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SYSTEMATIC REVIEW AND META-ANALYSIS

Atrial High-Rate Episode Duration Thresholds and Thromboembolic Risk: A Systematic Review and Meta-Analysis

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BACKGROUND: Available evidence supports an association between atrial high-rate episode (AHRE) burden and thromboembolic risk, but the necessary extent and duration of AHREs to increase the thromboembolic risk remain to be defined. The aim of this systematic review and meta-analysis was to identify the thromboembolic risk associated with various AHRE thresholds.

METHODS AND RESULTS: We searched PubMed and Scopus until January 9, 2020, for literature reporting AHRE duration and thromboembolic risk in patients with implantable electronic devices. The outcome assessed was stroke or systemic embolism. Risk estimates were reported as hazard ratio (HR) or relative risk alongside 95% CIs. We used the Paule-Mandel estimator, and heterogeneity was calculated with I^2 index. Among 27 studies including 61 919 patients, 23 studies reported rates according to the duration of the longest AHRE and 4 studies reported rates according to the cumulative day-level AHRE duration. In patients with cardiac implantable devices, AHREs lasting ≥30 seconds significantly increased the risk of stroke or systemic embolism (HR, 4.41; 95% CI, 2.32–8.39; I^2, 5.5%), which remained consistent for the thresholds of 5 minutes and 6 and 24 hours. Patients with previous stroke or transient ischemic attack and AHREs lasting ≥2 minutes had a marginally increased risk of recurrent stroke or transient ischemic attack. The risk of stroke or systemic embolism was higher in patients with cumulative AHRE ≥24 hours compared with those of shorter duration or no AHRE (HR, 1.25; 95% CI, 1.04–1.52; I^2, 0%).

CONCLUSIONS: This systematic review and meta-analysis suggests that single AHRE episodes ≥30 seconds and cumulative AHRE duration ≥24 hours are associated with increased risk of stroke or systemic embolism.

Key Words: atrial high-rate episode ■ embolism ■ implantable device ■ stroke

The increasing use of cardiac implanted electronic devices (CIEDs), such as pacemakers or implantable defibrillators and implantable loop recorders (ILRs), expanded our ability to assess the burden of atrial arrhythmias in a fully quantitative way. These devices can identify short episodes of subclinical atrial fibrillation (AF) and other atrial tachyarrhythmias, collectively described as atrial high-rate episodes (AHREs). To date, relevant studies have used different strategies to quantify and classify AHRE burden, with the 2 main approaches being the duration of the longest single AHRE and the overall time spent in atrial tachyarrhythmia during a day (or else, cumulative day-level AHRE duration).[1,2] The available evidence from studies using CIEDs and ILRs supports an association between AHRE burden and stroke or systemic embolism risk, but it is unclear how much or how little AHRE is necessary to increase the risk of thromboembolic events.[3]

The aim of this systematic review and meta-analysis was to identify the thromboembolic risk associated

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CLINICAL PERSPECTIVE

What Is New?

- Among patients with cardiac implantable devices taking part in 27 studies, single atrial high-rate episodes ≥30 seconds in length and cumulative atrial high-rate episode duration ≥24 hours are associated with increased risk of stroke or systemic embolism.
- In patients with previous cryptogenic stroke or transient ischemic attack monitored with an implantable loop recorder, atrial high-rate episodes lasting ≥2 minutes significantly increase the risk of recurrent stroke or transient ischemic attack.

What Are the Clinical Implications?

- Although short atrial high-rate episodes may increase the thromboembolic risk, it is still unclear whether this risk is high enough to allow for a potential beneficial effect of oral anticoagulation.

Nonstandard Abbreviations and Acronyms

AHRE	atrial high-rate episode
ILR	implantable loop recorder

with AHREs by deriving pooled estimates for various thresholds of AHRE burden.

METHODS

The authors declare that all supporting data are available within the article and its online supplementary file. This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement framework[4] and was registered in PROSPERO (CRD42020152057).

Search Strategy and Inclusion Criteria

We searched PubMed and Scopus until January 9, 2020, using the terms “atrial high rate episodes” or “subclinical atrial fibrillation” or “atrial tachyarrhythmia” or “occult atrial fibrillation” or “new-onset atrial fibrillation” or “atrial fibrillation duration” or “atrial fibrillation” and “device” or “implantable” or “loop recorder” or “continuous monitoring” and “stroke” or “embolism” or “transient ischemic attack.” In addition, we contacted experts in the field and searched the references of related letters, reviews, and editorials to identify potentially eligible studies. To be eligible for the present analysis, relevant studies had to be published as full-text articles in English language and report data on the burden of AHRE, as well as on the associated rates of thromboembolic events, reported as stroke or systemic embolism rates in adult patients with CIEDs or ILRs irrespective of the presence of previous cerebrovascular event.

Quality of Studies and Grading of Evidence

Two independent researchers (D.S. and K.P.) used the modified Newcastle Ottawa Scale to evaluate the quality of the nonrandomized studies included in this meta-analysis, as previously described.[5] The certainty of the body of evidence for the association between different thresholds of longest and cumulative AHRE and thromboembolic risk was adjudicated by the Grades of Recommendation, Assessment, Development, and Evaluation Working Group system, which takes into account 5 main domains (ie, risk of bias, consistency of effect, imprecision, indirectness, and publication bias).[6] Any discrepancy or uncertainty was resolved by consensus among all authors.

Definition of AHRE Burden, Outcome, and Data Extraction

Two indexes were used to quantify the burden of AHRE: the duration of the longest AHRE and the day-level cumulative duration of all AHREs. The outcome assessed was stroke or systemic embolism. Eligible studies were assessed independently by 2 authors (D.S. and G.G.), and data were extracted using a prespecified form.

Statistical Analysis

For each eligible study, we assessed the annual incidence rate for stroke or systemic embolism in (1) patients with AHRE burden above the reported AHRE threshold and (2) patients with AHRE burden below the reported AHRE threshold or no AHRE. The related risk estimates of stroke or systemic embolism in each study were reported as hazard ratio (HR) or as relative risk (RR) alongside 95% CIs.[7] If the risk estimates were not initially reported in the study, the raw events/nonevents were used to calculate the risk estimates [RR=Intervention Events (IE)×(Control Events (CE)+Control Nonevents (CN))/Control Events (CE)×(IE+Intervention Nonevents (IN))] and their SEs [(SElog RR)=$\sqrt{(IN/(IE(IE+IN))+CN/(CE(CE+CN)))}$] based on the binomial distribution. Where applicable, adjusted HRs were used in the meta-analysis. Among 2 studies conducted in the same patient population,[8,9]

the HR for the AHRE threshold of 6 minutes was extracted from the primary publication,[9] whereas RRs for the AHRE thresholds of 6 and 24 hours were calculated by the data provided from the secondary publication, which was a subanalysis.[8] For one study,[10] CIs around the mean estimates were calculated as previously suggested.[11] In one study,[12] we estimated the HR and 95% CI from the corresponding log-rank test.[13]

Meta-Analysis Technique

We performed meta-analyses separately for each index of AHRE burden (ie, the duration of the longest AHRE and the day-level cumulative duration of all AHREs) and for each available threshold of AHRE duration. In each meta-analysis, the comparator group was the patients without any AHRE or AHRE lasting less than the threshold that was under study. To test for heterogeneity, we used the I^2 index that permits quantification of discrepancy among studies.[7] Independently of the reported statistical significance of the I^2 index, we applied both random-effects and fixed-effects meta-analysis to minimize the risk of possible false-positive results. We used the Paule-Mandel estimator, which produces less biased results in case of limited number of studies that are available for synthesis.[14] The mean effect size and CIs of individual studies were illustrated with forest plots.

