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Screening for Atrial Fibrillation in Relation to Stroke and Mortality Risk

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There has been much advocacy for the implementation of screening strategies for asymptomatic atrial fibrillation (AF),[1] given the high health care burden associated with this common arrhythmia.[2] Importantly, AF can occur asymptomatically in up to 40% of the cases, even though no profound differences were reported between symptomatic and asymptomatic AF patients in terms of risk for adverse outcomes.[3,4] Based on this evidence, implementing screening strategies to effectively identify unknown AF patients has highlighted how structured screening strategies are effective in identifying a higher number of high-risk AF patients needing the prescription of oral anticoagulants (OACs), and that using such strategies to increase OAC can be cost-effective.[5–7] Notwithstanding this, most of the studies reported thus far have only focused on the diagnostic yield related to the screening procedure and were not designed or powered to identify a significant clinical benefit in reducing adverse events in screened patients compared with those incidentally diagnosed with AF.[1] On the basis of this lack of evidence, in 2018 the United States Preventive Services Task Force (USPSTF) released a statement which still did not recommend the use of large-scale systematic screening strategies to identify AF patients.[8,9]

In this issue of *Thrombosis and Haemostasis*, Wallenhorst and colleagues present an interesting and topical analysis[10] derived from the United Kingdom Clinical Practice Research Datalink, linked to the Hospital Episodes Statistics and the Office for National Statistics to gather information regarding hospital admissions and mortality data. In this analysis using International Classification of Diseases-10th Revision codes, the authors analyzed 22,035 adult (18–84 years old) subjects with incident AF from January 1, 2001 to October 31, 2009 categorized according to the mode of AF detection. Hence, the patients were divided as follows: (1) asymptomatic incidentally detected ambulatory AF (AA-AF) [$N = 5{,}409$, 24.5%)]; (2) symptomatic ambulatory AF (SA-AF) [$N = 5{,}913$, 26.8%]; (3) AF as primary hospital discharge diagnosis (PH-AF) [$N = 4{,}989$, 22.6%); (4) AF as nonprimary hospital discharge diagnosis (Non-PH-AF) [$N = 26.0\%$]. The study cohort was then analyzed and compared with 23,605 non-AF matched patients, regarding the occurrence of stroke and all-cause death during long-term follow-up. At baseline, AA-AF patients were found to be less affected by comorbidities, with an overall low thromboembolic risk, similarly to non-AF patients. Conversely, the non-PH-AF group showed the highest burden of comorbidities and the highest level of thromboembolic risk. SA-AF and PH-AF patients showed a mixed clinical profile being both moderately comorbid, but with PH-AF ones being younger and with the lowest thromboembolic risk. Over a 3-year follow-up, while the non-AF group was associated to lower risk of stroke occurrence, in a fully adjusted competitive risk analysis compared with the AA-AF group, all the other three groups (SA-AF, PH-AF, and Non-PH-AF) reported no differences in the association with stroke events, as compared with the asymptomatic patients.[10] Similar results were found when restricting the observation to high-risk patients only (males with CHA_2DS_2-VASc ≥ 2 and females with CHA_2DS_2-VASc ≥ 3).

Non-AF subjects were associated with a lower risk and the SA-AF and PH-AF ones showed no difference in association with all-cause death; however, non-PH-AF patients were associated with a higher risk of all-cause death compared with asymptomatic patients. Notably, the rate of OAC prescription was generally low (~29%), with no differences between low- and high-risk patients and both AA-AF and SA-AF having the same

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OAC prevalence, while non-PH-AF subjects were markedly less treated with OAC (~20%).

This article allows us to highlight several important considerations regarding the modern management of AF patients. First, even in an unselected real-world cohort of subjects with first diagnosed AF, the proportion of patients with completely asymptomatic AF, which were only incidentally diagnosed, remains quite consistent, being around one-quarter of the entire study cohort. Even though those patients appeared to be slightly less burdened with comorbidities, they still have an important thromboembolic risk with more than 70% with a CHA_2DS_2-VASc score $\geq$2. Indeed, stroke risk changes with aging and incident comorbidities[11,12] and the burden of symptoms does not necessarily influence the risk of outcomes, even in those who never have been symptomatic[4]; hence, asymptomatic AF patients should not be less intensively treated in comparison with symptomatic subjects.[3]

