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Prediction of atrial fibrillation in patients with hypertension: A comprehensive comparison of office and ambulatory blood pressure measurements

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Abstract

Hypertension is associated with the development of atrial fibrillation (AF). Evidence has shown that reverse dipping pattern, an abnormal increase of night-time blood pressure (BP) comparing to daytime BP, is associated with cardiovascular events. However, the relationship between diurnal changes in BP and AF has not been sufficiently explored. This paper aims to cross-sectionally explore the relationship between AF and ambulatory BP parameters, especially reverse dippers to the others, and further longitudinally analyze how BP patterns are associated to the risk of developing new-onset AF. Between February 2012 and March 2021, five out of 412 patients were identified of AF at baseline; four were reverse dippers (3.7%) and one was from the others (.3%). Cross-sectionally, the multivariate logistic regression analysis showed that reverse dippers were significantly more likely to have AF (odds ratio: 12.39, $p = .030$). After excluding patients with baseline AF, during the mean follow-up of 4.6 ± 3.0 years, seven patients developed AF. Longitudinally, the multivariate Cox regression analysis revealed that 24-h systolic BP (hazard ratio per 10 mmHg: 2.12, $p = .015$), night-time systolic BP (hazard ratio per 10 mmHg: 2.27, $p = .002$), and presentation of reverse dipping (hazard ratio: 5.25, $p = .042$) were independently associated with new-onset AF. None of the office BP measurements were associated with new-onset AF. While ambulatory BP measurements were better predictors for the incidence of AF, careful management is necessary for reverse dippers as they are at high risk of developing AF.

KEYWORDS
ambulatory blood pressure, atrial fibrillation, blood pressure, hypertension, reverse dipping

1 | INTRODUCTION

Atrial fibrillation (AF) is one of the most perturbed arrhythmias associated with increased risks of stroke and mortality.[1,2] A recent meta-analysis of 12 cohorts identified independent risk factors associated with the development of AF, and hypertension contributed the highest risk ratio (1.46) among the modifiable risk factors.[3]

Traditionally, hypertension is determined by office blood pressure (BP). However, many studies have shown the ambulatory BP measurement to be superior.[4–6] Daytime, night-time, 24-h, and diurnal BP can be measured ambulatorily, and current studies have shown evidence that the former three measurements might predict AF.[5,6] However, diurnal changes were omitted in the previous studies.

Diurnal BP shows the difference between daytime and night-time BP, and normal individuals, named "dippers" in this context, present with a nocturnal pressure drop of more than 10%.[7] "Non-dippers" refers to those who have a nocturnal pressure drop of less than 10%, whereas those with an increase in nocturnal pressure are called "reverse dippers." A reverse dipping pattern could predict stroke, cardiovascular events, and all-cause mortality.[8,9] Although both non-dipping and reverse dipping pattern were correlated with cardiovascular events, only the latter pattern was independently related with cardiovascular events after controlling other risk factors.[10]

To the best of our knowledge, only one study in 2008 identified that non-dippers had a higher risk of developing AF; however, the study did not compare the risk of development of AF with reverse dippers and other BP measurements.[11] A comprehensive comparison of different BP measurements and their predictiveness of AF is required to elucidate the mechanisms of the relationship between hypertension and AF.

This study aimed to cross-sectionally and longitudinally compare office and ambulatory BP measurements and test the risk of AF in patients with reverse dipping patterns. This study may facilitate the identification of patients at risk of AF, monitor hypertension treatment results, and suggest more aggressive treatments to prevent AF.

2 | METHOD

2.1 | Study population

Our study, conducted between February 2012 and March 2021, included patients with hypertension. The inclusion criteria were as follows: patients aged ≥20 years; those willing and capable of providing informed consent; those of Han Chinese descent; those who were official residents in Taiwan; those meeting one of the following hypertension criteria: (a) systolic BP (SBP) ≥140 mmHg or diastolic BP (DBP) ≥90 mmHg in at least two consecutive visits within 2 months or (b) intake of one or more antihypertensive medications; those with no medical history of severe diseases, including liver, renal, cardiac, and pulmonary failure and carcinoma; those without acute disease within 2 weeks; and those without secondary hypertension. Secondary hypertension was excluded by a series of examinations including blood chemistry tests, abdominal sonogram, and/or computed tomography, and/or magnetic resonance imaging, etc., to rule out chronic kidney disease, renal artery stenosis, endocrinopathy, and coarctation of aorta.

