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# Meta-Analysis of the Association Between Atrial Fibrillation, Hypertension, Sleep-Disordered Breathing, and Wake-Up Stroke

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## Abstract

**Background:** The occurrence of atrial fibrillation, circadian fluctuation in blood pressure, and oxygen desaturation at night is likely associated with the pathophysiology of wake-up stroke. Whether patients who experience wake-up strokes are candidates for thrombolysis treatment is a serious dilemma. The aim is to investigate the association between risk factors and wake-up stroke and to determine variations that are associated with the pathophysiology of wake-up stroke.

**Methods:** Five major electronic databases were searched using a fitted search strategy to identify relevant studies. Odds ratios with 95% CIs were used to calculate estimates, and the Quality Assessment for Diagnostic Accuracy Studies-2 tool was used to conduct the assessment quality.

**Results:** A total of 29 studies were included in this meta-analysis. Hypertension is not associated with wake-up stroke (odds ratio, 1.14 [95% CI, 0.94-1.37]; $P = .18$). Atrial fibrillation is an independent risk factor to wake-up stroke, with a statistically significant difference (odds ratio, 1.28 [95% CI, 1.06-1.55]; $P = .01$). Subgroup analysis showed a different result in patients with sleep-disordered breathing, although no significant difference was assessed.

**Conclusion:** This study revealed that atrial fibrillation is an independent risk factor for wake-up stroke and that patients with atrial fibrillation who also experience sleep-disordered breathing tend to have fewer wake-up strokes.

**Keywords:** Atrial fibrillation; wake-up stroke; meta-analysis

## Introduction

Wake-up stroke (WUS) refers to an ischemic stroke (IS) that occurs during sleep and is associated with neurological symptoms upon waking. Previously, by analyzing the onset of stroke at 3 different wakeup times, a consistent morning peak of stroke incidence was recorded, which supports a close association between stroke and morning awakening.[1] Studies on WUS report inconsistent physiological and clinical features but showed similar outcomes with awake-onset stroke.[2-5] However, no significant difference has yet been identified between the imaging features of IS distributions.[6] Whether patients with WUS ought to receive acute stroke treatment requires us to understand and be able to manage WUS. These patients have the lowest rate of intravenous thrombolysis treatment, accounting for only 0.3% to 2.1% of all patients who experience an IS.[4,5] The pathophysiology of WUS remains unclear. Still, WUS and non-WUS (NWUS) showed different characteristics, such as sex, severity syndromes, and sleep disorders.[3,7]

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Wake-up stroke is a subtype of IS with risk factors that are similar to those for IS. Numerous risk factors, such as atrial fibrillation (AF) and hypertension, cannot explain the occurrence of WUS. According to the special features of onset and exacerbation during sleep, it is supposed that a combination of oxygen desaturation at night, AF, and blood pressure (BP) fluctuation are the underlying reasons why WUS is so distinct from other types of IS.[8] Nocturnal oxygen desaturation may trigger cerebral ischemia or may increase the risk of stroke mediated by hypertension.[9] Patients with AF have a 5 times higher risk of having a stroke than do with those without AF.[10,11] Among those who experience stroke, cardiovascular disease–related IS usually results in more severe prognoses and is more frequently fatal than for those with non–cardiovascular disease.[12] Up to 20% of patients with IS have a history of AF and a high prevalence of hypertension (>80%); they also usually have higher rates of disability and fatality. Even though oral anticoagulant treatment can effectively prevent strokes related to AF, a large population-based and observational report showed that it is underused in patients with AF who are at risk for stroke.[13]

A national stroke registry study provided evidence that hypertension is highly prevalent in patients who experience stroke during sleep.[14] On the other hand, other studies have ascertained that a substantial proportion of patients who have had a stroke might have experienced unconscious paroxysmal asymptomatic AF before experiencing the stroke.[14,15] Nevertheless, a recent study reported that newly diagnosed AF was 3-fold higher among wake-up cerebrovascular events than among non–wake-up events.[16] Could AF and hypertension be underlying mechanisms that raise the risk of WUS or a patient with WUS having an increased risk of stroke following the occurrence of AF? Conclusions of the relevant studies are underpowered, owing to limited data and because the results of the studies conflict.[3,9,16] Therefore, the association between potential clinical factors and WUS raises a crucial problem that needs to be addressed to further clinical practice in prevention and anticoagulation treatment. This meta-analysis investigates the associations between hypertension, previously known AF (KAF), and WUS in an attempt to reach a unified conclusion among the differing results of previous studies. The secondary objective of this meta-analysis was to further investigate whether sleep-disordered breathing (SDB) contributes to this condition.

