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Oral anticoagulation for subclinical atrial tachyarrhythmias detected by implantable cardiac devices: an international survey of the AF-SCREEN Group

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ABSTRACT

Aims: At present, there is little evidence on how to treat subclinical atrial fibrillation (SCAF) or atrial high rate episodes (AHREs) detected by cardiac implantable electronic devices (CIEDs). Our aim was to assess current practice around oral anticoagulation (OAC) in such patients.
Methods: A web-based survey undertaken by 310 physicians: 59 AF-SCREEN International Collaboration members and 251 non-members.
Results: In patients with SCAF/AHRE and a $CHA_2DS_2VASc \geq 2$ in males or ≥ 3 in female the amount of SCAF/AHRE triggering use of OAC was variable but <2% of respondents considered that no AHRE would require OAC. Around one third (34%) considered SCAF/AHRE duration of >5–6 min as the basis for OAC prescription, while 16% and 18% required a burden of at least 5.5 h or 24 h, respectively. The propensity to prescribe OAC for a low burden of AHREs differed according to certain respondent characteristics (greater propensity to prescribe OAC for neurologists). When the clinical scenario included a prior stroke or a prior cardioembolic stroke, stated prescription of OAC was very high. More than 96% felt that any SCAF/AHRE should be treated with OAC.
Conclusions: There is substantial heterogeneity in the perception of the risk of stroke/systemic embolism associated with SCAF/AHRE of variable duration. The threshold of AHRE burden that would trigger initiation of OAC is highly variable, and differs according to the clinical scenario (lower threshold in case of previous stroke). Ongoing trials will clarify the real benefit and risk/benefit ratio of OAC in this specific clinical setting.

1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, with an epidemiological profile characterized by higher incidence and prevalence in the elderly, [1] and clinical relevance dominated by the associated increased risk of stroke/systemic embolism (SEE) [2–4]. AF is frequently asymptomatic with a similar if not higher risk of associated adverse outcome in terms of stroke and mortality than symptomatic AF [4,5].

Cardiac implanted electrical devices (CIEDs) with an atrial lead or with capability of rhythm discrimination (i.e. implantable cardiac monitors, ICM) extend the capability to detect atrial tachyarrhythmias since they allow continuous monitoring of cardiac rhythm, with detection of AF and atrial high-rate episodes (AHREs) coupled with storage of arrhythmia electrograms in device memory for review and specific diagnosis. AHREs, currently defined as

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episodes of at least 5 min of atrial tachyarrhythmias/AF with an atrial rate > 180 bpm, are usually asymptomatic, discovered during routine device follow-up and classified in terms of duration of the longest single episode, or time spent in atrial tachyarrhythmias during a day (from minutes to hours) [6–11]. The term "subclinical AF" (SCAF) is currently used for episodes of atrial tachyarrhythmias with duration between 5 min and 24 h, detected by a CIED in patients without clinical history or clinical symptoms of AF [4,9,10].

The association between CIED-detected atrial tachyarrhythmias of variable durations and stroke or systemic thromboembolism has been evaluated by several studies that together collected data on >22,000 patients [3,4,9,10,12,13]. These studies showed that AHREs with a duration ≥5–6 min are associated with a significant increase in the risk of stroke or systemic thromboembolism, although the risk is around half of the risk associated with clinical AF [14]. However, there is substantial uncertainty about management of these patients to reduce the risk of stroke or systemic embolism, and specifically about the risk-benefit ratio of oral anticoagulation in this specific setting [4,10]. At present, there is no evidence in support of or against prescription of oral anticoagulants (OAC) in patients at increased risk of stroke (intermediate to high risk according to CHA_2DS_2VaSC score) who present with AHREs of short duration, confirmed as atrial tachyarrhythmias/AF by electrogram assessment. Two randomized controlled trials are ongoing for evaluating the efficacy and risk-benefit ratio of oral anticoagulation vs no oral anticoagulation (aspirin alone as the comparator), in patients with CIED-detected AHRE (ARTESiA (NCT01938248) [15] and NOAH – AFNET 6 (NCT02618577) [16]. Before availability of the results of these randomized trials, we aimed to assess current practice around management of OAC therapy in patients with CIED-detected AHREs, using an on-line survey. Questions in the survey were designed to elucidate how physicians perceive the risk of stroke and systemic embolism in patient sub-groups with device-detected atrial tachyarrhythmias, focusing on decision making for anticoagulation.

