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A systematic review and meta-regression

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Original article

Epidemiology of subclinical atrial fibrillation in patients with cardiac implantable electronic devices: A systematic review and meta-regression

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ABSTRACT

Background: In recent years, attention to subclinical atrial fibrillation (SCAF), defined as the presence of atrial high-rate episodes (AHREs), in patients with cardiac implantable electronic devices (CIEDs), has gained much interest as a determinant of clinical AF and stroke risk. We aim to perform a systematic review and meta-regression of the available scientific evidence regarding the epidemiology of SCAF in patients receiving CIEDs.
Methods: PubMed and EMBASE were searched for all studies documenting the prevalence of AHREs in patients (n=100 or more, <50% with history of AF) with CIEDs from inception to 20th August 2021, screened by two independent blind reviewers. This study was registered in PROSPERO: CRD42019106994.
Results: Among the 2614 results initially retrieved, 54 studies were included, with a total of 72,784 patients. Meta-analysis of included studies showed a pooled prevalence of SCAF of 28.1% (95%CI: 24.3-32.1%), with high heterogeneity between studies (I^2=98%). A multivariable meta-regression was able to explain significant proportion of heterogeneity (R^2=61.9%, p<0.001), with age and follow-up time non-linearly, directly and independently associated with occurrence of SCAF. Older age, higher CHA_2DS_2-VASc score, history of AF, hypertension, CHF, and stroke/TIA were all associated with SCAF occurrence.
Conclusions: In this systematic review and meta-regression analysis, SCAF was frequent among CIED recipients and was non-linearly associated with age and follow-up time. Older age, higher thromboembolic risk, and several cardiovascular comorbidities were associated with presence of SCAF.

1. Introduction

In 1958 Senning and Elmqvist implanted the first permanent cardiac pacemaker (PM) to Arne Larsson, who survived for more than 40 years and ultimately died from different causes [1]. Since then, the use of cardiac implanted electronic devices (CIEDs) is widespread thanks to the technological advances that progressively introduced implanted cardioverter-defibrillator (ICD) and cardiac resynchronization therapy

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Table 1
General Characteristics of the Studies Included in the Systematic Review.

STUDY	Year	Geographic Location	Design	N	N SCAF	AGE (mean)	AF History	Atrial Rate Cut-Off (bpm)	Duration Cut-Off (min)	SCAF Confirmation	FU (years)
Arai [18]	2020	Asia	Observational Retrospective	153	75	65.6	No	180-200	5-6	Other/Unclear	4.17
Banerjee [19]	2019	Asia	Observational Retrospective	234	48	66.9	No	180-200	5-6	Manual Confirm	3.74‡
Benezet-Mazuecos [20]	2015	Europe	Observational Prospective	109	28	74	No	>200	5-6	Manual Confirm	1.42‡
Bertini [21]	2010	Europe	Observational Prospective	495	142	62.2	21%	180-200	>6	Other/Unclear	1.37‡
Boriani [22]	2014	Multinational	Observational Prospective	10016	4287	70§	24%	Other/ Unclear	Other/ Unclear	Other/Unclear	2§
Borleffs [23]	2009	Europe	Observational Retrospective	223	55	65	No	180-200	>6	Device-based	2.75‡
Bukari [24]	2018	North America	Observational Retrospective	322	199	68.8	23%	Other/ Unclear	<5	Manual Confirm	5.60‡
Campbell [25]	2014	Europe	Observational Retrospective	197	87	66.7	No	180-200	<5	Manual Confirm	2.80§
Cheung [26]	2006	North America	Observational Prospective	262	77	74	No	Other/ Unclear	5-6	Manual Confirm	1.63‡
Ghali [27]	2007	Multinational	Observational Prospective	427	232	75	23%	180-200	<5	Manual Confirm	1.75‡
Gonzalez [28]	2014	North America	Observational Retrospective	224	39	74	No	<180	5-6	Manual Confirm	0.5
Healey [29]	2012	Multinational	RCT	2580	261	76	No	180-200	5-6	Manual Confirm	0.25
Healey [30]	2013	North America	Observational Retrospective	445	246	73.1	25%	180-200	5-6	Manual Confirm	4.29‡
Ishiguchi [31]	2021	Asia	Observational Retrospective	710	350	78	29%	<180	5-6	Other/Unclear	4.5§
Kaplan [32]	2020	North America	Observational Retrospective	35779	12938	71.8	36%	Other/ Unclear	Other/ Unclear	Device-Based	0.5
Kawakami [33]	2017	Asia	Observational Retrospective	343	165	80	24%	<180	5-6	Device-Based	4.33‡
Kim [34]	2016	Asia	Observational Retrospective	880	122	62.7	No	180-200	5-6	Manual Confirm	4.6§
Kim [35]	2021	Asia	Observational Prospective	816	112	73§	No	>200	5-6	Manual Confirm	1.5§
Kishima [36]	2021	Asia	Observational Retrospective	147	50	75.2	No	180-200	5-6	Manual Confirm	3.19‡
Kirshnamoorthy [37]	2017	Europe	Observational Prospective	101	24	72.1	No	>200	<5	Device-Based	1
Li [38]	2019	Europe	Observational Retrospective	594	175	69	No	<180	5-6	Manual Confirm	4.2‡
Liao [39]	2019	Asia	Observational Prospective	171	66	74.1	12%	180-200	5-6	Device-Based	1.68§
Lima [40]	2016	Other	RCT	300	63	75.2	No	<180	<5	Manual Confirm	1.31‡
Lorenzoni [41]	2014	Europe	Observational Prospective	582	20	74§	30%	Other/ Unclear	Other/ Unclear	Manual Confirm	0.42
Lu [42]	2021	Asia	Observational Retrospective	481	112	77	26%	Other/ Unclear	5-6	Manual Confirm	3.32‡
Marijon [43]	2010	Europe	Observational Prospective	173	34	71	32%	<180	5-6	Manual Confirm	0.83‡
Mathen [44]	2020	Asia	Observational Retrospective	398	59	59.9	No	Other/ Unclear	Other/ Unclear	Device-Based	1.55§
Mittal [45]	2008	North America	Observational Prospective	1482	150	74	No	180-200	5-6	Device-Based	0.5‡
Miyazawa [46]	2018	Asia	Observational Retrospective	371	78	61	No	180-200	5-6	Manual Confirm	4.58§
Miyazawa [47]	2021	Multinational	RCT	2718	653	64.4	12%	180-200	5-6	Manual Confirm	2.0‡
Nishinarita [48]	2019	Asia	Observational Retrospective	104	34	75.1	No	<180	5-6	Manual Confirm	1
Palmisano [49]	2018	Europe	Observational Retrospective	770	88	65.5	15%	180-200	5-6	Other/Unclear	2.08§
Ricci [50]	2009	Europe	Observational Prospective	166	55	73.1	29%	<180	>6	Manual Confirm	1.34‡
Rovaris [51]	2018	Europe	Observational Prospective	2,410	962	70§	No	180-200	>6	Other/Unclear	2.01§
Rubio-Campal [52]	2018	Multinational	Observational Prospective	380	125	75	24%	>200	5-6	Manual Confirm	1.50‡
Russo [53]	2020	Europe	Observational Prospective	181	34	68.1	No	Other/ Unclear	<5	Manual Confirm	1