### Abbreviations and Acronyms

| | |
|---|---|
| AF | atrial fibrillation |
| BP | blood pressure |
| IS | ischemic stroke |
| KAF | previously known atrial fibrillation |
| NWUS | non–wake-up stroke |
| OR | odds ratio |
| WUS | wake-up stroke |

## Methods

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[17]

### Data Source and Search Strategy

Eligible studies were identified through electronic database searches using suitable search strategies and through cross-checking references of related papers before November 2021. The PubMed, ScienceDirect, Web of Science, Embase, and Cochrane Library databases were systematically searched using the following search terms: "wake-up stroke," "hypertension," and "atrial fibrillation." Detailed search items and strategies are displayed in the supplementary material (database search strategy).

### Inclusion and Exclusion Criteria

J.X. and A.C. independently collected data from the eligible studies into a standardized data collection form. The inclusion criteria for this meta-analysis were as follows: (1) studies on the associations between prior AF, hypertension, SDB, and WUS; (2) studies that stratify patients with stroke into a WUS group and an NWUS group; and (3) studies that prove almost comprehensive data were included when more than 1 study for the same population was published.

The exclusion criteria were as follows: (1) studies of a single rate or those without a control group of patients with NWUS; (2) studies with insufficient data or duplicate data; (3) studies that were not published in English or Chinese; (4) studies with a total sample size of fewer than 10; and (5) studies about animal experiments. Only original articles were considered, and other publications, such as letters, reviews, case reports, editorial articles, or unpublished articles/data were excluded. The 2 investigators reached a consensus on each item through discussion.

### Data Extraction and Quality Assessment

For each eligible study, the first author's name, publication year, country, demographic data (age, type of disease), study design, and sample size were noted. The primary outcome of the study was the number of patients with hypertension and prior AF in WUS and NWUS groups. The secondary outcome was the comparison of KAF and hypertension between patients with WUS and NWUS with SDB. The same 2 investigators used the Quality Assessment for Diagnostic Accuracy Studies-2 (QUADAS-2) tool by RevMan version 5.3 to assess the quality of the eligible studies. The risk of bias for each item was graded as "low," "unclear," or "high." J.X. and A.C. appraised the study quality independently, and discrepancies were resolved by discussion. Each study was ranked as having a high, low, or unclear risk of bias according to 6 different areas: (1) selection bias, (2) performance bias, (3) detection bias, (4) attrition bias, (5) reporting bias, and (6) other bias. The quality of each study was graded as having a "low," "unclear," or "high" risk of influencing the meta-analysis results. J.X. and A.C. appraised the study quality independently, and discrepancies were resolved by discussion.

### Statistical Analysis

Statistical analysis was performed using Stata version 15.1 (StataCorp LP). The odds ratios (ORs) were used to compare continuous and dichotomous variables with 95% CIs. Fixed- and random-effects models were used in this meta-analysis. The level of significance was set at $P < .05$. The heterogeneity of each group was tested using the $\chi^2$ test and the inconsistency index ($I^2$). An $I^2$ of greater than 50% and a $P$ value of $\chi^2$ less than .05 confirmed the existence of significant heterogeneity, and a random-effects model was used to pool the data. Otherwise, a fixed-effects model was used. The heterogeneity, sensitivity, and subgroup analyses were conducted to determine the potential sources of heterogeneity among the included studies. Subgroups were separated into patients with and without SDB. Publication bias was analyzed using the Deeks funnel plot and an asymmetry test. Interobserver reliability was assessed using Cohen κ, and the κ coefficients were interpreted accordingly.[18] Interobserver κ less than 0.20 was considered poor, 0.20 to 0.40 was fair, 0.40 to 0.60 was moderate, 0.60 to 0.80 was good, and 0.80 to 1.00 was excellent.

## Results

### Search Results

In total, the electronic search and cross-checking of related papers identified 2,037 studies, and after removing duplicates, 1,295 studies were left for screening. Based on titles and abstracts, 1,084 studies were excluded for the reasons of nonrelated topic with the study's meta-analysis (n = 740) and undesired article types (n = 344). After conducting this process, 52 studies were left. These underwent a thorough full-text review. Six studies were single case studies, 6 studies were animal experiments, and 3 used the same cohort as other studies; therefore, these 15 studies were excluded. Only the most comprehensive studies were included in the meta-analysis. In a secondary full-text review, 9 studies were further excluded owing to their ineligibility of reported data or because they were not published in English or Chinese. Ultimately, 29 studies were included in the study's meta-analysis.[1-3,9,14,16,19-41] Figure 1 presents the flowchart for this process.