We performed prespecified sensitivity analyses, where feasible, by (1) synthesizing only studies with adjusted risk estimates, (2) assessing patients with previous stroke or transient ischemic attack (TIA), and (3) synthesizing only studies reporting the outcome of stroke. The presence of publication bias was investigated graphically by funnel plots of precision and statistically by regression tests for asymmetry. The Egger and the Begg and Mazumdar test were implemented.

We conducted fixed-effect meta-regression analysis to assess the impact of increasing thresholds of longest AHRE on the association between higher arrhythmic burden and the risk of stroke/systemic embolism. We performed both linear and nonlinear meta-regression, including polynomials and splines, to capture possible complex associations.[15] In meta-regression analyses, each study was used once with respect to individual estimates of risk of thromboembolism corresponding to prespecified AHRE thresholds; thus, no overlap in individual studies and thresholds of AHRE burden was encountered.

Statistical analysis was performed with R, version 4.0.2 (R Core Team). The packages "metafor"[16,17] and "meta"[14] were used for performing the meta-analysis and producing the diagnostic measures in R. The level of statistical significance was set at $P<0.05$.

RESULTS

Literature Search Yield and Characteristics of Included Studies

The literature search identified 27 eligible studies with a total population of 61 919 patients[2,9,10,12,18–40] (flow diagram; Figure S1). Twenty-three studies reported rates of stroke or systemic embolism according to the duration of the longest AHRE,[9,10,12,19–35,37,39,40] and 4 studies reported rates according to the cumulative day-level AHRE duration.[2,18,36,38] Twenty-four studies reported data on stroke or systemic embolism in patients submitted to CIED implantation because of severe heart failure or history of symptomatic ventricular tachyarrhythmias,* whereas 3 studies reported results on recurrent cerebrovascular event in patients with previous embolic stroke of undetermined source or TIA, who were submitted to long-term monitoring with ILR.[23,26,35] The main characteristics of the included studies are summarized in Tables S1 and S2. Most studies were adjudicated as moderate to good quality according to the Newcastle Ottawa Scale (Table S3).

Stroke or Systemic Embolism According to the Duration of the Longest AHRE

Among 40 536 patients from 23 studies with available data for the longest AHRE duration,[8–10,12,19–35,37,39,40] 40 221 patients had CIED attributable to history of severe heart failure or ventricular tachyarrhythmias, and 315 patients attributable to prior embolic stroke of undetermined source or TIA. The incidence rates of stroke or systemic embolism per each threshold of longest AHRE duration are displayed in Figure 1 (top panel).

In 2 studies that investigated the AHRE thresholds of ≥10 and 20 seconds,[10,32] there was no difference in the risk of stroke or systemic embolism between patients with AHRE above this threshold and patients with AHRE of shorter duration or no AHRE (HR, 0.88; 95% CI, 0.55–1.41; and HR, 1.13; 95% CI, 0.58–2.28, for the random-effects model, respectively; Figure 2).

In 4 studies that investigated the AHRE threshold of ≥30 seconds,[21,27,34,39] the risk of stroke or systemic embolism was higher in patients with AHRE above this threshold and patients with AHRE of shorter duration or no AHRE (HR, 4.58; 95% CI, 2.52–8.34; I^2, 9.7%; and HR, 4.41; 95% CI, 2.32–8.39; I^2, 5.5%, for the fixed-effects and random-effects model, respectively; Figure 2). In the sensitivity analysis of 3 studies reporting results on stroke,[27,34,39] the results were similar (HR, 4.18; 95% CI, 1.92–9.11; I^2, 22.7% for the random-effects model).

In 12 studies that investigated the AHRE thresholds of ≥5 to 6 minutes,† the risk of stroke or systemic

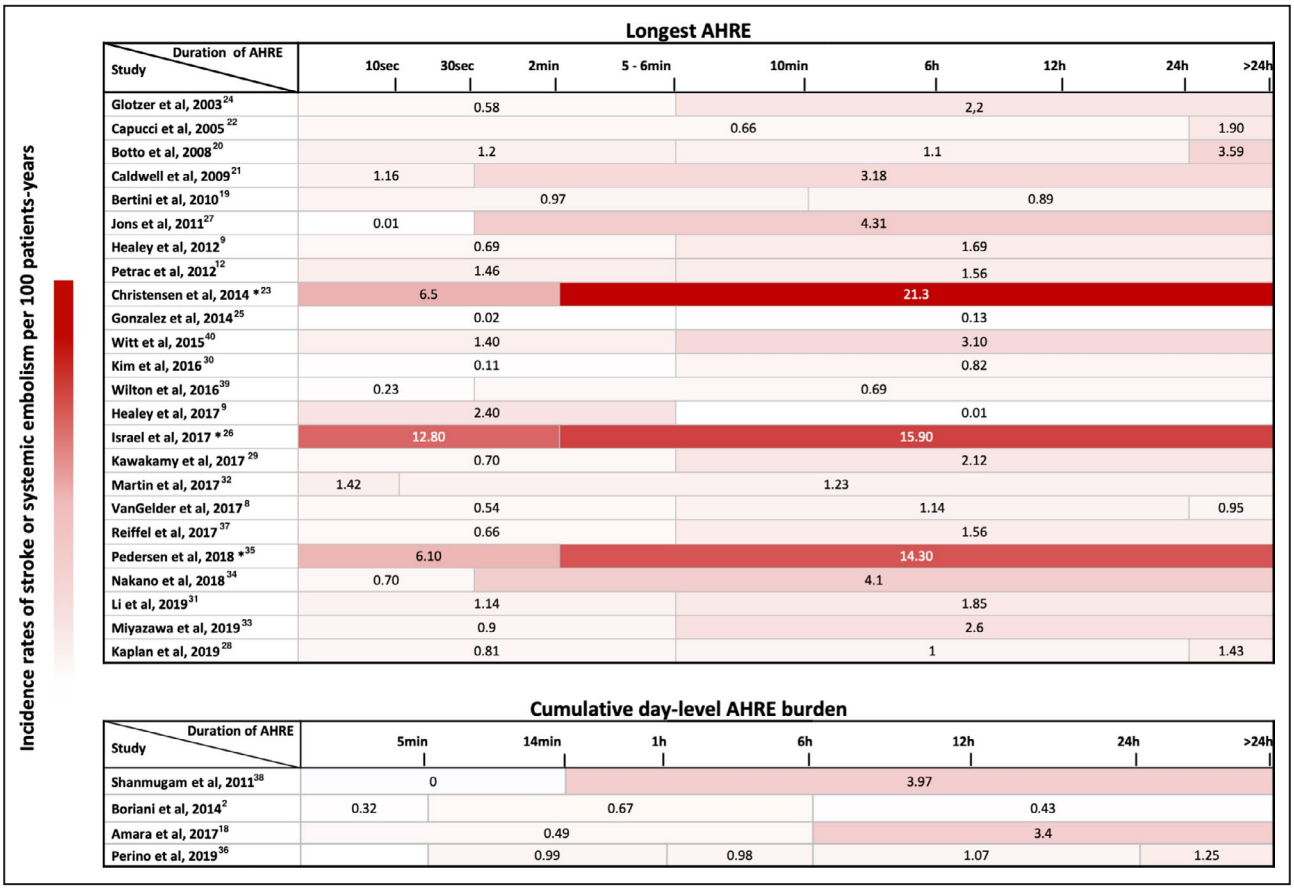

Figure 1. Incidence rates of stroke or systemic embolism per 100 patient-years in patients with atrial high-rate episode (AHRE) burden above the reported threshold (top panel) and patients with AHRE burden below the reported threshold or no AHRE (bottom panel).