2.2 | Study design

This study is divided into two parts: cross-sectional analysis of the BP patterns of recruited hypertensive patients and their relationship of baseline AF, and longitudinal analysis of the BP patterns of those recruited without baseline AF and the risk of new-onset AF. The study included a comprehensive evaluation of each participant's medical history and physical examination at the hypertension clinic of the hospital. Geographical characteristics were measured on enrollment as baseline profile, including age, sex, body mass index (BMI), presence of diabetes mellitus, smoking, SBP and DBP in office and ambulatory settings, lipid profile, renal function, and uric acid, renin, and aldosterone levels. Antihypertensive drug prescriptions, including angiotensin-converting enzyme inhibitor (ACEI), angiotensin II receptor antagonist (ARB), B-blocker, calcium channel blocker (CCB), and thiazide diuretics, were recorded once they were present. The patients underwent regular follow up at the outpatient clinic every 3 months.

The study protocol was approved by the Ethics Committee of Taipei Veterans General Hospital (2011-10-007IB). All participants agreed to participate after being informed of the nature and purpose of the study. This study was conducted in accordance with the principles of the Declaration of Helsinki.

2.3 | BP measurement

Office BP was measured according to a standardized protocol by a trained nurse with an electronic BP monitor (Omron HEM-7121, Omron Healthcare Taiwan Co., Songshan, Taipei, Taiwan, ROC; Importation of Medical Device License 026021 by Ministry of Health and Welfare) in the morning after the participants had been instructed to sit for 10 min in a quiet room. Three consecutive BP measurements were obtained from the same upper arm, with each measurement taken at 30-s intervals.

Patients were connected to an ambulatory BP monitoring device between 08:00 h and 10:00 h (WatchBP O3 ambulatory BP monitor, Microlife Corp., Neihu, Taipei, Taiwan, ROC; Medical Device License 004574 by Ministry of Health and Welfare). The device was programmed to record the BP every 15 min between 06:00 h and 22:00 h (daytime BP) and every 30 min from 22:00 h to 06:00 h (night-time BP). The average of all the SBP/DBP readings was the 24-h SBP/DBP, and the daytime and night-time average SBP/DBP were also calculated. Normal dipping pattern presents nocturnal BP fall between 10% and 20%.[12] Patients were classified as extreme dippers (nocturnal BP

fall ≥ 20%), dippers (≥10%–<20%), non-dippers (≥0%–<10%), and reverse dippers (nocturnal BP increase > 0%).[8]

2.4 | Event definition

All patients underwent 12-lead electrocardiogram at baseline and follow-up period. If AF symptoms and/or signs were identified, further Holter monitoring was performed. Electrocardiogram and Holter findings were interpreted by a cardiologist, and new-onset AF was documented if the results presented irregular R-R intervals, absence of distinct repeating P waves, and irregular atrial activity. The diagnosis of AF was in accordance with the American College of Cardiology/American Heart Association guidelines for AF management.[13]

2.5 | Statistical methods

Participant characteristics were summarized using descriptive statistics. Quantitative variables are expressed as mean ± standard deviation, and categorical variables are expressed as frequencies (percentages). Parametric continuous data between different groups were compared using the Student's *t*-test. Nonparametric data between different groups were compared using the Mann–Whitney test. Categorical variables were analyzed using the chi-square test or Fisher's exact test.

In the first part of the study, we performed cross-sectional analysis of patients on recruitment. The baseline characteristics in patients with and without AF at baseline were compared. Logistic regression was utilized to compare the risk of AF and different BP parameters. Univariate and multivariate analysis were done with SBP and DBP by office, 24-h, daytime, night-time, and reverse dipping pattern, whereas the latter one was done by adjusting age, male, BMI, smoking, ACEI/ARB, B-blocker, CCB, thiazide, and baseline estimated glomerular filtration rate (eGFR).

In the second part of the study, we performed longitudinal analysis of new-onset AF in patients without AF on recruitment. The baseline characteristics were analyzed in patients without AF at baseline. AF-free survival was assessed using the Kaplan–Meier curve, with significance determined based on the log-rank test findings. Reverse dippers were first compared with others, and further analysis was performed to compare reverse dippers to extreme dippers, dippers, and non-dippers. Cox proportional hazard regression analysis was performed to assess the independent effects of BP parameters and the risk of new-onset AF. The adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated after adjusting for potential confounding factors, including age, male, BMI, smoking, ACEI/ARB, B-blocker, CCB, thiazide, and baseline eGFR.

Statistical significance was defined as a two-sided *p*-value < .05. Statistical analysis was performed using the SPSS software (Version 21.0, SPSS Inc., Chicago, IL, USA).

