Current Atherosclerosis Reports (2020) 22: 14
https://doi.org/10.1007/s11883-020-0832-4

EVIDENCE-BASED MEDICINE, CLINICAL TRIALS AND THEIR INTERPRETATIONS (L. ROEVER, SECTION EDITOR)

Excessive Supraventricular Ectopic Activity and Adverse Cardiovascular Outcomes: a Systematic Review and Meta-analysis

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Published online: 21 May 2020

Abstract

Purpose of Review Excessive supraventricular ectopic activity (ESVEA), in the form of frequent premature atrial contractions (PACs) and runs of PACs, is commonly observed in clinical practice and is frequently considered to be benign. Yet, recent studies have demonstrated a link between ESVEA and adverse cardiovascular outcomes. The aim of this meta-analysis was to examine the association between ESVEA and the risk of atrial fibrillation (AF), stroke, and mortality.

Recent Findings A systematic search was performed in PubMed, EMBASE, and the Cochrane Library up to December 2017 to identify studies assessing adverse cardiovascular outcomes in patients with ESVEA, recorded on ambulatory electrocardiography. ESVEA was defined as a burden of PACs > 30 PACs/h or any runs of ≥20 PACs. The risk estimates for EVSEA and each clinical endpoint were pooled and analyzed separately.

Results Five studies comprising 7545 participants were included in this meta-analysis. The pooled analysis showed that ESVEA doubled the risk of AF (HR 2.19, 95% CI 1.70–2.82). ESVEA was also associated with a higher incidence of stroke (HR 2.23, 95% CI 1.24–4.02). Finally, ESVEA was associated with higher all-cause mortality (HR 1.61, 95% CI 1.25–2.07).

Summary Our meta-analysis found that ESVEA is closely associated with AF, stroke, and all-cause mortality. Further studies are required to examine the implication of therapeutic strategies in patients with ESVEA, in order to prevent potential subsequent adverse cardiovascular outcomes.

Keywords Excessive supraventricular ectopy · Atrial fibrillation · Stroke · Mortality

This article is part of the Topical Collection on *Evidence-Based Medicine, Clinical Trials and Their Interpretations*

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11883-020-0832-4) contains supplementary material, which is available to authorized users.

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Introduction

Premature atrial contractions (PACs) are a frequent electrocardiographic finding across all age groups, whereas the PAC burden shows a consistent increase with advancing age [1–6]. Although PACs have been considered benign for years [3, 7, 8], association with atrial fibrillation (AF) [9–15] as well as with traditional risk factors for cardiovascular disease has been shown in the last two decades [2]. These data may suggest that PACs could be an expression of underlying cardiac pathologies and a harbinger of future adverse clinical events.

The term "excessive supraventricular ectopic activity" (ESVEA) has been used in previous studies to describe a high burden of PACs, short supraventricular runs (SVRs), and/or runs of dozens of PACs. Population-based observational studies have shown that baseline PAC burden, whether recorded during rest [16–22] or with ambulatory electrocardiography [23–33], independently predicts new AF [20, 21, 24, 26, 27] and other cardiovascular outcomes [23–25, 28, 31]. The clinical significance of PACs has also been confirmed in a specific patient group with a high incidence of AF, such as in patients with stroke [34–38, 39••, 40], electrically cardioverted AF [41, 42], or post AF ablation [43, 44]. Other studies however failed to demonstrate a statistically significant association between ESVEA and cardiovascular outcomes especially after adjustment for covariates [26, 39••, 41, 45, 46].

Of note, most of the preceding studies are encumbered by a substantial heterogeneity regarding the demographics of the included population, the method of recording PACs/SVRs, the optimal cutoff points that characterize the supraventricular activity as "excessive," and the definitions of clinical endpoints. Thus, we sought to perform a systematic review and meta-analysis of all the relevant outcome data aiming to shed further light into the prognostic significance of ESVEA. Specifically, we investigated the association of ESVEA with increased risk of incident AF, stroke, and cardiovascular morbidity/mortality.

Methods

We analyzed relevant studies assessing adverse cardiovascular outcomes in patients with and without ESVEA on ambulatory electrocardiographic monitoring. We defined ESVEA as PACs burden > 30 per hour and/or runs of ≥ 20 PACs or PACs burden > 218 per 24 h according to the optimal cutoff values set in the recent studies reflecting the current perception of their clinical significance [23, 47, 48•]. We included studies presenting primary or secondary outcomes related to AF, myocardial infarction (MI), coronary artery disease, stroke/transient ischemic attack (TIA), cerebrovascular disease, heart failure, and mortality. We also included studies reporting a composite endpoint and we analyzed separately independent outcomes.

We systematically and independently interrogated the online databases of PubMed, Embase, and the Cochrane Database to identify relevant studies published up to December 2017. The search terms used were as follows: (atrial premature or atrial ectopy or supraventricular premature or supraventricular ectopy or atrioventricular junctional premature or atrioventricular junctional ectopy) and (atrial fibrillation or myocardial infarction or coronary heart disease or stroke or cerebrovascular disease or transient ischemic attack or heart failure or hospitalization rate or mortality). There were no restrictions with respect to the date of publication or language.

Two independent reviewers (L. M. and J. H.) screened the potentially eligible studies. Additionally, titles, abstracts, and references retrieved from relevant studies were searched for additional studies consistent with the inclusion criteria, while bibliographies of original articles were also manually reviewed. Potentially relevant reports were then retrieved as complete manuscripts and assessed for conformity with inclusion criteria. Uncertain ties or disagreements between reviewers were resolved through consensus after rechecking the source data and consultation with a third reviewer (T.L.).