Studies reporting on the longest single AHRE duration are summarized in the top panel, whereas studies reporting on the cumulative day-level AHRE burden are summarized in the bottom panel. The reported data from Swiryn et al [10] did not allow the calculation of incidence rates. *Denoted studies of patients with previous stroke or transient ischemic attack.

embolism was higher in patients with AHRE above this threshold and patients with AHRE of shorter duration or no AHRE (HR, 1.81; 95% CI, 1.51–2.16; I^2, 19.6%; and HR, 1.93; 95% CI, 1.55–2.40; I^2, 11.4%, for the fixed-effects and random-effects model, respectively; Figure 2). In the sensitivity analysis of studies reporting adjusted HRs,[24,29–31] patients with AHRE ≥5 minutes had significantly higher risk of stroke or systemic embolism compared with those with AHRE duration <5 minutes (adjusted HR, 1.91; 95% CI, 1.02–3.55; I^2, 52.7% for the random-effects model). We did not identify significant interaction between studies reporting adjusted and nonadjusted risk estimates (*P* for interaction, 0.827; nonadjusted HR/RR, 1.98; 95% CI, 1.42–2.78). In the sensitivity analysis of 6 studies reporting results on stroke,[12,20,24,25,30,37] patients with AHRE ≥5 to 6 minutes had higher risk of stroke compared with subjects without AHRE or with AHRE of shorter duration (HR, 2.83; 95% CI, 1.81–4.44; I^2, 0% for the random-effects model).

A single study used a threshold of 10 minutes and was not further synthesized.[19] A single study reported data that allowed the calculation of RR on the risk of stroke or systemic embolism for the threshold of 6 hours and was not further synthesized.[8]

In 4 studies that investigated the AHRE threshold of ≥24 hours,[8,20,22,28] the risk of stroke or systemic embolism was higher in patients with AHRE above this threshold and patients with AHRE of shorter duration or no AHRE (HR, 1.99; 95% CI, 1.53–2.59; I^2, 48%; and HR, 2.39; 95% CI, 1.53–3.74; I^2, 32.4%, for the fixed-effects and random-effects model, respectively; Figure 2).

Studies in Patients After Stroke or TIA

In 3 studies using ILRs in patients after an embolic stroke of undetermined source or TIA,[23,26,35] patients with at least one AHRE ≥2 minutes had a marginally higher risk of recurrent stroke or TIA compared with patients with lower burden (HR, 1.96; 95% CI, 1.04–3.68; and HR,

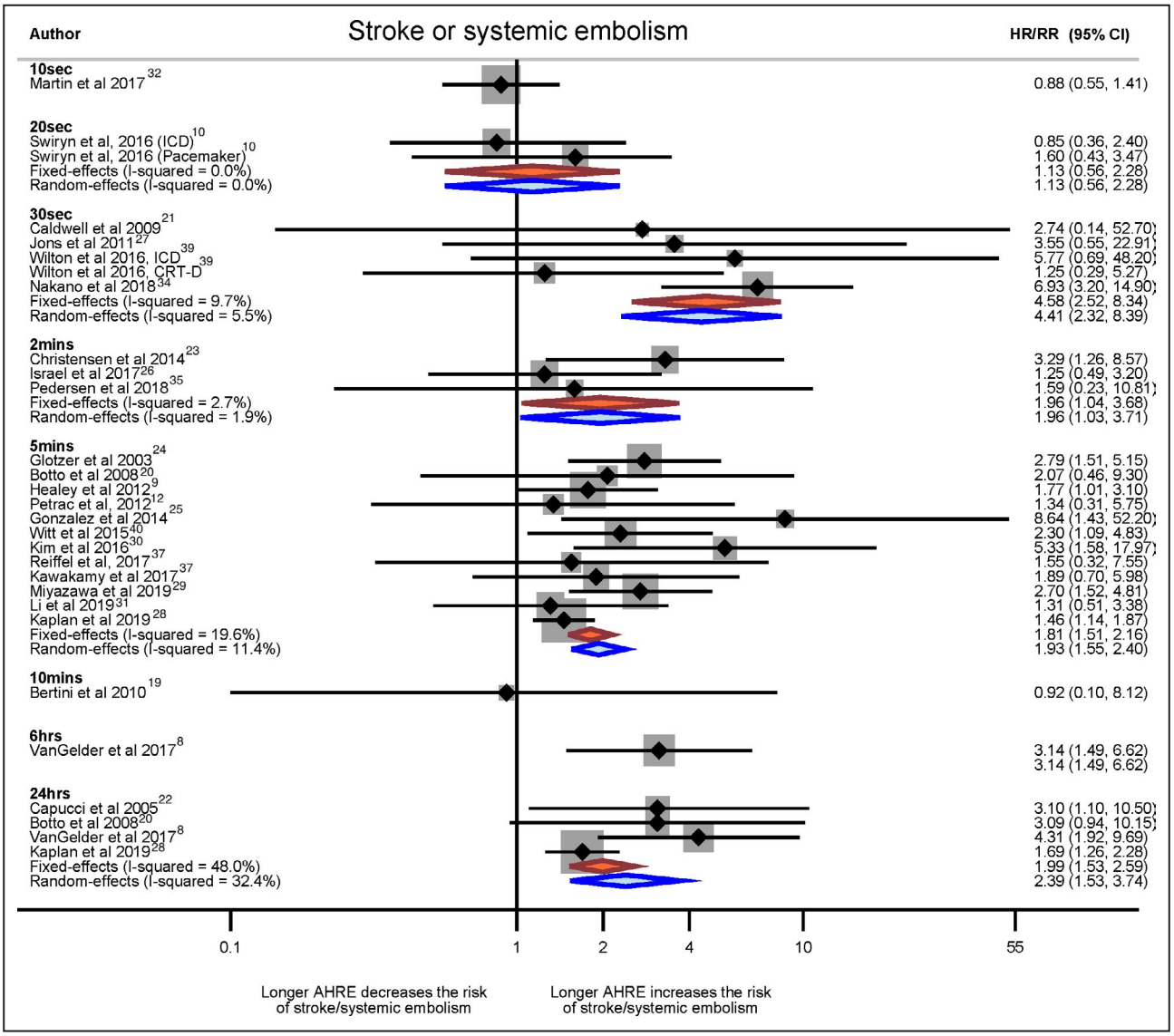

Figure 2. Risk estimates (hazard ratio [HR]/relative risk [RR]) and 95% CIs for the risk of stroke or systemic embolism based on the duration of the longest atrial high-rate episode (AHRE).
Studies are listed by the AHRE threshold. Boxes represent the HRs/RRs and lines represent the 95% CIs for individual studies. All patients included in the analysis for the threshold of 2 minutes had prior embolic stroke of undetermined source or transient ischemic attack and were monitored with implantable loop recorders. All other patients included in this analysis had a cardiac implantable electronic device because of heart failure or significant dysrhythmias.

