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ABOUT COVER

Editorial Board Member of *World Journal of Clinical Cases*, M Anwar Iqbal, PhD, Professor, Department of Pathology and Laboratory Medicine, University of Rochester Medical Center, Rochester, NY 14642, United States. anwar_iqbal@urmc.rochester.edu

AIMS AND SCOPE

The primary aim of *World Journal of Clinical Cases* (*WJCC*, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

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The *WJCC* is now indexed in Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, PubMed, and PubMed Central. The 2021 Edition of Journal Citation Reports® cites the 2020 impact factor (IF) for *WJCC* as 1.337; IF without journal self cites: 1.301; 5-year IF: 1.742; Journal Citation Indicator: 0.33; Ranking: 119 among 169 journals in medicine, general and internal; and Quartile category: Q3. The *WJCC*'s CiteScore for 2020 is 0.8 and Scopus CiteScore rank 2020: General Medicine is 493/793.

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SYSTEMATIC REVIEWS

Atrial fibrillation burden and the risk of stroke: A systematic review and dose-response meta-analysis

Sheng-Yi Yang, Min Huang, Ai-Lian Wang, Ge Ge, Mi Ma, Hong Zhi, Li-Na Wang

ORCID number: Sheng-Yi Yang 0000-0002-5841-4674; Min Huang 0000-0003-3092-2105; Ai-Lian Wang 0000-0002-2821-3863; Ge Ge 0000-0002-5733-2634; Mi Ma 0000-0003-2791-0998; Hong Zhi 0000-0001-7462-325X; Li-Na Wang 0000-0003-3665-5706.

Author contributions: Yang SY and Huang M designed the search strategy, performed the literature search and collected the data; Yang SY wrote the manuscript; Ma M checked the data; Ge G performed quality assessment and reviewed the level of evidence; Wang LN designed the project and edited the manuscript; Zhi H helped revised the manuscript for language; Wang AL checked the data; all authors read and approved the manuscript.

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Sheng-Yi Yang, Min Huang, Ge Ge, Mi Ma, Department of Epidemiology and Biostatistics, Southeast University, Nanjing 210009, Jiangsu Province, China

Ai-Lian Wang, Yaohua Community Healthcare Center, Nanjing 210046, Jiangsu Province, China

Hong Zhi, Department of Cardiology, Zhongda Hospital, Nanjing 210009, Jiangsu Province, China

Li-Na Wang, School of Public Health, Southeast University, Nanjing 210009, Jiangsu Province, China

Corresponding author: Li-Na Wang, Doctor, Associate Professor, School of Public Health, Southeast University, No. 87 Ding Jiaqiao Road, Nanjing 210009, Jiangsu Province, China. lnwang@seu.edu.cn

Abstract

BACKGROUND

The increased stroke risk associated with atrial fibrillation (AF) burden exceeding 5 min is a matter of debate. In addition, the potential linear or nonlinear relationship between AF burden and stroke risk has been largely unexplored.

AIM

To determine the association between AF burden > 5 min and the increased risk of stroke and explore the potential dose-response relationship between these two factors.

METHODS

Sixteen studies from six databases with 53141 subjects (mean age 65 years) were included. Fifteen studies were observational studies, and one was a randomized controlled trial study. The potential nonlinear dose-response association was characterized using a restricted cubic splines regression model. AF burden for each 1 h and 2 h was associated with an increased risk of stroke. Trial sequential analysis with a random-effect model was used to evaluate the robustness of the evidence from the included 16 studies.

RESULTS

AF burden > 5 min was associated with an increased risk of clinical AF [adjusted risk ratio (RR) = 4.18, 95% confidence interval (CI): 2.26-7.74]. However, no

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association was found with an increased risk of all-cause mortality (adjusted RR = 1.55, 95%CI: 0.87-2.75). Patients with AF burden > 5 min had an increased risk of stroke (adjusted RR = 2.49, 95%CI: 1.79-3.47). Moreover, a dose-response analysis showed that the increased stroke risk was paralleled by an increase in AF burden at a rate of 2.0% *per* hour ($P_{nonlinear}$ = 0.656, RR = 1.02, 95%CI: 1.01-1.03). Trial sequential analysis provided robust evidence of the association between AF burden > 5 min and an increased risk of stroke.

CONCLUSION
AF burden was a significant risk factor for clinical AF and future stroke. A significant linear association was documented between increased AF burden and risk of future stroke.

Key Words: Atrial fibrillation; Stroke; Dose-response; Meta-analysis; Risk

Core Tip: We performed a systematic review and meta-analysis to determine whether atrial fibrillation (AF) burden > 5 min was associated with increased risk of stroke and to explore the dose response effect of AF burden on the future stroke. A significant linear association was documented between increased AF burden and risk of future stroke.

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INTRODUCTION

Atrial fibrillation (AF) is one of the most frequent cardiac arrhythmias. Reports suggest that an estimated 12.1 million people will suffer from this condition in the United States by 2030 and 17.9 million people in Europe by 2060[1,2]. It has been established that patients with AF have a 3 to 5-fold increased risk of stroke, and subjects with AF-related embolic stroke have a worse progression than those who experience stroke not related to AF[3-5]. With the widespread use of cardiac implantable electronic devices (CIEDs) and wearable devices, it is now possible to monitor the time and frequency of AF episodes. The American Heart Association recommends that the AF burden should be defined as the duration of the longest AF episode during a defined monitoring period[6].

