

Association of clinic and ambulatory blood pressure with new-onset atrial fibrillation: A meta-analysis of observational studies

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Abstract

The aim of this study was to perform a meta-analysis of studies evaluating the association of clinic and daytime, nighttime, and 24-h blood pressure with the occurrence of new-onset atrial fibrillation. We conducted a literature search through PubMed, Web of science, and Cochrane Library for articles evaluating the occurrence of new-onset atrial fibrillation in relation to the above-mentioned blood pressure parameters and reporting adjusted hazard ratio and 95% confidence interval. We identified five studies. The pooled population consisted of 7224 patients who experienced 444 cases of atrial fibrillation. The overall adjusted hazard ratio (95% confidence interval) was 1.05 (0.98-1.13), 1.19 (1.11-1.27), 1.18 (1.11-1.26), and 1.23 (1.14-1.32), per 10-mmHg increment in clinic, daytime, nighttime, and 24-h systolic blood pressure, respectively. The degree of heterogeneity of the hazard ratio estimates across the studies (Q and I-squared statistics) were minimal. The results of this meta-analysis strongly suggest that ambulatory systolic blood pressure prospectively predicts incident atrial fibrillation better than does clinic systolic blood pressure and that daytime, nighttime, and 24-h systolic blood pressure are similarly associated with future atrial fibrillation.

1 | INTRODUCTION

Various studies have shown that hypertension,^{1,2} through different mechanisms,³ is an important risk factor for incident atrial fibrillation (AF) which in turn increases cardiovascular risk.⁴

Clinic blood pressure (BP) recording is traditionally used for diagnosis and management of hypertension. However, it has been largely reported that ambulatory BP is superior to clinic BP in predicting cardiovascular outcome.⁵⁻¹¹

In such a context, some studies have also evaluated whether ambulatory BP is superior to clinic BP in predicting new-onset AF.¹²⁻¹⁸ It has been reported that daytime,¹⁶⁻¹⁸ nighttime,¹⁵⁻¹⁸ and 24-h BP¹³⁻¹⁸ are independent predictors of new-onset AF and that these ambulatory BP measures tend to be superior to clinic BP¹⁶⁻¹⁸ in predicting future AF. However, as there is still little information on this subject,¹⁹ pooling all available evidence could allow for a more robust assessment of the association between AF and clinic and ambulatory BP.

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The aim of this study was to perform a meta-analysis of studies evaluating the association of clinic and daytime, nighttime, and 24-h BP with the occurrence of new-onset AF.

2 | METHODS

The study was performed in accordance with the recommendations of the Meta-analysis of Observational Studies in Epidemiology Group.²⁰ Original studies were approved by the institutional review committees and patients gave informed consent.

2.1 | Search strategy

We conducted a literature search through PubMed, Web of science, and Cochrane Library for articles evaluating the occurrence of new-onset AF according to clinic, daytime, nighttime, and 24-h BP up to January 15, 2021. The terms used to identify studies were “clinic blood pressure,” “ambulatory blood pressure,” “daytime blood pressure,” “diurnal blood pressure,” “nighttime blood pressure,” “nocturnal blood pressure,” “twenty-four-hour blood pressure,” “24-h blood pressure,” and “atrial fibrillation.” Two reviewers (FC and AMP) independently screened titles and abstracts to identify eligible studies. Disagreement between the two reviewers was resolved by a third reviewer. Reference lists of included articles were also examined for additional studies. If necessary, supplementary data were obtained through personal contact with the investigators of the selected studies.