1.96; 95% CI, 1.03–3.71; I^2, 1.9%, for the fixed-effects and random-effects model, respectively; Figure 2).

Meta-Regression

In the linear meta-regression, we did not identify a significant association between increasing AHRE thresholds and the risk of stroke or systemic embolism (HR, 1.08 per 1 log minute increase; 95% CI, 0.93–1.26) (Figure S2). Respectively, nonlinear meta-regression did not indicate a significant association between increasing AHRE thresholds and the risk of stroke or systemic embolism (Figure S2).

Stroke or Systemic Embolism According to the Cumulative Day-Level AHRE Duration

Four studies including 21 695 patients reported rates of stroke or systemic embolism according to the cumulative day-level burden of AHRE.[2,18,36,38] The incidence rates of stroke or systemic embolism per available threshold of cumulative day-level AHRE burden are presented in Figure 1 (bottom panel).

For each of the thresholds of 5 minutes and 3.8 hours,[2,38] we identified only a single study, which were not further synthesized.

In 3 studies that investigated the threshold of a cumulative day-level AHRE duration of ≥6 hours,[2,18,36] the risk of stroke or systemic embolism was higher in patients with AHRE above this threshold based on the fixed-effects model (HR, 1.19; 95% CI, 1.03–1.38; I^2, 48.2%; Figure 3). Interestingly, this effect did not remain consistent in the random-effects model (HR, 1.52; 95% CI, 0.81–2.87; I^2, 63.7%; Figure 3). In 2 studies that investigated the threshold of a cumulative day-level AHRE duration of ≥24 hours,[2,36] the risk of stroke or systemic embolism was higher in patients with AHRE above this threshold and patients with AHRE of shorter duration or no AHRE (HR, 1.25; 95% CI, 1.04–1.52; I^2, 0%, in both the fixed-effects and random-effects model; Figure 3).

Publication Bias and Grade of Evidence

Diagnostics were performed for the main meta-analyses of the article. On the basis of the funnel plots and regression tests, the least evidence for publication bias appears in the meta-analyses of the thresholds of 30 seconds, 5 minutes, and 24 hours of longest AHRE, whereas visual and statistical evidence for publication bias appears in the meta-analyses of the threshold of 5 hours of cumulative AHRE (Egger and Begg and Mazumdar tests, $P<0.01$; Figure S3).

On the basis of the Grades of Recommendation, Assessment, Development, and Evaluation Working Group system, the degree of certainty was moderate for the association between AHREs lasting ≥30 seconds and ≥5 minutes and the risk of stroke or systemic embolism; high for the association between AHREs lasting ≥24 hours and the risk of stroke or systemic embolism; and moderate for the association between cumulative day-level AHRE burden ≥24 hours and the incidence of stroke or systemic embolism (Table S4).

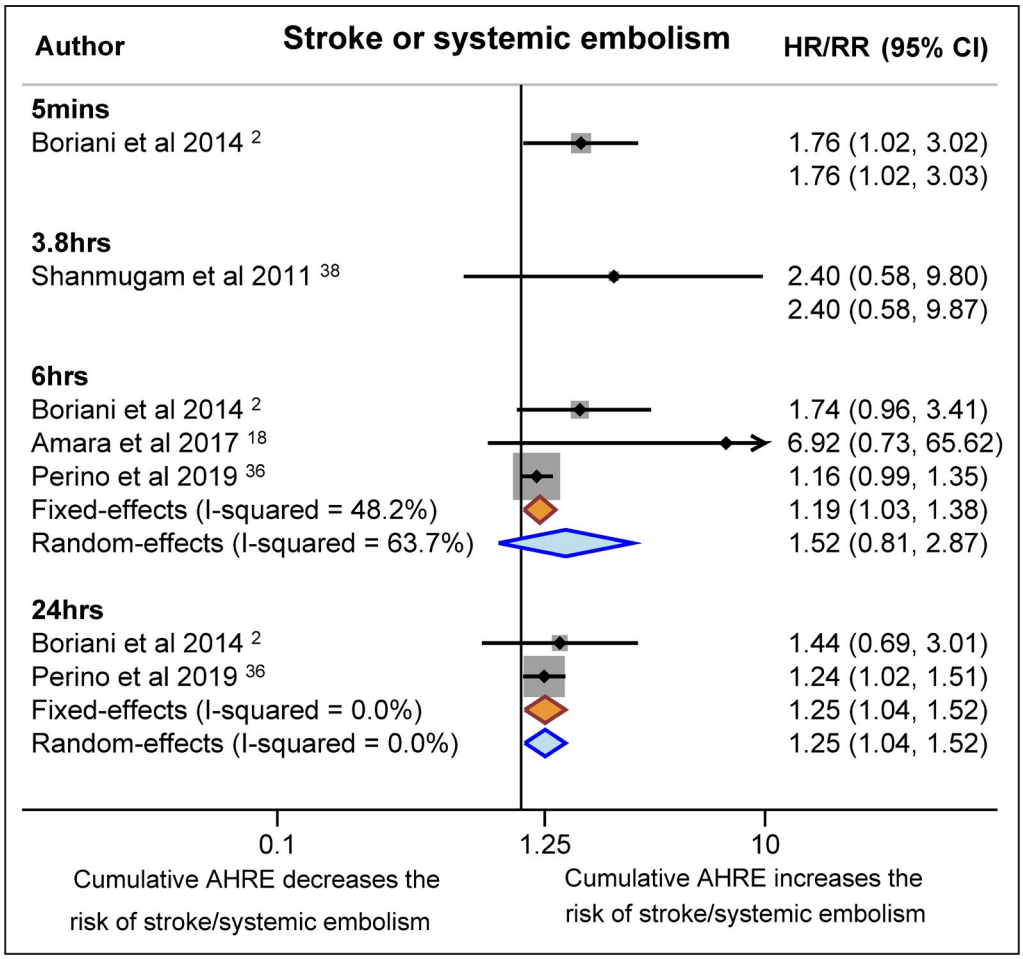

Figure 3. Risk estimates (hazard ratio [HR]/relative risk [RR]) and 95% CIs for the risk of stroke or systemic embolism based on the cumulative day-level duration of atrial high-rate episodes (AHREs).

Studies are listed by the AHRE threshold. Boxes represent the HR and lines represent the 95% CIs for individual studies. All studies reported risk estimates for stroke, except from the study of Shanmugam et al.[38]

DISCUSSION

The present systematic review and meta-analysis of 27 studies including 61 919 patients with CIEDs and ILRs suggests that single AHRE episodes ≥30 seconds and cumulative AHRE duration ≥24 hours are associated with increased risk of stroke or systemic embolism. The increased risk of stroke or systemic embolism remained consistent also for single AHRE episodes of ≥5 to 6 minutes, ≥6 hours, and ≥24 hours.

A previous meta-analysis suggested that AHREs lasting <1 minute were related to higher risk of thromboembolic events, but it did not differentiate between lower thresholds, like 10, 20, and 30 seconds.[41] We analyzed these thresholds separately and concluded that the AHRE threshold >30 seconds is associated with increased risk of stroke or systemic embolism, but not shorter AHREs. Whether there is an association between even shorter AHRE thresholds and thromboembolic risk that was not evident because of lack of statistical power needs further evaluation in future studies.

