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Commentary

Systematic screening of atrial fibrillation works, but is this our current priority?

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Prevalence and incidence of atrial fibrillation (AF) increase with age, making it the most common cardiac arrhythmia in older people and a growing burden for healthcare services in developed countries [1]. Although AF has been associated with an increased risk of several adverse outcomes (systemic embolism, mortality, heart failure, hospitalization, symptom burden and poor quality of life, cognitive impairment and dementia), ischemic stroke (IS) represents its most feared consequence, accounting for roughly one third of ISs in the elderly. Because of their greater net clinical benefit over vitamin K antagonists (VKAs) [2], direct oral anticoagulants (DOACs) are currently recommended for patients with clinically documented non-valvular AF (NVAF) and a CHA_2DS_2-VASc score ≥ 2 in men and ≥ 3 in women [3]. In keeping with these recommendations, the increasing use of DOACs in recent years has been associated with declining rates of IS in the general population [4]. Despite these encouraging findings, IS remains the first clinical presentation of undiagnosed/asymptomatic AF in a not negligible proportion of patients [5], underscoring the need of investigating the feasibility and clinical implications of an early diagnosis of AF in older people. The improvements and wider availability of technologies for early detection of AF has sparked the interest and research in AF screening techniques among older patients. Unfortunately, studies on the topic have yielded inconclusive findings at the moment. Indeed, the European Society of Cardiology guidelines recommend routine screening of AF in patients older than 75 years at high risk of stroke [6], whereas the US Preventive Service Task Force does not recommend routine screening due to insufficient evidence [7].

In this context, the paper from Elbadawi et al. in this Journal [8] is a timely and relevant contribute to this topic. In their network meta-analysis, the Authors compared both systematic (i.e., inviting the whole target population) and opportunistic (i.e., screening patients fortuitously presenting to clinical practice) screening strategies, with no screening on AF detection rate and clinical outcomes among subjects aged 65 years and older enrolled in RCTs studying different non-invasive technologies. The final analysis included 9 RCTs (most of them conducted in recent years) with a total of 85 209 patients (mean age 73.4 years, 45.6% males): 22 803 underwent systematic screening, 23 532 received opportunistic screening and 38 873 were not screened. Regarding the primary outcome – the rate of new AF detection in patients screened – Elbadawi et al. demonstrated that any AF screening was associated with a mildly higher AF detection rate compared with no screening (1.8% vs 1.3%; risk ratio [RR] 2.10; 95% confidence interval [CI] 1.20–3.65). However, compared with no AF screening, new AF detection rate was higher only in the systematic screening group (RR 2.73; 95% CI 1.62–4.59). With respect to the secondary outcomes (OAT initiation, all-cause mortality, and acute cerebrovascular events), a higher likelihood for initiation of OAT was associated only with systematic screening (RR 5.67; 95% CI 2.68–11.99). Although largely relying on data from one single study (STROKESTOP), there was no significant difference between any AF screening vs no screening in all-cause mortality or acute cerebrovascular events.

To put these studies in the right context, we must remember that, according to the World Health Organization (WHO), the aim of screening is to identify apparently healthy people who are at higher risk of a health problem or a condition, so that an early treatment or intervention can be offered with the potential of improving health outcomes for some of the screened individuals [9]. In Western countries screening programmes are part of a long public health tradition, recognized and valued by citizens as an essential part of health care. As part of this approach, there has been considerable interest in introducing new screening programmes for various conditions along the life-course, ultimately including AF. However, screening is not synonymous of early diagnosis: screening invites people who do not have symptoms to