2. Methods

The survey was distributed in two steps. First the invitation to participate in this anonymous, web-based survey was sent in August 2018 by email to the 158 members of the AF-SCREEN International Collaboration, a group created in 2016 to promote discussion and research about screening for unknown or undertreated atrial fibrillation as a way to reduce stroke and death [4] (http://www.afscreen.org/). A few weeks later, in October 2018, the same invitation was distributed through e-mails by AF-SCREEN members to a "convenience sample" of physicians, nurses or allied professional colleagues involved in care of patients with arrhythmias or stroke. The analysis of the survey was managed in an anonymous way. We present numbers and percentages for answers each of the survey questions (Figs. 1 and 2).

3. Results

Overall, 310 physicians completed the survey (59 AF-SCREEN members and 251 non-members). The geographical region of respondents was Europe in 76%, Asia/Oceania in 15% and North America in 8%. Survey respondent characteristics are shown in Table 1.

In the whole group, 20% of the respondents reported to be currently involved in the ARTESiA trial (22% among AF SCREEN members), 8.1% in NOAH trial (12% among AF SCREEN members), 3.5% in both trials (3.4% among AF SCREEN members), while 69% were not involved in either of these trials (63% among AF SCREEN members).

The answer to the general question whether device-detected atrial tachyarrhythmias [subclinical AF/AHRE (Atrial High Rate Episodes)] require medical attention and specific decision-making even if asymptomatic was quite homogeneous, since among respondents ($N = 309$) 96% answered yes and only 4% answered no (95% and 5%, respectively among AF SCREEN members).

\The approach to SCAF/AHRE with a duration between 30 s and 5 min documented in device logs, included a variety of behaviours (Fig. 1, Panel A), though a large majority considered a "wait and see" approach as clinically indicated, deferring any decision to the time of occurrence of device detected episodes of longer duration or to the occurrence of clinical AF. Checking the EGMs stored in the device memory for arrhythmia confirmation was indicated by >60% of respondents, but it is noteworthy that in >30% of answers it was considered necessary to order a Holter recording. In case of device detection of SCAF/AHRE with a duration between 5 min and 24 h the approach substantially changed (Fig. 1, Panel B), and waiting for device-detected episodes of longer duration or for clinical AF was reported in only 28% of the answers. A check of the EGMs was considered necessary by most, but not all respondents.

With regard to the amount of AF considered sufficient to recommend the use of long-term OAC, despite supportive evidence from a clinical trial, in a patient with a pacemaker, cardioverter defibrillator or ICM with detection of SCAF/AHRE and with a $CHA_2DS_2VASc = 1$ in males or $= 2$ in females, a wide variability in approaches emerged (Fig. 1, Panel C). At this level of stroke risk, the current ESC and ACC/AHA/HRS guidelines state that OAC should be considered, rather than a recommendation for OAC therapy. The heterogeneity is quite evident considering that 13% of the respondents replied that no amount of AHRE would require OAC in this clinical context, while at the opposite end of the spectrum, 16% considered that any SCAF/AHRE requires OAC. Also, for the respondents who considered as critical the attainment of a specific threshold of AHRE burden, a substantial heterogeneity was found, with at least 20% choosing either 5–6 min, or, alternatively, 5.5 h or 24 h as the basis for instituting OAC.

The same question on the amount of SCAF/AHRE which would trigger use of chronic OAC in the context of a higher CHA_2DS_2VASc (≥2 in males or ≥3 in females, for which ESC guidelines recommend OAC treatment) showed a shift to a much higher propensity towards treatment (Fig. 1, Panel D). Very few (<2% of respondents) considered that no amount of AHRE would require OAC in this context. Around one third of responders considered a burden of SCAF/AHRE of 5–6 min as the basis for OAC prescription, while around 16–18% required at least 5.5 h or 24 h, respectively. If the categories of any duration of AHREs, or AHREs of >5–6 min are combined, 64% of respondents would prescribe OAC for SCAF/AHREs >5–6 min, and about half of these would prescribe OAC for any AHREs, no matter how brief. The proportion of physicians prescribing OAC for any duration of AHREs, or AHREs of >5–6 min differed according to certain respondent characteristics. The percentage for AF-SCREEN members was lower (54%, 32/59) than non-members (67%, 167/249), and was lower for electrophysiologists (56%, 97/173), than cardiologists (69%, 52/75), or internal medicine physicians/general practitioners (80%, 12/15), or neurologists (86%, 31/36). The percentage was lower in respondents from Canada or Australia (19%, 4/21, and 52% (12/23 respectively) than in respondents from continental Europe (75%, 123/164), or Ireland/UK (81%, 26/32) or Japan/Korea (75%, 12/16).