The meta-regression graphically suggested a linear association between AHRE threshold and stroke risk, although the statistical result was not significant. Although this result may be limited by the potential overlap of the various duration thresholds, it suggests a potential dose-dependent relation between AHRE duration and thromboembolic risk and generates the hypothesis that AHRE may need to be considered as a continuous variable.

Traditionally, when it comes to treatment decisions on stroke prevention, AF is considered in a binary manner (ie, present or absent), without taking into consideration the burden of AF. In specific, the pattern of AF (ie, paroxysmal or permanent) is not taken into consideration to guide decisions about antithrombotic treatment, as it is believed that it does not add significantly to the assessment of risk based on patient characteristics (ie, the CHA_2DS_2-VASc score). Despite the evidence that AHRE of short duration increases the thromboembolic risk, it is still unclear whether this risk is high enough to allow for a potential beneficial effect of oral anticoagulation that would exceed the associated bleeding risk.[42] Although in some of the included studies patients were treated with anticoagulants, there is still no evidence to prove the efficacy and safety of anticoagulation in patients with subclinical AF, and this is investigated in the ongoing (Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation) and NOAH-AFNET (the Non–vitamin K antagonist Oral anticoagulants in patients with Atrial High rate episodes-Atrial Fibrillation NETwork) trials.[43,44] Currently, the assessment of the thromboembolic risk in patients with subclinical AF is based on the individualized thromboembolic risk (ie, the CHA_2DS_2-VASc score), and anticoagulation may only be considered in specific patients with longer AHREs (≥24 hours).[42] The initiation of anticoagulation after a cumulative AF >24 hours was recently associated with reduced stroke risk, although this was only significant when AF lasted at least 6 minutes.[36] Also, we are dealing with a heterogeneous and dynamic arrhythmia, and what is 30-seconds duration at one monitoring period may be 30 hours at the next monitoring period.

Strengths and Limitations

Among the strengths of our study is that we investigated 2 indexes of AHRE burden and several duration thresholds for each index. We used adjusted risk estimates and accounted for the duration of follow-up where possible. We also provided sensitivity analyses to confirm or explore specific findings for thresholds with sufficient number of available studies and critically reviewed the quality of the outcomes of this meta-analysis based on Grades of Recommendation, Assessment, Development, and Evaluation Working Group guidelines.

Although some studies provided results-adjusted risk estimates for the use of anticoagulants, the CHA_2DS_2-VASc, and the existence of previous paroxysms of AF, this was not consistent across all studies. The absence of detailed report on the vascular risk factors based on the CHA_2DS_2-VASc score and the use of anticoagulation in some of the included studies may have affected the synthetized thromboembolic risk of the study. The inherent limitations of all meta-analyses apply also to the present meta-analysis, such as variations in the definitions of AHRE and comorbidities used in the studies, differences in the selection criteria among trials, differences in outcomes definition across the studies, and differences in the length of follow-up. Finally, the risk of stroke in patients with heart failure, which represented a large proportion of the patients included in this meta-analysis, may be associated not only with the presence of AHRE but also with the presence of heart failure.[45,46]

CONCLUSIONS

The present study suggests that single AHREs ≥30 seconds and cumulative AHRE duration ≥24 hours are associated with increased risk of stroke or systemic embolism. The increased risk of stroke or systemic embolism remained consistent also for single AHRE episodes of ≥5 to 6 minutes, ≥6 hours, and ≥24 hours.

ARTICLE INFORMATION

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Supplementary Material

Tables S1–S4
Figures S1–S3

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Supplemental Material

Table S1. Basic characteristics of the included studies.

Study	Study design	Patients included	Age	Prior stroke/TIA n (%)	Recorder type	Indication for device implantation	Anticoagulation n (%)	AHRE definition	Time cut offs	Follow-up (months)	Outcome	Study population
Glotzer et al 2003	Randomized	312	74	55 (17,6)	PMs	sinus node dysfunction	NA	longest episode	5 min	27	Stroke	MOST
Capucci et al 2005	Observational Prospective	725	71 ±11	13 (1,8)	PMs	class I or II ACC/AHA indication for dual-chamber pacing: node disease (82.8%) AV block (4.7%), drug-induced bradycardia in (4.4%), other (8.1%)	261(36,4)	longest episode	24 h	22 (16-30)	Stroke	NA
Botto et al 2008	Observational,retrospective	568	70 ± 10	8 (1,4)	PMs	bradycardia according to current guidelines	165 (29)	longest episode	>5 min >24 h	12	Stroke/ TIA	NA
Caldwell et al 2009	Observational, retrospective	162	66 ±1.8	NA	CRT	HF NYHA class III –IV CHF	NA	longest episode	30 sec	14.1 ±1	Stroke or SE	NA
Bertini et al 2010	Observational,prospective	495	62.2 ±11.7	NA	ICD	heart failure according to the current AHA/ACC/ESC guidelines	263(54)	longest episode	10 min	16.4 ±11.2	Stroke or SE	NA
Shanmugan et al 2011	Observational,prospective	560	66 ± 10	1 (0.18)	CRT	HF with no history of AF	67 (12.0)	day-level cumulative burden	14 min (3.8 h as threshold)	12.3 (IQR 8.4-13)	Stroke or SE	EVEREST
Jons et al 2011	Randomized	271	63,3 ± 11	NA	ICM	post MI ≤40% EF	56 (20,6)	longest episode	30 sec	24	Stroke	CARISMA
Healey et al 2012	Prospective Observational	2580	76 ± 7	312 (12,1)	PMs or ICD	sinus-node or atrioventricular-node disease or any indication for ICD	0(0)	longest episode	6 min	30	Stroke or SE	ASSERT*
Petrac et al, 2012	Observational, retrospective	308	67 ± 10	NA	PMs	second- or third-degree AV block	48 (15,6)	longest episode	5min	36 ± 20	Stroke	NA
Gonzalez et al 2014	Observational,retrospective	224	74 ± 12	13 (6)	PMs	Sinus node dysfunction AV block	7 (3.1)	longest episode	5 min	79.2 ± 24	Stroke	NA
Christensen et al 2014	Observational,prospective	85	56,7	85 (100)	ILR	cryptogenic stroke	18 (20,7)	longest episode	2 min	19 ±10.3	Stroke	SURPRISE
Boriani et al 2014	Observational, pooled analysis from five prospective studies	10016	70	589(6)	CIEDs	class I/II indication for an implantable cardiac rhythm device	1822(18)	day-level cumulative burden	5 min 1 h 6 h 12 h 23 h	24 (14–40)	Stroke	TRENDS, PANORAMA
Witt et al 2015	Observational, retrospective	394	67 (59-74)	58 (14,7)	CRT	HF (standard indication for CRT treatment)	56(14,2)	longest episode	6 min	50.4 (IQR 30–79.2)	Stroke or SE	NA
Kim et al 2016	Observational,retrospective	880	62,7 ± 14	70 (8)	PM, ICDs, and CRTs	classes I-II recommendation of the current ACCF/AHA/HRS guidelines for device implantation	40 (4,5)	longest episode	5 min	55 (20-90.2)	Stroke	NA
Wilton et al 2016	Randomized, prospective	972	66.1	NA	ICDs and CRTs	HF	286 (29,4)	longest episode	30 sec	41± 19	Stroke	RAFT
Swiryn et al, 2016	Observational,	5379	69,7	186 (5.9%)	PMs and ICDs	indication for a cardiac rhythm management	823 (15,3)	longest episode	>20 sec	22,9	Stroke or SE	RATE