Articles were included if they met the following inclusion criteria: (a) the study design was a prospective or retrospective cohort analysis; (b) PAC burden at baseline and during follow-up was measured using Holter or other ambulatory ECG recording methods, and PAC burden was greater than 30 PACs per hour and/or runs of ≥ 20 PACs or PACs burden > 218 per 24 h; (c) predefined clinical outcomes were assessed during follow-up; (d) the hazard ratios (HRs) and the corresponding 95% confidence intervals (CI) were reported for ESVEA and adverse outcomes. Regarding multiple articles originating from the same cohort and reporting the same event, only those with the largest sample and the longest follow-up duration were included. In addition, only studies of patients with no history of previous AF were included.

Two blinded reviewers (L. M. and J. H.) independently extracted the demographic and clinical outcome data from the selected studies using a standard data extraction form. From each study, we collected information on data on study design, number of participants, male/female ratio, mean age, duration of follow-up, study population, methods of ESVEA detection, and type of ESVEA. We also collected information on pre-specified adverse outcomes, i.e., the incidence of adverse events, the unadjusted and adjusted hazard ratios and their 95% CIs, and the variables used in multivariate analyses.

To limit heterogeneity in study designs, the methodological quality of included articles was assessed by applying the Newcastle-Ottawa Score (NOS) checklist [49]. We graded quality as good (≥ 7 stars), fair (4–6 stars), and poor (< 4 stars).

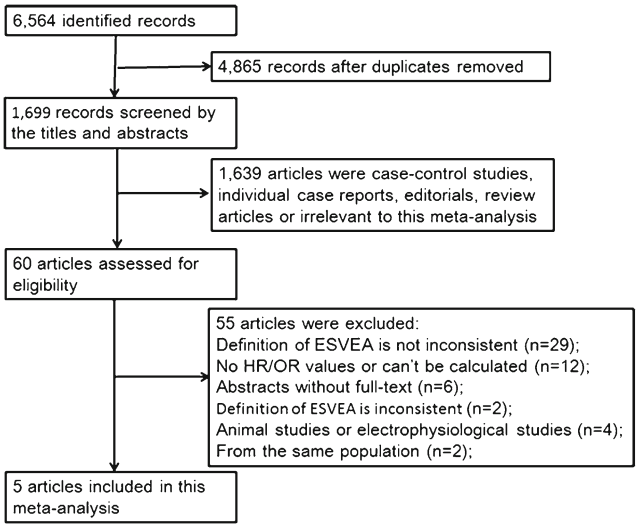

Fig. 1 Study selection flow diagram of the meta-analysis

The demographic characteristics of included patients were described as mean ± SD, median (interquartile range), or percentages as appropriate. According to the different adverse outcomes, we pooled the risk estimates for ESVEA and each clinical endpoint separately. The primary adverse outcomes assessed in this meta-analysis were the relative risk for AF, stroke, and mortality.

Pooled effect sizes were presented as the HR with 95% CI for each trial, using a random effects model. Since the related data were occasionally absent, we utilized raw data to calculate unadjusted risk estimates. We used the random effects model for pooling effect sizes because of the wide range of sample populations contained in the included studies.

Statistical heterogeneity across studies was assessed by ÷2 test and quantified with the use of the I^2 statistic. An $I^2 > 50\%$ is indicative of at least moderate heterogeneity. To assess the effect of individual studies on the estimated relative risk, we also performed a sensitivity analysis by recalculating the pooled relative risk after omitting one study at a time and checking the consistency of the overall effect estimate. Furthermore, publication bias was evaluated by inspecting the funnel plot for each outcome. Statistical significance was defined as a 2-tailed p value of 0.05. All statistical analyses were performed with the Review Manager, version 5.3 (Revman; The Cochrane Collaboration, Oxford, UK).

Results

The flow diagram of our literature search is shown in Fig. 1. A total of 6564 studies were retrieved by using our predefined search criteria. After removing 4865 duplicate records, we further excluded 1639 studies, as they were irrelevant, case-control or cross-sectional studies, individual case reports, editorials, and review articles. Among the remaining 60 original studies, 55 articles were further excluded for the following reasons: the definition of ESVEA in 29 studies was inconsistent, 12 had no outcome estimates in details, and the values could not be retrieved from raw data; 6 were abstracts without full-texts; 2 had no clear definition of ESVEA; 4 were animal studies or electrophysiological studies; and 2 were derived from the same study population. Finally, a total of 5 studies with 7545 patients were included in our meta-analysis: 3 prospective cohort studies [24, 26, 48] and 2 retrospective cohort studies [27, 30].

Baseline characteristics of included studies are listed in Table 1; the proportion of male participants ranged from 44 to 96%, and mean age from 61 to 66 years. The average follow-up duration varied from a minimum of 6.1 years to a

Table. 1 Characteristics of the studies included in the meta-analysis

Author, year	Location	Study design	Subject no.	Male/female (%)	Age (years)	Follow-up	Detection of PACs	Study population
Binici, 2010 [24]	Denmark	PS	678	59/41	64.5 ± 6.8	14.4 years	48-h Holter	Participants in the Copenhagen Holter Study cohort free of CVD, stroke, or AF
Chong, 2012 [26]	China	PS	428	44/56	66.7 ± 10.2	6.1 years	24-h Holter	Patients without AF or structural heart disease
Acharya 2015 [30]	USA	RS	706	96/4	63.7 ± 12.5	13 years	24-h Holter	Veterans free of AF at baseline
Lin, 2015 [27]	Taiwan	RS	5371	60/40	61.76 ± 18.57	10 years	24-h Holter	AF-free patients who underwent clinically indicated Holter monitoring
Marinheiro, 2017 [48•]	Portugal	PS	362	56/44	NA	7.1 years	24-h Holter	Patients without stroke or AF between 2005 and 2010 in a single center

Values represent means ± SD

AF atrial fibrillation, *CVD* cardiovascular disease, *NA* not available, *PAC* premature atrial complexes, *PS* prospective cohort study, *RS* retrospective cohort study

Table 2 Study characteristics in terms of ESVEA definition, studied outcomes, and risk ratios