Second, no differences in the risks of ischemic stroke between asymptomatic presentation of AF and other presentations have important clinical correlates regarding the application of opportunistic and/or systematic screening procedures in the general population. Indeed, those 5,409 asymptomatic patients who were found to be in AF were only accidentally diagnosed, mimicking what could be obtained by using an opportunistic screening applied to the entire population. If such patients had not been found in AF, none of them could have been prescribed with OAC and then an even larger number of strokes would have been recorded. In the 2020 European Society of Cardiology (ESC) clinical guidelines, the need for screening has been strongly emphasized.[13] Notwithstanding this, the ESC guidelines still recommend the use of opportunistic screening only in patients age $\geq$65 years, even though with a "B" level of evidence, while the use of systematic screening is suggested to be considered in subjects $\geq$75 years or with a high burden of stroke risk factors, again with a low quality of evidence (class II, level B).[13] Currently the USPSTF is considering an update of its recommendations about screening strategies for AF (https://www.uspreventiveservicestaskforce.org/uspstf/draft-recommendation/screening-atrial-fibrillation), and while this update is still ongoing, the evidence review still underlines that the direct evidence regarding the benefit of AF screening is still lacking, since no completed trials have assessed the benefits and harms of anticoagulation treatment among screen-detected AF. Consequently, systematic population screening for AF is still not recommended.

This situation appears paradoxical, given the large evidence regarding the positive diagnostic yield obtained by screening strategies[1,5] and with a "major" scientific society recommending AF screening, even though with a low degree of direct evidence. This situation is due to the lack of solid data regarding the reduction of adverse clinical outcomes in subjects undergoing screening. Indeed, most of the studies published thus far focused exclusively on the diagnostic yield, not considering the long-term follow-up. Only few studies (►**Table 1**, upper panel) currently report data about adverse events, again with conflicting and inconsistent data. While some of the studies were small in size and reported a very low number of events with little or no differences between subjects diagnosed by screening and by usual care,[14,15] other recent data seem to indicate a more significant benefit. The follow-up data from the STROKESTOP program, recently presented during the European Heart Rhythm Association 2021 online congress, showed a significant reduction of the composite outcome of adverse events, even though the Kaplan–Meier curves appeared to diverge only after 4 years of follow-up and with a small reduction in terms of relative risk.[16] Conversely, the mSToPS trial[17] seems to indicate a more important reduction of the risk over the 3 years of follow-up.

Additionally, more data are needed on the effects of screening on patient anxiety, as a consequence of a positive screening, as one of the criticisms raised by the first assessment done by the USPSTF,[9] even if it is reasonable to expect that this can be easily managed through adequate patient information in the context of a clinically structured integrated approach.[18] The current scenario suggests that even if the efficacy of screening in terms of diagnostic yield is quite solidly reported by several studies, the real impact on risk reduction is yet to be determined.

In the next few years, at least four large studies specifically investigating this issue would ultimately clarify whether to diagnose AF by screening campaigns would be useful or not (►**Table 1**, lower panel). Indeed, the STROKESTOP II,[19,20] the SAFER (ISRCTN Registry: ISRCTN72104369), the GUARD-AF (ClinicalTrials.gov: NCT04126486), and the HEARTLINE (ClinicalTrials.gov: NCT04126486) studies all are going to include very large number of patients and have been specifically conceived and powered to determine the impact of the screening strategies on clinical events.

Last, while the absence of a significant difference in all-cause mortality between AA-AF, SA-AF, and PH-AF patients only emphasizes what we discussed above, regarding the evidence that those patients found in AF during hospitalization, but not as primary diagnosis, have a higher risk of all-cause death. This allows us to further emphasize the need for more structured management of "clinically complex AF" patients. The burden of clinical complexity is associated with AF pathophysiology and arrhythmia course over time,[21] as well as with an increased risk of adverse outcomes (particularly all-cause death)[22,23] and the prescription and quality of OAC therapy.[22–24] Despite the significant uptake of OAC observed in recent years and the consequential reduction of stroke risk,[25] the risk of all-cause death has remained steadily high over the years, but has also increased in terms of absolute numbers.[26,27] The recent ESC guidelines have underlined the importance to manage AF patients in an integrated and holistic way, by using the "Atrial fibrillation Better Care (ABC)" pathway, which was proposed to streamline the application of integrated care in AF patients[28] with a major impact on reducing AF-related mortality, stroke, bleeding, and hospitalizations.[29–32] Wider application of the ABC pathway, together with a better AF patient evaluation and characterization using the 4S-AF scheme,[33] will help