	prospective					implantable device						
Reiffel et al, 2017	Observational, prospective	326	71,5 ± 9.9	80 (20.3)	ICM (Reveal XT or Reveal LINQ; Medtronic) .	high risk patients for AF	72 (56,3)	longest episode	6 min	22,5	Stroke	REVEAL AF
Israel et al 2017	Observational, prospective	123	65 ± 9	123 (100)	ILR	ESUS	NA	longest episode	2 min	12.7 ±5.5	Stroke	NA
Amara et al 2017	randomized, single-blind	595	79 ± 8	60 (10,1)	PMs	Sinus node dysfunction, AV block and other conduction defects	0(0)	day-level cumulative burden	6 h	12.8 ± 3.3	Stroke	SETAM
Kawakamy et al 2017	Observational, retrospective	343	80±7	52 (15)	PMs	sinus node disease or atrioventricular block	53 (15)	longest episode	6 min	52± 30	Stroke or SE	NA
Martin et al 2017	Randomized	2718	64,4	243(8,9)	ICD and CRTs	Current clinical class I or II indications for ICD / CRT implantation	302 (11)	longest episode	10 sec	24	Stroke or SE	IMPACT
VanGelder et al 2017	Observational, prospective	2455	76,3 ± 6,7	297 (12)	PMs and ICD	PCM for sinus node or AV node disease, ICD for any indication	0	longest episode	6 h 24h	30	Stroke or SE	ASSERT*
Nakano et al 2018	Observational, retrospective	348	70±16	NA	PMs ICDs, and CRTs	Class I or IIa indication according to the Japanese Circulation Society	0(0)	longest episode	30 sec	65±58	Stroke	NA
Pedersen et al 2018	Observational, prospective	105	65.4 (27.2 - 0.8)	105 (100)	ILR	TIA patients . CHA_2DS_2-Vasc 4	0(0)	longest episode	2 min	12.7 (12.4-13)	Stroke	NA
Perino et al 2019	Observational, retrospective	10212	72±10	0 (0)	CIEDs	Database of CIEDs (not mentioned)	1032 (10)	day-level cumulative burden	6 min 1h 6 h 24 h	45	Stroke	Veterans Affair National Patient Care Database
Li et al 2019	Observational, prospective	594	69 ± 14	59 (9.9)	PMs, ICDs, CRTs	NA	NA	longest episode	5 min	50.4	Stroke or SE	NA
Kaplan et al 2019	Observational, retrospective	21768	68.6±12.7	3047 (14)	IPMs, ICDs, CRTs	according to ACC/AHA guidelines	0(0)	longest episode	6 min and 23.5 h	6 months	Stroke or SE	Optum© Electronic Health Record database, Medtronic CareLinkTM database of CIEDs
Miyazawa et al 2019	Observational, retrospective	856	72.0 (62.0–80.0)	92 (10.7)	ICDs, CRT	current indications for ICD / CRT implantation according to ESC guidelines	151 (19.7)	longest episode	5 min	48.2 ± 32.3	Stroke or SE	NA

CIEDs: cardiac implantable electronic devices, PM: pacemaker, ICD: implantable cardioverter defibrillators, ICM: impantable cardiac monitor, CRT: cardiac resynchronization therapy, ILR: implantable loop recorder, ESUS: embolic stroke of undetermined source, NA: not applicable
***: Both studies conducted in the ASSERT population**

Table S2. Studies providing raw events or incidence rates.

Author	Thresholds	Patients included	Relative Risk (95% CI)		Events	IR (%/yr)
		30 sec				
Caldwell et al 2009	<30sec	74	2,74	0,14 - 52,70	0.86*	1,16
	≥30sec	27			0.86*	3,18
Nakano et al 2018	<30sec	293	6,93	3,20 - 14,90	10	0.7
	≥30sec	55			13	4.3
		2min				
Christensen et al 2014	<2min	69	3,29	1,26 - 8,57	7	6.5
	≥2min	18			6	21.3
Israel et al 2017	<2min	94	1,25	0,49 - 3,20	13	12.8
	≥2min	29			5	15.9
Pedersen et al 2018	<2min	98	1,59	0,23 - 10,81	6	6.1
	≥2min	7			1	14.3
		5min				
Botto et al 2008	<5min	166	2,07	0,46 - 9,30	2	1.2
	≥5min	402			10	2.48
Petrac et al, 2012	<5min	274	1,34	0,31 - 5,75	12	1.46
	≥5min	34			2	1.56
Reiffel et al, 2017	<6min	198	1,55	0,32 - 7,55	3	0.66
	≥6min	128			3	1.56
Kaplan et al 2019	<6min	19443	1,46	1,14 - 1,87	158	NA
	≥6min	8589			102	
		10 min				
Bertini et al 2010	<10min	309	0,92	0,10 - 8,12	4	0.97
	≥10min	84			1	0.89
		6h				
VanGelder et al 2017	<6h	2121	3,14	1,49 - 6,62	13.3*	NA
	≥6h	234			4.9*	
		24h				
Botto et al 2008	<24h	345	3,094	0,94 - 10,15	4	NA
	≥24h	223			8	
VanGelder et al 2017	<24h	2226	4,31	1,92 - 9,69	14.3*	NA
	≥24h	129			3.9*	
Kaplan et al 2019	<24h	24270	1,691	1,26 -2,28	206	NA
	≥24h	3762			54	

*** Corresponding events based on provided incidence rate**
IR: incidence rate

Table S3. Quality assessment of the selected studies based on the Newcastle-Ottawa Scale (NOS).

Study	Selection ☆☆☆☆/★★★★				Comparability ☆☆/★★	Outcome ☆☆☆/★★★			Overall stars	Quality Assessment
	Is the Case Definition Adequate?	Representativeness of the Cases	Selection of Controls	Definition of Controls	Comparability of Cases and Controls on the Basis of the Design or Analysis	Ascertainment of Exposure	Same method of ascertainment for cases and controls	Non-Response Rate		
Swiryn et al 2017	★	★	★	★	★★	★	★	★	9/9	Good quality
Study	**Selection ☆☆☆☆/★★★★**				**Comparability ☆☆/★★**	**Outcome ☆☆☆/★★★**			**Overall stars**	**Quality Assessment**
	Representativeness of the exposed cohort	**Selection of the non-exposed cohort**	**Ascertainment of exposure**	**Demonstration that outcome of interest was not present at the start of the study**	**Comparability of cohorts on the basis of the design or analysis controlled for confounders**	**Assessment of outcome**	**Was follow-up long enough for outcomes to occur**	**Adequacy of follow-up of cohorts**		
Botto et al 2008		★	★		★	★		★	5/9	Medium quality
VanGelder et al 2017	★	★	★	★	★★	★	★	★	9/9	Good quality
Perino et al 2019		★	★	★	★★	★	★		7/9	Good quality
Boriani et al 2014	★	★	★	★	★★		★		7/9	Good quality
Li et al 2019	★	★	★	★	★★	★	★		8/9	Good quality
Kim et al 2016	★	★	★	★	★★	★	★		8/9	Good quality
Jons et al 2011		★	★	★	★	★	★		6/9	Fair quality
Israel et al 2017		★	★	★			★	★	5/9	Medium quality
Gonzalez et al 2014	★	★	★	★	★★	★	★		8/9	Good quality
Glotzer et al 2003	★	★	★	★	★★	★	★		8/9	Good quality
Christensen et al 2014		★	★	★	★★	★		★	7/9	Good quality
Capucci et al 2005		★	★	★	★★		★		6/9	Fair quality
Amara et al 2017	★	★	★	★		★	★	★	7/9	Good quality
Kaplan et al 2019	★	★	★	★	★★	★	★	★	9/9	Good quality
Bertini et al 2010		★	★		★★	★	★		6/9	Fair quality
Caldwell et al 2009		★	★	★		★	★		5/9	Medium quality
Kawakamy et al 2017	★	★	★	★	★★	★	★		8/9	Good quality
Martin et al 2017	★	★	★	★	★★	★	★	★	9/9	Good quality
Miyazawa et al 2019	★	★	★	★	★★	★	★		8/9	Good quality
Nakano et al 2018	★	★	★	★	★★	★	★		8/9	Good quality
Ogino et al 2017	★	★	★	★	★★	★	★	★	9/9	Good quality
Pedersen et al 2018		★	★	★		★	★	★	6/9	Fair quality
Shanmugan et al 2011	★	★	★		★★	★	★		7/9	Good quality
Wilton et al 2016	★	★	★		★★	★	★	★	8/9	Good quality
Witt et al 2015	★	★	★	★	★★	★	★	★	9/9	Good quality
Healey et al 2012	★	★	★	★	★★	★	★		8/9	Good quality
Petrac et al 2012		★	★	★		★	★	★	6/9	Fair quality
Reiffel et al 2017		★	★	★		★	★		5/9	Medium quality

