic investigations, and non-invasive ambulatory blood pressure monitoring were undertaken on all patients.

The criteria for inclusion were as follows: ≥ 18 years of aged or older of patients, of both genders, HF_rEF event in life, ABPM at admission or one day after admission, and stable heart failure with $\leq 40\%$ of EF in New York Heart Association functional classification (NYHA) II-IV. The criteria for exclusion were: patients < 18 years old, with incomplete ambulatory blood pressure (ABP) recordings, infection, and dialysis. The local institutional ethics committee approved the research.

2.2 Ambulatory blood pressure monitoring (ABPM)

24-h monitoring of ambulatory blood pressure was undertaken as previously determined in chronic HF (Goyal, Macfadyen, Watson, & Lip, 2005) using the oscillometer technique of the A&D TM-2430 (Palatini et al., 1998). Blood pressure was taken every 15 minutes between 7:00 a.m. and 9:59 p.m. throughout the day and every 30 minutes between 10:00 p.m. and 6:59 a.m. during the night. The BP was measured in millimetres of mercury (mmHg).

A trained nurse fitted the ABPM devices on the right arms of the patients 24 hours after their admission. During the test, patients were instructed to relax their cuffed arms, after which they were given a dairy sheet each to help keep track of any unexpected events.

Diurnal (awake period), nocturnal (asleep period), and 24-hour systolic and diastolic blood pressures were assessed as ambulatory blood pressure parameters. As previously mentioned, we measured blood pressure variability using the 24-hour systolic BP of average real variability (ARV) (Coccina et al., 2019). The ARV 24-hour calculates the average of successive measures of the absolute differences and thereby adjusts the sequence in which the BP readings were taken. It is computed using the formula below (L. Mena et al., 2005):

$$ARV = \frac{1}{N - 1} \sum_{K=1}^{N-1} |BP_{K+1} - BP_K|$$

N represents the valid number of BP readings, and K denotes the sequence of readings from each monitored participant.

In this present research, the effect of ARV on 24-hour SBP was investigated. Subjects with ARV 24-hour systolic BP less than or greater than the medium (0.772 mmHg or 0.772 mmHg) were identified as having the lowest or the highest BP variability, respectively. If systolic BP, or diastolic BP, or pulse pressure was more 260 or less 70 mmHg, or was more 150 or less 40 mmHg, or more 150 or less 20 mmHg, respectively (Pierdomenico et al., 1995); automatic editing was performed on recordings (i.e. removed).

Patients had high-quality technical recordings (at least 20 valid measurements while awake with 2 measurements per hour, at least 7 valid measures were taken at night with 1 valid measurement per hour, and 70% of the 24-hour predicted measurements must be valid).

2.3 Follow-up of patients

Patients were contacted by phone by the study's author during the follow-up phase or via interactions with family members. Subjects who did not provide new information after ABPM in the preceding month were judged missing for follow-up. During 15 months of follow-up, the occurrence outcomes consisted of a combination of cardiovascular events involving cardiac death and myocardial infarction, stroke, and hospitalization.

2.4 Statistical analysis

The mean and standard deviation were used to present continuous data. Percentages were used to express categorical data. The comparison of the two groups was made using an unpaired t-test and χ^2 -test. We analyzed the receiver operating characteristic (ROC) curve. The factors affecting the outcomes were studied using multiple linear regression. The sensitivity and specificity of the tested parameters were determined using ROC curves. SPSS 25 was used, and the value of $p < 0.05$ had statistical significance.

3. Result

Characteristics of baseline and blood pressure values of participants following 24-h systolic ARV are reported in Table 1. The allocated medicine diuretics beta-blockers were highly significant in patients with low 24-h systolic ARV. BMI and digoxin as allocated medicine were significantly low in patients with low 24-h systolic ARV. Ambulatory blood pressure monitoring (ABPM), daytime systolic BP, daytime diastolic BP, night-time systolic BP, night-time diastolic BP, 24-hour systolic BP, 24-h diastolic BP were significantly low in patients with low 24-h systolic ARV compared with those with high systolic ARV.

During the follow-up, of 156 subjects included, 107 cardiovascular events occurred; among them 29 (19%) of cardiac death, 18 (12%) of myocardial infarction, 9 (6%) of stroke, and 51 (33%) of hospitalization for worsened heart failure specifically, with an average follow-up of 7.6 ± 3.6 months. There was not anyone who missed a follow-up.