(*continued on next page*)

Table 1 (*continued*)

STUDY	Year	Geographic Location	Design	N	N SCAF	AGE (mean)	AF History	Atrial Rate Cut-Off (bpm)	Duration Cut-Off (min)	SCAF Confirmation	FU (years)
Sandgren [54]	2018	Europe	Observational Retrospective	411	125	76.4	No	Other/ Unclear	5-6	Other/Unclear	3.17§
Satilmis [55]	2018	Other	Observational Prospective	203	51	67.5	No	>200	5-6	Other/Unclear	0.5
Tekkesin [56]	2017	Other	Observational Prospective	355	107	67.5	No	>200	5-6	Other/Unclear	0.5
Thomas [57]	2019	North America	Observational Prospective	150	16	59	No	180-200	<5	Other/Unclear	1§
Tsai [58]	2008	Asia	RCT	106	59	71	N/A	180-200	<5	Manual Confirm	1
Tse [59]	2005	Asia	Observational Retrospective	226	99	70.9	38%	Other/ Unclear	Other/ Unclear	Device-Based	7.0‡
Ugurlu [60]	2018	Other	Observational Prospective	191	44	64.7	No	Other/ Unclear	5-6	Manual Confirm	1.60‡
Van Velzen [61]	2017	Europe	Observational Retrospective	132	29	52	30%	180-200	<5	Manual Confirm	2.8§
Verbrugge [62]	2014	Europe	Observational Prospective	118	53	70	No	180-200	<5	Manual Confirm	2.17‡
Wali [63]	2018	North America	Observational Retrospective	166	78	71	27%	Other/ Unclear	<5	Manual Confirm	5.8‡
Wilton [64]	2016	Multinational	RCT	972	465	66	No	<180	<5	Manual Confirm	3.42§
Witt [65]	2015	Europe	Observational Retrospective	394	79	67	No	Other/ Unclear	5-6	Device-Based	0.5
Wu [66]	2021	Asia	Observational Prospective	219	56	67.4	No	180-200	5-6	Device-Based	2.42‡
Xie [67]	2012	Asia	Observational Prospective	110	32	70.5	15%	>200	5-6	Device-Based	1
Xu [68]	2019	Asia	Observational Retrospective	110	31	62	No	180-200	5-6	Device-Based	1.75‡
Younis [69]	2020	Multinational	RCT	1500	286	62.8	15%	<180	<5	Manual Confirm	1.42‡
Zakeri [70]	2020	Europe	RCT	1561	350	69.4	43%	Other/ Unclear	5-6	Manual Confirm	1
Zhang [71]	2016	Asia	RCT	116	34	65.1	No	180-200	5-6	Manual Confirm	2

Legend: ‡Mean; §Median; AF= Atrial Fibrillation; BPM= Beat Per Minute; FU= Follow-Up; N/A= Not Available; RCT= Randomized Controlled Trial; SCAF= Subclinical Atrial Fibrillation.

(CRT) with only pacing activity (CRT-P) or also defibrillation (CRT-D) [2], with increasing clinical indications [3–5]. Despite some geographical variability [6], in recent years increasing use of CIEDs is evident [2,7].