Author, year	Definition	Definition of outcome	Total events/ participants	Unadjusted risk[2] (95% CI)	Adjusted risk[2] (95% CI)
Binici 2010 [24]	ESVEA (SVEC ≥ 30/h or as any episodes with runs of ≥ 20 SVEC)	All-cause mortality	87/678	HR 2.12 (1.30–3.47)	HR 1.40 (0.83–2.36)
		Death or stroke	105/678	HR 2.54 (1.66–3.90)	HR 1.64 (1.03–2.60)
		AF	22/678	HR 3.19 (1.30–7.86)	HR 2.78(1.08–6.99)
		Stroke	27/678	HR 3.88(1.78–8.48)	HR 2.37(1.02–5.50)
Chong, 2012 [26]	PACs ≥ 100/24 h	AF incidence	60/428	NA	HR 3.22 (1.9–5.5)
		Composite endpoint of IS, CHF, or death	99/428	NA	HR 1.6 (1.04–2.44)
		Ischemic stroke	41/428	NA	HR 2.1 (1.1–4.8)
		CHF	35/428	NA	HR 2.2 (1.2–5.6)
		Death	60/428	NA	HR 1.8 (1.1–3.6)
		CVD	75/428	NA	HR 1.95 (1.37–3.50)
Acharya, 2015 [30]	PACs > 100/24 h	Incident AF	108/706	HR 3.37 (2.18–5.22)	HR 2.87 (1.65–4.98)
Lin, 2015 [27]	PACs > 76/24 h	All-cause mortality	1209/5371	HR 2.188 (1.953–2.451)	HR 1.384 (1.230–1.558)
		CVD hospitalization	1166/5371	HR 1.744 (1.555–1.957)	HR 1.284 (1.137–1.451)
		All-cause hospitalization	3104/5371	HR 1.436 (1.338–1.542)	HR 1.060 (0.983–1.143)
		AF incidence	418/5371	HR 2.305 (1.898–2.799)	HR 1.757 (1.427–2.163)
Marinheiro, 2017 [48•]	EAEA$^{\pm}$ (PACs = 30–97/h)	AF	13/114	HR 1.68(1.05–2.69)	HR 1.90 (1.10–2.78)
		All-cause death	42/114	HR 1.69 (1.06–2.72)	HR 2.01 (1.06–2.52)

AF atrial fibrillation, *CHF* chronic heart failure, *CVD* cardiac vascular disease, *EAEA* excessive atrial ectopic activity, *ESVEA* excessive supraventricular ectopic activity, *HR* hazard ratio, *IS* ischemic stroke, *NA* not available, *PAC* premature atrial complexes, *SVEC* supraventricular ectopic complexes

maximum of 14.4 years. The methods of ESVEA detection included 24-h or 48-h Holter recordings. Table 2 provides a description of different ESVEA definitions among included studies, examined outcomes, and risk ratios according to the presence of ESVEA. The main potential confounders used in multivariate analysis and the quality of the included studies in terms of NOS are shown in Table 3.

All the included studies investigated the potential association between ESVEA and the risk of AF [24, 26, 27, 30, 48]. The pooled analysis showed that ESVEA increased the risk of AF (HR 2.19, 95% CI 1.70–2.82), with slight heterogeneity across studies ($I^2 = 41\%$, $p < 0.00001$) (Fig. 2). Sensitivity and subgroup analyses were performed to find the origin of heterogeneity in the studies for investigating the potential association between ESVEA and the risk of AF. After removing the study by Lin et al. [27], which had the largest number of enrolled patients, significant difference was found on heterogeneity across the remaining studies ($I^2 = 3\%$, $p < 0.00001$),

Table 3 Potential confounders and Newcastle-Ottawa Scale (NOS) of included studies

Study	Confounders used in multivariate analysis	NOS	Quality
Binici, 2010 [24]	Age, sex, smoking habits, diabetes mellitus, systolic blood pressure, and total cholesterol	9	Good
Chong, 2012 [26]	Age, sex, smoking status, hypertension, diabetes, and coronary artery disease	9	Good
Acharya, 2015 [30]	Demographics, medication use, co-morbidities, laboratory, and echocardiographic findings	8	Good
Lin, 2015 [27]	Age, sex, hypertension, coronary heart disease, previous myocardial infarction, heart failure, use of antihypertensive medication	9	Good
Marinheiro 2017 [48•]	Sex, age, body mass index, current smoking, hypertension, diabetes mellitus, blood glucose, creatinine, low-density lipoprotein (LDL) cholesterol, coronary or peripheral arterial disease and heart failure	8	good