Some studies demonstrated an association between AF burden and stroke risk, but few mentioned the existence of a dose-response effect. The Italian AT 500 registry study showed that patients with device-detected AF episodes of > 24 h had a 3.1-fold increased risk of stroke. In contrast, patients with AF episodes of > 5 min and < 24 h experience no significant increase in stroke risk[7]. Moreover, the ASSERT Clinical Trial reported episodes lasting > 6 min were associated with an increased risk of ischemic stroke or systemic embolism[8]. A recent systematic review demonstrated the AF burden exceeding different thresholds was associated with an increased risk of stroke; however, they did not provide a definite threshold for AF burden at stroke risk [9]. It is a matter of controversy whether an AF burden of > 5 min can increase the risk of stroke, and no studies have reported the potential dose-response effect on stroke. Accordingly, we performed a systematic review and meta-analysis to determine the association between AF burden > 5 min and the increased risk of stroke and explored the dose-response effect between these two factors.

MATERIALS AND METHODS

This systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines[10].

Search strategy

The literature search was performed by two researchers (YSY and HM) with the help of an experienced medical reference librarian. Studies were retrieved by searching electronic databases (PubMed, EMBASE, Medline, Cochrane, Web of Science) from inception until February 28, 2020. The following search terms were used: AF, physiological monitoring, implantable cardiac monitor, artificial pacemaker, electrocardiograph, burden, stroke, cerebrovascular disorders, brain infarction and thromboembolic event. The language of publication was restricted to English. We also retrieved the reference lists of included articles and previous reviews to identify potential studies as comprehensively as possible. All retrieved references were exported to EndNote X9, and duplicate citations were removed.

Inclusion criteria and exclusion criteria

Two investigators (YSY, HM) independently assessed the eligibility of the studies identified. The inclusion criteria included: (1) Studies that described AF burden within 1 d or more; (2) Studies that described the method used to quantify AF burden such as a pacemaker, implantable cardioverter-defibrillator and cardiac-resynchronization device; and (3) Studies where clinical outcomes included stroke, ischemic stroke, systematic embolism, transient ischemic attack or other thromboembolic events. The combined endpoint of these outcomes was also included: (1) Studies that directly and/or indirectly provided the relative risk of the outcome, including hazard ratio (HR), risk ratio (RR) and odds ratio (OR) values; (2) Observational studies or randomized controlled trials (RCTs); and (3) Studies where the study design and methods were described in detail.

However, reviews, conference abstracts, editorials, case reports, duplicate publications and cross-sectional studies were excluded.

Data extraction

Two researchers (YSY and HM) independently extracted the following information from the included studies: Study type, significant AF burden definition, adverse outcomes, sample size, follow-up period, the method for AF monitoring and others. The number of cases and HR, RR, OR for the risk of the adverse outcomes for different AF burdens were also recorded. HRs provided by original studies were considered as adjusted RRs. We also contacted the authors for additional data or any clarification if necessary. Disagreements were resolved by a consensus-based discussion.

Quality assessment and the level of evidence

The quantitative assessment tool 'QualSyst'[11] and the Oxford Centre for Evidence-Based Medicine 2009 Level of Evidence Tool[12] were used to assess the methodological quality and the evidence levels of the included studies by two researchers (YSY and HMJ). The 'QualSyst' scoring system included 14 criteria with three possible answers: Yes, No, and Partial. "Yes" = 2 points, "No" = 0 points and "Partial" = 1 points. Items not applicable to a particular study design were marked 'NA' and were excluded from calculating the summary score. A summary score was calculated for each article based on the evaluation criteria. A score greater than 75% of the summary score indicated strong quality, a score ranging from 55% to 75% indicated moderate quality, and a score lower than 55% indicated poor quality. The level of evidence was assessed according to the type of study, and each subgroup level included five levels.

Data synthesis and statistical analysis

Sufficient data were obtained to calculate the incidence of AF burden and stroke. Adjusted RRs and 95% confidence interval (CI) were extracted from each study. A meta-analysis was used to pool the relative risks of each study. Chi-squared-based Q test and the I^2 value were used to evaluate the heterogeneity within the studies. The random-effects meta-analysis model was used when the heterogeneity was statistically significant ($I^2 > 50\%$, $P < 0.05$)[13]. Publication bias was assessed by Egger's test. A P value < 0.05 was statistically significant.

The potential linear or nonlinear dose-response effect was evaluated using a restricted cubic splines regression model, where the AF burden was associated with an increased risk of stroke every 1 min[14]. We further explored the increased risk of

stroke *per* hour. Four knots at the 5th, 35th, 65th and 95th percentiles of AF burden were used in the regression model. The nonlinear *P* value was calculated by testing the null hypothesis that the second spline coefficient was equal to zero[15]. If $P_{nonlinear}$ was greater than 0.05, the linear dose-response effect was statistically significant.

Moreover, when the AF burden was not a definite value, the midpoint between the upper and lower boundaries was considered as the average AF burden; when the lowest level was an open interval, the lowest dose was assumed to be 0; when the highest category was open-ended, a value with 1.5 times of the boundary of the highest dose was considered the dose[16]. Trial sequential analysis (TSA) was used to evaluate the statistical power of the current sample size and provide robust evidence of the effect of AF burden on the stroke risk[17]. Heterogeneity-adjusted required information size was calculated with $\alpha = 0.05$, $\beta = 0.2$ and a relative risk reduction of 30%.

The meta-analysis was conducted using Review Manager (v5.3). The potential dose-response association was conducted by STATA software (v15.0, College Station, TX, United States). TSA was conducted with TSA 0.9.5.10 Beta software (http://www.ctu.dk.tsa)[18].

RESULTS

Identification of studies

The search strategy yielded a total of 10479 abstracts from five English databases, while a manual search of the references cited in other available included articles and previous reviews yielded an additional 372 abstracts. After removing duplicates, 7827 studies remained. After abstract screening, 7004 studies were excluded. The remaining 823 full-texts were assessed for eligibility based on the inclusion and exclusion criteria, and 807 studies were excluded for the following reasons: 412 were not original articles, 218 lacked detailed data on AF burden and 126 did not provide information on the clinical outcomes, 44 had a history of AF or stroke, and seven were cross-sectional studies. Finally, 16 studies were included in the quantitative synthesis (Figure 1).