The increasing use of CIEDs and atrial leads for sensing purposes led to the identification of a clinical entity, the CIED-detected atrial high-rate episodes (AHRE) [8]. The occurrence of AHRE, which is nowadays assimilated as the term of 'subclinical atrial fibrillation (SCAF), is defined as asymptomatic atrial tachyarrhythmias detected only with long-term continuous cardiac monitoring and not through usual electrocardiographic means [8]. In this clinical context, AHRE/SCAF has been associated with an increased risk of developing clinical AF and an increased risk of stroke and systemic embolism [8,9]. Thus far, a highly variable incidence of AHRE/SCAF has been reported, basically depending on patients' clinical characteristics [8].

In this study, we performed a systematic review of all studies reporting about AHRE/SCAF prevalence in patients with CIEDs and provide pooled estimates to obtain a comprehensive assessment of its' epidemiology. Second, we performed a meta-regression analysis to investigate study setting and clinical factors that would be more likely associated with AHRE/SCAF.

2. Methods

This systematic review was performed according to the 'Meta-analysis Of Observational Studies in Epidemiology' guidelines [10] and reported according to the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' guidelines [11]. A protocol for this systematic review has been registered into the international prospective register of systematic reviews PROSPERO (Center for Reviews and Dissemination, University of York) (CRD42019106994).

We performed a systematic and comprehensive literature search PubMed and EMBASE databases from inception up to 20th August 2021. The search was performed combining the terms 'AHRE', 'SCAF', and 'CIED'. The full search strategy is reported in the Supplementary Materials (Supplemental Table 1).

2.1. Studies selection

Two co-authors (MB and GFR) independently screened the search results. Disagreements were resolved by discussion with a third author (MP). All articles retrieved from the searches were evaluated according to titles and abstracts sequentially. From here on, for simplicity and consistency, only the term SCAF will be used.

Full-text eligibility was assessed independently by two co-authors (MB and GFR). Disagreements were resolved by discussion with a third author (MP). All full-texts that: (i) reported data about the prevalence of SCAF in patients implanted with PM, ICD, CRT-P or CRT-D; (ii) evaluated SCAF according to a reliable assessment of episodes; (iii) included <50% of patients with a history of AF; and (iv) included at least 100 patients were included. Exclusion criteria were: (i) conference abstracts, letters, comments, case reports, editorials; (ii) studies not

published in English; (iii) all the studies that defined SCAF only based on algorithms (e.g., atrial mode switch episodes). To improve consistency among the studies included in the analysis, we also excluded studies reporting only SCAF of very short or long duration (i.e., <30 s and >15 min).

2.2. Data extraction and quality assessment

Data were extracted independently by two of the co-authors (MB and GFR), alongside the supervision of a third author (MP). The following data were extracted: sample size, SCAF events and follow-up time, SCAF definition, type of CIED implanted, geographical location, study design and patients clinical characteristics in the overall cohort and according to SCAF presence (age, sex, body mass index [BMI], hypertension, diabetes, coronary artery disease [CAD], chronic heart failure [CHF], history of atrial fibrillation, history of stroke/transient ischemic attack [TIA], chronic kidney disease, left ventricular ejection fraction [LVEF], baseline treatments). SCAF definition was subdivided according to a atrial rate (<180 bpm, 180–200 bpm, >200 bpm and other/unclear definition) and a duration (<5 min, 5, 6 min, >6 min, and other/unclear definition) criterion, according to the cut-offs adopted by the included studies.

All studies were evaluated independently to assess risk of bias by two co-authors (MB and GFR), according to the Newcastle-Ottawa Scale for cross-sectional studies, composed of 5 items across three domains (Selection, Comparability, Outcome), with a maximum of 5 points. Any study with a score equal or less than 3 was categorized as high risk of bias.

2.3. Data synthesis and analysis

We calculated the pooled prevalence of SCAF as reported in the original studies included, with a generalised linear mixed model (random intercept logistic regression model) [12] using logit transformation of proportions.

Mean age, CHA_2DS_2-VASc, BMI and LVEF differences, number of males, and number of patients with a history of hypertension, diabetes mellitus, CAD, CHF, history of stroke/TIA, and history of atrial fibrillation were pooled and compared between SCAF and non-SCAF patients using random-effect models. For continuous outcomes, mean, SD and total number in each group were pooled and compared with the inverse variance method. Pooled estimates were reported as Odds Ratios (OR) and 95% confidence intervals (CI), or mean difference and 95% CI for continuous variables.

The inconsistency index (I^2) was calculated to measure heterogeneity. According to pre-specified cut-offs, low heterogeneity was defined as an I^2 of <25%, moderate heterogeneity as I^2 between 25 and 75%, and high heterogeneity when I^2 was >75%.

For the pooled prevalence rate of SCAF, a pre-specified sensitivity analysis was performed with a "leave-one-out" approach, in which all studies are removed iteratively one at a time to evaluate their influence on the pooled estimate and heterogeneity.

To account for potential sources of heterogeneity in the pooled prevalence of SCAF, we performed several subgroup analyses, according to geographical location, study design, risk of bias, atrial rate and duration cut-offs for SCAF, and type of SCAF definition (manual review vs. device-based).

We also performed a multivariable meta-regression, with relevant baseline characteristics of the included studies. To account for the potential non-linear relationship between continuous variables and pooled effect size, we fitted meta-regression with the use of restricted cubic splines [13], with default placement of 3 knots. All analyses were conducted with R version 4.0.3, using the 'meta', [14] 'metafor', [15] 'dmetar' [16] and 'rms' [17] packages.

Table 2
Subgroup Analyses for SCAF Prevalence.