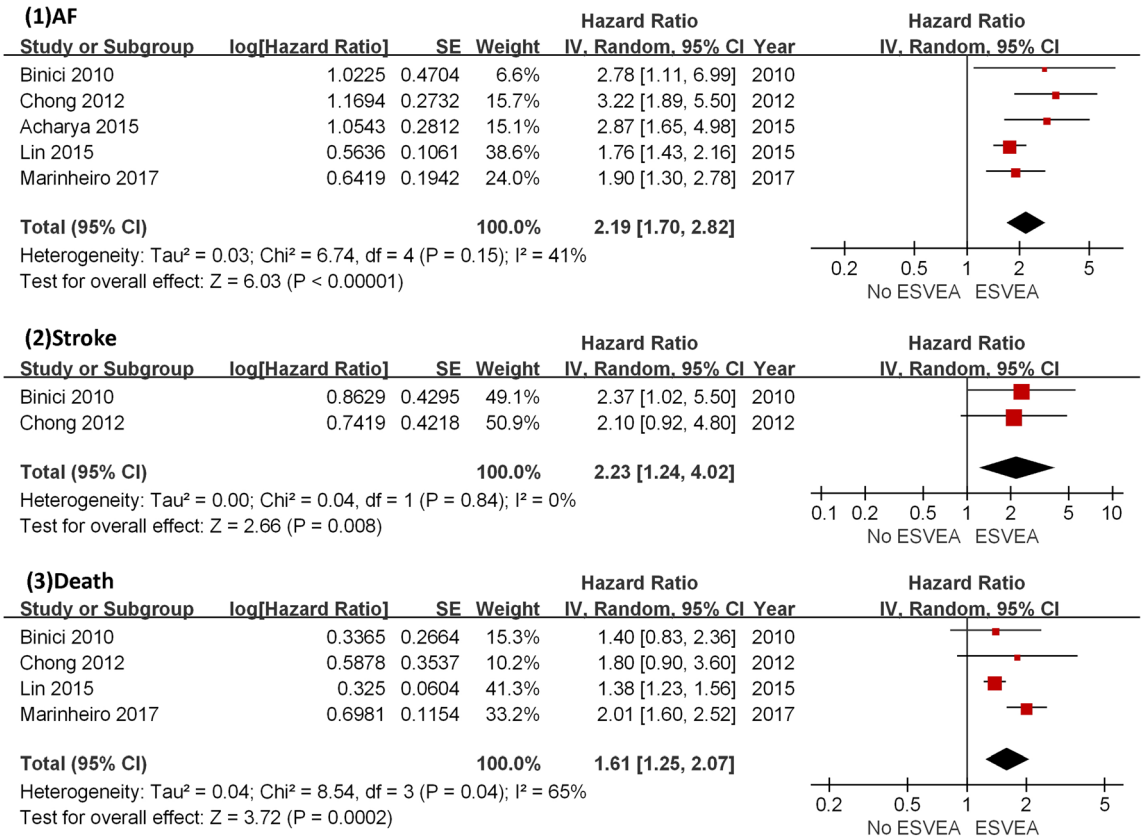

Fig. 2 Risk estimates for the association between ESVEA and the risk of (1) AF incidence, (2) stroke, and (3) death. AF, atrial fibrillation; ESVEA, excessive supraventricular ectopic activity

but the overall results remained the same (HR 2.44, 95% CI 1.87 to 3.18).

Two studies assessed the association between ESVEA and the risk of stroke [24, 26]. The study by Binici et al. demonstrated an association between ESVEA and stroke (HR 1.64, 95% CI 1.03–2.60) [24] and a similar finding was reported by Chong et al. (HR 2.1, 95% CI 1.1–4.8) [26]. Collectively, the above studies showed an overall association between ESVEA and stroke (HR 2.23, 95% CI 1.24–4.02), with no heterogeneity across studies ($I^2 = 0\%$, $p = 0.008$) (Fig. 2). However, the pooled analysis showed that there was no association between ESVEA and all-cause mortality (HR 2.10, 95% CI 0.92–4.80).

Four studies assessed the association between ESVEA and all-cause mortality [24, 26, 27, 48•]. The pooled analysis of all studies showed that ESVEA increased the risk of all-cause mortality (HR 1.61, 95% CI 1.25–2.07), with moderate heterogeneity across studies ($I^2 = 65\%$, $p = 0.0002$) (Fig. 2). We also performed sensitivity and subgroup analyses to find the origin of heterogeneity. Similarly, after removing the study by Lin et al. [27], which had the largest number of enrolled patients, significant difference was found on heterogeneity across the remaining studies ($I^2 = 0\%$, $p < 0.00001$), and the overall results remained the same (HR 1.89, 95% CI 1.55 to 2.31).

We also performed the predefined subgroup analyses using different definitions of ESVEA and the type of studies (retrospective versus prospective). Firstly, we classified studies into two groups: in group 1, ESVEA is defined based on PACs burden per 24 h, while in group 2, ESVEA is defined based on PACs burden per hour and/or runs of PACs as detailed in the "Methods" section. In group 1, the pooled analysis showed that there was an association between ESVEA and AF incidence (HR 2.38, 95% CI 1.55 to 3.66) and the same also applied for group 2 (HR 2.01, 95% CI 1.41 to 2.86, Appendix Fig. 4. In addition, the subgroup analysis showed that ESVEA is predictive of all-cause mortality in both groups (group 1 HR 1.39 95% CI 1.24 to 1.57, group 2 HR 1.82 95% CI 1.32 to 2.50, Appendix Fig. 5. Then, we also classified studies into the retrospective or prospective groups depending on the types of study. In Appendix Fig. 6, the pooled analysis showed that there was an association between ESVEA and AF incidence, no matter in retrospective or prospective groups (HR 2.09, 95% CI 1.32 to 3.31 vs. HR 2.39, 95% CI 1.66 to 3.43). In addition, the pooled analysis showed that ESVEA is predictive of all-cause mortality in both groups (retrospective group: HR 1.38, 95% CI 1.22 to 1.56; prospective group: HR 1.89, 95% CI 1.55 to 2.31; Appendix Fig. 7. Finally, the results of the funnel plot suggested that little publication bias was present (Fig. 3).

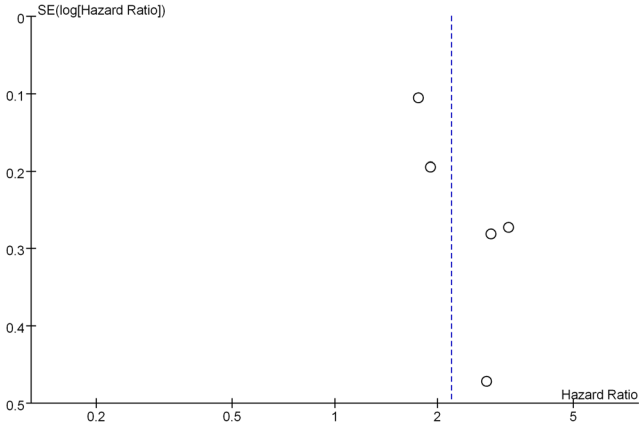

Fig. 3 The funnel plot for estimating the association between ESVEA and the risk of AF incidence

Discussion

The present meta-analysis including 5 studies with 7545 participants shows that ESVEA is associated with the following: (i) a 2-fold increased risk of incident AF, (ii) a higher likelihood of stroke, and (iii) increased risk of all-cause mortality. Even though several original studies have examined the potential association of ESVEA with AF and other cardiovascular outcomes, this systematic analysis is the first to synthesize all available data and produce pooled risk estimates on cardiovascular outcomes in a group of individuals with a considerable burden of PACs.