Table S4. Certainty assessment of the selected studies based on the GRADING system.

Number of studies	Study design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty
Risk of stroke or systemic embolism based on the duration of longer AHRE							
30 seconds AHRE duration							
4	Observational and Randomized (1:1)	Few concerns	Low	Low	Moderate	Low publication Bias	Moderate
5 to 6minutes AHRE duration							
13	Observational	Low	Moderate	Low	Moderate	Low publication Bias	Moderate
24 hours AHRE duration							
5	Observational	Low	Moderate	Low	Low	Low publication Bias	High
Risk of stroke or systemic embolism based on the cumulative day-level AHRE burden							
24 hours AHRE duration							
2	Observational	Few concerns	Low	Low	Moderate		Moderate

Figure S1. Flow diagram of studies identified, screened and included in the meta-analysis.

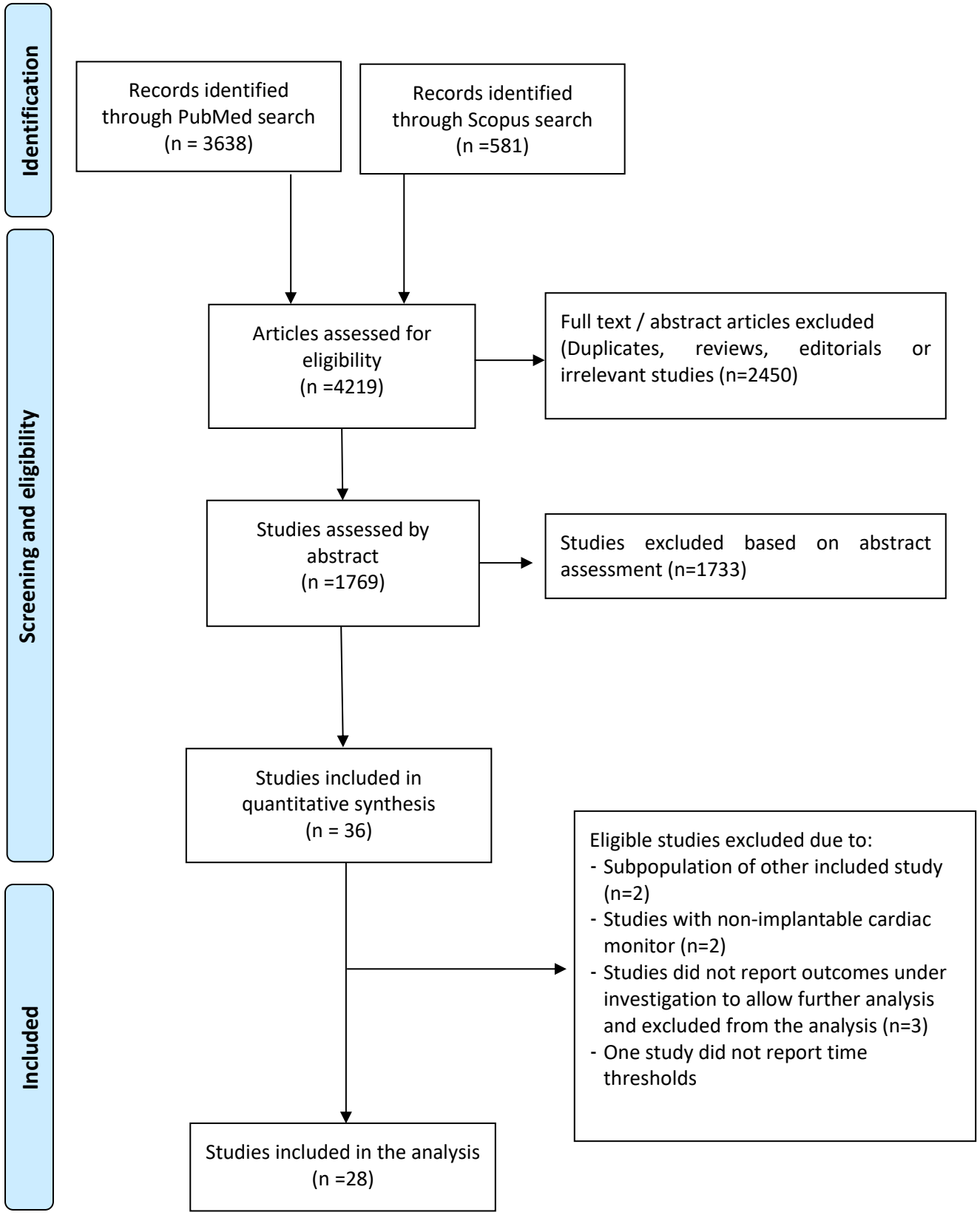