Characteristics of the involved studies

Table 1 shows the characteristics of the included 16 studies, all except one were RCT studies[7,8,19-32]. The detected devices for AF burden included one or more of the three following devices: Pacemaker, implantable cardioverter-defibrillator and cardiac-resynchronization device. The 16 studies included 53141 subjects with mean or median ages > 65 years. Except for case-crossover study, subjects in all studies were followed up for at least 1 year to ascertain the clinical outcomes[25]. Four studies were multinational consortium studies; six were conducted in European countries, four in North American countries and two in Asian countries.

Table 2 shows the quality evaluation and the evidence level for each study. Twelve studies were associated with scores higher than 21. The levels of evidence ranged from 1b to 3a, and most were considered level 2b evidence.

The incidence of AF burden > 5 min and stroke

Eleven studies provided data on the incidence of AF burden > 5 min. The detectable rate of AF burden > 5 min ranged from 10.12% to 70.77% among CIED patients, and AF burden > 24 h ranged from 6.70% to 39.26%. Overall, AF burdens > 5 min and > 24 h were detected in 26% (95%CI: 1%-52%) and 15% (95%CI: 6%-35%) of patients within the follow-up period, respectively, and the pooled incidence of stroke was 2.80% (95%CI: 1.56%-4.03%).

Association between AF burden > 5 min and future stroke risks

Sufficient data were obtained to calculate the crude RR for stroke associated with AF burden > 5 min in each study. The average follow-up for the 11 studies ranged from 12 to 67 mo (mean = 36.18 mo). The random-effects pooled analysis revealed that patients with AF burden > 5 min had a 67% increased risk of stroke (RR = 1.67, 95%CI: 1.25-2.25) compared with patients with AF burden < 5min (Figure 2A). Significant heterogeneity was found within the included studies ($I^2 = 52\%$, $P = 0.020$). The funnel plot was symmetrical, and Egger's test showed no significant publication bias ($t = 1.56$, $P = 0.150$).

Six of the included studies provided adjusted RRs on the strength of association between AF burden > 5 min and the stroke risk. In these six studies, the average

Table 1 Characteristics of the included 16 studies, all except 1 were randomized controlled trial studies

Ref.[1]	Study type	Significant AF burden definition	Adverse outcomes	Sample size	Follow-up period	AF monitoring	Age (male/female)	Nation	Population
Glotzer *et al*[19], 2003, Ancillary MOST	Secondary analysis of multicenter RCT	AF rate > 220 bpm, AF burden ≥ 5 min	Stroke/systematic embolism	312	Median: 27 mo	PM	74 yr (141/171)	United States	Patients with sinus node disease who required PM for bradycardia and a history of AF
Capucci *et al*[7], 2005, Italian AT 500 Registry	Prospective, observational study	AF rate > 174 bpm, AF burden ≥ 5 min or ≥ 1 d	Thromboembolic event	725	Median: 22 mo	PM	72 yr (360/365)	Italy	Patients with symptomatic atrial tachyarrhythmias and a history of AF. Permanent AF were excluded
Botto *et al*[20], 2009, NA	Prospective, observational study	AF rate > 174 bpm, AF burden ≥ 5 min or ≥ 1 d	Stroke/systematic embolism	568	Mean: 1 yr	PM	70 yr (NA)	Italy	Patients with a class I or II American College of Cardiology/American Heart Association indication for dual-chamber PM, symptomatic atrial tachyarrhythmias and a history of AF. Permanent AF were excluded
Glotzer *et al*[21], 2009, TRENDS	Prospective, observational study	AF rate > 175 bpm, AF burden ≥ 20 s	Ischemic stroke, TIA, and systemic embolism	2486	Mean: 1.4 yr	PM, ICD or CRT	70 yr (1650/836)	International	Patients with an established class I/II indication for an ICD or stroke risk factor and a history of AF. Permanent AF were excluded
Healey *et al*[8], 2012, ASSERT ClinicalTrials	Prospective, observational study	AF rate > 190 bpm, AF burden□6 min	Ischemic stroke or systemic embolism	2580	Mean: 2.5 yr	PM or ICD	77 yr (1506/1074)	International	Patients who had a history of hypertension, but no AF
Shanmugam *et al*[22], 2012, Home Monitor CRT	Prospective, observational study	AF rate > 180 bpm, AF burden > 14 min	Thromboembolic event	560	Median: 370 d	PM or ICD	66 yr (434/136)	Europe	Patients with a heart failure, CRT and a history of AF. Permanent AF were excluded
Gonzalez *et al*[23], 2014, NA	Retrospective, observational study	AF rate > 178 bpm, AF burden ≥ 5 min	Stroke and all-cause mortality	224	Median: 6.6 yr	PM	74 yr (118/106)	United States	Consecutive patients with no history of AF who underwent dual-chamber PM implantation
Boriani *et al*[24], 2014, SOS AF project (PANORAMA, TRENDS, ClinicalService)	Prospective studies	AF rate > 175 bpm, AF burden > 5 min	Ischemic stroke or TIA events	10016	Median: 2 yr	PM or ICD	70 yr (6859/3157)	International	Patients who had at least months of follow-up and with a history of AF. Permanent AF were excluded
Turakhia *et al*[25], 2015, NA	Case-Crossover	AF burden > 5.5 h in a day during a defined 30-d period	Ischemic Stroke	9850	Case period: 1-30 d Control period: 91-120 d	PM or ICD	NA	United States	Patients with CIEDs remotely monitored in the Veterans Administration Health Care System and a history of AF
Witt *et al*[26], 2015, NA	Retrospective, observational study	AF burden > 6 min	Thromboembolic events	394	Median: 4.2 yr	CRT	67 yr (290/104)	Denmark	Patients with a CRT device, and no history of AF
Benezet-Mazuecos *et al*[27], 2015, NA	Prospective, observational study	AF rate > 225 bpm, AF burden ≥ 5 min	Silent ischemic brain lesions	109	Median: 2 yr	PM, ICD or CRT	74 yr (61/48)	Europe	Patients with PMs, ICDs, and CRT capable of atrial activity monitoring, and with no history of AF
Van Gelder *et al*[28], 2017, ASSERT ClinicalTrials	Prospective, observational	AF rate > 190 bpm, AF burden > 6 min	Ischemic stroke or systemic embolism	2455	Mean: 2.5 yr	PM or ICD	NA	International	Patients with hypertension but no prior AF requiring medical therapy