2.2 | Eligibility criteria

Inclusion criteria for entry in the present meta-analysis were as follows: (a) full-text paper published in a peer-reviewed journal; (b) any language of publication; (c) study on adult population; (d) prospective study; (e) follow-up of at least 1 year; (f) use of ambulatory BP monitoring; (g) assessment of new-onset AF; (h) availability of

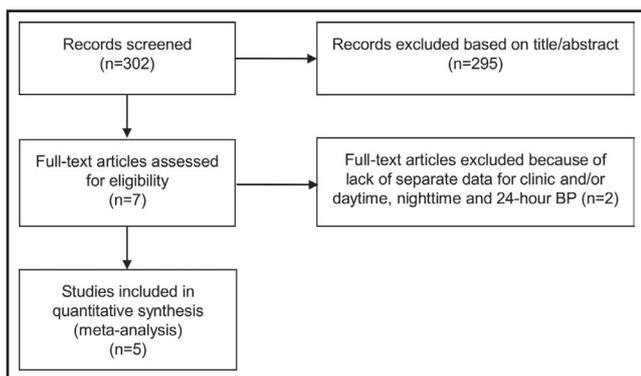


FIGURE 1 Flowchart showing selection of publications. BP, blood pressure

TABLE 1 Main characteristics of selected studies

Study	Patients/ Events	Entry age/ mean age (years)	Men (%)	DM (%)	Clinic BP mmHg	Day BP mmHg	Night BP mmHg	24-h BP mmHg	Mean FU (years)	Ethnicity	Population NTN/HTN/T (%)
Pierdomenico et al ¹⁴	1141/43	>40/53	55	6.6	154/97	144/91	126/76	140/87	6	Caucasian	0/100/0
Perkiömäki et al ¹⁵	903/91	40-59/51	49	—	—	135/85	117/70	130/81	16	Caucasian	51/49/—
Tikhonoff et al ¹⁶	2776/111	>18/44	48	3.5	126/78	126/78	109/62	119/72	13	Caucasian	71/29/16
Matsumoto et al ¹⁷	769/83	>55/70	40	29	136/79	128/74	119/66	125/71	9.5	Hispanic/Other	23/77/53
Coccina et al ¹⁸	2135/116	>40/61	46	9.3	148/89	134/81	120/69	130/78	9.7	Caucasian	0/100/100

Abbreviations: —, not available; BP, blood pressure; DM, diabetes mellitus; FU, follow-up; HTN, hypertension; NTN, normotension; T, treated at baseline.

adjusted hazard ratio (HR) and 95% confidence interval (CI) for new-onset AF according to increments of clinic and/or daytime, nighttime, and 24-h BP.

2.3 | Study selection, data extraction, and quality evaluation

The first literature search identified 302 studies. Of these, 7 were eligible after revision of titles and abstracts.¹²⁻¹⁸ Two studies^{12,13} were excluded because they did not report separate data for clinic and/or daytime, nighttime and 24-h BP. Thus, 5 studies¹⁴⁻¹⁸ were included. Selection of publications is summarized in Figure 1.

Two reviewers (FC and AMP) independently extracted relevant data from selected studies. Disagreement between the two reviewers was resolved by a third reviewer.

The quality of included studies was evaluated using the Newcastle-Ottawa scale²¹ for assessable items.

2.4 | Statistical analysis

To address confounding from other risk factors, we used the adjusted HR and 95% CI of the individual studies to calculate the overall adjusted HR and 95% CI. For Pierdomenico and colleagues,¹⁴ HRs and 95% CIs for clinic, daytime, and nighttime BP were recalculated from the original database. For Perkiömäki and colleagues,¹⁵ values of log hazard ratio and standard error were extrapolated from published HRs and 95% CIs by using the Comprehensive Meta-Analysis software and normalized to 1 unit; then, HRs and 95% CIs were expressed per 10 mmHg increments of BP by means of a dedicated software, and finally, they were used for the meta-analysis. We used the random effects model.²² Tests of heterogeneity were performed using the Cochrane Q statistic and I² statistic.²³ Subgroup meta-analysis, which is equivalent to meta-regression with categorical (or categorized) variables, was also performed to analyze potential

sources of heterogeneity.²⁴ Individual studies were removed one at a time to evaluate the influence of that study on the pooled estimate. Usually, tests for funnel plot asymmetry are used when approximately 10 studies are included in the meta-analysis, because when there are few studies the power of the tests is too low to distinguish chance from real asymmetry; thus, due to the relatively low number of studies available in the literature, the above-mentioned statistical approach was not performed. Statistical significance was defined as $p < .05$ (2-tailed tests). Analyses were done using the Comprehensive Meta-Analysis software version 2 (Biostat).