3 | RESULTS

3.1 | Cross-sectional analysis of 412 patients on recruitment

The mean age of the 412 patients was 61.8 years, and 58% of them were male. Approximately 11.4% of the patients had diabetes mellitus, and 5.1% smoked cigarettes. When categorizing reverse dippers (n = 107), SBP by daytime (121.9 ± 10.3 mmHg vs. 124.6 ± 12.0 mmHg, p = .030) and night-time (125.9 ± 12.0 mmHg vs. 114.6 ± 12.1 mmHg, p < .001) and DBP by night-time (75.3 ± 9.1 mmHg vs. 67.6 ± 8.8 mmHg, p < .001) showed significant differences from the others (n = 305), whereas office BP exhibited no significant difference. We observed a significant between-group difference in terms of the use of thiazides (28.0% vs. 15.7%, p = .005) and eGFR (82.4 ± 17.1 ml/min/1.73 m^2 vs. 87.6 ± 19.8 ml/min/1.73 m^2, p = .009) but no significant difference in terms of other demographical characteristics such as age, diabetes mellitus, smoking, lipid profiles, and electrolytes. Five out of 412 patients (1.2%) were identified of AF during screening, and four of them were reverse dippers (3.7%) and one was from the others (.3%). Details of the geographical characteristics are shown in Table 1.

When comparing different BP measurements with risk of AF, univariate analysis by logistic regression showed that reverse dippers had significantly higher risk of underlying AF (odds ratio: 11.81, 95% CI: 1.30–106.83, p = .028). After adjusting age, male, BMI, smoking, antihypertensive drugs, and baseline eGFR, multivariate analysis showed that reverse dippers were significantly more likely to have AF (odds ratio: 12.39, 95% CI: 1.28–119.65, p = .030). Details of the univariate and multivariate analysis are shown in Table 2.

3.2 | Longitudinal analysis of 407 patients without AF on recruitment

After excluding five patients with underlying AF, all profile remained similar to the one with all patients mentioned in Table 1. The mean age of the 407 patients was 61.6 years, and 58% of them were male. The significant differences between reverse dippers (n = 103) and the others (n = 304) were noted in BP measurements of SBP by daytime (121.9 ± 10.2 mmHg vs. 124.7 ± 11.9 mmHg, p = .024) and night-time (125.9 ± 11.8 mmHg vs. 114.6 ± 12.1 mmHg, p < .001) and DBP by night-time (75.4 ± 9.1 mmHg vs. 67.6 ± 8.8 mmHg, p < .001), the use of thiazides (27.2% vs. 15.8%, p = .010), and baseline eGFR (82.7 ± 17.3 ml/min/1.73 m^2 vs. 87.7 ± 19.9 ml/min/1.73 m^2, p = .016). No significant difference was noted in age, diabetes mellitus, smoking, lipid profiles, electrolytes, and follow-up duration. Details of the geographical characteristics are shown in Table 3.

During the mean follow-up of 4.6 ± 3.0 years, 59 patients received Holter exams due to symptoms and/or signs. Of all patients without AF at baseline screening, four patients were diagnosed of AF via Holter exam, and the other three were diagnosed via 12-lead

TABLE 1 Baseline geographical characteristics in all patients ($n = 412$)