Subgroups	N° Studies	Pooled Prevalence	95% CI	I^2
Geographical Location (p for subgroup differences=0.512)				
North America	8	30.2%	18.2-45.8%	98.8%
Europe	18	24.4%	19.1-30.7%	96.3%
Asia	18	31.0%	25.0-37.6%	96.8%
Other	10	28.0%	20.3-37.2%	99.3%
Study Type (p for subgroup differences=0.115)				
Obs. Retrospective	30	31.8%	27.1-36.8%	96.7%
Obs. Prospective	16	22.5%	16.3-30.2%	63.9%
RCT	8	26.5%	18.0-37.2%	98.8%
Definition of SCAF (p for subgroup differences=0.837)				
Manual Confirm	31	27.1%	22.1-32.7%	97.8%
Device-based	13	29.0%	22.2-36.9%	98.0%
Other/Unclear	10	30.0%	21.8-39.6%	97.7%
Type of Device (p for subgroup differences=0.233)				
Pacemaker	23	32.2%	26.2-38.8%	97.6%
CRT	7	28.8%	21.5-37.3%	91.3%
ICD	4	18.7%	9.8-32.9%	97.2%
Mixed	20	25.5%	19.9-32.0%	98.9%
Atrial Rate Cut-Off (p for subgroup differences=0.632)				
>200 bpm	7	25.0%	20.1-30.7%	91.5%
180-200 bpm	22	26.8%	21.2-33.3%	98.3%
<180 bpm	10	30.7%	23.6-38.8%	97.7%
Other/Unclear	15	29.6%	21.1-39.8%	98.2%
Duration Cut-Off (p for subgroup differences=0.191)				
>6 min	4	31.8%	26.2-38.0%	92.2%
5-6 min	32	25.7%	22.1-29.7%	98.3%
<5 min	13	34.3%	25.3-44.6%	97.7%
Other/Unclear	5	25.4%	9.8-51.6%	98.7%
AF History (p for subgroup differences=0.066)				
Yes	22	32.2%	25.2-40.1%	98.4%
No	31	24.6%	20.9-28.6%	97.6%
Risk of Bias (p for subgroup differences=0.653)				
Low Risk	39	27.6%	23.1-32.6%	98.5%
High Risk	15	29.4%	23.2-36.5%	96.9%

Legend: AF= Atrial Fibrillation; BPM= beats per minute; CI= Confidence Interval; CRT= Cardiac Resynchronization Therapy; ICD=Implantable Cardiac Defibrillator; MIN=minute; SCAF= Subclinical Atrial Fibrillation.

3. Results

After the electronic search, we retrieved 1486 articles from PubMed and 1128 articles from EMBASE. After the selection process, a total of 205 full-text articles were assessed for inclusion in the systematic review and meta-analysis (Supplemental Fig. 1). Fifty-four papers were included in the analysis, with a total of 72784 patients. [1871] Baseline characteristics of the studies included are reported in Table 1.

Among the papers included 8 papers derived from randomized controlled trials; 30 from observational retrospective studies; and 16

Table 3
Association between clinical characteristics and SCAF Presence.

Categorical Variable	Number of studies	OR	Lower 95%CI	Upper 95%CI	I^2
AF History	15	4.39	2.73	7.07	85%
Male Sex	39	1.08	0.95	1.23	63%
Hypertension	35	1.14	1.04	1.25	23%
Diabetes	33	0.96	0.86	1.06	39%
CHF	18	1.39	1.06	1.83	62%
CAD	29	1.01	0.89	1.14	30%
History of Stroke/ TIA	23	1.17	1.03	1.33	0%
Treatments					
Beta-Blockers	27	1.12	0.92	1.37	69%
Statins	14	0.93	0.81	1.06	2%
Amiodarone	8	1.26	0.71	2.25	79%
ACEi/ARBs	25	1.11	0.98	1.27	37%
Continuous Variables	Number of studies	MD	Lower 95%CI	Upper 95%CI	I^2
Age	35	1.36	0.40	2.32	85%
CHA_2DS_2-VASc	15	0.23	0.14	0.32	39%
LVEF	23	-0.70	-1.45	0.05	61%
BMI	12	0.31	-0.14	0.75	48%

Legend: ACEi= Angiotensin Converting Enzime Inhibitors; AF= Atrial Fibrillation; ARB= Angiotensin II Receptor Blocker; BMI= Body Mass Index; CAD= Coronary Artery Disease; CHF= Congestive Heart Failure CI= Confidence Interval; LVEF= Left Ventricular Ejection Fraction; MD= Mean Difference; OR= Odds Ratio; TIA= Transient Ischemic Attack.

from observational prospective studies. Of the included studies, 18 studies were conducted in Europe; 18 in Asia; 8 in North America, and 10 in other geographical locations, including multinational studies. Twenty-three studies involved patients implanted with PM; 7 studies with patients implanted with CRT; 4 studies involved patients implanted with ICD; and remaining 20 studies involved patients which were not selectively implanted with a specific type of CIED.

Of note, 31 studies adopted manual confirmation of SCAF, while 13 studies used device-based definition, and the remaining 10 articles used other or unclear assessments. Different durations were used to define SCAF. Four studies used duration of ≥6 min; in 13 cohorts a duration of <5 min was adopted, while 32 used cut-offs between 5 and 6 min. In 5 studies, other or unclear duration of SCAF was reported. As for the atrial rate, 10 studies adopted a cut-off of less than 180 beats per min (bpm); 7 studies used a cut-off over 200 bpm, 22 studies used a cut-off comprised between 180 and 200 bpm, and in 15 studies other or unclear velocity cut-offs were used. Overall, 15 (28%) studies were considered at significant risk of bias. All the other studies (39 out of 53) were considered at low risk of bias (Supplemental Table 2).