3 | RESULTS

Main characteristics of selected studies are reported in Table 1. The pooled population consisted of 7224 patients who experienced 444 cases of AF. The majority of the studies,^{14,15,17,18} except one,¹⁶ included subjects aged ≥ 40 years. Mean follow-up ranged from 6 to 16 years. Four studies^{14-16,18} included Caucasian individuals, and one study¹⁷ included mainly Hispanic subjects. One study¹⁴ evaluated untreated hypertensive patients, one study¹⁸ assessed treated hypertensive patients, and three studies¹⁵⁻¹⁷ comprised subjects with normotension and hypertension in different percentages.

Covariates included in the multivariate analysis of selected studies are reported in Table 2. Though there were some differences across the studies, a set of covariates including the main determinants of AF was used in multivariate analysis in the various studies.

According to the Newcastle-Ottawa scale, for assessable items, all the included studies were of good quality (Table S1).

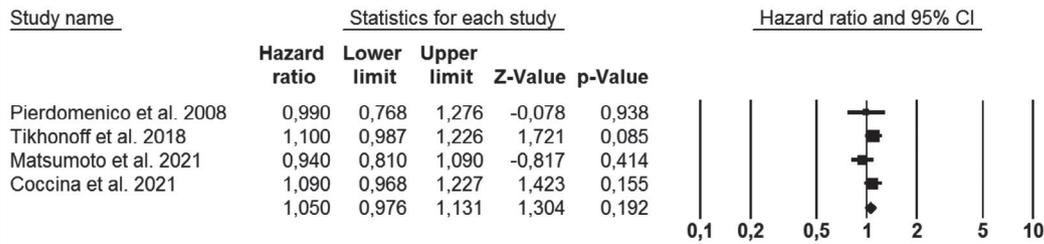
Figure 2 gives the adjusted HR and 95% CI of the individual studies and of the overall analysis. The overall adjusted HR (95% CI) was 1.05 (0.98-1.13), 1.19 (1.11-1.27), 1.18 (1.11-1.26), and 1.23 (1.14-1.32), per 10-mmHg increment in clinic, daytime, nighttime, and 24-h systolic BP, respectively. The degree of heterogeneity of the HR estimates across the studies (Q and I-squared statistics) were minimal. To further explore this aspect, subgroup meta-analysis was

Study	Covariates
Pierdomenico et al ¹⁴	Age, sex, family history of premature CV disease, smoking habit, BMI, low-density lipoprotein cholesterol, creatinine, DM, LA enlargement or LVH, nondipping, and antihypertensive drug class at follow-up
Perkiömäki et al ¹⁵	Age, sex, BMI, height, smoking, alanine aminotransferase, uric acid, glucose
Tikhonoff et al ¹⁶	Age, sex, BMI, serum cholesterol, tobacco and alcohol use, history of CV disease and DM and antihypertensive drug treatment
Matsumoto et al ¹⁷	Age, sex, race, and hypertension status at baseline
Coccina et al ¹⁸	Age, BMI, family history of CV disease, DM, eGFR, LVH, LA enlargement, ALVSD, number of antihypertensive drugs

TABLE 2 Covariates included in the multivariate analysis of selected studies

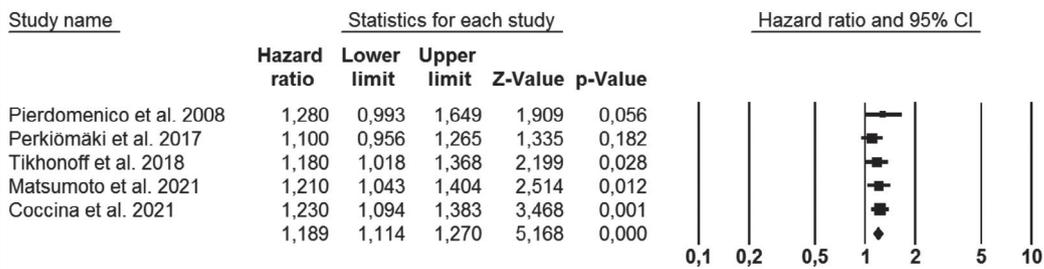
Abbreviations: ALVSD, asymptomatic left ventricular systolic dysfunction; BMI, body mass index; CV, cardiovascular; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; LA, left atrial; LVH left ventricular hypertrophy.