	All ($n = 412$)	Reverse dipper ($n = 107$)	Others ($n = 305$)	p-value
Age, years	61.8 ± 14.2	62.8 ± 14.5	61.5 ± 14.1	.433
Male, *n*(%)	239 (58.0%)	66 (61.7%)	173 (56.7%)	.371
BMI, kg/m^2	26.1 ± 3.8	26.6 ± 4.2	25.9 ± 3.6	.118
DM, *n*(%)	47 (11.4%)	13 (12.1%)	34 (11.1%)	.779
Smoking, *n*(%)	21 (5.1%)	5 (4.7%)	16 (5.2%)	.817
BP parameters				
Office SBP, mmHg	131.9 ± 16.9	129.7 ± 17.2	132.6 ± 16.7	.120
Office DBP, mmHg	81.8 ± 10.5	81.0 ± 12.2	82.0 ± 9.9	.394
24-h SBP, mmHg	121.9 ± 11.3	123.3 ± 10.5	121.4 ± 11.5	.112
24-h DBP, mmHg	73.1 ± 8.2	74.3 ± 8.7	72.7 ± 8.1	.103
Daytime SBP, mmHg	123.9 ± 11.6	121.9 ± 10.3	124.6 ± 12.0	.030
Daytime DBP, mmHg	74.7 ± 8.4	73.7 ± 8.7	75.1 ± 8.3	.156
Nighttime SBP, mmHg	117.5 ± 13.1	125.9 ± 12.0	114.6 ± 12.1	<.001
Nighttime DBP, mmHg	69.6 ± 9.5	75.3 ± 9.1	67.6 ± 8.8	<.001
Diurnal changes of SBP, %	5.0 ± 7.3	−3.3 ± 5.1	8.0 ± 5.5	<.001
Diurnal changes of DBP, %	6.8 ± 8.3	−2.3 ± 5.3	10.0 ± 6.6	<.001
Antihypertensive drugs				
ACEI/ARB, *n*(%)	273 (66.3%)	77 (72.0%)	196 (64.3%)	.147
Beta-blocker, *n*(%)	101 (24.5%)	31 (29.0%)	70 (23.0%)	.213
CCB, *n*(%)	304 (73.8%)	75 (70.1%)	229 (75.1%)	.313
Thiazide, *n*(%)	78 (18.9%)	30 (28.0%)	48 (15.7%)	.005
Laboratory data				
Cholesterol, mg/dL	184.0 ± 31.1	181.0 ± 31.9	185.1 ± 30.9	.257
Triglyceride, mg/dL	130.5 ± 90.5	122.9 ± 83.3	133.2 ± 92.9	.288
HDL-C, mg/dL	48.7 ± 13.1	46.9 ± 12.0	49.3 ± 13.5	.088
LDL-C, mg/dL	111.8 ± 27.2	111.6 ± 27.2	111.9 ± 27.3	.913
Creatinine, mg/dL	.9 ± .2	.9 ± .3	.8 ± .2	.038
eGFR, ml/min/1.73 m^2	86.3 ± 19.3	82.4 ± 17.1	87.6 ± 19.8	.009
Sodium, mmol/L	140.9 ± 2.5	140.8 ± 2.9	141.0 ± 2.3	.476
Potassium, mmol/L	3.9 ± .7	3.9 ± .5	3.9 ± .7	.947
Uric acid, mg/dL	6.1 ± 1.5	6.2 ± 1.5	6.0 ± 1.5	.271
Renin, pg/mL	47.4 ± 183.3	37.2 ± 51.0	51.0 ± 210.7	.299
Aldosterone, pg/mL	125.0 ± 73.3	120.5 ± 76.7	126.6 ± 72.1	.479
Baseline AF, *n*(%)	5 (1.2%)	4 (3.7%)	1 (.3%)	.017

Abbreviations: ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; AF, atrial fibrillation; BMI, body mass index; CCB, calcium channel blockers; DBP, diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

electrocardiogram. The incidence rate of new-onset AF in reverse dippers was 3.9% (four events/103 participants), and that in others was 1.0% (three events/304 participants). In the Kaplan–Meier survival curves of AF-free duration for reverse dippers and the others (Figure 1), the difference was significant (log-rank test, $p = .050$). There was no significant difference between the three survival curves when those other than dippers were further subdivided as extreme dippers, dippers, and non-dippers.

Univariate analysis showed that 24-h SBP (HR per 10 mmHg: 2.11, 95% CI: 1.24–3.59, $p = .006$), daytime SBP (HR per 10 mmHg: 1.81, 95% CI: 1.06–3.10, $p = .031$), and night-time SBP (HR per 10 mmHg: 2.07, 95% CI: 1.36–3.17, $p = .001$) were associated with new-onset AF.

TABLE 2 Risk of baseline atrial fibrillation in all patients ($n = 412$)

	Univariate analysis			Multivariate analysis		
	OR	(95% CI)	*p*-value	OR	(95% CI)	*p*-value
Office SBP, 10 mmHg	.77	(.45–1.33)	.354	.56	(.30–1.07)	.078
Office DBP, 10 mmHg	.76	(.32–1.79)	.527	.98	(.36–2.65)	.965
24-h SBP, 10 mmHg	.74	(.32–1.72)	.482	.63	(.26–1.53)	.305
24-h DBP, 10 mmHg	.49	(.15–1.54)	.219	.82	(.21–3.23)	.776
Daytime SBP, 10 mmHg	.60	(.26–1.39)	.235	.52	(.21–1.29)	.158
Daytime DBP, 10 mmHg	.36	(.11–1.14)	.083	.51	(.13–2.06)	.347
Night-time SBP, 10 mmHg	1.11	(.59–2.11)	.742	.98	(.50–1.92)	.951
Night-time DBP, 10 mmHg	1.03	(.41–2.60)	.955	1.70	(.63–4.56)	.294
Reverse dipper (yes vs. no)	11.81	(1.30–106.83)	.028	12.39	(1.28–119.65)	.030

Note: Multivariate analysis: adjusted for age, male, body mass index, smoking, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, B-blocker, calcium channel blockers, thiazide, and baseline estimated glomerular filtration rate.
Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; OR, odds ratio; SBP, systolic blood pressure.