A causal relationship between PACs and initiation of AF has been proposed since 1965 [9, 50]. Contemporary research has unanimously recognized PACs critical to AF pathogenesis having considered data from Holter recordings [9, 11, 13, 15, 51] and electrophysiological studies [20]. Indeed, Vincenti et al. found 95% of AF episodes to be preceded by a triggering PAC, while PAC frequency was significantly increased before the AF episode [51]. Pulmonary veins have been consistently shown to be the focus of most AF-triggering PACs either clinically [10, 14] or experimentally [12]. More complex supraventricular activity than single PACs, namely atrial bigeminy and short atrial runs, have also been shown to precede AF [15].

Regarding the observed association of ESVEA with incident stroke or TIA, various pathophysiologic mechanisms have been proposed. The most widely accepted theory involves the development of subclinical AF because of atrial ectopic triggers [52]. Increased atrial ectopy has also been associated with traditional risk factors for cardiovascular disease (low HDL, physical inactivity, existing cardiovascular disease, NT-proBNP) [2]. Therefore, ESVEA may be a surrogate marker of a poor cardiovascular risk factor profile, potentially responsible for an increased propensity for subsequent stroke. Larsen et al. [25] reported an association between ESVEA and stroke beyond manifest AF. Atrial electrical instability, exhibited as ESVEA, together with hypertension and other cardiovascular risk factors, can lead to left atrial dilatation, wall fibrosis, and a hypercoagulable state [53, 54]. The ESVEA-stroke association, as it was shown in our meta-analysis, may imply that ESVEA can be considered as an emerging risk factor for stroke, independent of concomitant AF.

Our meta-analysis also revealed a significant association between ESVEA and all-cause mortality. Excessive atrial ectopy, as mentioned before, may represent a surrogate marker of a constellation of cardiovascular risk factors, hidden heart disease, and an unfavorable cardiovascular profile in general. Furthermore, AF, associated with ESVEA as shown above, is well-known to increase cardiovascular mortality, myocardial infarction, sudden cardiac death, and stroke mortality [55, 56]. Left ventricular diastolic dysfunction either detected echocardiographically [57] or on the basis of elevated natriuretic peptide levels [2, 24] has been additionally correlated with ESVEA.

Prior to this meta-analysis, many original studies varied significantly in the definition of ESVEA, thereby impeding definite conclusions and the suggestion of universal cutoff points. In the majority of Holter studies, cutoff points were derived from the > 90th percentile [24, 25, 31], the top quartile [26, 32, 35, 40], or quintile [23] of observed values. Other researchers treated PAC counts as continuous variables [28, 29], thus reporting risk ratios for every doubling of PACs [29]. The resultant cutoff points ranged from 70 [27] to 720 PACs/day in the Copenhagen Holter Study [24, 25, 31], with most of them varying around 100 PACs/day. We chose a PACs burden of > 30 per hour or > 218 per 24 h as optimal cutoffs for ESVEA to avoid inclusion of non-clinically significant PAC occurrences. It would be challenging to define universal cutoff points for ESVEA, especially considering that PACs increase with progressing age. Another consideration relates to the fact that in some studies, participants were suffering from a specific disease (e.g., hypertension, cryptogenic stroke, or cardioverts AF) in various proportions. These discrepancies may have affected both the outcomes and the generalizability of respective studies. Of note, a recent meta-analysis assessing the effects of PACs on cardiovascular outcomes, reported an association with atrial fibrillation, first stroke and all-cause mortality. This meta-analysis however was also limited by the considerable variations in the definitions of PACs burden, especially in cases where the PACs were treated as dichotomous variable [58••].

As this meta-analysis unveils a potential implication of ESVEA on cardiovascular outcomes, future studies are warranted to explore the impact of appropriate therapeutic interventions. Prospective studies, possibly using

clinically indicated antiarrhythmic therapy or radiofrequency ablation, would be of utmost importance in elucidating a potential clinical benefit of ESVEA suppression on AF, stroke, and death incidence. Furthermore, the effects of anticoagulation or antiplatelet therapy in preventing cerebrovascular events in individuals with ESVEA should be investigated.

With regard to the limitations of this meta-analysis, a degree of publication bias cannot be excluded. Significant differences in the studies composing this meta-analysis were noted, such as the duration of follow-up (2 to 10 years) and the study population (number of participants and baseline characteristics). These variations might have affected our results. In addition, since this was a meta-analysis of published studies as opposed to an individual patient-level meta-analysis, they could not adjust for potential confounders beyond what each of the individual studies did. In that respect, some of the potential confounders (e.g., presence of structural heart disease, ejection fraction, and various cardiovascular risk factors) were not uniformly adjusted for across studies and could potentially confound the association or the effect size.

Conclusions

In conclusion, our meta-analysis found that ESVEA is closely associated with AF, stroke, and all-cause mortality. Further studies are required to examine the implication of therapeutic strategies in patients with ESVEA, to prevent ESVEA-related adverse cardiovascular outcomes.

Funding Information This work was supported by the National Natural Science Foundation of China (81970270, 81570298, 30900618, and 81270245 to T.L.), the Tianjin Natural Science Foundation (16JCZDJC34900 to T.L.), and the Croucher Foundation of Hong Kong (Clinical Assistant Professorship to GT).