Risk of New-Onset Atrial Fibrillation (Per 10-mmHg Increment in Clinic Systolic Blood Pressure)



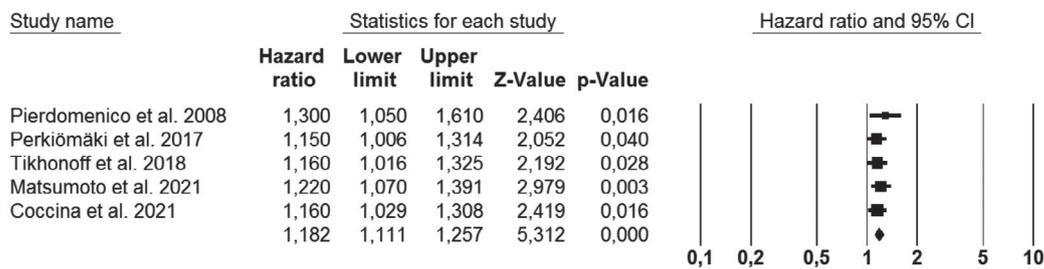
Q=3.42; P=0.33
I-squared=12.268

(Per 10-mmHg Increment in Daytime Systolic Blood Pressure)



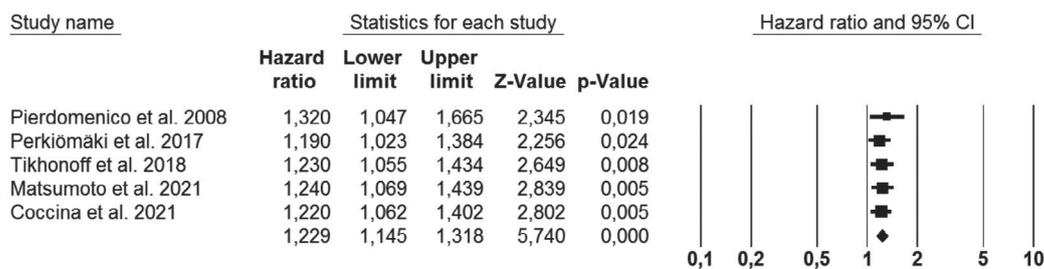
Q=1.90; P=0.75
I-squared=0.000

(Per 10-mmHg Increment in Nighttime Systolic Blood Pressure)



Q=1.32; P=0.86
I-squared=0.000

(Per 10-mmHg Increment in 24-hour Systolic Blood Pressure)



Q=0.56; P=0.97
I-squared=0.000

FIGURE 2 Forest plot showing the adjusted hazard ratio (HR) and 95% confidence interval (CI) per 10-mmHg increment in clinic, daytime, nighttime, and 24-h systolic blood pressure (BP). For Pierdomenico et al (Ref. 14), HRs and 95% CIs for clinic, daytime, and nighttime BP were recalculated from the original database. For Perkiömäki et al (Ref. 15), values of log hazard ratio and standard error were extrapolated from published HRs and 95% CIs by using the Comprehensive Meta-Analysis software and normalized to 1 unit; then, HRs and 95% CIs were expressed per 10 mmHg increments of BP by means of a dedicated software and finally they were used for the meta-analysis. For Tikhonoff et al (Ref. 16), HRs and 95% CIs per 10-mmHg increment of BP were provided by the authors

performed according to mean age at entry and prevalence of hypertension in the studied populations (Table 3). Though some differences were observed, there was no evidence of heterogeneity with respect to either.

Sensitivity analysis (Figure 3) indicated that none of the studies had a significant influential effect on the overall estimate for daytime, nighttime, and 24-h BP and that only one study¹⁷ had a significant influential effect on the overall estimate for clinic BP.