	study								
Chu *et al*[29], 2020, NA	Retrospective, observational study	AF rate > 250 bpm, AF burden > 6 min	Ischemic stroke, transient ischemic attack, or systemic embolism	152	Median: 67 mo	PM	73.2 yr (86/66)	China	Patients who were with a dual-chamber PM and a history of AF
Kaplan *et al*[30], 2019, NA	Retrospective, observational study	AF burden > 6 min	Ischemic Stroke and systemic embolism	21768	NA	PM, ICD or CRT	68.6 yr (13611/8157)	United States	Patients who had a cardiovascular diagnosis code or had a cardiovascular related procedure performed during the data collection period and with a history of AF
Li *et al*[31], 2019, The West Birmingham Atrial Fibrillation Project	Prospective, observational study	AF rate > 175 bpm, AF burden > 5 min	Thromboembolic event	594	Median: 4.2 yr	PM, ICD or CRT	69 yr (360/234)	United Kingdom	Patients receiving a PM, ICD, or CRT between Januar1999 and January 2017
Nakano *et al*[32], 2019, NA	Retrospective, observational study	AF rate > 200 bpm	Embolic stroke	348	Median: 65 mo	PM or ICD	70 yr (224/124)	Japan	Patients receiving PMs and ICDs between May 1980 and May 2016

[1]Healey *et al*[8], 2012 and Van Gelder *et al*[28], 2017 were both from ASSERT clinical Trials and were used for analysis the association between atrial fibrillation burden > 5 min and future stroke, the dose-response association, respectively. PM: Pacemaker; ICD: Implantable cardioverter-defibrillator; CRT: Cardiac-resynchronization device; NA: Not applicable; AF: Atrial fibrillation.

follow-up time ranged from 24 to 67 mo (mean = 36.90 mo). Notwithstanding that Li *et al*[31] found a higher annual incidence of stroke in patients with AF burden > 5 min (1.85% *vs* 1.14%), the difference was not statistically significant (adjusted RR = 1.31, 95%CI: 0.51-3.38)[31]. The other five studies indicated that the annual incidence of stroke for AF burdens > 5 min and < 5 min ranged from 1.69 to 3.1 and 0.58 to 1.4 *per* 100 patient-years, respectively. The fixed-effect pooled analysis revealed that patients with AF burden > 5 min had a 2.49-fold increase in the risk of stroke (adjusted RR = 2.49, 95%CI: 1.79-3.47) compared with patients with AF burden < 5min (Figure 2B). There was no significant heterogeneity (I^2 = 0%, P =0.620) and publication bias (t = 1.08, P = 0.340) among these studies.

TSA of ten studies showed that 71.5% (37144 out of 51978 patients) of the heterogeneity-adjusted information size required was accrued. We also found that the cumulative Z curve crossed the trial sequential monitoring boundary, providing robust evidence of the association between the AF burden > 5 min and increased risk of stroke based on the sample size (Figure 3).

Subgroup analyses of association between AF burden > 5 min and the future stroke risk

The fixed-effect pooled analysis performed with adjusted RRs revealed that patients with AF burden > 5 min had a 1.23-fold increase in risk of stroke (RR = 2.23, 95%CI: 1.48-3.35), compared to AF burden < 5 min among patients with no history of AF. Moreover, patients with AF burden > 5 min had a 2.14-fold increase in the risk of stroke (adjusted RR = 2.14, 95%CI: 1.23-3.72) compared to AF burden < 5 min among patients not on anticoagulation therapy. The detailed results of subgroup analyses

Table 2 Quality evaluation and the evidence level for each study

Ref.	Question described	Appropriate study design	Appropriate subject selection	Characteristics described	Random allocation	Investigators blinded	Subjects blinded	Outcome and measures well defined and robust to bias	Sample size appropriate	Analytic methods appropriate	Estimate of variance reported	Controlled for confounding	Results reported in detail	Conclusion supported by results?	Rating	Levels of evidence
Glotzer *et al* [19], 2003	2	2	2	2	2	NA	2	2	2	2	2	2	2	2	S	1b
Capucci *et al* [7], 2005	2	2	1	1	0	NA	0	2	2	2	2	2	2	2	M	2b
Botto *et al* [20], 2009	2	2	2	2	0	NA	0	2	2	2	2	1	2	2	S	2b
Glotzer *et al* [21], 2009	2	2	1	2	0	NA	0	2	2	2	2	1	2	2	M	2b
Healey *et al* [8], 2012	2	2	2	2	1	NA	2	2	2	2	2	2	2	2	S	2b
Shanmugam *et al*[22], 2012	2	2	1	2	0	NA	0	2	2	2	2	2	2	2	S	2b
Gonzalez *et al*[23], 2014	2	2	1	1	0	NA	0	2	1	2	2	2	2	2	M	2b
Boriani *et al* [24], 2014	2	2	1	2	0	NA	0	2	2	2	2	2	2	2	S	2b
Turakhia *et al*[25], 2015	2	2	2	2	0	NA	0	2	2	2	2	2	2	2	S	3a
Witt *et al* [26], 2015	2	2	2	2	0	NA	0	2	2	2	2	2	2	2	S	2b
Benezet-Mazuecos *et al*[27],	2	2	2	2	0	NA	0	2	1	2	2	2	2	2	S	2b
Van Gelder *et al*[28], 2017	2	2	2	2	1	NA	2	2	2	2	2	2	2	2	S	2b
Chu *et al*	2	2	1	1	0	NA	0	2	1	2	2	2	2	2	M	2b