When the clinical scenario included a prior stroke or a prior cardioembolic stroke (Fig. 2, Panel A and B) the propensity to recommend prescription of OAC in case of SCAF/AHRE detected by a CIED or ICM was very high. Conversely, only 2.6% of respondents in case of a prior stroke and 3.2% in case of a prior cardioembolic stroke, respectively, considered that in these scenarios no amount

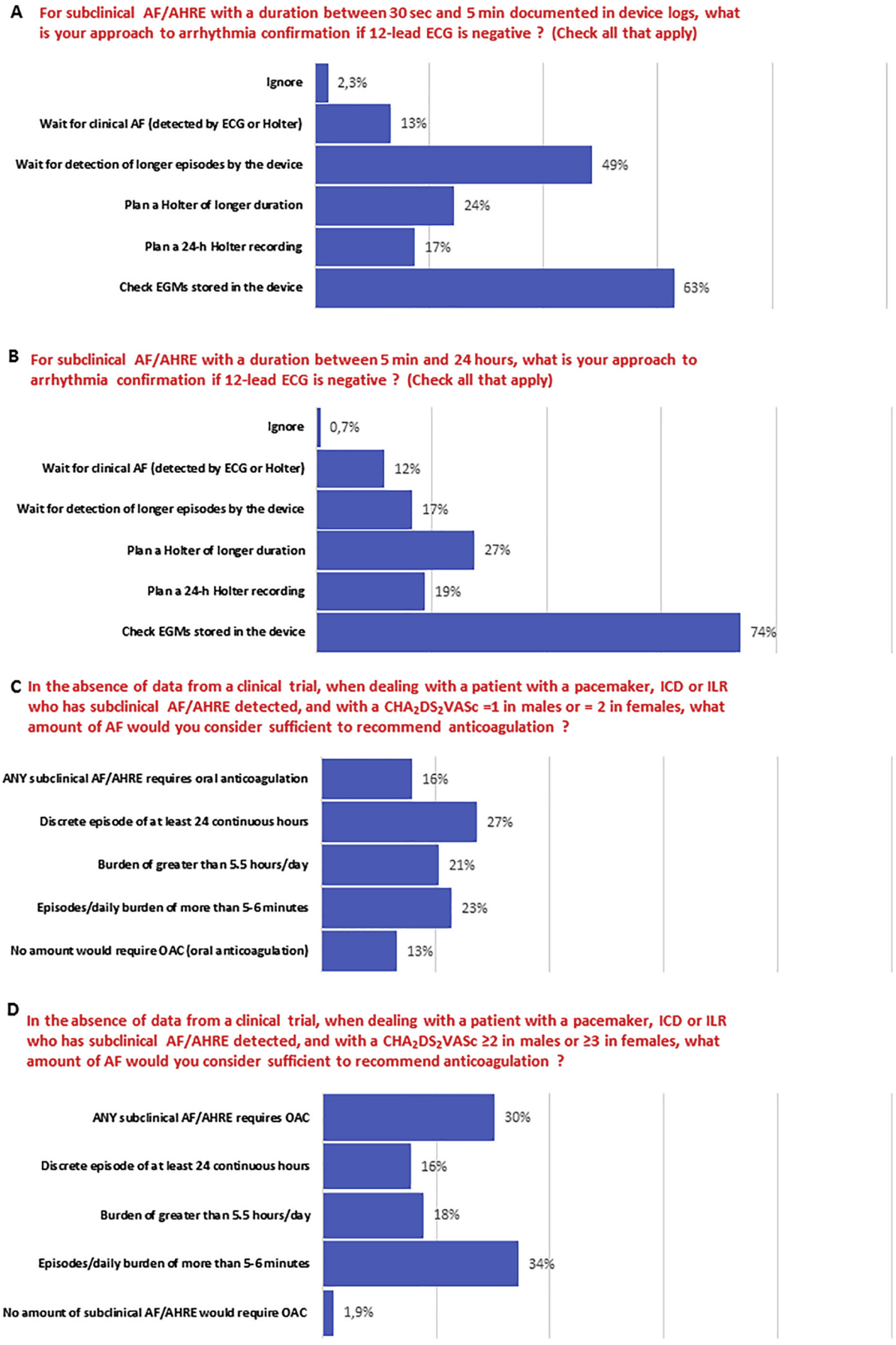

Fig. 1. Results of our survey. Legend: AF: atrial fibrillation; AHRE: atrial high-rate episodes; ICD: implantable cardioverter-defibrillator; ILR: implantable loop recorder.