### Study Characteristics

The 29 included studies represented a total of 12,790 patients, of which 2,510 were patients with WUS and 10,280 were patients with NWUS. The included studies were conducted in Asia, the United States, and Europe over more than a decade (2005-2020). Among the included studies, patients' age varied widely, ranging from 21 to 89 years. The interobserver reliability κ agreement for study selection was 0.65. Detailed information is summarized in Table I.[1-3,9,14,16,19-41]

### Quality Assessment

Regarding the quality of the included studies, the results are presented by the QUADAS-2 tool, as illustrated in Figure 2. Seven studies were judged to have low risk of bias in all bias detection areas; 7 studies were judged to have 1 domain at high risk of bias; and 5 studies were at high risk of bias in more than 1 domain (2 domains). Among the 6 studies judged to have a high risk of bias in more than 1 domain, most were in the domains of selection bias, performance bias, and detection bias, owing to the fact that it was not mentioned whether those studies used randomization or blinding in their methodology (Fig. 2).

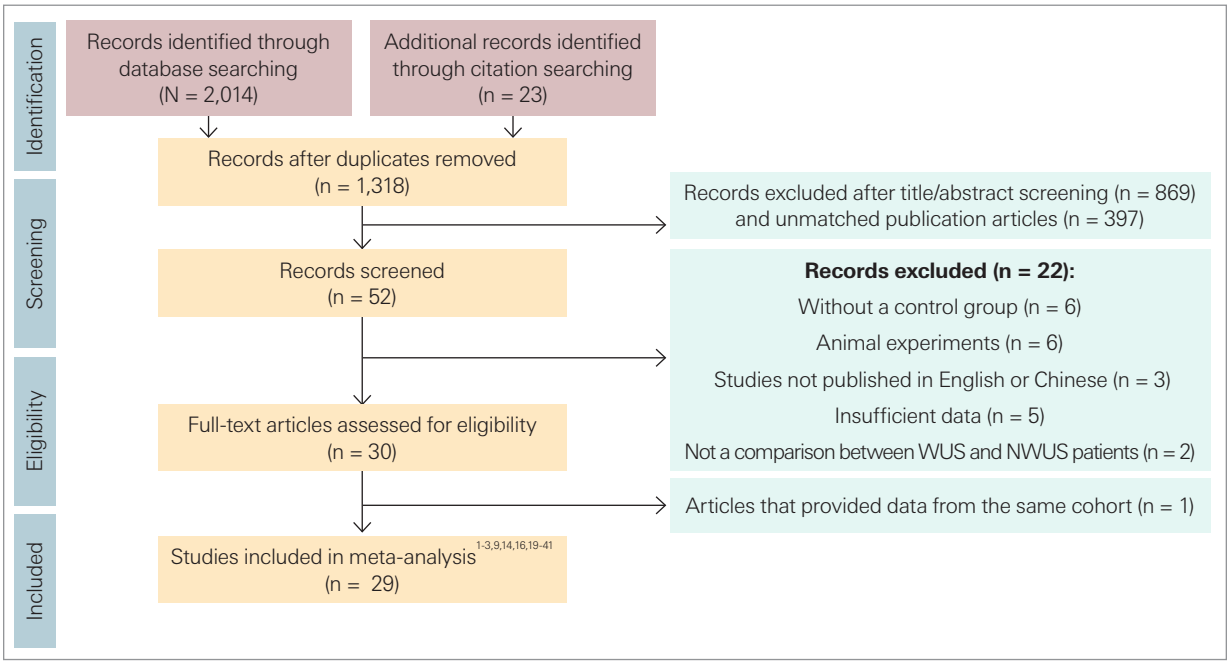


**Fig. 1** Flow diagram of the study selection process.

NWUS, non–wake-up stroke; WUS, wake-up stroke.

### Hypertension

A total of 28 studies reported hypertension data among patients with IS. The overall results revealed that the percentage of individuals with a history of hypertension with WUS was higher than that of those with NWUS (OR, 1.14 [95% CI, 0.94-1.37]; $P = .18$; Fig. 3). However, no significant difference between the 2 groups was assessed. Also, a random-effects model was used and heterogeneity was high ($I^2 = 63\%$; $P < .001$). Subgroup analysis showed that in patients with SDB, a similar result was observed: hypertension predominated in patients with WUS compared with patients with NWUS (Table II), whereas no significant difference was assessed (Supplemental Fig. 1). Sensitivity analysis was also conducted to identify sources of heterogeneity. After removing each study from the analysis, the study by Bian et al[40] was found to be a potential source of heterogeneity; omitting this study decreased heterogeneity from 63% to 50.8%. The slight difference was assessed, but the heterogeneity among the included studies persisted.