The higher risk of having cardiovascular events in patients with the lowest and highest 24-hours systolic average real variability is reported in Table 2. Myocardial infarction (MI) and Cardiac death were significantly related with blood pressure variability index in low 24-h systolic ARV ((adjusted odd ratio =AOR) AOR= 3.5 (1.1-11.6), $P=0.03$, AOR= 0.3 (0.1-0.8), $P=0.02$; AOR= 3.5 (1.1-11.6), $P=0.03$) respectively.

According to multivariate logistic regression analysis, all unfavorable outcomes were independently related to age, medical history of coronary artery disease and valvular cardiomyopathy, daytime systolic BP, daytime diastolic BP, and 24-hour diastolic BP. The independent variables for negative outcomes were reported in Table 3.

After adjusting for variables related to poor prognosis in subjects with HFrE; (age, EF, daytime SBP, daytime DSP, daytime PP, night-time SBP, night-time DBP, night-time PP, 24-h SBP, 24-h DBP, and 24-h PP), Four independent factors were discovered to be very sensitive and specific for predicting poor outcomes in subjects with HFrE: daytime SBP (sensitivity 88%, specificity

59%: under area curve = 0.794, 95% CI: 0.659-0.928, p =0.003), nighttime SBP (sensitivity 88%, specificity 74%; area under curve = 0.746, 95 % CI: 0.577-0.915, p = 0.013), 24-h SBP (sensitivity 88%, specificity 63%; area under curve = 0.784, 95 % CI: 0.645-0.923, p = 0.004) and 24-h SBP (sensitivity 88%, specificity 55%; area under curve = 0.741, 95 % CI: 0.611-0.872, p = 0.015). The sensitivity and specificity of short-term BPV's prognostic impact as a predictive contributing factor for cardiovascular events were explored by a receiver operating characteristic (ROC) analysis. (Figure 1)

Table1: Baseline characteristics according to 24-hours systolic average real variability ARV

Parameters	Low 24hoursystolic ARV n=78	High 24-hour systolic ARV n=78	P
Gender, n (%)			
Men	58 (74.4)	46 (59)	0.042
Female	20(25.6)	32 (41)	
Age, years Mean ± SD	58 ± 14	62 ± 15	0.822
BMI, kg/m2 Mean ± SD	24 ± 3	25 ± 4	0.019
Ejection Fraction, Mean ± SD	30 ± 6	31 ± 6	0.735
NYHA Class, n (%)			
II	4 (5.1)	14 (17.7)	0.039
III	26 (33.3)	20 (25.6)	
IV	48 (61.5)	44 (56.4)	
Medical history			
Hypertension n (%)	33 (42.3)	46 (59)	0.037
Smoker, n (%)	13 (16.7)	8 (10.3)	0.241
Congestive heart failure, n (%)	14 (17.9)	21 (26.9)	0.179
Diabetes mellitus, n (%)	17 (21.8)	24 (30.8)	0.203
Valvular cardiomyopathy,n (%)	6 (7.7)	7 (9)	0.772
Dilated cardiomyopathy, n (%)	50 (64.1)	37 (47.4)	0.036
Atrial fibrillation, n (%)	23 (29.5)	20 (25.6)	0.591
Coronary artery disease, n (%)	18 (23.1)	27 (34.6)	0.112
Allocated treatment			
Diuretics, n (%)	78 (100)	67 (85.9)	0.000

CAEI, n (%)	52 (66.7)	52 (66.7)	1
Beta-blocker	73 (93.6)	62 (79.5)	0.01
Aspirin, n (%)	23 (29.5)	35 (44.9)	0.047
Statin, n (%)	25 (32.1)	27 (34.6)	0.734
Digoxin, n (%)	23 (29.5)	14 (17.9)	0.090
ABPM			
Daytime SBP, mmHg, M ± SD	110 ± 16	113 ± 18	0.008
Daytime DBP, mmHg, M ± SD	65 ± 6	68 ± 8	0.006
Daytime PP, mmHg, M ± SD	74 ± 10	75 ± 11	0.414
Nighttime SBP, mmHg, M ± SD	110 ± 15	112 ± 15	0.027
Nighttime DBP, mmHg, M ± SD	66 ± 11	67 ± 12	0.010
Nighttime PP, mmHg, M ± SD	71 ± 14	72 ± 14	0.195
24-h SBP, mmHg, M ± SD	110 ± 7	113 ± 9	0.014
24-h DBP, mmHg, M ± SD	66 ± 8	69 ± 10	0.028
24-h PP, mmHg, M ± SD	73 ± 11	74 ± 11	0.791
Dipping, mmHg, M ± SD	1±.49	1±.41	0.047

NYHA: New York Heart Association functional class, BMI: Body mass index, CAEI: Angiotensin-converting enzyme inhibitor, ARV: Average real variability, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, PP: Pulse pressure, M: Mean, SD: Standard deviation.