[29], 2020																
Kaplan *et al* [30],	2	2	2	2	0	NA	0	2	2	2	2	2	2	2	S	2b
Li *et al*[31], 2019	2	2	2	2	0	NA	0	2	2	2	2	1	2	2	S	2b
Nakano *et al* [32], 2019	2	2	2	2	0	NA	0	2	2	2	2	1	2	2	S	2b

The quantitative assessment tool 'QualSyst' and the Oxford Centre for Evidence-Based Medicine (OCEBM) 2009 Level of Evidence Tool were used to access the methodological quality and the evidence levels. NA: Not applicable; 2 indicates yes, 1 indicates partial, 0 indicates no. Quality scores: ≥ 75% strong (S), 55%-75% moderate (M), ≤ 55% weak (W).

with different populations are shown in Supplementary Table 1.

Does-response relationship between AF burden and the future stroke risk

Seven studies were included in the dose-response meta-analysis on the association between AF burden and stroke. The potential linear or nonlinear dose-response association was evaluated using a restricted cubic splines regression model. A linear dose-response relationship ($P_{nonlinear}$ = 0.656) was found (Figure 4), and AF burden was associated with 2.0% and 3.0% increased risks of stroke for every 1 h (RR = 1.02, 95%CI: 1.01-1.03) and 2 h (RR = 1.03, 95%CI: 1.02-1.05), respectively.

AF burden and risk of clinical AF

Three of the included studies, including 3286 patients, provided adjusted RRs values of the AF burden > 5 min on the risk of clinical AF. The random-effect pooled analysis reveal that patients with AF burden > 5 min had a 3.18 fold increased risk of clinical AF (adjusted RR = 4.18, 95%CI: 2.26-7.74) compared with the patient suffering AF burden < 5 min (Figure 5). The heterogeneity was significant among the different study designs (I^2 = 77%, P = 0.010), RCT[19] and two retrospective observational studies[8,26]. The funnel plot was symmetrical and no significant publication bias was found in the Egger's test (t = 0.80, P = 0.570).

AF burden and the risk of all-cause mortality

The reported adjusted RRs for the strength of association between AF burden > 5 min and risk of all-cause mortality in three studies differed. An ancillary study of the Mode Selection Trial trial[19] included patients with sinus node disease who were in sinus rhythm at the time of pacemaker implantation and aged > 21 years. Two studies[23,26] included patients with no history of AF. The random-effects pooled analysis found that patients with AF burden > 5 min had a 55% increased risk of all-cause mortality (adjusted RR = 1.55, 95%CI: 0.87-2.75) (Figure 6); however, significant heterogeneity (I^2 = 68%, P = 0.040) and publication bias (t = -21.13, P = 0.030) were present in this

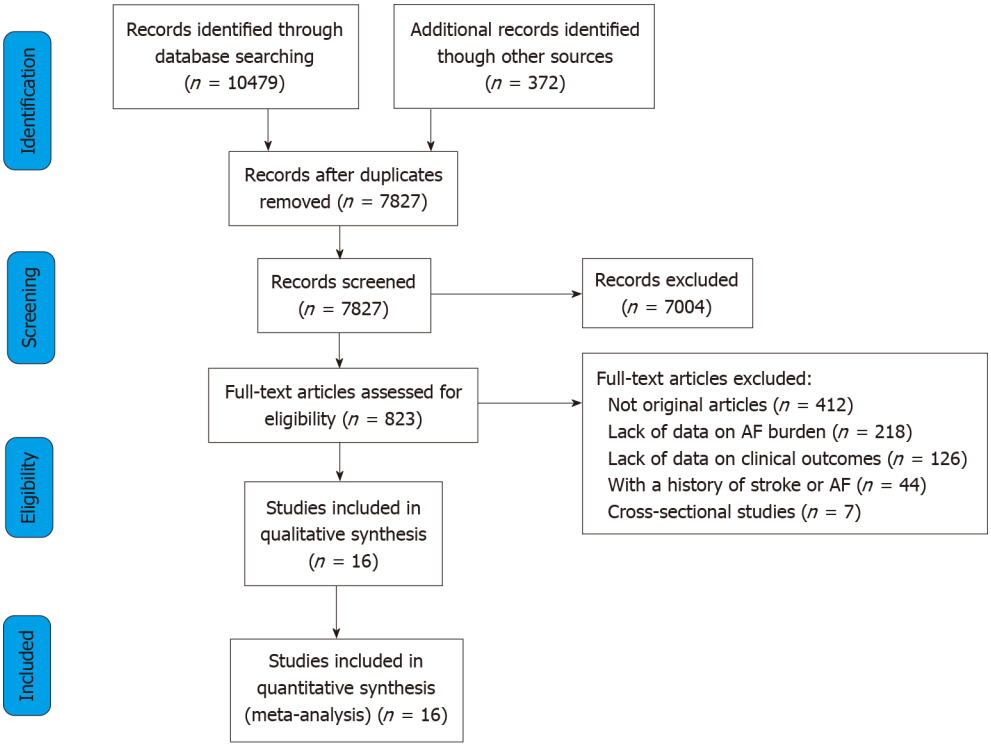

Figure 1 Flow diagram of the study selection process.

analysis.