### Atrial Fibrillation

A total of 27 studies reported AF data among patients with IS (of 12,488 patients, 2,484 with WUS, 10,004 with NWUS). The overall meta-analysis results assessed a significant difference between patients with WUS and those with NWUS (OR, 1.28 [95% CI, 1.06-1.55]; $P = .01$; Fig. 4), revealing that AF is a risk factor in the incidence of WUS. During the subgroup analysis, a different result was observed: the presence of AF was more frequent in patients with NWUS (OR, 0.72 [95% CI, 0.48-1.10]; $P = .12$; Table II; Supplemental Fig. 2) even though there was no statistically significant difference between the 2 groups. Sensitivity analysis was also conducted for heterogeneity by omitting each study from the analysis, though omitting each study did not affect the results greatly.

### Publication Bias

Deeks' funnel plot asymmetry test detected no publication bias among the studies with hypertension ($P = .44$; Supplemental Fig. 3) and AF ($P = .3$; Supplemental Fig. 4), as displayed in the supplementary material.

## Discussion

As advanced noninvasive and implanted monitors become more available, the detection of AF is increasing. The idea that prompt anticoagulant therapy might affect the impact of stroke prognosis is being questioned. Studies have suggested a strong association of AF with

**TABLE I. Characteristics of Included Studies**

| Reference | Country of origin | n | | Age, mean (SD), y | | Study design |
|---|---|---|---|---|---|---|
| | | WUS | NWUS | WUS | NWUS | |
| Nadeau et al[2] (2005) | Canada | 349 | 2,236 | 73 | 71 | Prospective |
| Jiménez-Conde et al[35] (2007) | Spain | 127 | 686 | 75.39 (9.96) | 73.26 (12.40) | Prospective |
| Silva et al[26] (2010) | Brazil | 131 | 420 | 68.8 (15.4) | 67.5 (15.2) | Prospective |
| Mackey et al[3] (2011) | USA | 273 | 1,581 | 72.3 (0.83) | 70.0 (0.48) | Retrospective |
| Hsieh et al[9] (2012) | China | 26 | 45 | 65.7 (11.1) | 67.8 (10.7) | Prospective |
| Jung et al[34] (2013) | Switzerland | 55 | 22 | 61.9 (14.5) | 63.5 (10.2) | Prospective |
| Manawadu et al[28] (2013) | UK | 68 | 326 | 73.9 (15.6) | 72.8 (14.7) | Prospective |
| Riccio et al[16] (2013) | Chile | 41 | 315 | 72 (11.11) | 72 (11.11) | Prospective |
| Turin et al[14] (2013) | Japan | 127 | 1,105 | NA | NA | Retrospective |
| Nahrir et al[1] (2014) | UK | 65 | 154 | 62.62 | 61.012 | Retrospective |
| Tan et al[25] (2014) | Singapore | 213 | 429 | 64 (13.33) | 65 (12.59) | Cross-sectional analysis |
| Tanimoto et al[24] (2014) | USA | 28 | 44 | NA | NA | Prospective |
| Aghaebrahim et al[41] (2015) | USA | 78 | 128 | 67 (13.8) | 64 (13.6) | Retrospective |
| Zhai et al[22] (2015) | China | 17 | 90 | ≥80 | ≥80 | Retrospective |
| Kim et al[33] (2016) | Korea | 79 | 219 | 67.6 (12.5) | 67.7 (12.6) | Retrospective |
| Koo et al[32] (2016) | USA | 50 | 114 | 61.5 (10.7) | 62.2 (11.6) | Cross-sectional analysis |
| Liu et al[31] (2016) | China | 22 | 74 | 64.6 (9.6) | 61.0 (10.8) | Retrospective |
| Zhai et al[21] (2016) | China | 103 | 317 | 69.4 (11.9) | 69.4 (11.5) | Prospective |
| Lundholm et al[29] (2017) | USA | 78 | 291 | 69.0 (16.6) | 63.8 (6.77) | Prospective |
| Dankbaar et al[37] (2018) | Netherlands | 26 | 123 | 65 (14.06) | 69 (14.81) | Prospective |
| Brown et al[39] (2018) | USA | 136 | 307 | 66 (9.63) | 65 (13.33) | Retrospective |
| Zhang et al[20] (2018) | China | 70 | 204 | 66 (12) | 68 (13) | Prospective |
| Bian et al[40] (2019) | China | 27 | 196 | 67 (16) | 60 (15) | Retrospective |
| Fu et al[36] (2020) | China | 34 | 85 | 59.2 (11.5) | 59.7 (12.5) | Cross-sectional analysis |
| Mohammad et al[27] (2019) | Saudi Arabia | 40 | 67 | NA | NA | Case-control study |
| Wang et al[23] (2019) | China | 40 | 127 | NA | NA | Prospective |
| Colon-Feliciano et al[38] (2020) | USA | 38 | 102 | NA | NA | Cross-sectional analysis |
| Ye et al[30] (2020) | China | 37 | 132 | 55.38 (4.67) | 55.90 (4.89) | Retrospective |
| Zhang et al[19] (2020) | China | 132 | 341 | 68.4 (11.8) | 66.4 (13.0) | Prospective |

NA, not available; NWUS, non–wake-up stroke; WUS, wake-up stroke.