Table 2: Risks of cardiovascular events (negative outcomes) for the low vs High 24-hours systolic average real variability

	Participants N= (156), %	LSARV	HSARV	AOR	95% CI	P-value
Cardiac death	29 (18.5)	16	13	0.35	0.15-0.84	0.02
MI	18 (11.5)	11	7	3.58	1.10-11.64	0.03
Stoke	9 (5.7)	7	2	0.17	0.03-1.00	0.05
Hospitalization	51(32.6)	27	24	0.89	0.4-1.8	0.76

MI: myocardial infarction, **LSARV:** Low systolic average real variability, **HSARV:** High systolic average real variability **AOR:** Adjusted odds ratio, **CI:** Confidence interval.

We adjusted the blood pressure variability index: daytime systolic blood pressure, daytime diastolic blood pressure, daytime pulse pressure, night-time systolic blood pressure, night-time diastolic blood pressure, night-time pulse pressure, 24-h systolic blood pressure, 24-h diastolic Blood pressure, 24-h pulse pressure.

Table 3: Multiple logistic regression for poor outcomes and cardiac death

Parameters	Negative outcomes		Cardiac death	
	OR (95%CI)	P	OR (95%CI)	P
Gender	1.33 (0.33-5.37)	0.68	0.41 (0.13-1.25)	0.11
Age	1.08 (1.01-1.15)	0.01	0.99 (0.95-1.04)	0.92
Hypertension	2.41 (0.68-8.46)	0.17	2.32 (0.78-6.92)	0.12
EF	1.07 (0.96-1.19)	0.21	1.00 (0.91-1.09)	0.99
Smoking	0.76 (0.23-2.44)	0.64	0.58 (0.09-3.42)	0.52
Body mass index	1.06 (0.87-1.31)	0.52	0.98 (0.85-1.11)	0.76
Dilated cardiomyopathy	1.45 (0.52-4.04)	0.47	0.43 (0.11-1.71)	0.23
Coronary artery disease	0.34 (0.12-0.98)	0.04	0.41 (0.09-1.84)	0.24
Diabetes mellitus	1.43 (0.56-3.60)	0.44	1.70 (0.53-5.40)	0.36
Congestive heart failure	0.93 (0.29-2.97)	0.91	1.78 (0.39-8.06)	0.45
Valvular cardiomyopathy	0.08 (0.09-0.82)	0.03	0.13 (0.01-1.42)	0.09
Beta-blocker	1.11 (0.92-1.85)	0.93	0.78 (0.17-3.51)	0.75
Aspirin	2.32 (0.62-8.64)	0.20	0.51 (0.12-2.14)	0.63
Diuretics	0.31 (0.03-2.69)	0.29	0.79 (0.19-3.19)	0.74
ACEI	2.46 (0.60-9.99)	0.20	1.72 (0.42-6.95)	0.44
Daytime SBP	0.92 (0.77-1.09)	0.35	1.25 (1.04-1.49)	0.01
Daytime DBP	1.10 (1.02-1.20)	0.01	1.07 (1.00-1.14)	0.04
Nighttime SBP	0.97 (0.94-1.02)	0.30	0.99 (0.89-1.11)	0.98
Nighttime DBP	0.95 (0.89-1.03)	0.24	1.02 (0.85-1.22)	0.80
24-hour SBP	1.99 (0.94-1.06)	0.96	0.95 (0.81-1.10)	0.52
24-hour DBP	1.10 (0.99-1.21)	0.06	1.12 (1.02-1.22)	0.01

Poor outcomes combined with cardiac death, myocardial infarction, stroke and hospitalization. EF: Ejection fraction, AOR: Adjusted odds ratio, CI: Confidence interval, ACEI: Angiotensin-converting enzyme inhibitors, SBP: Systolic blood pressure, DBP: diastolic blood pressure