DISCUSSION

In this systematic review and dose-response meta-analysis on the association between AF burden and the risk of stroke, 16 original studies were included, including 53141 CIED patients. First of all, we found that patients with an AF burden > 5 min had an increased risk of stroke. Moreover, a linear dose-response relationship was found; the risk of stroke was increased by 2.0% *per* hour among subjects with AF burden > 5 min. Last but not least, we found AF burden > 5 min was associated with a significantly increased risk of clinical AF but not associated with an increase in all-cause mortality.

AF burden: A significant risk factor for stroke

Data from each study were extracted to calculate the crude RRs without considering the time-to-event endpoints. The pooled results indicated that patients with AF burden > 5 min had a higher stroke risk. That significant heterogeneity was detected for the pooled analysis of the relationship between AF burden and stroke risk (I^2 = 52%, P = 0.02). The heterogeneity might be associated with the variations in patient populations, hypertension, prior AF and antithrombotic therapy, *etc*.[33]. The population included in our study had different comorbidities, including patients with symptomatic atrial tachyarrhythmias[7,20], sinus node disease[19] and heart failure[22]. Moreover, some studies provided no information on patient history of AF[8,23,26-28]. Besides, in the study by Chu *et al*[29], patients with oral anticoagulants for any reason were excluded. However, even though anticoagulants were used in different proportions of patients at baseline, we found that the heterogeneity was not significant. With the pooled data of HRs adjusted for one or more known embolism predictors [including age, sex, heart failure, prior stroke diabetes, congestive heart failure, hypertension, age 75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65 to 74 years, sex category (CHA2DS2-VASc) score], we found that an AF burden > 5 min was associated with an increased risk of stroke (I^2 = 0, P = 0.62).

We found that subjects with AF burden of > 5 min had a 67% increased risk of stroke. Recently, a meta-analysis also found that subclinical AF (pooled with highest AF duration cut-off values from the original studies) was associated with a 2.4-fold increased risk of stroke[9]. These results indicated that the risk of stroke was higher among the subjects with the serious AF burden. This finding provides novel insights

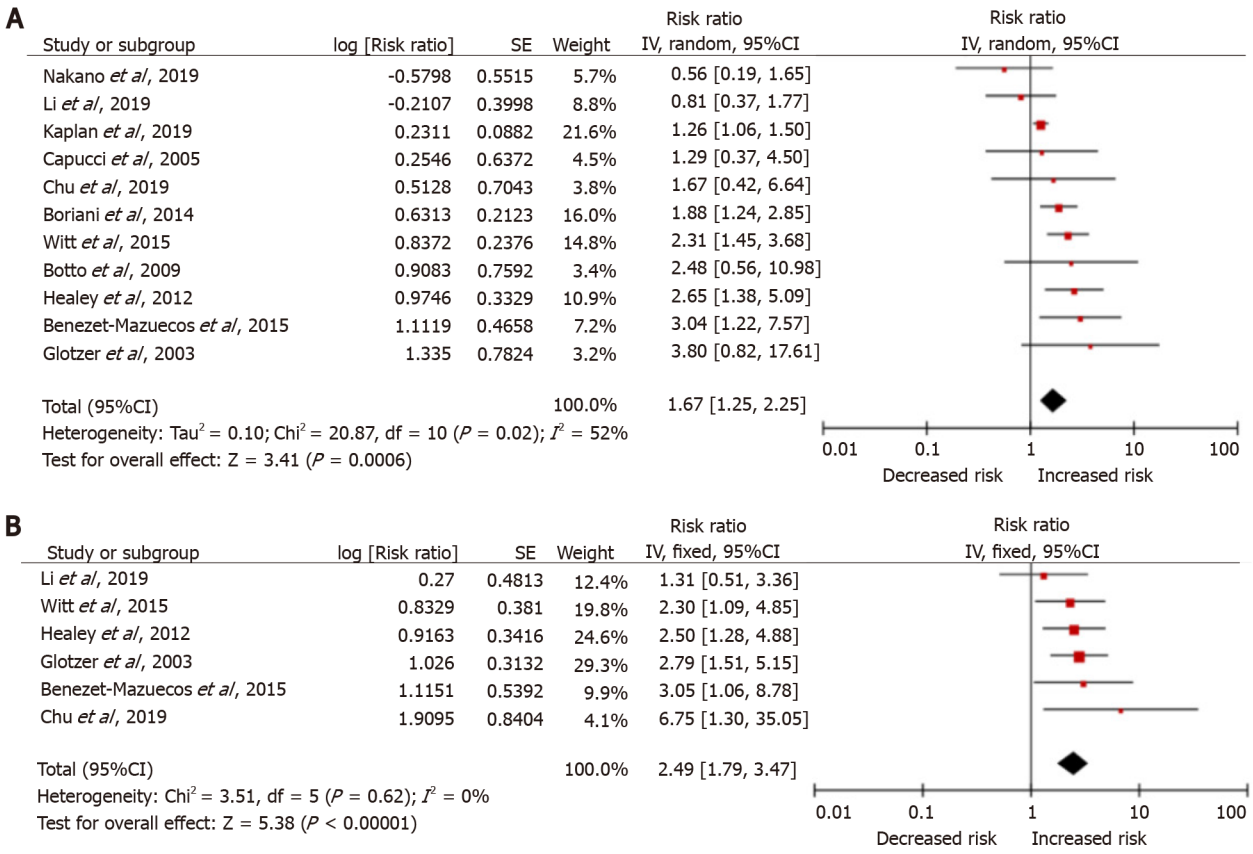

Figure 2 Meta-analysis forest plot: Atrial fibrillation burden and the risk of future stroke. A: Crude risk ratio (RR) model; B: Adjusted RR model; SE: Stand error; CI: Confidence interval.