IS and its WUS subtype. The potential pathophysiological mechanism underlying WUS is assumed to be related to 3 aspects: changes in BP, overnight oximetry, and newly occurring AF.[8] Yet no consensus has been reached on how AF should be investigated in patients with stroke, and its prevalence after a stroke remains uncertain. Thus, this study aims to investigate the association between hypertension, KAF, and WUS.

First, the prevalence of AF in patients with IS was observed to range from 24.6% to 30.7%.[10,11] Our study confirmed the hypothesis that the prevalence of AF is substantially different in patients with WUS and those without WUS. Patients with AF have significantly increased risk of having a WUS, confirming that AF is significantly associated with WUS. According to the pooled OR estimates, there was an approximate 1.28-fold increase in the risk of WUS induced in patients who had KAF. Previous research mentioned that the onset time of WUS presents a circadian curve, with a peak frequency in the morning hour.[1,42] Moreover, circadian variations in the frequency of paroxysmal AF have also been demonstrated, with peaks occurring dur-

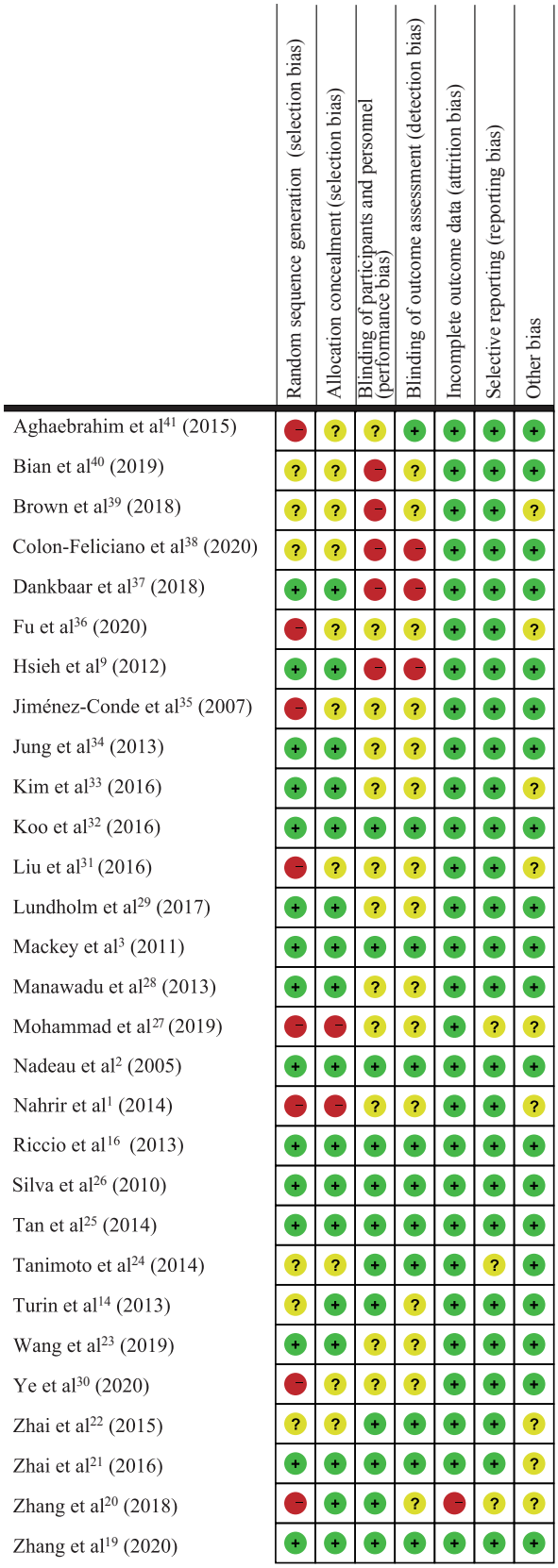


**Fig. 2** Risk of bias for each of the 29 included studies (red = high, yellow = unclear, green = low).

ing the night and early morning hours. The circadian rhythm of AF and WUS warrants careful consideration and further investigation. In response to this issue, Riccio et al's study[16] investigating newly diagnosed AF after WUS demonstrated that newly diagnosed AF might be the expression of an unconscious and unnoticed episode of paroxysmal AF that occurred before the onset of WUS and that this unnoticed AF is the potential cause of stroke. Nocturnal sleep may trigger cardiac electrical instability; thus, in patients with unconscious AF, it could lead to transient reductions of cardiac output that cause fluctuations in the volume and velocity of blood flow.[42,43] Therefore, a paroxysmal episode of AF that occurs in the comparable time with WUS is worthy to be considered a participant in the formation of cardiac emboli.