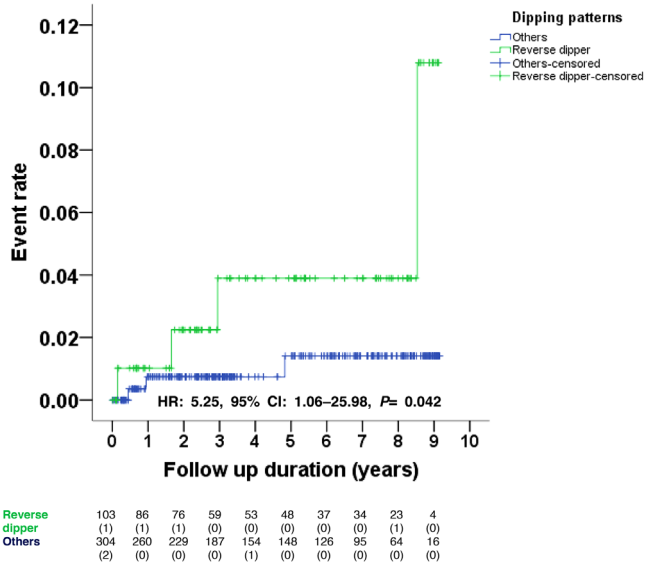

FIGURE 1 Kaplan–Meier curves of the risk of new-onset atrial fibrillation (AF) according to the dipping patterns in patients with hypertension. All participants were divided into two groups according to the dipping patterns. The green line represents the patient group with reverse dippers. The blue line represents the patient group without reverse dippers. The differences were compared using the log-rank test ($p = .042$)

Reverse dipping patterns was not significantly associated with new-onset AF in univariate analysis (HR: 3.98, 95% CI: .89–17.8, $p = .070$) (Table 4). When adjusting baseline characteristics in the multivariate Cox regression analysis, 24-h SBP (HR per 10 mmHg: 2.12, 95% CI: 1.16–3.87, $p = .015$), night-time SBP (HR per 10 mmHg: 2.27, 95% CI: 1.35–3.83, $p = .002$), and reverse dipping patterns (HR: 5.25, 95% CI: 1.06–25.98, $p = .042$) were independently associated with new-onset AF. Neither office SBP nor office DBP was significant in either analysis (Table 4).

4 | DISCUSSION

This study comprehensively compared office and ambulatory BP measurements to predict AF events. The main results of the study showed that ambulatory BP measurement (24-h SBP and night-time SBP) was superior to office BP in predicting the development of AF. In addition, patients with reverse dipping patterns had a higher risk of developing AF when compared with their counterparts.

4.1 | Office and ambulatory BP measurements

Hypertension is a public concern due to the risk of cardiovascular diseases, and office BP is measured in most practices. However, the one-off measurement might raise concerns of white coat hypertension or masked uncontrolled hypertension.[14] Ambulatory BP measurements are more reliable for predicting cardiovascular events,[4–6] and some guidelines have emphasized the monitoring of ambulatory BP as an important modality to manage hypertension.[15–18] Many studies have shown that 24-h SBP is more accurate in predicting cardiovascular events than office SBP.[19–21] There is increasing evidence that night-time BP is an independent predictor of cardiovascular events.[22,23] It might be vital to identify patients with masked nocturnal hypertension by monitoring ambulatory BP because their risk of developing cardiovascular disease was higher than that of hypertensive patients with controlled BP.[22] In addition, ambulatory BP monitoring can identify the dipping patterns in patients. The reverse dipping pattern has been shown to be associated with a higher risk of developing cardiovascular diseases.[24] Previous studies and this study contributes additional evidence to prove the ability of dipping patterns in predicting AF.[11] Therefore, it is important to use ambulatory BP measurements to identify masked uncontrolled hypertension, night-time hypertension, and reverse dippers.

TABLE 3 Baseline geographical characteristics of patients without AF ($n = 407$)