4 | DISCUSSION

This meta-analysis shows that ambulatory BP is a stronger predictor of new-onset AF than clinic BP. Moreover, though there were slight differences across the studies regarding the impact of the ambulatory BP parameters, our results suggest that daytime, nighttime, and 24-h systolic BP are similarly associated with future AF.

To the best of our knowledge, this is the first meta-analysis in the literature evaluating this topic. Our pooled data reinforce findings from single studies.¹⁴⁻¹⁸

At present, it is unclear why ambulatory BP is a stronger predictor of new-onset AF than clinic BP. It could be speculated that ambulatory BP is superior to clinic BP in detecting and integrating potential mechanisms implicated in the pathogenesis of AF.¹⁹

Some studies have evaluated the impact of BP control on future occurrence of AF but results are debated.²⁵⁻²⁹ These controversial findings may partly be related to the partial ability of clinic BP to detect real BP status/control unlike ambulatory BP.^{8,30,31} Therefore, future research to evaluate the impact of ambulatory BP control, in comparison with clinic BP control, on the occurrence of new-onset AF might be helpful in order to find the best preventive strategy.

This study has some limitations. First, there are few studies in the literature about the topic. Second, studied populations tended to be heterogeneous including both normotensive subjects and untreated or treated hypertensive patients; however, the vast majority of individuals had hypertension. Third, the set of covariates included in multivariate analyses tended to be heterogeneous; however, the main determinants of AF were included in the various studies. In any case, despite the aforesaid limitations, the heterogeneity of the HR estimates across the studies was minimal

TABLE 3 Random effects meta-analysis according to mean age at entry and prevalence of hypertension in the studied populations

	Studies	Subjects/Events	Adjusted HR (95% CI)	p
Clinic blood pressure				
Age <60 years	2	3917/154	1.07 (0.94-1.22)	.59
Age >60 years	2	2904/199	1.02 (0.91-1.15)	
HTN <50%	1	2776/111	1.10 (0.96-1.25)	.37
HTN >50%	3	4045/242	1.02 (0.92-1.13)	
Daytime blood pressure				
Age <60 years	3	4820/245	1.16 (1.05-1.27)	.41
Age >60 years	2	2904/199	1.22 (1.11-1.34)	
HTN <50%	2	3679/202	1.14 (1.03-1.26)	.25
HTN >50%	3	4045/242	1.23 (1.13-1.34)	
Nighttime blood pressure				
Age <60 years	3	4820/245	1.18 (1.08-1.28)	.90
Age >60 years	2	2904/199	1.19 (1.09-1.30)	
HTN <50%	2	3679/202	1.15 (1.05-1.27)	.52
HTN >50%	3	4045/242	1.20 (1.11-1.31)	
24-h blood pressure				
Age <60 years	3	4820/245	1.23 (1.11-1.35)	.99
Age >60 years	2	2904/199	1.23 (1.11-1.36)	
HTN <50%	2	3679/202	1.21 (1.09-1.35)	.70
HTN >50%	3	4045/242	1.24 (1.13-1.36)	

Abbreviation: HTN, hypertension.

