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Natural History of 'Silent' Atrial Fibrillation from Subclinical to Asymptomatic State of the Art and Need for Research

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Milan, 23rd October 2022

To Professor Giancarlo Agnelli
Editor-in-Chief
European Journal of Internal Medicine

Dear Prof. Agnelli,
RE: Natural History of 'Silent' Atrial Fibrillation from Subclinical to Asymptomatic: State of the Art and Need for Research

Dear Prof. Agnelli,

Please find attached my Clinical Insight about silent atrial fibrillation (AF) and screening strategies.

I hope you would like to consider the manuscript acceptable for your authoritative journal.

Look forward to receive your decision.

Kind Regards
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Natural history of 'silent' atrial fibrillation from subclinical to asymptomatic: state of the art and need for research

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In the last 30th years clinical research in the atrial fibrillation (AF) field has seen a great advance both in terms of productivity and heterogeneity of areas that developed significant new knowledge and evidence. Indeed, it is very easy to verify how in the last 3 decades the number of articles regarding AF registered in MEDLINE has increased exponentially overtime. This large amount of evidence led to significant changes in the guidelines, with an improvement of the overall quality of recommendations and an increase in the high-quality recommendations (despite being still generally low)[1,2]. Several areas about AF clinical management are now largely assessed and established, as the need for oral anticoagulant (OAC) prescription, the preference of the non-vitamin K antagonist oral anticoagulants over vitamin k antagonist ones, as well as the assessment of thromboembolic and bleeding risks[3,4]. Also, the need for implementation of integrated care, emerged as the main AF management strategy in the last guidelines, is now largely assessed and evidence based[4–6].

Despite this large amount of evidence produced over the years, various areas are still not completely elucidated. Among them, the need to prescribe OAC in patients with a cardiac implantable electronic device (CIEDs) presenting subclinical AF (SCAF)[7] and the choice of the optimal AF screening strategies[8] are two of the most currently active and fertile. The aim of this manuscript is to discuss the main papers included in this Collection of *European Journal of Internal Medicine* focusing on these two clinical research themes, to put them in the context of the current knowledge and discuss the clinical correlates.

Subclinical atrial fibrillation in context

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The last decades saw a great technological expansion related to CIEDs, with devices more and more complex and smaller. Contemporary, clinical research expanded its knowledge about their implementation in clinical practice, with a progressive increase in indications to propose and implant a CIED[9–12]. This led to the discovery of a new previously unknow clinical entity, which was denominated SCAF[7]. The presence of SCAF is defined by the occurrence of asymptomatic fast atrial tachyarrhythmias which is only detected by continuous long-term monitoring. In 2012 the landmark 'Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial' (ASSERT) study demonstrated that the presence of SCAF is associated with an increased risk of developing clinical AF and thromboembolic events[13].

A recent systematic review and meta-analysis published in EJIM reported that, among 54 studies including 72,784 patients, prevalence of SCAF was equal to 28.1% (95% confidence interval [CI] 24.3-32.1%), with a non-linear association between increasing age and follow-up time and increasing prevalence[14]. In this paper the authors also showed how patients found with SCAF have a significant higher risk profile, with higher prevalence of several comorbidities associated with a higher thromboembolic risk[14]. In another meta-analysis, Vitolo and colleagues demonstrated that patients with SCAF have a significant higher risk for thromboembolic events (approximately 2 fold, irrespective of AF previous history) and clinical AF (more than 3 fold)[15]. Really interesting, Ungar and colleagues also demonstrated that in a real-world cohort of patients diagnosed with cryptogenic stroke which received a CIED implant after the clinical event, up to 31.5% of patients were found with SCAF over a 24 months of follow-up[16].

The high prevalence of this condition together with the higher risk of adverse outcomes demonstrated in patients with SCAF, as underlined by the data reported above, posed a reasonable question of whether oral anticoagulation prescription would be indicated in these patients. Nowadays clinical guidelines are not entirely solid in recommending the use of oral anticoagulant drugs. On the basis of the evidence that the risk appears to be higher as longer the burden of SCAF[17,18], the last European Society of Cardiology (ESC) guidelines recommend, even though with a Level IB of evidence, the prescription of oral anticoagulant drugs in all those patients presenting with a burden of SCAF ≥24 hours, that also present a high baseline risk of thromboembolic events (CHA_2DS_2-VASc ≥2 for males and ≥3 for females)[4]. So far, it is not yet established if shorter episodes of SCAF would still bring the same amount of risk for adverse outcomes.

To elucidate this, two studies have been designed and started recruitment a few years ago (Table 1). In the 'Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation' (ARTESiA) trial, patients with AHRE ≥6 minutes and <24 hours and thromboembolic risk factors were randomized to receive apixaban vs. acetylsalicylic acid 81 mg[19], while in the 'Non–vitamin K antagonist Oral anticoagulants in patients with Atrial High rate episodes' (NOAH-AFNET 6) trial, patients with AHRE ≥6 minutes and thromboembolic risk factors were randomized to receive edoxaban vs. placebo[20]. Data from these two trials are eagerly awaited to understand what the risk/benefit ratio of treating patients with shorter SCAF episodes might be. Even though recently the NOAH-AFNET 6 was stopped due to futility and safety concerns (https://www.kompetenznetz-

vorhofflimmern.de/en/artikel/286), the full analysis of the study, together with the full results of the ARTESiA trial, which is now near completion, are needed to fully understand and elucidated this important issue.