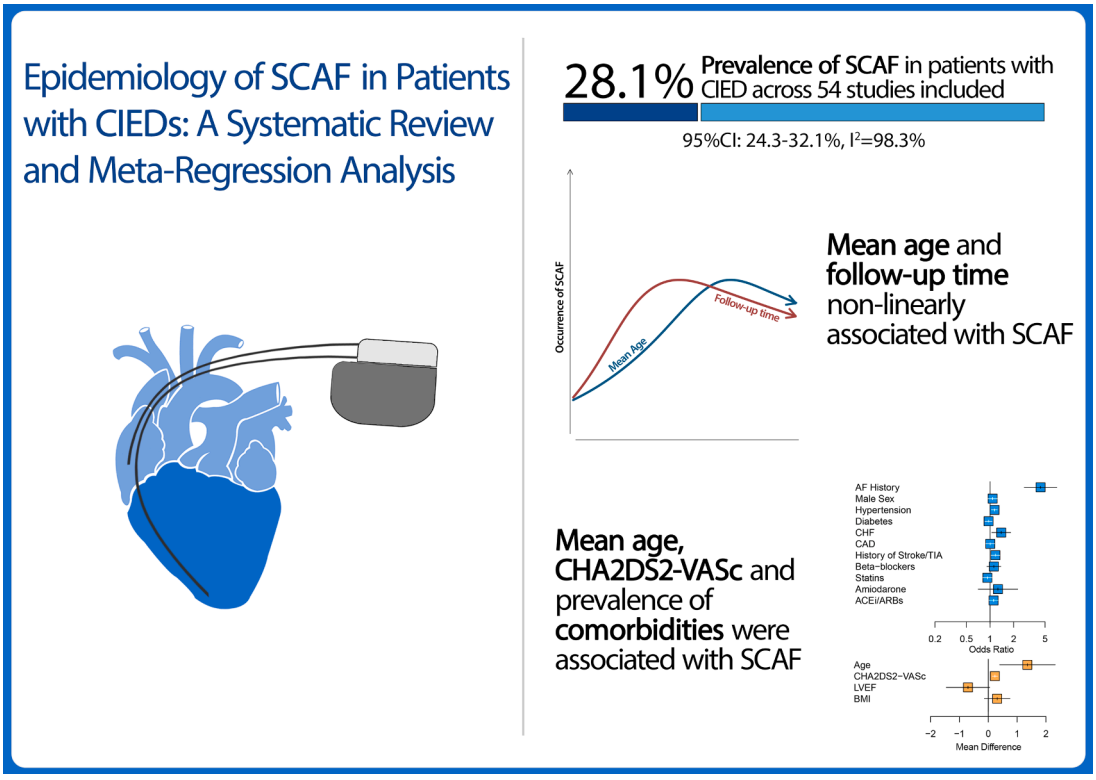
3.1. SCAF prevalence

The overall prevalence of SCAF across the 54 included studies included was 28.1% (95% CI: 24.3-32.1%), with a high heterogeneity detected (I^2=98.3%) (Fig. 1). According to the pre-specified 'leave-one-out' analysis reported in Supplemental Fig. 2, we did not find any significant influence of individual studies on pooled estimates or heterogeneity.

Subgroup analyses for the prevalence of SCAF are reported in Table 2. We did not observe any significant differences across the subgroups explored, except for a non-significant trend for higher SCAF prevalence in patients with previous history of AF.

3.2. Meta-regression analysis

A multivariable model comprised of cut-offs of SCAF duration and atrial rate, type of study, level of bias, the inclusion of patients with previous history of AF, and age and follow-up times (both modelled as restricted cubic splines) was able to explain a significant proportion of the heterogeneity observed (R^2=61.9%, p<0.001; Supplementary Table 3). A graphical representation of the marginal relationship between follow-up times and age, modelled as restricted cubic splines, and the



Central Illustration. Epidemiology of Subclinical Atrial Fibrillation in Patients with CIEDs: A Systematic Review and Meta-RegressionLegend: CIEDs= Cardiac Implanted Electronic Devices; IR= Incidence Rate; SCAF= Subclinical Atrial Fibrillation.

prevalence of AHRE is reported in Fig. 2, panel A and B, respectively. Prediction of SCAF prevalence according to the multivariable model, according to mean age and different follow-up times, is reported in Fig. 3.

3.3. Clinical variables associated with SCAF

We calculated pooled estimates for several characteristics comparing patients with SCAF vs. patients without SCAF (Table 3). The occurrence of SCAF was significantly associated with older age, higher CHA_2DS_2-VASc score, and clinical history of atrial fibrillation, hypertension, heart failure, and history of stroke/transient ischemic attack; however, male sex, body mass index, diabetes and coronary artery disease were not associated with SCAF. We did not observe any significant association between SCAF and pharmacological treatments.