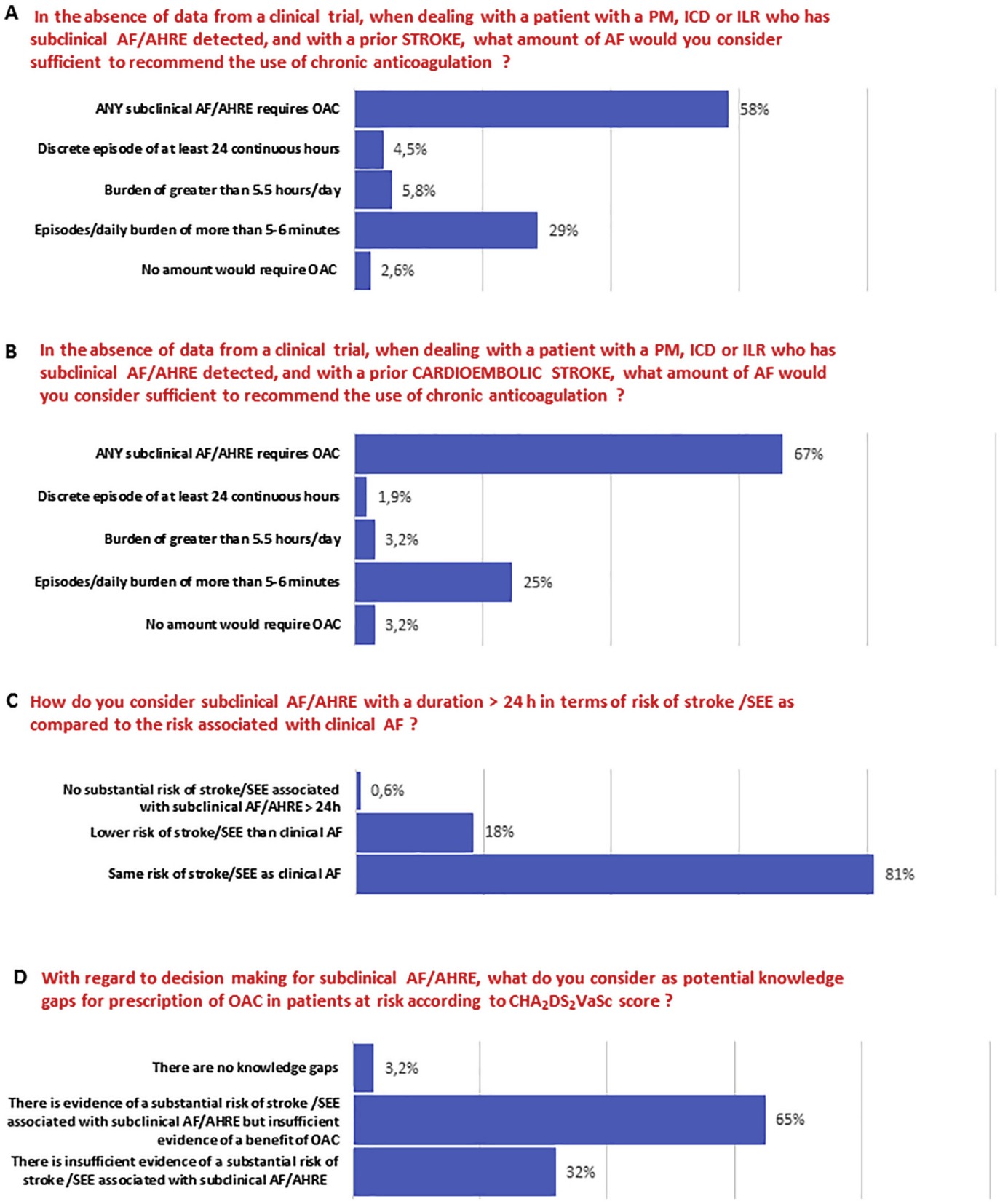

Fig. 2. Results of our survey. Legend: AF: atrial fibrillation; AHRE: atrial high-rate episodes; ICD: implantable cardioverter-defibrillator; ILR: implantable loop recorder.

of SCAF/AHRE would require OAC. The large majority of respondents (58% and 67%, respectively) considered that in these contexts any SCAF/AHRE would necessitate institution of OAC. If the categories of any duration of AHRE, or AHREs of >5–6 min are combined as above, then 87% (268/308) would recommend OAC in the case of prior stroke and 92% (282/308) in a prior cardioembolic

Table 1
Survey respondent characteristics.