Screening for asymptomatic atrial fibrillation: look harder, better, longer

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Beyond the clinical classification of AF endorsed by the ESC guidelines (first detected, paroxysmal, persistent, long-term persistent, permanent)[4], it is now largely assessed that a consistent part of AF patients present clinically asymptomatic, estimated as more than 40% of the overall patients[21]. This evidence led to a great expansion of the concept that systematic screening of AF was needed in order to identify all the potential patients due the prescription of OAC to reduce the risk of adverse events[8].

A large amount of studies have been produced to support the idea of implementation of systematic screening of AF, all demonstrating a significant uptake in the yield of diagnosis in general, unselected populations[22,23], as well as in elderly subjects, particularly by implementing systematic rather than opportunistic screening programmes[24]. Moreover, the technological development also provided a larger range of possibilities, with a long list of specific screening devices, all performing substantially very well in identifying subjects with undiagnosed AF[23,25]. The developing of mobile-based and wearable-based strategies to identify alterations in cardiac rhythm provided further means to expand the implementation of screening strategies[26]. Indeed, the use of the so-called ‘consumer-led screening’ strategies appear nowadays a feasible approach to identify new AF cases, even though the great diffusion of these devices need the careful planning of specific assistance

pathways to manage the great number of potential patients that could reach the clinical services[26–28].

Another important piece of evidence is related to the data showing that asymptomatic AF patients carry exactly the same baseline thromboembolic risk and also experience the same level of adverse outcomes risk over follow-up observation, as recently clearly demonstrated by Sgreccia and colleagues[29]. Hence, the most important question has become to understand whether the use of screening strategies, beyond the high yield of screening and the high uptake of OAC in this patients would also be effective in reducing the occurrence of stroke and other adverse outcomes[23]. For this purpose, a number of specific studies have been designed, having the reduction of thromboembolic events as the main outcome of the screening strategy.

So far, two papers have been published reporting the results of the STROKESTOP and LOOP studies[30,31]. Notwithstanding both the studies failed to achieve the reduction of the primary outcome, there is consistent evidence that actually the use of the screening strategy can actually reduce the occurrence of adverse outcomes, in particular when focusing on the ‘on-treatment’ analysis of the STROKESTOP study, that documented a 25% relative risk reduction of the primary composite outcome in subjects that underwent the screening procedure[30]. Furthermore, the implementation of digital strategies to detect AF, combined with the application of an integrated care strategy, already demonstrated a significant reduction in the risk of adverse outcomes in AF patients[32,33]. These data are also reinforced by a recent systematic review and meta-analysis, which actually demonstrated how the use of

AF screening strategies actually reduce the risk of stroke occurrence of around 10% of relative risk[34]. Notwithstanding this, such data are not enough to support the large scale implementation of AF screening strategies, as recently assessed by the United States Preventive Services Task Force (USPSTF), which claimed the lack of randomized trial that solidly proved the reduction of adverse outcomes after screening implementation[35], despite several clinical international guidelines already recommend the use of both opportunistic and systematic screening[4,36,37]. Other very large randomized controlled trials are currently ongoing, as the SAFER study[38] which will randomise more than 100,000 subjects, or the HEARTLINE study (https://www.heartline.com) which will implement a large scale screening programme in ≥65 years subjects through the use of mobile-health devices.

As underlined by the evidence provided by this clinical insight commentary, usually our “standard” symptomatic AF patients represent only the “tip of the iceberg”, and while a lot of work to increase the knowledge about these different forms of “silent AF” has been done, a lot is still have to come to understand the best clinical and management approaches.

CONFLICT OF INTERESTS

I declare no conflict of interests to be reported.

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Table 1: Randomized Clinical Trials about Oral Anticoagulant Drugs in Patients with SCAF

Study Name	Type of Study	N	Inclusion Criteria	Intervention	Control	Estimated FU
ARTESiA[19]	Double Blind	4,000	i) AHRE ≥6 minutes and <24 hours AND ii) ≥75 years OR iii) previous stroke/TIA/TE (+ ≥55 years) OR iv) 55-64 + 3 risk factors* OR v) 65-74 + 2 risk factors	Apixaban	ASA 81 mg	3 years 248 Events
NOAH-AFNET 6[20]	Double Blind	3,400	i) AHRE ≥6 minutes AND ii) ≥75 years OR iii) ≥65 years + ≥1 risk factor†	Edoxaban	Placebo	3 years 222 Events

Legend: *are intended as risk factors: hypertension, heart failure, diabetes mellitus, vascular disease, female sex; †are intended as risk factors: hypertension, heart failure, diabetes mellitus, stroke/TIA/TE, vascular disease, female sex; AHRE= Atrial High-Rate Episodes; ASA= Acetylsalicylic Acid; FU= Follow-Up; TE= Thromboembolic Event; TIA= Transient Ischemic Attack.