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undergo testing, whereas early diagnosis is intended to detect conditions as early as possible among people with symptoms [9]. Therefore, early detection of AF might qualify as a "screening" intervention (i.e., identification of short runs of asymptomatic AF of uncertain clinical significance in persons at risk) as well as an "early diagnosis" intervention, when symptoms suggestive of AF should prompt immediate testing for AF documentation. The latter is not feasible at the moment in real-world clinical practice, even if improvement in accuracy and availability of wearable tools may change this scenario in a very short period. Therefore, if screening had to be the mainstay for early detection of AF, the Authors must be commended for their effort in performing this large meta-analysis, whose findings consolidate the role of systematic screening in improving AF detection. At the same time some limitations, some of which recognized by the Authors themselves, should be highlighted. First, the high heterogeneity among studies included in this meta-analysis would suggest focusing on the confirmed greater efficacy in AF detection of systematic screening vs no screening/opportunistic screening. This is not a hard clinical endpoint, but rather a preliminary or intermediate step in building an effective screening intervention (Box 1). Secondary endpoints of these studies have limited clinical implications and should be wisely considered. There is no apparent clinical background for the higher OAT initiation rate only in patients with AF detected through systematic screening. Few, highly heterogeneous studies have contributed to the analysis for secondary outcomes, which largely relies on data from the recent STROKESTOP study, mainly including young-older and "fit" persons and with a follow-up of about 7 years. With the exception of this latter study, the weighted median follow-up time was only 12 months, and the Authors recognize that these analyses are likely underpowered. Different screening tools were used across these open-label studies, and no specialist referral was planned in case of AF detection. With these limitations, it is difficult to hypothesize a significant clinical benefit on hard clinical outcomes.

However, even assuming that systematic screening is the best strategy for improving AF detection, it remains a long way to build an effective screening program for AF. Indeed, if we consider the Wilson & Jungner's basic principles for an appropriate screening program for public health (Box 1) [10], we have to sadly recognize that we still lack conclusive evidence for several points of this decalogue applied to AF screening. Notably, the best tools and scheduling for systematic screening are not defined; settings, facilities, referrals, and cost/sustainability of case findings have not been addressed; the natural history of "latent" or "subclinical" AF, and its temporal and causal association with the risk of ischemic stroke are not completely understood. Most importantly, the clinical consequences of, and the best therapeutic approach to short episodes of AF detected through screening are not clear, and we have limited information about which patients may derive a net clinical benefit from OAT initiation in this setting, and whether other medical interventions or procedures (e.g., rhythm control, AF ablation) might provide additional benefits. Moreover, as recognized by the Authors, AF screening or early diagnosis comes at a cost. False positive results are however possible, and the incorrect labeling of a patient as suffering from AF (and therefore at risk of stroke) may induce anxiety, thereby worsening perceived health status and quality of life and, ultimately, leading to an increased possibility of AF recurrence and chronicization [11]. Therefore, as it is true for most of available screening programmes, we still need validated tools for early AF detection in real-world clinical practice, as well as robust clinical evidence about the best medical options for these patients and a proof of benefit. Still, as screening tools keep proliferating, healthcare professionals, policymakers and some citizens are pondering whether "doing more" actually means "doing better" [9]. For these reasons, population-based AF screening in asymptomatic patients remains controversial [12], as reflected by divergent contemporary recommendations from international expert panels [6,7]. RCTs and pragmatic clinical trials with large number of subjects enrolled from different real-life scenarios, well-defined screening interventions and data collection over a long follow-up period hopefully will shed some light on this topic.

Box 1
Wilson & Jungner's principles of screening (from Wilson, Jungner & WHO, 1968).

1.	The condition should be an important health problem.
2.	There should be an accepted treatment for patients with recognized disease.
3.	Facilities for diagnosis and treatment should be available.
4.	There should be a recognizable latent or early symptomatic phase.
5.	There should be a suitable test or examination.
6.	The test should be acceptable to the population.
7.	The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8.	There should be an agreed policy on whom to treat as patients.
9.	The cost of case-finding (including a diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10.	Case-finding should be a continuous process and not a "once and for all" project.

Meanwhile, it is our opinion that other priorities should draw our attention and efforts as clinicians to increase access to already well-proven and effective stroke prevention strategies in AF patients. More than a decade since the first DOAC has been released in the market, recent population studies from England, Canada and the USA have reported dishearteningly low rates of OAT prescription (53.1%, 50.1% and 65.0%, respectively) in older adults with documented AF [13–15]. In an Italian cohort study still unpublished including more than 170 000 patients with a hospital discharge diagnosis of AF, only 63% of them received OAT (Bo M, Marchionni N, unpublished data). Such a dismal clinical scenario should prompt that all or at least a great deal of our clinical efforts should be made to comply with current international recommendations on stroke prevention in AF.

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