4. Discussion

This systematic review and meta-regression analysis about the epidemiology of SCAF in patients with CIEDs found an overall prevalence of 28.1% of patients presenting AHREs among the over 72000 patients with CIEDs. While no significant differences were found in prevalence among the subgroups examined, meta-regression analysis found that both patients' age and length of follow-up were significantly, independently and non-linearly associated with SCAF prevalence. Furthermore, the analysis of clinical characteristics revealed that patients presenting SCAF, beyond having a more frequent AF history, were older, more likely hypertensive, affected with congestive heart failure and with an history of stroke/transient ischemic attack. Accordingly, SCAF patients had an overall higher CHA_2DS_2-VASc score [Central Illustration].

Our findings have important epidemiological and clinical implications. First, the pooled estimate we provided adds an important piece of information in understanding the natural course of this condition. Thus far, no accurate evaluation of SCAF epidemiology has been provided by any study. Available studies have shown large variability in reporting the occurrence of SCAF [72] and differences in studies design, patients' characteristics and follow-up duration limit the generalizability of any of the previous studies to the general population of patients receiving a CIED implant.

The finding that 28% of patients receiving a CIED report SCAF after receiving the device is highly relevant. First, it gives us a reliable appraisal of the real "size of the problem". Second, it allows us to make some considerations in terms of patients' care. Indeed, the presence of SCAF significantly increases the risk of developing incident clinical AF. Some recent estimates showed that presence of SCAF entails more than 3-fold higher risk of clinical AF [9]. Overall, the findings that almost 1 in every 3 patients receiving a CIED could be at high risk for developing clinical AF clearly underlines the importance of performing more accurate monitoring for this condition and the need for proper dissemination of information about its impact on patients.

Furthermore, as shown in the ASSERT trial and further underlined by other studies and meta-analyses, the presence of SCAF increases the risk of stroke by more than 2 fold and the risk of all-cause death and other outcomes, particularly in those patients with a high baseline thromboembolic risk [8,9,22,29,73]. Data from European Society of Cardiology countries reported that almost 750,000 patients received a CIED [2], extrapolating our findings suggests that more than 210,000 patients would report SCAF and consequently have such a higher risk for clinical AF and stroke, also progressively increasing with age and throughout time, with important implications for patients' management and health-care services resources use. These numbers highlight the need for further data regarding the use of oral anticoagulants in patients with SCAF. While not all the guidelines discuss this issue, use of oral anticoagulant is recommended only in patients with high stroke risk and longer ($\geq$24 h) episodes of AHRE [72,74,75]. Uncertainty still exists in patients with shorter AHRE episodes. Two currently ongoing randomized trials will provide important evidence to elucidate this important issue [76,77].

Our findings regarding the relationship between increasing age and SCAF occurrence underlines how SCAF shares similar risk factors with clinical AF, and extends our knowledge on SCAF epidemiology beyond the estimate of prevalence per se. Indeed, is well-known that increasing older age is a pivotal risk factor for AF [78], and our multivariate analysis elucidates that the contribution of increasing age to the risk of developing SCAF is pivotal. Also, the non-linear association between follow-up time and SCAF prevalence suggests that the observation period is likely to play a role in determining the prevalence observed in CIED recipients. The combination of increasing age and longer follow-up, concurrently with the higher prevalence of comorbidities, which we found associated with presence of SCAF, could underline how these factors combine together to determine the development of an atrial arrhythmogenic substrate [78]. Indeed, also the association with increasing age could be a proxy of a generally more complex and impaired clinical situation with no specific risk factor driving the occurrence of SCAF (as underlined by the results of meta-regression analysis), but with the overall progressively higher amount of exposure to risk factors determining the arrhythmogenic substrate. As the occurrence of clinical AF is multifactorial and related to various risk factors [79], the relationship between age, exposure and comorbidities together lead to SCAF, through the mechanism of developing atrial cardiomyopathy and further strengthening the relationship between SCAF, clinical AF and higher risk of thromboembolic events [78,80–82].

These findings may have significant implications in the management of patients receiving CIEDs, underlining the importance of close observation for SCAF occurrence. Further studies are required to expand and corroborate these hypotheses, and to clarify whether specific subgroups of patients may have a different risk(s) of SCAF. Indeed, it should be noted that few studies focused on very elderly CIED recipients, and therefore our estimates for this group of patients were broad, underlining the need for specific studies aiming at evaluating the epidemiology of SCAF in elderly patients, as well as other high-risk subgroups which may experience a different burden of SCAF.

We also observed that patients presenting with SCAF were found to have a higher burden of risk factors and comorbidities, eventually resulting in a higher CHA_2DS_2-VASc score, conferring greater thromboembolic risk compared to patients without SCAF. This evidence supports the current knowledge about the increased risk of stroke and thromboembolic events in patients with SCAF, underlining the need for more data about oral anticoagulant and supporting current recommendations on prescribing oral anticoagulant drugs in SCAF patients with very high thromboembolic risk [72].

In the latest European Society of Cardiology clinical guidelines on the management of patients with AF, the nosological entity of SCAF is by definition identifiable only in patients who have no previous history of AF [72]. In our meta-analysis we also included patients with previous history of AF. While also other meta-analyses about SCAF included patients with previous history of AF [9], the approach of excluding patients with history of AF has been only recently adopted, hence excluding all studies with such patients would have excluded large part of previous evidence about SCAF. While overall 22/54 studies (41%) included patients with previous history of AF, only 10/54 studies (19%) included more than 25% of patients with previous history of AF, thus with a limited contribution of the group of previously diagnosed AF patients in most of these cohorts. While the subgroup analysis reported a non-significant trend in higher SCAF prevalence in those patients with previous history of AF, the presence of SCAF was clinically more associated with the previous history of AF.