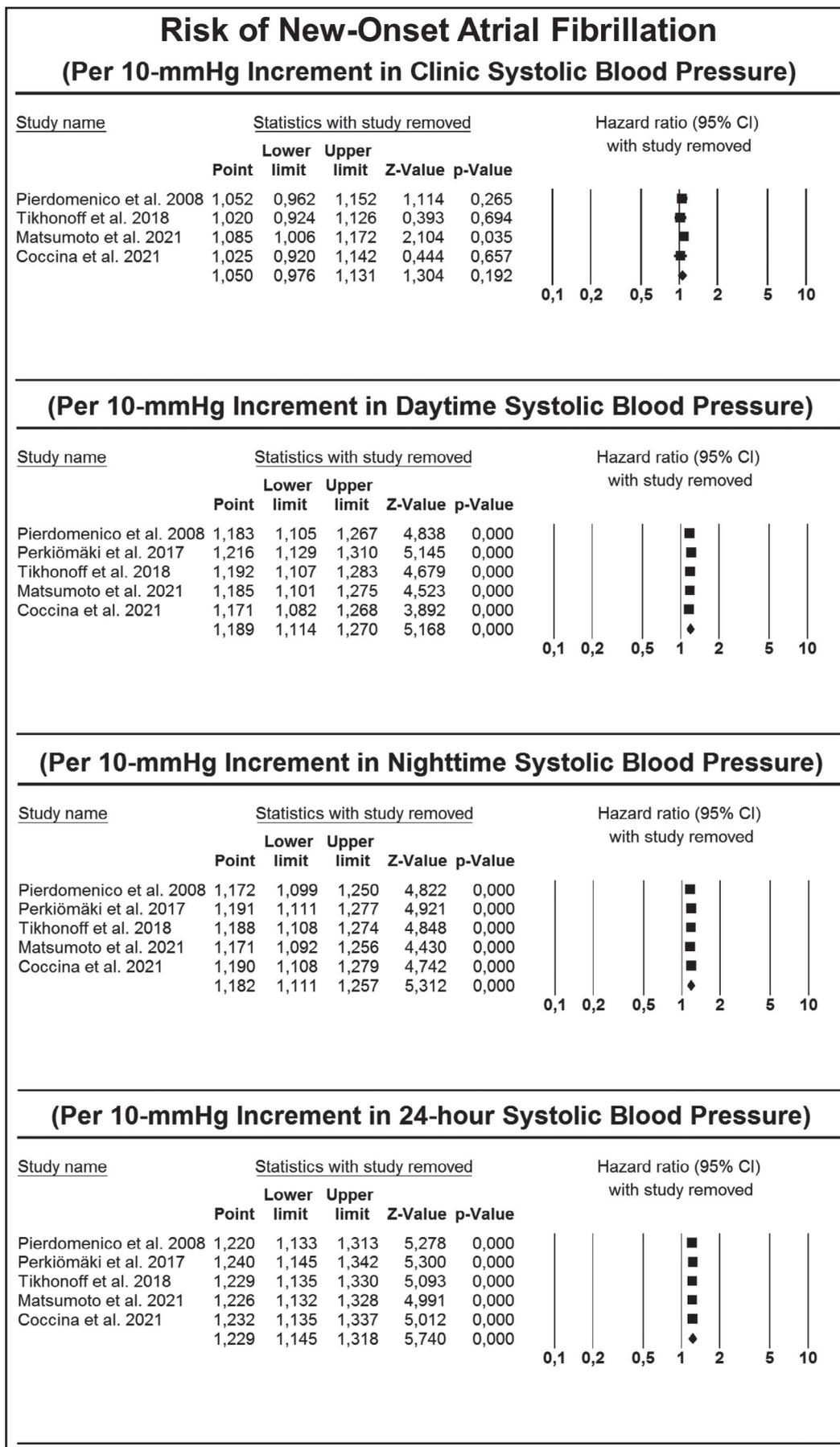


FIGURE 3 Forest plot showing the influence of each study on the overall estimate. CI, confidence interval

suggesting that ambulatory is stronger than clinic BP in different contexts.

In conclusion, the results of this meta-analysis strongly suggest that ambulatory systolic BP prospectively predicts incident atrial fibrillation better than does clinic systolic BP and that daytime, nighttime, and 24-h systolic BP are similarly associated with future AF. In this context, further research may be needed to evaluate whether ambulatory BP lowering over time is stronger than clinic BP lowering in reducing new-onset AF.

ACKNOWLEDGMENT

Thanks are due to Tatiana Kuznetsova for providing the results of their study.

CONFLICT OF INTEREST

The authors have no conflict of interest.

AUTHOR CONTRIBUTIONS

Francesca Coccina collected the data, 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 collected the data, 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. Matteo De Rosa 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. Chiara Cuccurullo 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. Sante D. Pierdomenico designed the study, collected the data, performed statistical analysis, 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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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Coccina F, Pierdomenico AM, De Rosa M, Cuccurullo C, Pierdomenico SD. Association of clinic and ambulatory blood pressure with new-onset atrial fibrillation: A meta-analysis of observational studies. *J Clin Hypertens*. 2021;23:1104-1111. <https://doi.org/10.1111/jch.14256>