	All ($n = 407$)	Reverse dipper ($n = 103$)	Others ($n = 304$)	p-value
Age, years	61.6 ± 14.2	62.1 ± 14.4	61.5 ± 14.1	.685
Male, *n*(%)	236 (58.0%)	63 (61.2%)	173 (56.9%)	.449
BMI, kg/m^2	26.1 ± 3.8	26.6 ± 4.2	25.9 ± 3.6	.131
DM, *n*(%)	47 (11.5%)	13 (12.6%)	34 (11.2%)	.693
Smoking, *n*(%)	21 (5.2%)	5 (4.9%)	16 (5.3%)	.887
BP parameters				
Office SBP, mmHg	132.0 ± 16.9	129.6 ± 17.4	132.8 ± 16.6	.110
Office DBP, mmHg	81.8 ± 10.6	81.1 ± 12.4	82.0 ± 9.9	.434
24-h SBP, mmHg	121.9 ± 11.2	123.3 ± 10.4	121.5 ± 11.4	.137
24-h DBP, mmHg	73.2 ± 8.2	74.4 ± 8.7	72.7 ± 8.0	.084
Daytime SBP, mmHg	124.0 ± 11.6	121.9 ± 10.2	124.7 ± 11.9	.024
Daytime DBP, mmHg	74.8 ± 8.4	73.9 ± 8.7	75.1 ± 8.3	.204
Night-time SBP, mmHg	117.5 ± 13.0	125.9 ± 11.8	114.6 ± 12.1	<.001
Night-time DBP, mmHg	69.6 ± 9.5	75.4 ± 9.1	67.6 ± 8.8	<.001
Diurnal changes of SBP, %	5.1 ± 7.3	−3.3 ± 5.1	8.0 ± 5.5	<.001
Diurnal changes of DBP, %	6.9 ± 8.3	−2.2 ± 5.3	10.0 ± 6.6	<.001
Antihypertensive drugs				
ACEI/ARB, *n*(%)	270 (66.3%)	74 (71.8%)	196 (64.5%)	.171
Beta-blocker, *n*(%)	100 (24.6%)	31 (30.1%)	69 (22.7%)	.132
CCB, *n*(%)	300 (73.7%)	72 (69.9%)	228 (75.0%)	.310
Thiazide, *n*(%)	76 (18.7%)	28 (27.2%)	48 (15.8%)	.010
Laboratory data				
Cholesterol, mg/dL	184.1 ± 31.0	181.7 ± 31.8	184.9 ± 30.8	.373
Triglyceride, mg/dL	130.4 ± 90.8	123.0 ± 84.3	132.9 ± 92.9	.319
HDL-C, mg/dL	48.7 ± 13.2	46.9 ± 11.9	49.3 ± 13.5	.093
LDL-C, mg/dL	112.1 ± 27.2	112.2 ± 27.2	112.0 ± 27.3	.972
Creatinine, mg/dL	.9 ± .2	.9 ± .3	.8 ± .2	.054
eGFR, ml/min/1.73 m^2	86.4 ± 19.3	82.7 ± 17.3	87.7 ± 19.9	.016
Sodium, mmol/L	140.9 ± 2.4	140.7 ± 2.8	141.0 ± 2.3	.458
Potassium, mmol/L	3.9 ± .7	3.9 ± .5	3.9 ± .7	.989
Uric acid, mg/dL	6.1 ± 1.5	6.2 ± 1.5	6.0 ± 1.5	.325
Renin, pg/mL	47.6 ± 184.4	37.1 ± 51.0	51.0 ± 211.1	.299
Aldosterone, pg/mL	125.0 ± 73.6	121.1 ± 77.9	126.4 ± 72.2	.551
Follow-up duration, years	4.6 ± 3.0	4.6 ± 3.0	4.7 ± 3.0	.766

Abbreviations: ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; BMI, body mass index; CCB, calcium channel blockers; DBP, diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

4.2 | Comparison with previous studies

Although our study had a shorter follow-up duration (4.6 years) compared with previous studies (6.1–16.4 years), some results regarding office and ambulatory BP parameters for AF prediction were similar (Table 5). In previous studies, the 24-h SBP was significantly related to higher HR for the development of AF (HR between 1.09 and 1.42),[4–6,11,25,26] whereas a higher value (HR: 2.12) was seen in our study. However, the predictive value of daytime SBP is controversial. Although three studies concluded a significantly higher HR ($p < .05$),[4–6] another study and our study do not support this argument.[25] On the other hand, night-time SBP might be a better

TABLE 4 Risk of new-onset atrial fibrillation in patients without atrial fibrillation ($n = 407$)

	Univariate analysis			Multivariate analysis		
	HR	(95% CI)	*p*-Value	HR	(95% CI)	*p*-Value
Office SBP, 10 mmHg	1.38	(.92–2.07)	.118	1.36	(.85–2.19)	.205
Office DBP, 10 mmHg	1.12	(.55–2.25)	.759	1.16	(.56–2.39)	.688
24-h SBP, 10 mmHg	2.11	(1.24–3.59)	.006	2.12	(1.16–3.87)	.015
24-h DBP, 10 mmHg	1.14	(.46–2.82)	.781	1.82	(.57–5.86)	.312
Daytime SBP, 10 mmHg	1.81	(1.06–3.10)	.031	1.77	(.99–3.16)	.053
Daytime DBP, 10 mmHg	.86	(.35–2.14)	.745	1.08	(.32–3.67)	.904
Night-time SBP, 10 mmHg	2.07	(1.36–3.17)	.001	2.27	(1.35–3.83)	.002
Night-time DBP, 10 mmHg	1.54	(.72–3.32)	.268	2.46	(.93–6.51)	.070
Reverse dipper (yes vs. no)	3.98	(.89–17.8)	.070	5.25	(1.06–25.98)	.042