As a potential risk factor for IS, it is said that hypertension and the biological effect of the circadian rhythm of BP and heart rate may contribute to the occurrence of IS.[15] The circadian rhythm of BP is typically lower at night and increases upon awakening. For patients with hypertension, the long-term, intensive BP on the heart and vessels decreases flexibility of arterial elasticity and causes various pathological changes in the target organ (the heart and brain in this case); for those impaired organs, BP fluctuation further exacerbates blood perfusion and eventually induces IS. There are 2 schools of thought about the changes of BP among patients with WUS. The studies by Turin et al[15] and Nadeau et al[2] reported a higher systolic BP among patients with WUS, whereas Wang et al[23] conducted research that contradicted these findings. No significant role of hypertension was observed in the current study on the incidence of WUS. Similar results were determined in the subgroup analysis (Table II). The lack of association indicates that neither morning BP surge nor nocturnal dipping patterns that occur in patients with hypertension are associated with the occurrence of WUS. In a case report that used BP monitoring to examine the variations in nocturnal BP among patients with IS, evidence suggests that BP is elevated after waking up and not before in patients with WUS, which supports the lack of association with the peak frequency of WUS occurrence during nocturnal sleep.[44] Thus, larger and prospective studies on this topic are needed to determine whether BP and WUS occurrence are associated.

Sleep disorders may have a substantial impact on the autonomic nervous system and cardiac function. Sleep-disordered breathing is considered a potential risk factor for the incidence of stroke and, subsequently, WUS.[3]