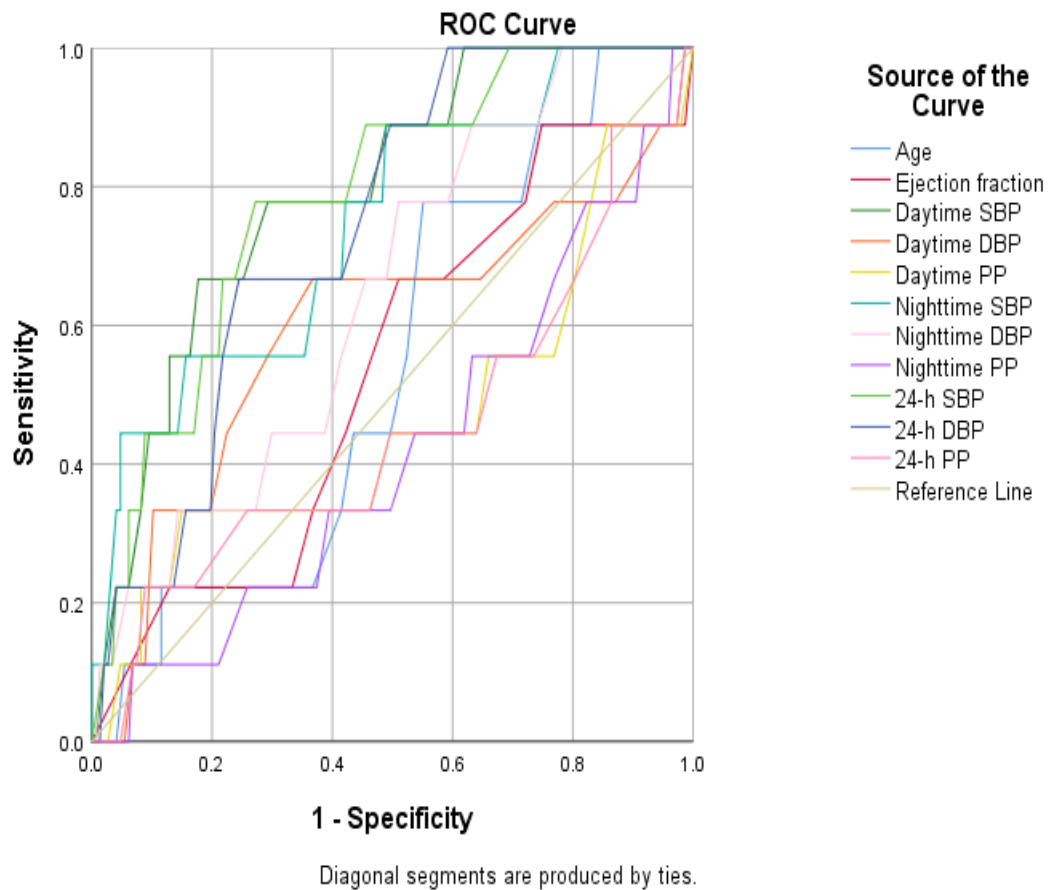


Figure 1: A receiver operating characteristic study determines the prognostic significance of short-term blood pressure variability in patients with endpoints. EF: ejection fraction, daytime SBP: daytime systolic blood pressure, daytime DBP: Daytime diastolic Blood pressure, daytime PP: daytime pulse pressure, night-time SBP: Night-time systolic blood pressure, night-time DBP: Night-time diastolic Blood pressure, night-time PP: night-time pulse pressure, 24-h SBP:24-h systolic blood pressure, 24-h DBP: 24-h diastolic Blood pressure, 24-h PP: 24-h pulse pressure.

4. Discussion

The current study sheds significant light on the prognosis impact of short-term BP Variability and its effect on HFrEF patients. This research reports that low ARV of 24-hour systolic BP is related to greater chronic heart failure (HFrEF) patients, regardless of risk markers. Daytime SBP variability, daytime DBP variability, night-time SBP variability, 24-h SBP and 24-h DBP variability were independently related to negative outcomes of HFrEF patients.