5. Limitations

The main limitation is the high heterogeneity reported in our pooled

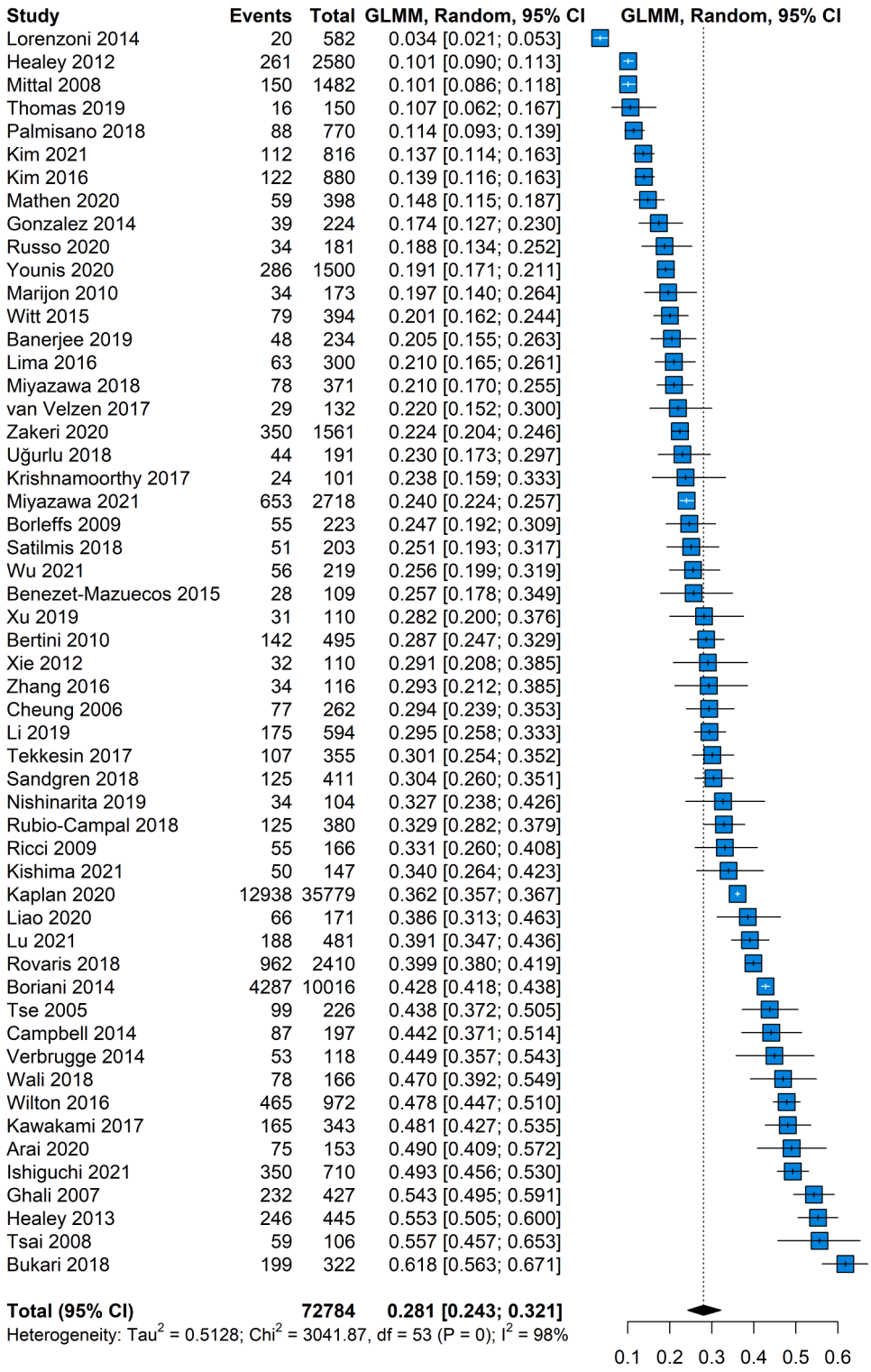


Fig. 1. Pooled Prevalence of SCAF across the Included Studies.
CI= Confidence Interval; GLMM= General Linear Mixed Model.

estimates. However, high heterogeneity is a common concern in epidemiological meta-analysis exploring the prevalence of several conditions, in which we expect the results to vary consistently in each study [83–85]. This also reflect the clinical heterogeneity found in clinical practice, with SCAF prevalence highly likely to be influenced by several determinants. Furthermore, we performed additional analyses to account for heterogeneity, including the multivariable meta-regression which allows us to account for roughly 60% of the observed heterogeneity in the pooled estimate for SCAF prevalence. Although we cannot exclude the contribution of other, unaccounted confounders in influencing our findings, the results of the meta-regression clearly underline the impact of age and follow-up time in determining the occurrence of SCAF, representing, together with the epidemiological data about the clinical profile of SCAF patients, the most relevant evidence provided by our work.