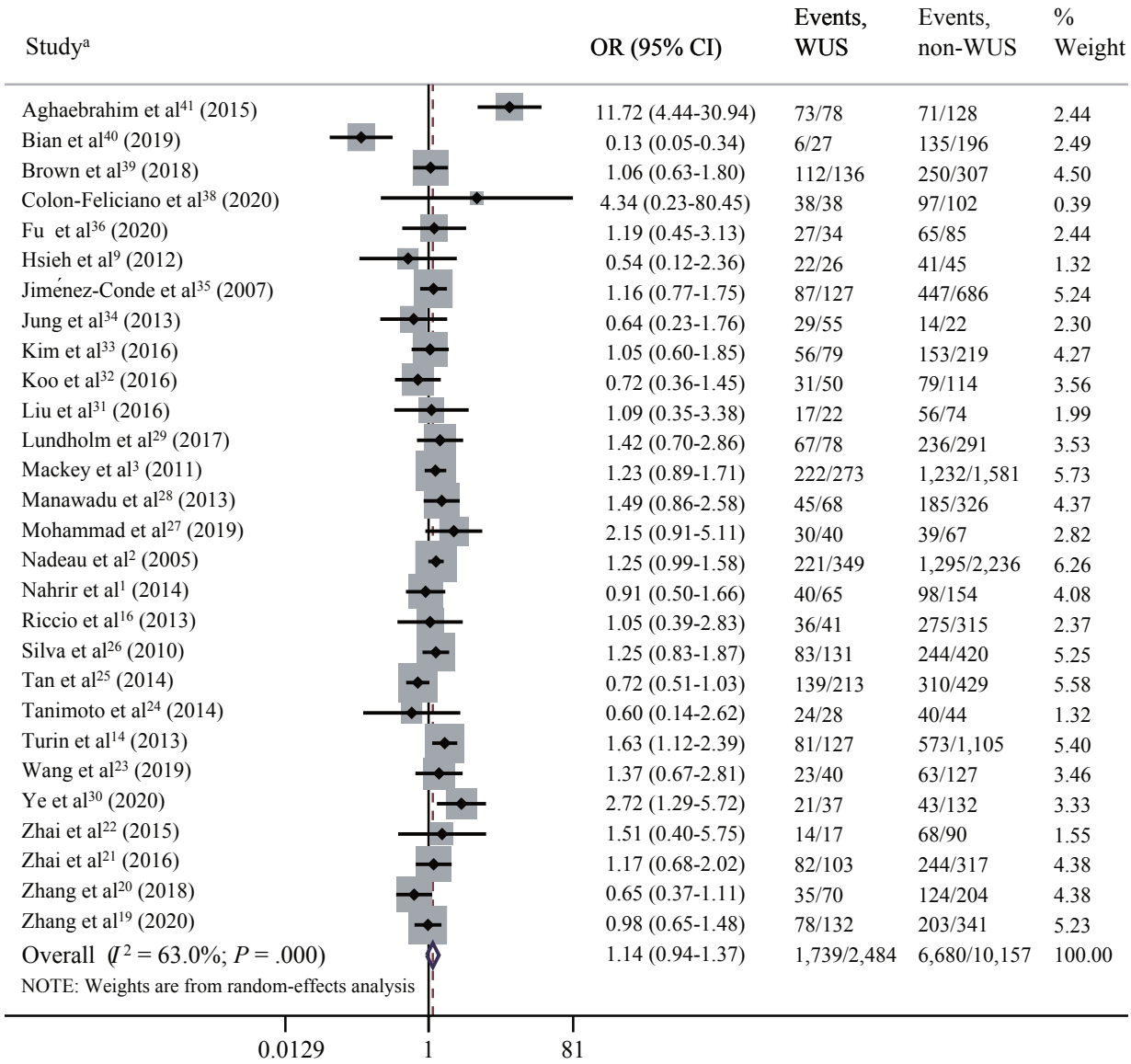


**Fig. 3** Forest plot that shows that the pooled results cross the null line, indicating no significant difference of preexisting hypertension ($P$ = .18) between patients with WUS and those with NWUS. $P \leq .05$ was considered statistically significant. The existence of hypertension was not considered an important factor in the occurrence of WUS.

[a] The study by Dankbaar et al[37] provided no relevant data on hypertension and therefore was not included in the analysis.

NWUS, non–wake-up stroke; OR, odds ratio; WUS, wake-up stroke.

Current evidence has noted that patients with WUS who have severe SDB status have a higher apnea-hypopnea index and oxygen desaturation index than do those with NWUS, indicating a possible factor that distinguishes WUS from IS.[36,45] Obstructive sleep apnea has been established as the only risk factor for WUS, particularly in those patients with moderate to severe stroke.[9] The coexistence of SDB as a possible mechanism underlying the pathophysiology of WUS has been proposed in various studies. Furthermore, SDB has been proven to be specifically associated with WUS.[45] However, in the subgroup analysis on those patients with SDB, a lower prevalence of KAF was detected than with the NWUS group (11.7% vs 20.3%, respectively) (OR, 0.72 [95% CI, 0.48-1.09]; Table II), and no statistical significance was observed ($P$ = .12); this result is very

**TABLE II. Results of Subgroup Analysis**

| Cardiovascular factor | Category | No. of studies | OR (95% CI) | *P* value |
|---|---|---|---|---|
| Hypertension | No SDB | 21 | 1.17 (0.94-1.47) | .16 |
| | SDB | 8 | 1.02 (0.76-1.38) | .90 |
| Atrial fibrillation | No SDB | 21 | 1.39 (1.14-1.69) | .001[a] |
| | SDB | 7 | 0.72 (0.48-1.09) | .12 |

OR, odds ratio; SDB, sleep-disordered breathing.

[a] $P < .05$ represents statistical significance.

different from the overall result. Among patients with SDB, the occurrence of preexisting AF and hypertension did not significantly differ between patients with WUS and those with NWUS. For patients with an accompanying sleep problem, the reciprocal association among AF/hypertension, SDB, and WUS should be considered cautiously and separately.

This study had several limitations that should be considered when interpreting the meta-analysis results. First, the high heterogeneity observed in the hypertension analysis implies that hypertension could also be a potential factor for the incidence of WUS. Even though sensitivity and subgroup analyses were conducted, the long time span of the included studies and experiment details (2005-2020) should be considered a potential source of heterogeneity. Second, the meta-analysis was conducted concerning cardiac factors that received high interest in the included studies. Third, the included studies were conducted in different regions (the Middle East, East and Southeast Asia, North and South America, Europe) that have different medical treatment levels.

## Conclusion

Today, the pathophysiology of WUS remains unclear; no single factor is likely to explain WUS. Hypertension is a causal implication to be elucidated to the occurrence of WUS. Atrial fibrillation is one of the most common reasons for cardiogenic stroke, with more severe and complicated high outcomes of mortality and hemorrhage rates. In summary, this study demonstrates that hypertension is not a risk factor for WUS even though there was a high prevalence of hypertension in patients with WUS. In addition, this study confirms that AF is an important risk factor for WUS. Further prospective studies are needed to explore the circadian variation similarity between AF and WUS and well as the pathophysiologic relationships among AF, WUS, and other clinical variations, such as SDB.

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**Author Contributions:** J.Z. is responsible for conceptualization, methodology, writing of the original draft, and project administration. J.X. is responsible for verification of the results, formal analysis, review of the writing, and editing. A.C. is responsible for investigation, resources, and software. Y.K. contributed a substantive effort for literature selection in databases, data curation, review of the writing, and editing. X.L. is responsible for visualization of the data in figures and tables, data curation, updated imaging, and writing of the original draft. M.M. contributed a substantive effort for verification of the results, interpretation of data, and writing of the original draft. S.S. is responsible for methodology, supervision of the research activity planning and execution, review of the writing, and editing. All authors have approved the final version of the manuscript.