Compliance with Ethical Standards

Conflict of Interest Lei Meng, Georgios Tsiaousis, Jinli He, Gary Tse, Konstantinos P. Letsas, Adrian Baranchuk, Wenwei Qi, Zhiwei Zhang, Enzhao Liu, Gang Xu, Yunlong Xia, Guangping Li, Leonardo Roever, Nikolaos Fragakis, and Tong Liu each declare that they have no conflict of interest. Antonios P. Antoniadis reports personal fees from PromoPharma SA, outside the submitted work Panagiotis Korantzopoulos reports personal fees from MEDTRONIC, personal fees from PFIZER, personal fees from BAYER, and personal fees from BOEHRINGER-INGELHEIM, outside the submitted work. Gregory YH Lip has served as a consultant for Bayer/Janssen, Bristol-Myers Squibb/Pfzer, Biotronik, Medtronic, Boehringer Ingelheim, Novartis, Verseon, and Daiichi Sankyo, and as a speaker for Bayer, Bristol-Myers Squibb/Pfzer, Medtronic, Boehringer Ingelheim, and Daiichi Sankyo.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Folarin VA, Fitzsimmons PJ, Kruyer WB. Holter monitor findings in asymptomatic male military aviators without structural heart disease. Aviat Space Environ Med. 2001;72(9):836–8.
2. Conen D, Adam M, Roche F, Barthelemy JC, Felber Dietrich D, Imboden M, et al. Premature atrial contractions in the general population: frequency and risk factors. Circulation. 2012;126(19):2302–8. https://doi.org/10.1161/CIRCULATIONAHA.112.112300.
3. Fleg JL, Kennedy HL. Long-term prognostic significance of ambulatory electrocardiographic findings in apparently healthy subjects greater than or equal to 60 years of age. Am J Cardiol. 1992;70(7):748–51.
4. Glasser SP, Clark PI, Applebaum HJ. Occurrence of frequent complex arrhythmias detected by ambulatory monitoring: findings in an apparently healthy asymptomatic elderly population. Chest. 1979;75(5):565–8.
5. Kantelip JP, Sage E, Duchene-Marullaz P. Findings on ambulatory electrocardiographic monitoring in subjects older than 80 years. Am J Cardiol. 1986;57(6):398–401.
6. Camm AJ, Evans KE, Ward DE, Martin A. The rhythm of the heart in active elderly subjects. Am Heart J. 1980;99(5):598–603.
7. Taylor IC, Stout RW. The significance of cardiac arrhythmias in the aged. Age Ageing. 1983;12(1):21–8.
8. Fleg JL, Kennedy HL. Cardiac arrhythmias in a healthy elderly population: detection by 24-hour ambulatory electrocardiography. Chest. 1982;81(3):302–7.
9. Bennett MA, Pentecost BL. The pattern of onset and spontaneous cessation of atrial fibrillation in man. Circulation. 1970;41(6):981–8.
10. Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med. 1998;339(10):659–66. https://doi.org/10.1056/nejm199809033391003.
11. Kolb C, Nurnberger S, Ndrepepa G, Zrenner B, Schomig A, Schmitt C. Modes of initiation of paroxysmal atrial fibrillation from analysis of spontaneously occurring episodes using a 12-lead Holter monitoring system. Am J Cardiol. 2001;88(8):853–7.
12. Gong Y, Xie F, Stein KM, Garfinkel A, Culianu CA, Lerman BB, et al. Mechanism underlying initiation of paroxysmal atrial flutter/atrial fibrillation by ectopic foci: a simulation study. Circulation. 2007;115(16):2094–102. https://doi.org/10.1161/circulationaha.106.656504.
13. Jensen TJ, Haarbo J, Pehrson SM, Thomsen B. Impact of premature atrial contractions in atrial fibrillation. Pacing Clin Electrophysiol. 2004;27(4):447–52. https://doi.org/10.1111/j.1540-8159.2004.00462.x.
14. Chen SA, Hsieh MH, Tai CT, Tsai CF, Prakash VS, Yu WC, et al. Initiation of atrial fibrillation by ectopic beats originating from the pulmonary veins: electrophysiological characteristics, pharmacological responses, and effects of radiofrequency ablation. Circulation. 1999;100(18):1879–86.
15. Waktare JE, Hnatkova K, Sopher SM, Murgatroyd FD, Guo X, Camm AJ, et al. The role of atrial ectopics in initiating paroxysmal atrial fibrillation. Eur Heart J. 2001;22(4):333–9. https://doi.org/10.1053/euhj.2000.2517.
16. Cheriyath P, He F, Peters I, Li X, Alagona P Jr, Wu C, et al. Relation of atrial and/or ventricular premature complexes on a two-minute