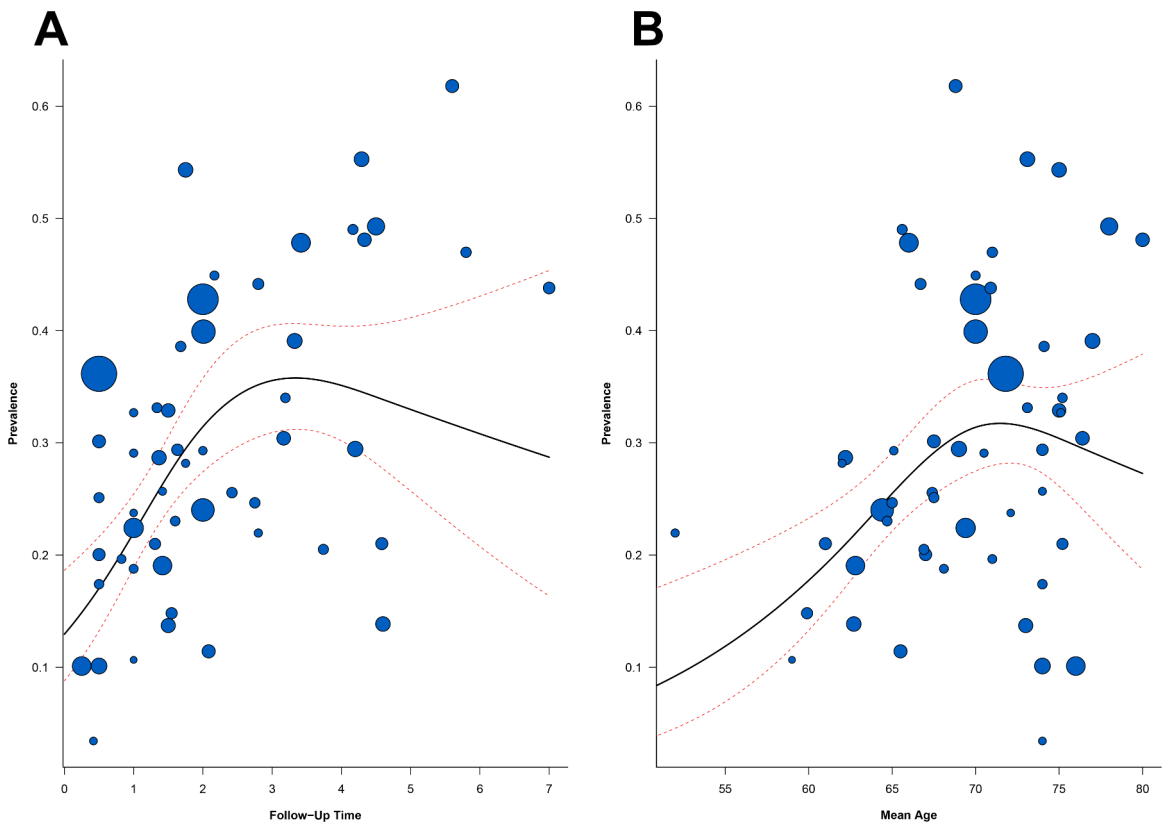


Fig. 2. Marginal Relationship between Follow-up times and Mean Age of the included studies and SCAF prevalence.
Panel A) Years of Follow-Up; Panel B) Age.

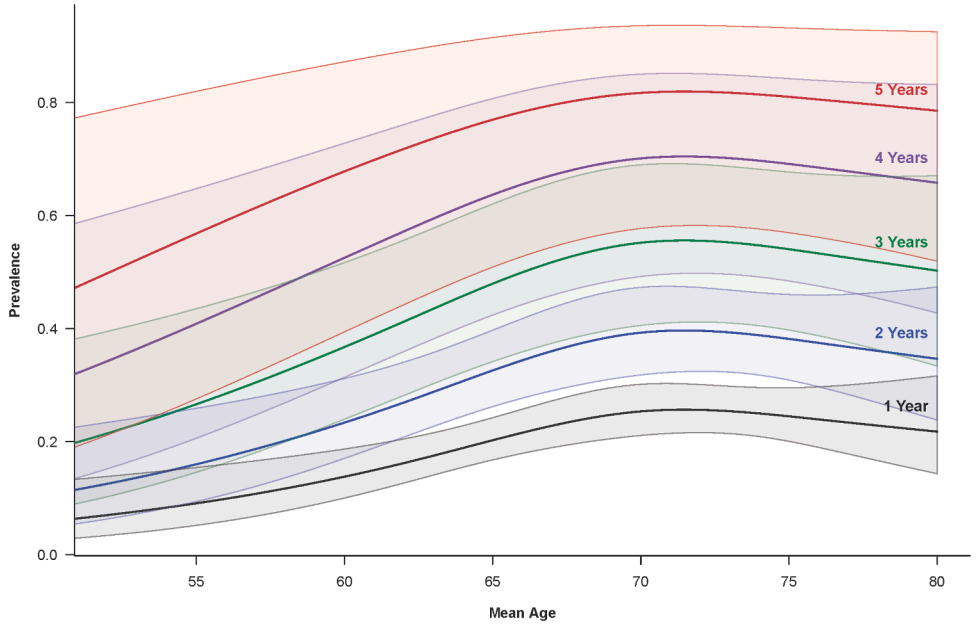


Fig. 3. Prevalence of SCAF according to mean age at different follow-up times.
Each curve is a graphical representation of SCAF incidence rate at each year of follow-up according to patients' age.

6. Conclusions

In this systematic review and meta-regression analysis, SCAF increased with age and decreased over longer follow-up times, both being independently associated with its prevalence. The presence of SCAF is associated with higher age, more prevalent comorbidities, and higher thromboembolic risk.

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Declaration of Competing Interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2022.06.023.

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