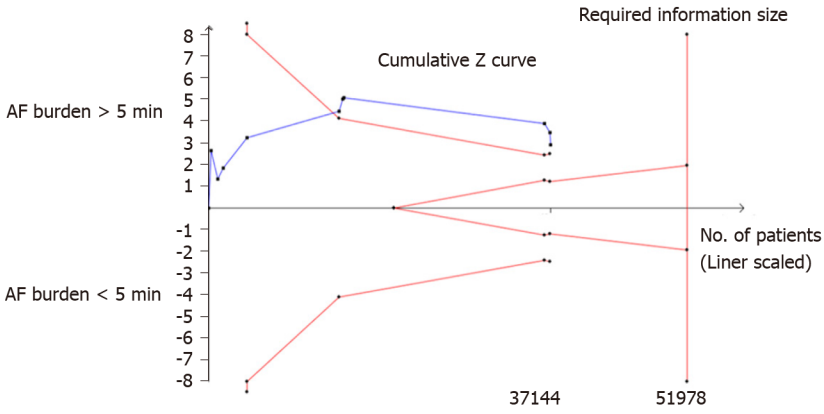

Figure 3 Trial sequential analysis of atrial fibrillation burden > 5 min. Heterogeneity adjusted required information size of 51978 participants calculated on basis of incidence of 2.37% in control group, relative risk reduction of 30%, α = 5%, β = 20%, and I^2 = 30%. Actually, accrued number of participants was 37144, 71.5% of required information size. AF: Atrial fibrillation.

that can be used to develop stroke prophylaxis approaches for AF patients.

Consistently, Shanmugam *et al*[22] found that a higher AF burden (AF burden > 3.8 h) was associated with a 9.4-fold risk of stroke among CIED patients. Two studies[28, 30] also reported that patients with AF burden > 24 h had an increased risk of stroke. However, these results were inconsistent with a study by Healey *et al*[8], which could be accounted for by the fact that patients who experienced long periods of sinus rhythm and the better treatment of stroke had no history of AF[8].

The European and American[34] guidelines recommend estimating stroke risk in AF patients based on the CHA2DS2-VASc score. Moreover, an oral anticoagulant is recommended to reduce thromboembolic stroke risk in patients with AF, especially male patients with a CHA2DS2-VASc score of 1 and female patients with a CHA2DS2-

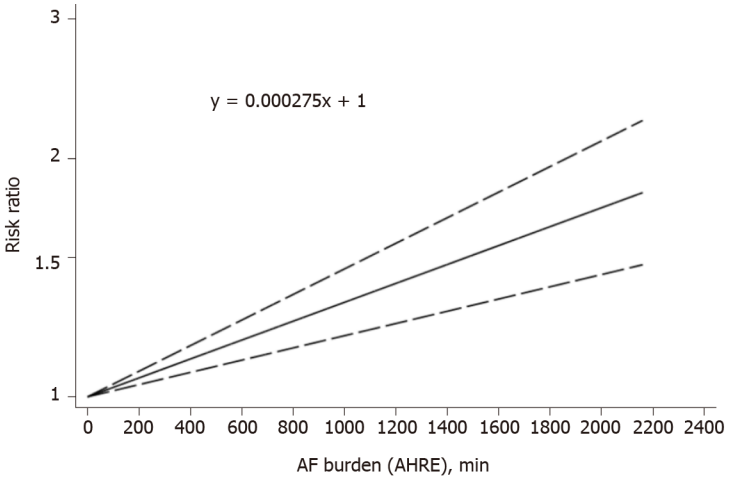

Figure 4 Random-effects liner dose-response association between atrial fibrillation burden and the risk future stroke ($P_{nonlinear}$ = 0.656). AF: Atrial fibrillation.

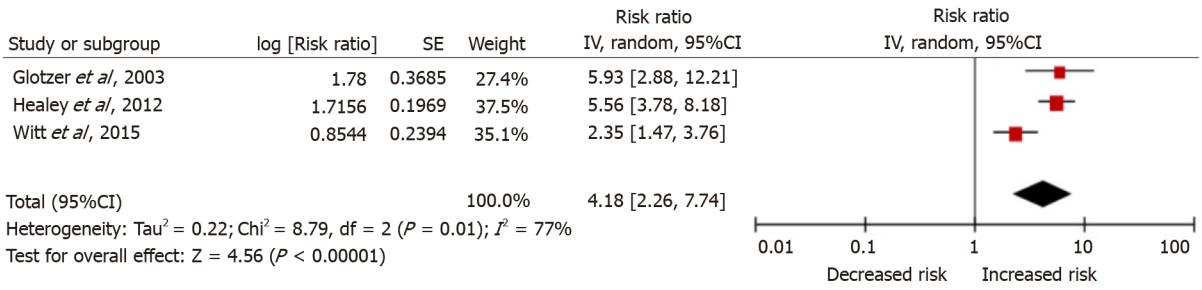

Figure 5 Adjusted risk ratio meta-analysis forest plot: Atrial fibrillation burden and the risk of clinical atrial fibrillation. SE: stand error; CI: confidence interval.