rhythm strip to the risk of sudden cardiac death (the Atherosclerosis Risk in Communities [ARIC] study). Am J Cardiol. 2011;107(2):151–5. https://doi.org/10.1016/j.amjcard.2010.09.002.
17. Ofoma U, He F, Shaffer ML, Naccarelli GV, Liao D. Premature cardiac contractions and risk of incident ischemic stroke. J Am Heart Assoc. 2012;1(5):e002519. https://doi.org/10.1161/JAHA.112.002519.
18. Inohara T, Kohsaka S, Okamura T, Watanabe M, Nakamura Y, Higashiyama A, et al. Long-term outcome of healthy participants with atrial premature complex: a 15-year follow-up of the NIPPON DATA 90 cohort. PLoS One. 2013;8(11):e80853. https://doi.org/10.1371/journal.pone.0080853.
19. Qureshi W, Shah AJ, Salahuddin T, Soliman EZ. Long-term mortality risk in individuals with atrial or ventricular premature complexes (results from the Third National Health and Nutrition Examination Survey). Am J Cardiol. 2014;114(1):59–64. https://doi.org/10.1016/j.amjcard.2014.04.005.
20. Murakoshi N, Xu D, Sairenchi T, Igarashi M, Irie F, Tomizawa T, et al. Prognostic impact of supraventricular premature complexes in community-based health checkups: the Ibaraki Prefectural Health Study. Eur Heart J. 2015;36(3):170–8. https://doi.org/10.1093/eurheartj/ehu407.
21. Perez MV, Dewey FE, Marcus R, Ashley EA, Al-Ahmad AA, Wang PJ, et al. Electrocardiographic predictors of atrial fibrillation. Am Heart J. 2009;158(4):622–8. https://doi.org/10.1016/j.ahj.2009.08.002.
22. Nguyen KT, Vittinghoff E, Dewland TA, Dukes JW, Soliman EZ, Stein PK, et al. Ectopy on a single 12-lead ECG, incident cardiac myopathy, and death in the community. J Am Heart Assoc. 2017;6(8). https://doi.org/10.1161/JAHA.117.006028.
23. Engstrom G, Hedblad B, Juul-Moller S, Tyden P, Janzon L. Cardiac arrhythmias and stroke: increased risk in men with high frequency of atrial ectopic beats. Stroke. 2000;31(12):2925–9.
24. Binici Z, Intzilakis T, Nielsen OW, Kober L, Sajadieh A. Excessive supraventricular ectopic activity and increased risk of atrial fibrillation and stroke. Circulation. 2010;121(17):1904–11. https://doi.org/10.1161/CIRCULATIONAHA.109.874982.
25. Larsen BS, Kumarathurai P, Falkenberg J, Nielsen OW, Sajadieh A. Excessive atrial ectopy and short atrial runs increase the risk of stroke beyond incident atrial fibrillation. J Am Coll Cardiol. 2015;66(3):232–41. https://doi.org/10.1016/j.jacc.2015.05.018.
26. Chong BH, Pong V, Lam KF, Liu S, Zuo ML, Lau YF, et al. Frequent premature atrial complexes predict new occurrence of atrial fibrillation and adverse cardiovascular events. Europace. 2012;14(7):942–7. https://doi.org/10.1093/europace/eur389.
27. Lin CY, Lin YJ, Chen YY, Chang SL, Lo LW, Chao TF, et al. Prognostic significance of premature atrial complexes burden in prediction of long-term outcome. J Am Heart Assoc. 2015;4(9):e002192. https://doi.org/10.1161/JAHA.115.002192.
28. Dewland TA, Vittinghoff E, Mandyam MC, Heckbert SR, Siscovick DS, Stein PK, et al. Atrial ectopy as a predictor of incident atrial fibrillation: a cohort study. Ann Intern Med. 2013;159(11):721–8. https://doi.org/10.7326/0003-4819-159-11-201312030-00004.
29. Nguyen KT, Vittinghoff E, Dewland TA, Mandyam MC, Stein PK, Soliman EZ, et al. Electrocardiographic predictors of incident atrial fibrillation. Am J Cardiol. 2016;118(5):714–9. https://doi.org/10.1016/j.amjcard.2016.06.008.
30. Acharya T, Tringali S, Bhullar M, Nalbandyan M, Ilineni VK, Carbajal E, et al. Frequent atrial premature complexes and their association with risk of atrial fibrillation. Am J Cardiol. 2015;116(12):1852–7. https://doi.org/10.1016/j.amjcard.2015.09.025.
31. Kumarathurai P, Mouridsen MR, Mattsson N, Larsen BS, Nielsen OW, Gerds TA, et al. Atrial ectopy and N-terminal pro-B-type natriuretic peptide as predictors of atrial fibrillation: a population-based cohort study. Europace. 2017;19(3):364–70. https://doi.org/10.1093/europace/euw017.
32. Suzuki S, Sagara K, Otsuka T, Kano H, Matsuno S, Takai H, et al. Usefulness of frequent supraventricular extrasystoles and a high CHADS2 score to predict first-time appearance of atrial fibrillation. Am J Cardiol. 2013;111(11):1602–7. https://doi.org/10.1016/j.amjcard.2013.01.335.
33. Johnson LS, Juhlin T, Juul-Moller S, Hedblad B, Nilsson PM, Engstrom G. A prospective study of supraventricular activity and incidence of atrial fibrillation. Heart Rhythm. 2015;12(9):1898–904. https://doi.org/10.1016/j.hrthm.2015.04.042.
34. Miller DJ, Khan MA, Schultz LR, Simpson JR, Katramados AM, Russman AN, et al. Outpatient cardiac telemetry detects a high rate of atrial fibrillation in cryptogenic stroke. J Neurol Sci. 2013;324(1–2):57–61. https://doi.org/10.1016/j.jns.2012.10.001.
35. Wallmann D, Tuller D, Wustmann K, Meier P, Isenegger J, Arnold M, et al. Frequent atrial premature beats predict paroxysmal atrial fibrillation in stroke patients: an opportunity for a new diagnostic strategy. Stroke. 2007;38(8):2292–4.
36. Yodogawa K, Seino Y, Ohara T, Hayashi M, Miyauchi Y, Katoh T, et al. Prediction of atrial fibrillation after ischemic stroke using P-wave signal averaged electrocardiography. J Cardiol. 2013;61(1):49–52. https://doi.org/10.1016/j.jjcc.2012.08.013.
37. Pinho J, Braga CG, Rocha S, Santos AF, Gomes A, Cabreiro A, et al. Atrial ectopic activity in cryptogenic ischemic stroke and TIA: a risk factor for recurrence. J Stroke Cerebrovasc Dis. 2015;24(2):507–10. https://doi.org/10.1016/j.jstrokecerebrovasdis.2014.09.029.
38. Sudacevschi V, Bertrand C, Chadenat ML, Tarnaud C, Pico F. Predictors of occult atrial fibrillation in one hundred seventy-one patients with cryptogenic transient ischemic attack and minor stroke. J Stroke Cerebrovasc Dis. 2016;25(11):2673–7. https://doi.org/10.1016/j.jstrokecerebrovasdis.2016.07.014.
39.•• Vinther KH, Tveskov C, Moller S, Auscher S, Osmanagic A, Egstrup K. Excessive premature atrial complexes and the risk of recurrent stroke or death in an ischemic stroke population. J Stroke Cerebrovasc Dis. 2017;26(6):1163–70. https://doi.org/10.1016/j.jstrokecerebrovasdis.2016.10.038 **A prospective cohort study investigated the potential association of premature atrial complexes (> 14 PAC per hour and three or more runs of premature atrial complexes per 24 h) between recurrent stroke or death in patients with ischemic stroke. These results confirmed excessive premature atrial complexes were associated with a higher risk of recurrent stroke or death.**
40. Kochhauser S, Dechering DG, Dittrich R, Reinke F, Ritter MA, Ramtin S, et al. Supraventricular premature beats and short atrial runs predict atrial fibrillation in continuously monitored patients with cryptogenic stroke. Stroke. 2014;45(3):884–6. https://doi.org/10.1161/STROKEAHA.113.003788.
41. Chong JJ, Kumar S, Thomas L, Thomas S. Supraventricular ectopy and recurrence of atrial fibrillation after electrical cardioversion. Europace. 2006;8(5):341–4. https://doi.org/10.1093/europace/eul008.
42. Varounis C, Dagres N, Maounis T, Panagiotakos D, Cokkinos DV. Atrial premature complexes and heart rate have prognostic significance in 1-month atrial fibrillation recurrence after electrical cardioversion. Europace. 2007;9(8):633–7. https://doi.org/10.1093/europace/eum090.
43. Kim IS, Yang PS, Kim TH, Park J, Park JK, Uhm JS, et al. Clinical significance of additional ablation of atrial premature beats after catheter ablation for atrial fibrillation. Yonsei Med J. 2016;57(1):72–80. https://doi.org/10.3349/ymj.2016.57.1.72.
44. Gang UJ, Nalliah CJ, Lim TW, Thiagalingam A, Kovoor P, Ross DL, et al. Atrial ectopy predicts late recurrence of atrial fibrillation after pulmonary vein isolation. Circ Arrhythm Electrophysiol. 2015;8(3):569–74. https://doi.org/10.1161/CIRCEP.114.002052.