Note: Multivariate analysis: adjusted for age, male, body mass index, smoking, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, B-blocker, calcium channel blockers, thiazide, and baseline estimated glomerular filtration rate.
Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; HR, hazard ratio; SBP, systolic blood pressure.

predictor of AF events (HR: 1.07–1.42, $p < .05$) in other studies and our study (HR: 2.27, $p = .002$).[4–6,25] Office SBP was not significant in previous studies and our study.[4–6] However, most studies did not analyze diurnal changes in BP, except for one study in 2008.[11]

In terms of dipping patterns and the incidence of AF, the study in 2008 divided patients into dippers and non-dippers.[11] Their results of AF-free duration of non-dippers were similar to that of our reverse dippers, approximately 90% at the eighth year of follow-up. On the other hand, our study showed a higher HR (HR: 5.25, 95% CI: 1.06–25.98, $p = .042$) in reverse dippers (Table 4) than in non-dippers (HR: 2.02, 95% CI: 1.08–3.79, $p = .028$) in their study (comparison see Table 5). However, their study did not compare diurnal patterns to other ambulatory BP measurements.[11]

4.3 | Pathophysiology of reverse dipping pattern

The pathophysiology of reverse dipping pattern is yet not fully understood. Regarding dipping pattern, relationship between the nocturnal BP drop and the decrease of sympathetic nerve activity is generally acknowledged, supported by the observation of decrease levels of norepinephrine and epinephrine during night-time,[12] and the discovery of baroreflex reset during nighttime.[27] Therefore, one of the proposed pathophysiology of reverse dipping pattern was related to abnormal sympathetic abnormality at night, and one study reassured this hypothesis by assessing muscle sympathetic nerve traffic.[28] Another hypothesis was the impaired renal capacity to excrete sodium.[29] Due to decreased daytime sodium excretion, an increase of night-time BP may facilitate pressure-natriuresis mechanism to achieve sodium balance.[30] However, these hypotheses of pathophysiology could not explain the relationship between reverse dipping pattern and AF.

4.4 | Possible mechanisms from reverse dipping to AF

The contribution of hypertension to AF has been widely discussed; however, the mechanism by which reverse dipping pattern results in AF is not well understood. Normally, diurnal changes serve as a compensatory activity to generate lower BP compared with daytime BP.[31] However, reverse dippers suffer from contrary effects with higher BP overnight, and this induces a higher risk of left ventricular hypertrophy and left atrial diastolic dysfunction.[32,33] Left ventricular hypertrophy induces sympathetic overactivity and provokes the renin-angiotensin-aldosterone system, both increasing left atrial and ventricular filling pressures, which exacerbate pre-existing left ventricular hypertrophy and left atrial diastolic dysfunction.[34] Consequently, adverse cardiac remodeling and left atrial and ventricular dysfunction increase the arrhythmic burden toward AF.[35,36]

As left ventricular hypertrophy and diastolic dysfunction could worsen in reverse dippers, these cardiopathies could increase left atrial strain, fibrosis, and dilation.[36,37] Left atrial fibrosis and dilation might lead to atrial ischemia and electrical remodeling, and many studies have shown that an increase in maximum P wave conduction time and P dispersion was observed in non-dippers.[38–40] It was demonstrated that atrial electromechanical delays were significantly prolonged in patients with AF,[41] and non-dippers tended to have prolonged atrial electrophysiologic activity and might develop into AF in the subsequent years.[38,39]

The reverse dipping pattern is adversely associated with sleep quality and time.[42] Some studies discovered that a reverse dipping pattern was more likely to be associated with obstructive sleep apnea,[43,44] and sleep fragmentation, and intermittent hypoxia might trigger sympathetic activity and result in elevated BP at night.[45] In a retrospective cohort study, obstructive sleep apnea was a significant predictor of AF incidence (HR 2.18, 95% CI: 1.34–3.54).[46] Therefore, the association

TABLE 5 Comparison of studies on ambulatory blood pressure and incident of newly onset atrial fibrillation