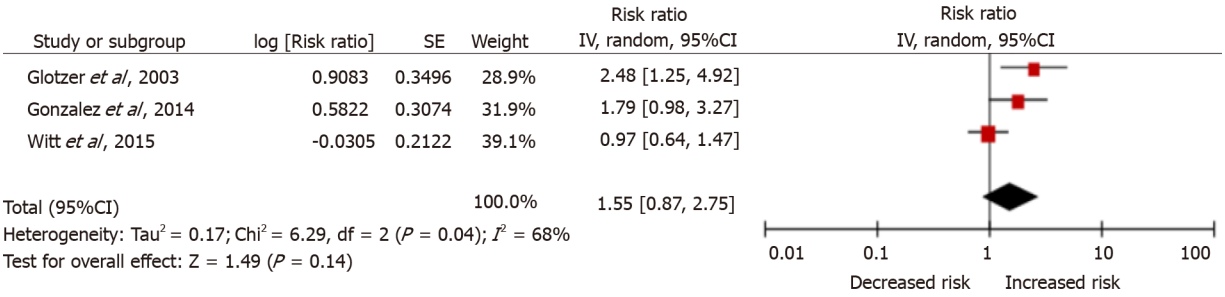

Figure 6 Adjusted risk ratio meta-analysis forest plot: Atrial fibrillation burden and the risk of all-cause mortality. SE: Stand error; CI: Confidence interval.

VASc score of 2. Interestingly, some studies explored the association between AF burden and CHA2DS2-VASc scores. Botto *et al*[20] indicated that patients with a CHADS2 score of 1 or 2 had either a high or low stroke risk consistent with a high or low detected AF duration, respectively. Kaplan *et al*[30] also found an interaction between AF duration and CHA2DS2-VASc score. The risk of systemic embolism in patients with intermediate CHA2DS2-VASc scores was variable and correlated with the maximum AF burden. Accordingly, the stroke risk among AF patients should be evaluated based on the CHA2DS2-VASc score and AF burden to provide better personalized anticoagulation decisions.

Association between AF burden and risk of clinical AF or all-cause mortality

Clinical AF is a chaotic heart rhythm characterized by an irregular and often rapid heart rate documented with a 12-lead electrocardiogram. Electrocardiogram-documented AF was confirmed in 38.9% of patients with AF burden and 2.1% without

AF burden[19]. Our study found that AF burden > 5 min was associated with an increased risk of clinical AF. Furthermore, progression from paroxysmal to persistent or permanent AF might be faster in patients with subclinical AF who did not receive treatment. Consequently, more emphasis should be placed on screening patients with AF burden > 5 min and providing timely therapy.

Our study demonstrated that AF burden was not associated with all-cause mortality. However, there was significant heterogeneity in this meta-analysis. Indeed, further research is required to explore the role of AF burden on all-cause mortality.

Limitations

Even though this meta-analysis was performed utilizing crude RRs and adjusted RRs, there are still some limitations. Owing to the lack of adjusted RRs corresponding to three or more groups of AF burden, this meta-analysis was conducted without considering the time-to-event points and adjusting for confounding factors. Furthermore, patients with CIEDs might have diabetes, hypertension and other stroke risk factors, which might lead to an overestimation of the effect of AF on stroke. Underreporting of stroke and prescribing an oral anticoagulant to patients with higher AF burden might also lead to underestimating the impact of AF burden on the stroke risk. However, anticoagulation was used in the different subgroups of patients who had comorbidities at the baseline. Finally, publication bias was present in this study. Our results might have been influenced by non-published studies or language bias as we only included studies published in English.

CONCLUSION

This meta-analysis demonstrated that AF burden is a significant risk factor for clinical AF and stroke. There is a linear dose-response between AF burden and risk of stroke. Further studies are needed to validate this effect and evaluate the cut-off value for AF burden among patients requiring anticoagulation treatment.

ARTICLE HIGHLIGHTS

Research background

With the widespread use of cardiac implantable electronic devices and wearable devices, it is nowadays possible to monitor the atrial fibrillation (AF) burden. However, whether an AF burden of > 5 min can increase the risk of stoke is still highly controversial, and the potential linear or nonlinear relationship between them remains largely unexplored.

Research motivation

A comprehensive systemic review and meta-analysis can summarize the results of available studies and help doctors in the clinical decision-making process.

Research objectives

This meta-analysis aimed to determine the association between AF burden > 5 min and the increased risk of stroke and explore a dose-response effect of AF burden on the risk of stroke.

Research methods

Studies were identified by searching electronic databases (PubMed, EMBASE, Medline, Cochrane and Web of Science) from inception until February 28, 2020. The potential nonlinear dose-response association was evaluated using a restricted cubic splines regression model. AF burden was associated with an increased risk of stroke for every 1 h and 2 h. Trial sequential analysis with a random-effect model was used to evaluate the robustness of the evidence from the included 16 studies. Data from these studies were pooled using RevMan software and Stata.

Research results

The meta-analysis indicated that an AF burden > 5 min was associated with an increased risk of clinical AF [adjusted risk ratio (RR) = 4.18, 95% confidence interval (CI): 2.26-7.74] but was not associated with an increased risk of all-cause mortality

(adjusted RR = 1.55, 95%CI: 0.87-2.75). Patients with an AF burden > 5 min had an increased risk of stroke (adjusted RR = 2.49, 95%CI: 1.79-3.47). The linear dose-response analysis showed that the risk of stroke was increased by 2.0% *per* hour as the AF burden was increased ($P_{nonlinear}$ = 0.656, RR = 1.02, 95%CI: 1.01-1.03). Trial sequential analysis provided robust evidence of the association between AF burden > 5 min and increased risk of stroke.

Research conclusions

AF burden is a significant risk factor for clinical AF and stroke. A significant linear association is present between increased AF burden and the risk of stroke.

Research perspectives

More emphasis should be laid on patients with AF burden to minimize the stroke risks.

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