The investigations were undertaken to ascertain the impacts of ambulatory BP fluctuation variability in HF patients with reduced EF (Gibelin, Spillner, Bonnan, & Chevallier, 2003) (Berry et al., 2016). Gilberl in et al. (Gibelin et al., 2003) discovered that 154 individuals with

chronic HF had a worsening prognosis of low BP variability followed up for an average of 565±215 days. The results were confirmed by Berry et al. (Berry et al., 2016); their study showed that low daytime BP variability was linked to the prognosis in systolic heart failure patients, which was confirmed by large recruitment after following up an average of 4.4 years. Our study confirms the results after assessing the impact of BP variability in 156 subjects followed up for mean of 7.6 months. In our study low BP variability was in the daytime systolic BP, night-time systolic BP, 24-hour systolic BP and 24-hour Diastolic BP. Thus, in contrast to earlier research on the predictive significance of BP variability in hypertension, we have revealed a counterintuitive prognostic effect of blood pressure fluctuation in HF with reduced EF for the occurrence of cardiac death, myocardial infarction, stroke and hospitalization.

4.1 Factors influencing BPV in CHF

Low BPV in subjects with Congestive HF is elaborated. Radaelli et al. (Radaelli et al., 1999) found a change in BPV in nine subjects with congestive HF during vigorous activity, with the variability ranging from BP 15 to 41 mmHg in subjects with congestive HF and control healthy controls (Cowburn, Cleland, Coats, & Komajda, 1998). The unsolved question is: What causes the reduction of BPV in CHF processes? Although blood pressure components such as systemic vascular resistance or cardiac output are well defined in CHF patients, the mechanism that causes their fluctuations are incompletely clear.

Intrinsic elements such as baroreflex sensitivity (Lanfranchi & Somers, 2002), autonomic nervous system integrity (Grassi, Bombelli, Seravalle, Dell'Oro, & Quarti-Trevano, 2010), circadian hormonal secretion, myocardial contractile reserve, and pre-load volume (Giles, Roffidal, Quiroz, Sander, & Tresznewsky, 1996) are possible routes that might contribute to BPV. Additionally, the aggregate of reactions to external pressor stimuli, spontaneously and regulatory variations due to central nervous system influences, mechanical forces created by breathing, and impacts of humoral and local vasomotor processes determine daily BP variation involved in BPV in systolic CHF patients (L. J. Mena, Felix, Melgarejo, & Maestre, 2017).

4.2 BPV prognostic Paradox

Over the last decades, many investigations have denoted that the typical risk factors for cardiovascular disease have become favorable prognostic indicators for CHF patients. In a CHF population, high blood pressure, hypercholesterolemia, and a high BMI are all connected to survival (Berry et al., 2016). Furthermore, BPV is required for survival in various complex physiologic adaptive systems (Lanfranchi & Somers, 2002); a greater level of BPV worsens the prognosis of patients with hypertension (Chen, 2008), while a low amount worsens the CHF prognosis. On the contrary, another paradigm in CHF and BPV must be regarded as part of the epidemiological reversal of traditional risk factors for CHF (Kalantar-Zadeh, Block, Horwich, & Fonarow, 2004).

4.3 Limitation

Although this was single retrospective cohort research with a short median follow-up, it is impossible to exclude measurement mistakes caused by technical difficulties such as the size of

the cuff or the position of the cuff displacement, which may occur in certain individuals. The monitoring device records the pressure measurements gathered, which should be done by the calibrator often before and during the study using a mercury sphygmomanometer to make sure that the information acquired is accurate. Prospective studies are required to corroborate these findings.

5. Conclusion

Low ARV of 24-hour systolic BP may be linked to the cardiovascular risk indicators daytime systolic BP variability, night-time systolic BP variability, 24-h systolic BP variability, and 24-h diastolic BP variability with HF with reduced EF patients.

Abbreviations

ABPM: Ambulatory blood pressure monitoring
AOR: Adjusted odds ratio
AM: Ante meridiem
ARV: average real variability
BMI: Body mass index
BBP: systolic blood pressure
BP: Blood pressure
BPV: Blood pressure variability
CAEI: Angiotensin-converting enzyme inhibitors
CHF: chronic heart failure
CI: Confidence interval
DBP: diastolic blood pressure
EF: Ejection fraction
HF: heart failure
HFrEF: heart failure with reduced ejection fraction
HSARV: High systolic Average real variability
LSARV: Low systolic Average real variability
LUSH: Lanzhou University second hospital
mmHg: Millimeters of mercury
M: Mean
MI: Myocardial infarction
NYHA: New York Heart Association functional class
OR: Odds ratio
PM: Post meridiem
PP: pulse pressure
ROC: receiver operating characteristic curve
SD: standard deviation

SPSS: Statistical Package for the Social Sciences

Conflict of Interest

The author stated that they have no competing interests.

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