**Statement of Ethics:** The present study was based on previously published articles and, as such, did not require ethics approval or patient consent.

**Conflict of Interest Disclosure:** The authors have no conflicts of interest to declare.

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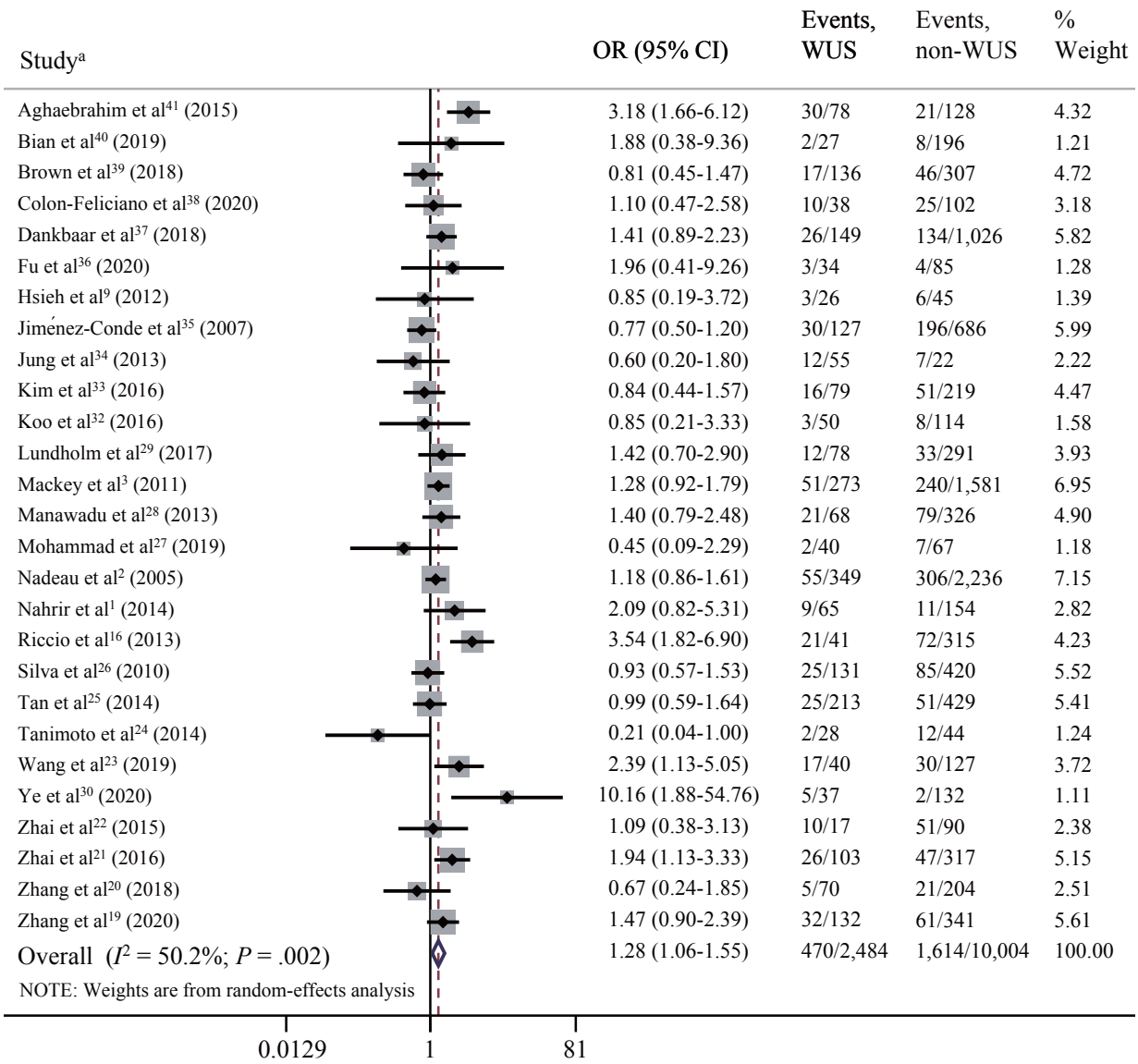


**Fig. 4** Forest plot that shows a significantly higher prevalence of AF ($P$ = .01) among patients with WUS than those with NWUS. $P \leq .05$ was considered statistically significant. Atrial fibrillation was considered a potential risk factor in the occurrence of WUS.

[a] The studies of Turin et al[14] and Liu et al[31] provided no relevant data on AF and therefore were not included in the analysis.

AF, atrial fibrillation; NWUS, non–wake-up stroke; OR, odds ratio; WUS, wake-up stroke.


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