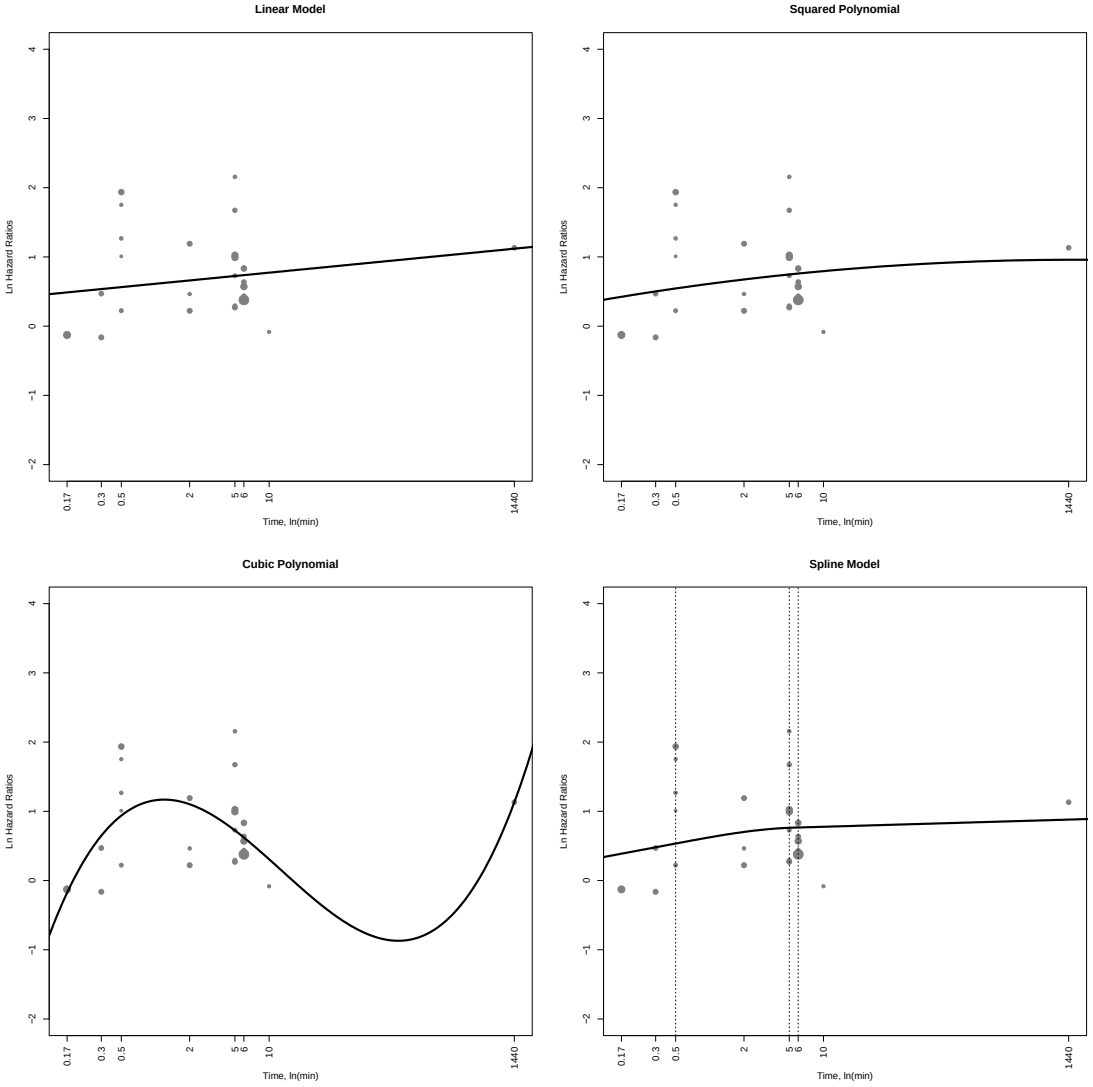
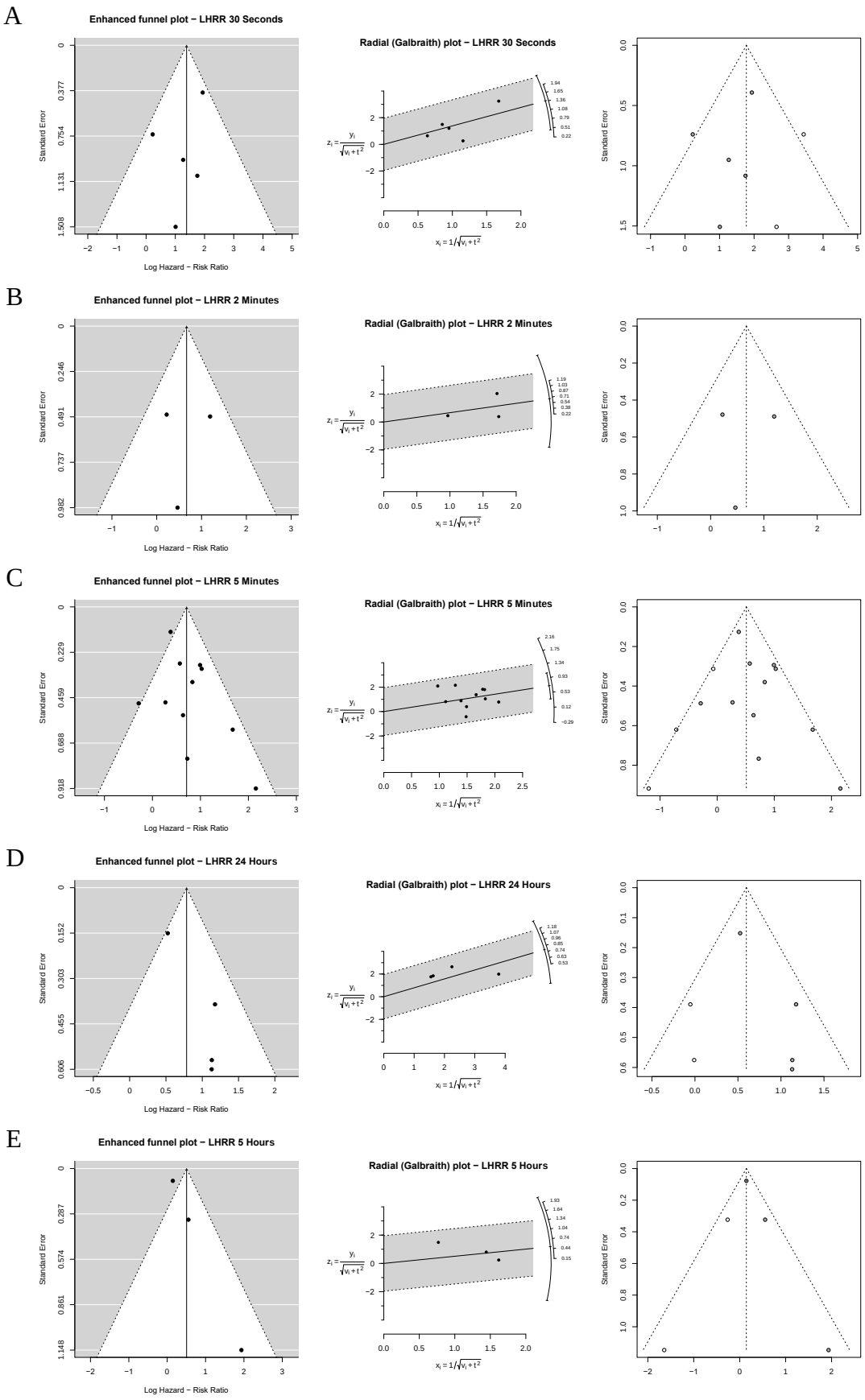


Figure S2. Linear and non-linear fixed effects meta regression based on the threshold of the longest AHRE duration.



When the high-leverage study from Capucci et al 2005 was excluded there was still no significant association between increasing AHRE thresholds and the risk of stroke or systemic embolism (HR per 1 ln min increase=1.09, 95% CI 0.878-1.36, P=0.412).

Figure S3. Diagnostic plots for each time threshold.



A: funnel plots and regression tests for the threshold of 30 seconds; B: funnel plots and regression tests for the threshold of AHRE >2 minutes; C: funnel plots and regression tests for the threshold of AHRE >5 minutes; D: funnel plots and regression tests for the threshold AHRE >24 hours; E: funnel plots and regression tests for the threshold cumulative day-level AHRE burden ≥24 hours