Category	Whole group	AF SCREEN Members	Non members
	% of Total (N)	% of the Subgroup (N)	% of the Subgroup (N)
Electrophysiologist	56.1% (174)	44.1%(26)	59.0% (148)
General cardiologist	24.5%(76)	30.5% [18]	23.1% (58)
Neurologist/stroke physician	11.6% (36)	8.5% [5]	12.4% (31)
Primary care physician/general practitioner	2.9% [9]	6.8% [4]	2.0% [5]
Internal medicine physician	1.9% [6]	3.4% [2]	1.6% [4]
Nurse/allied health professional	0.6% [2]	1.7% [1]	0.4% [1]
Other	2.3% [7]	5.1% [3]	1.6% [4]
Total	100% (310)	(59)	(251)

stroke. The percentages were slightly lower for AF-SCREEN members (79%, 46/58 in a prior stroke and 89%, 222/250 in a prior cardioembolic stroke, respectively) than for non-members (89%, 222/250 in a prior stroke and 93%, 231/249 in a prior cardioembolic stroke, respectively). The percentages did not differ greatly between the different physician categories (82–93% in a prior stroke and 88–97% in a prior cardioembolic stroke, respectively). Only Canada had a relatively low percentage in the case of a prior stroke (57%, 12/21), but had 76% (16/21) in a prior cardioembolic stroke. Little difference was detected between the other regions (range 87–94% in a prior stroke, and 91–97% in a prior cardioembolic stroke, respectively).

An additional question asked whether the current ESC consensus guidelines on atrial fibrillation are considered as sufficiently clear for helping decision making on SCAF/AHREs. Only 8.1% of respondents perceived the recommendations as very clear, with 67% as not completely clear and 25% as unclear.

The risk of stroke/systemic embolism posed by episodes of SCAF/AHRE with a duration >24 h were considered to be the same as clinical AF by 81% of respondents (Fig. 2, Panel C), to carry a lower risk as compared to clinical AF by 18.4%, while only 0.6% considered that no substantial risk was associated with this long duration of device detected atrial tachyarrhythmia.

Finally, we investigated what potential knowledge gaps could be identified for decision making on prescription of OAC in patients with SCAF/AHRE considered at increased risk according to CHA_2DS_2VaSc score. As shown in Fig. 2, Panel D, 65% of the respondents considered that at present there is evidence of a substantial risk of stroke /SEE associated with SCAF/AHRE but insufficient evidence of a benefit of OAC. Nevertheless, 32% responded that there is insufficient evidence of a substantial risk of stroke /SEE associated with SCAF/AHRE. Only 3% felt that there were no knowledge gaps in the field.

4. Discussion

There is growing interest on the significance and management of atrial tachyarrhythmias detected by implanted devices, which is not surprising considering their frequent occurrence and association with an increased risk of stroke/SEE [4,9,10,12,13]. However, the relationship with stroke events appears to be complex, with evidence of a temporal dissociation between stroke and AHRE occurrence [4,7,17,18], and other indicators that SCAF and AHRE are acting both as risk factor and risk marker for stroke [4,7].

The present survey highlights that despite consensus guidelines and position papers that summarize current knowledge about SCAF and AHRE [2–4] decision making on how to approach this topic remains highly variable, with heterogeneous stated behaviours among physicians involved in patient care. Most, but not all, of the respondents considered confirmation by EGMs stored in the device as an important first step, and this appears as an appropriate approach in view of the need to exclude double counting or artefacts [2,10]. A “wait and see” approach was presented as the dominant strategy in patients with SCAF/AHRE with a duration between 30 s and 5 min. Again, this appears reasonable and appropriate in patients with a CIED and no previous stroke, since no data are available on the relationship between these findings and either clinical AF or stroke. However, it is noteworthy that in CRYSTAL AF, the trial comparing implant of an ICM to standard monitoring in patients with previous cryptogenic stroke, the maximum 1-day duration of atrial fibrillation detected by the ICMs in the 12-month follow up was between 2 and 5 min in 7.7% of the patients and between 6 and 60 min in 19.2% of patients randomized to ICM, respectively [19].