45. Chun KJ, Hwang JK, Choi SR, Park SJ, On YK, Kim JS, et al. Electrocardiogram PR interval is a surrogate marker to predict new occurrence of atrial fibrillation in patients with frequent premature atrial contractions. J Korean Med Sci. 2016;31(4):519–24. https://doi.org/10.3346/jkms.2016.31.4.519.
46. Chun KJ, Hwang JK, Park SJ, On YK, Kim JS, Park KM. Electrical PR interval variation predicts new occurrence of atrial fibrillation in patients with frequent premature atrial contractions. Medicine (Baltimore). 2016;95(14):e3249. https://doi.org/10.1097/MD.0000000000003249.
47. Mattsson N, Kumarathurai P, Larsen BS, Nielsen OW, Sajadieh A. Mild hypokalemia and supraventricular ectopy increases the risk of stroke in community-dwelling subjects. Stroke. 2017;48(3):537–43. https://doi.org/10.1161/STROKEAHA.116.015439.
48.• Marinheiro R, Parreira L, Amador P, Sa C, Duarte T, Caria R. Excessive atrial ectopic activity as an independent risk factor for ischemic stroke. Int J Cardiol. 2017;249:226–30. https://doi.org/10.1016/j.ijcard.2017.08.054 **This study included in this meta-analysis demonstrated that in the patients without stroke or AF, having > 30 PACs/h was independently associated with a higher risk of AF and death but only subjects with > 97 PACs/h had a higher risk of ischemic stroke.**
49. Madigan E, Schmotzer BJ, Struk CJ, DiCarlo CM, Kikano G, Pina IL, et al. Home health care with telemonitoring improves health status for older adults with heart failure. Home Health Care Serv Q. 2013;32(1):57–74. https://doi.org/10.1080/01621424.2012.755144.
50. Killip T, Gault JH. Mode of onset of atrial fibrillation in man. Am Heart J. 1965;70:172–9.
51. Vincenti A, Brambilla R, Fumagalli MG, Merola R, Pedretti S. Onset mechanism of paroxysmal atrial fibrillation detected by ambulatory Holter monitoring. Europace. 2006;8(3):204–10. https://doi.org/10.1093/europace/euj043.
52. Hohnloser SH, Healey JS, Gold MR, Israel CW, Yang S, van Gelder I, et al. Atrial overdrive pacing to prevent atrial fibrillation: insights from ASSERT. Heart Rhythm. 2012;9(10):1667–73. https://doi.org/10.1016/j.hrthm.2012.06.012.
53. Hirsh BJ, Copeland-Halperin RS, Halperin JL. Fibrotic atrial cardiomyopathy, atrial fibrillation, and thromboembolism: mechanistic links and clinical inferences. J Am Coll Cardiol. 2015;65(20):2239–51. https://doi.org/10.1016/j.jacc.2015.03.557.
54. Watson T, Shantsila E, Lip GY. Mechanisms of thrombogenesis in atrial fibrillation: Virchow's triad revisited. Lancet. 2009;373(9658):155–66. https://doi.org/10.1016/s0140-6736(09)60040-4.
55. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur J Cardiothorac Surg. 2016;50(5):e1–e88. https://doi.org/10.1093/ejcts/ezw313.
56. Soliman EZ, Safford MM, Muntner P, Khodneva Y, Dawood FZ, Zakai NA, et al. Atrial fibrillation and the risk of myocardial infarction. JAMA Intern Med. 2014;74(1):107–14. https://doi.org/10.1001/jamainternmed.2013.11912.
57. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2016;17(12):1321–60. https://doi.org/10.1093/ehjci/jew082.
58.•• Himmelreich JCL, Lucassen WAM, Heugen M, Bossuyt PMM, Tan HL, Harskamp RE, et al. Frequent premature atrial contractions are associated with atrial fibrillation, brain ischaemia, and mortality: a systematic review and meta-analysis. Europace. 2019;21(5):698-707. https://doi.org/10.1093/europace/euy276 **This was one of the most recent meta-analysis comparing the association between PACs on ECG as well as PAC-count on Holter and AF, brain ischemia and all-cause mortality in patients without a history of AF, showing that frequent PACs on 24–48 h Holter were significantly associated with AF, stroke, and mortality.**