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Table 1 Current and future studies about AF screening strategies and risk of adverse outcomes

Current studies					
Study	**Year**	**Study design**	***N***	**Outcomes**	**Main results**
REHEARSE-AF[14]	2017	≥65 year subjects with CHA_2DS_2-VASc ≥2 with no AF and no OAC or pacing randomized to 30 seconds single-lead handheld ECG twice weekly or usual care	1,004	Clinical events at 1 year FU	Despite a numerically lower number of most of the clinical events examined, no significant difference was found between the two groups
Engdahl[15]	2018	74–75 year-old inhabitants from one Swedish municipality screened with 12-lead ECG + handheld ECG for 2 weeks	106	Ischemic stroke at 5 year FU	At 5-year follow-up rates of ischemic stroke significantly decreased in the screening area, while no changes were found in a control geographical area where no screening had been performed
STROKESTOP[16,34]	2021	All residents from 2 Swedish regions aged 75–76 randomized to single-lead ECG twice daily for 14 days or usual care	27,975	Combined endpoint of ischemic stroke, systemic embolism, severe bleeding, and all-cause death at 5 year FU	Subjects randomized to screening had a lower risk of the composite endpoint throughout the follow-up observation (HR: 0.96, 95% CI: 0.920–0.999, $p = 0.045$)[a]
mSToPS[17,35]	2021	Claims database participants ≥75 years or males ≥55 years/females ≥ 65 years with one risk factor/comorbidity randomized in 1:2 ratio to ECG skin patches monitoring for 2 weeks + 2 weeks after 3 months	5,214	Combined endpoint of ischemic stroke, systemic embolism, myocardial infarction, all-cause death at 3 years FU	Subjects randomized to screening has a lower risk of the combined endpoint (8.4 vs. 13.8 per 100 person-years; HR: 0.53, 95% CI: 0.40–0.78; $p < 0.01$)[b]
Future studies					
Study	**Year**	**Study design**	***N***	**Outcomes**	**Trial registration**
STROKESTOP II[19,20]	2017	75–76 years Stockholm region inhabitants, randomized to receive screening procedure or usual care; subjects randomized to screening were assigned to handheld ECG monitoring either intermittent for 2 weeks or one-stop screening according to NT-proBNP levels	28,800	Primary outcome is stroke or systemic embolism; secondary outcome is stroke, systemic embolism, or all-cause death over 5 year FU	ClinicalTrials.gov: NCT02743416
SAFER	2017	≥70 year subjects from a primary care unit network randomized to receive screening through a single-lead handheld ECG 4 times daily for 3 weeks; the study comprises two feasibility phases and one large interventional trial	126,000	Ischemic and haemorrhagic stroke over 5 years of FU	ISRCTN: ISRCTN72104369
GUARD-AF	2019	≥70 year subjects from a primary care unit network randomized to receive screening through an ECG skin patch with no AF and no OAC	52,000	Stroke leading to hospitalisation and bleeding leading to hospitalisation over 2 year FU	ClinicalTrials.gov: NCT04126486
HEARTLINE	2020	≥65 year-old subjects randomized to receive screening through a smart watch device and a healthy heart engagement program	150,000	Composite of cerebrovascular events and all-cause death over 3 years of FU	ClinicalTrials.gov: NCT04126486

Abbreviations: AF, atrial fibrillation; CI, confidence interval; ECG, electrocardiogram; FU, follow-up; HR, hazard ratio; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; OAC, oral anticoagulant.

[a]Data on outcomes presented at the European Heart Rhythm Association 2021 Online Congress, not yet fully published.

[b]Data on outcomes presented at the American Heart Association Scientific Sessions 2020, not yet fully published.

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improve our management and reduce the risk of adverse clinical events in AF patients.

Conflict of Interest

M.P. declares no conflict of interest. G.B. declares small speaker fee from Medtronic, Boston, Boehringer Ingelheim, and Bayer.

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