According to the literature, SCAF/AHRE with a duration >5–6 min are associated with an increased risk of stroke/SEE [9,13] but the survey clearly shows that there is substantial uncertainty in our group of respondents, with an important heterogeneity on the specific threshold of AF burden or episode duration that may trigger OAC prescription. In patients with SCAF/AHRE and a $CHA_2DS_2VASc \geq 2$ in males or ≥ 3 in females, around 98% of respondents would initiate OAC, even if the threshold of AF burden justifying OAC could vary from 5 to 6 min to >24 h. The propensity to treat with OAC with a relatively low burden of SCAF/AHRE >5–6 min but <5.5 h is appreciable, even in patients with only modestly elevated CHA_2DS_2VASc scores (1 male, 2 female), but much greater in patients with higher CHA_2DS_2VASc (2 male and 3 female), and even more so in those with previous stroke, especially if cardioembolic.

While the risk of stroke associated with detection of SCAF/AHRE is significantly increased, it appears lower than the risk associated with clinical AF (2.4-fold vs. 5-fold [14]. In the survey we examined the perceived significance of SCAF/AHRE of long duration, i.e. longer than 24 h, since in the post-hoc analysis of ASSERT this duration identified a subgroup of patients with AHRE carrying the higher risk [20]. The interesting finding is that for 81% of the respondents, these episodes were perceived to carry the same stroke/SEE risk as clinical AF.

Prescription of OAC in patients with SCAF/AHRE is currently considered on an individual basis, taking into account the clinical context and the profile of risk expressed by the CHA_2DS_2VASc score [10]. As the survey highlights, there is a knowledge gap on the benefit of OAC in this setting and direct evidence is needed. ARTESiA (NCT01938248) [15] and NOAH – AFNET 6 (NCT02618577) [16] are two ongoing randomized controlled trials planned to evaluate the efficacy and risk-benefit ratio of OAC vs. no oral anticoagulation (aspirin only) in patients with CIED-detected AHRE. The results are expected to provide evidence on the appropriate clinical management of these patients. This survey clearly shows that planning of these trials was absolutely needed. Before completion of these trials clinical evaluation of patients with SCAF/AHRE should consider the risk profile and potential risk-benefit ratio of OAC [4,10] taking into account that treatment may be reasonable when SCAF/AHRE burden is above some of the defined

thresholds in subjects with a profile at higher risk. In this perspective educational initiatives from the AF-SCREEN International Collaboration (http://www.afscreen.org/), as well as from Scientific Associations in the field of Cardiology and Arrhythmia management, are needed to provide the basis for a fine tuning of patient-tailored decision-making.

This survey has inherent limitations linked to the voluntary participation, the convenience sample nature of non-member respondents, and the different profile of participants. On the other hand, it is likely that only members who manage patients with CIEDs or ICMs responded, in view of their interest and involvement in this topical issue.

5. Conclusions

There is substantial heterogeneity in the perception of the risk of stroke/SEE associated with SCAF/AHRE of variable duration and this results in different propensity to institute OAC therapy in patients at risk, as assessed by the CHA_2DS_2VASc score. The threshold of AHRE burden or episode duration that would trigger institution of OAC is highly variable, and differs according to the clinical scenario (lower threshold in case of previous stroke), and in some cases according to specialty and geographic region of practice. The results of ongoing randomized trials are awaited, and will be required to define the benefit and risk/benefit ratio of OAC in this specific clinical setting.

Declaration of Competing Interest

GB reported speaker's fees of small amount from Biotronik, Boehringer Ingelheim, Boston and Medtronic.

JSH reported research grants Bristol-Myers Squibb, Pfizer, Bayer, Boehringer Ingelheim, Medtronic, Boston Scientific, and St Jude Medical.

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HC reported consultancies with honoraria from Biosense Webster, Medtronic, Abbott Medical, Adagio, speaker's fees from Biosense Webster, Medtronic, Abbott Medical, Adagio Medical, Boehringer Ingelheim and research support from Boston Scientific, Biosense Medical and Medtronic.

JAC reported consultancies with honoraria from Actelion Pharmaceuticals, Daiichi-Sankyo, Eli Lilly, GileadSciences, Inc., Heart Metabolics, InCardaTherapeutics, InfoBionic, Johnson and Johnson, Medtronic, Milestone, Pfizer, Boehringer Ingelheim, Boston Scientific, Novartis, Bayer, speaker's fees from Daiichi-Sankyo, Servier, Bayer/ScheringPharma, Boehringer Ingelheim, and research grants from Boehringer Ingelheim, Daiichi-Sankyo, and Pfizer.

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