Reference	Patients/ Events	Age at entry (years)	Mean age	Mean follow-up (years)	Office SBP HR (95% CI)	Daytime SBP HR (95% CI)	Night-time SBP HR (95% CI)	24-h SBP HR (95% CI)	Non-dipper/ Reverse dipper HR (95% CI)
Ciaroni and colleagues (2004)[26]	597/28	>50	66	7.0	–	–	–	1.16 (1.06–2.47)	–
Pierdomenico and colleagues (2008)[11]	1141/43	≥40	53.4	6.1	–	–	–	1.32 (1.05–1.67)	2.02 (1.08–3.79)
Perkiömäki and colleagues (2017)[25]	903/91	40–59	51.4	16.4	–	1.05 (.98–1.13)	1.07 (1.004–1.15)	1.09 (1.01–1.17)	–
Tikhonoff and colleagues (2018)[4]	2276/111	>18	43.1	14.0	1.19 (.99–1.43)	1.22 (1.02–1.46)	1.20 (1.02–1.42)	1.27 (1.07–1.51)	–
Matsumoto and colleagues (2021)[5]	769/83	≥40	70.5	9.5	.96 (.82–1.11)	1.24 (1.06–1.45)	1.24 (1.08–1.43)	1.27 (1.09–1.49)	–
Coccina and colleagues (2021)[6]	2135/116	≥40	61.3	9.7	1.09 (.97–1.23)	1.23 (1.10–1.39)	1.16 (1.03–1.31)	1.22 (1.06–1.40)	–
Our study	407/7	≥20	61.6	4.6	1.36 (.85–2.19)	1.77 (.99–3.16)	2.27 (1.35–3.83)	2.12 (1.16–3.87)	5.25 (1.06–25.98)

Note: Table was adapted from Pierdomenico, Ianni, De Rosa, Coccina.[52] SBP HR was assessed per 10 mmHg in all studies except Perkiömäki and colleagues (2017)[25] and Tikhonoff and colleagues (2018)[4] which was expressed per 5 mmHg increment and one standard deviation (≈12 mmHg), espectively. Patients number in our study represents those without atrial fibrillation at baseline.

between the reverse dipping pattern, obstructive sleep apnea, and AF should not be underestimated, and measurement of diurnal BP might be useful to predict the other two diseases. Further investigation is required to elucidate the relationship between these three conditions.

4.5 | Limitations

This study has several limitations. First, the sample size and the number of incident AF was relatively small. Further studies with larger sample sizes are required to confirm our results. Second, hypertension was defined by office BP ≥ 140/90 mmHg or the use of antihypertensive medications in our study. Currently, the BP levels for hypertension have been changed; out-of-hospital BP measurements were also suggested for the diagnosis of hypertension by current hypertension guidelines.[47,48] Since all our participants received antihypertensive drugs, the diagnosis of hypertension was according to the use of antihypertensive medications but not BP criteria. Third, both smoking and drinking had been reported to be risk factors for AF.[49–51] Although we had provided the information of smoking status, we did not collect the information of drinking status. Further studies are still indicated to include these risk factors. Fourth, all our participants were of Han Chinese descent, and the results might not be applicable to patients from other ethnic groups. Further studies involving patients with different ethnic backgrounds should be conducted. Fifth, paroxysmal AF might go undetected in asymptomatic patients; hence, the incidence of AF might be underestimated in both cross-sectional and longitudinal analysis. However, this study could still represent permanent or symptomatic paroxysmal AF. Sixth, due to the low incidence rate, the impact of non-dippers with 0%–10% diurnal variation on the development of AF could not be concluded in this study. Further studies are required to overcome these limitations. Finally, AF is related to multiple risk factors whereas mechanism of reverse dipping is not fully understood,[3,32] and we could not induce the causal relationship between reverse dipping and AF merely based on our results. Further in-depth study is warranted if causal relationship is to be established between reverse dipping pattern and AF.

5 | CONCLUSIONS

This study comprehensively compared office BP and ambulatory BP with the incidence of AF. The results confirmed the superiority of using ambulatory BP measurements over office BP measurements to predict the development of AF. Furthermore, patients with a reverse dipping pattern had a higher risk of AF. More aggressive survey for AF in reverse dipper is recommended, and further cost-benefit analysis is warranted to determine whether regular Holter exam is needed for asymptomatic or paroxysmal AF. The findings of our study highlight the importance of out-of-hospital BP monitoring to identify patients with masked nocturnal uncontrolled hypertension and provide appropriate treatment to these patients.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Pin-Hsiang Huang contributed to conception and design, interpretation of data, and drafted the manuscript. Chin-Chou Huang contributed to conception, data acquisition, analysis and interpretation of data, drafted and critically revised the manuscript. Shing-Jong Lin contributed to conception and design, data acquisition, and drafted the manuscript. Jaw-Wen Chen contributed to conception and design, data acquisition, and drafted the manuscript. All authors gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy

PATIENT CONSENT STATEMENT

All participants agreed to participate after being informed of the nature and purpose of the study.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

No material used from other sources.

CLINICAL TRIAL REGISTRATION

No registration for clinical trial.

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