Diving to the foot of an iceberg: The SEARCH for undiagnosed atrial fibrillation

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Atrial fibrillation (AF) currently affects nearly 2% of the general adult population, and its prevalence is rising (1, 2). Compared with individuals in sinus rhythm, AF patients have impaired quality of life, a five-fold increased risk of stroke, a three-fold higher risk of heart failure and a two-fold greater mortality (3). Hence, AF is a major health problem.

Poor AF outcomes are highly preventable by timely and appropriately initiated medical treatment. Strokes related to AF are generally more severe and more often fatal or disabling than strokes of other aetologies (4) but can be effectively prevented with oral anticoagulant therapy, either vitamin K antagonists or non-vitamin K antagonist oral anticoagulant drugs (NOACs) - direct thrombin inhibitor dabigatran or direct factor Xa inhibitors rivaroxaban, apixaban and edoxaban. Compared to placebo, warfarin reduces the risk of stroke by 67% (5), and NOACs were at least as effective as warfarin or in some cases even better, altogether achieving a 19% relative risk reduction compared to warfarin (p<0.0001) (6). Due to their pharmacology and favourable safety profiles, NOACs offer a greater net clinical benefit compared to warfarin (particularly in patients at increased risk of bleeding) (7, 8).

At present, comprehensive treatment of underlying cardiovascular risk factors and/or structural diseases, adequate thromboprophylaxis and rate control are the cornerstones of AF treatment (9-11). Rhythm control is recommended for patients with intolerable AF symptoms (or complications) despite ventricular rate control, and the concept of an early rhythm control (to prevent adverse AF outcomes by termination of recent onset AF and maintenance of sinus rhythm) is currently being investigated in a randomised trial (12).

Ideally, AF should be eradicated by the primary prevention but the second best option would be active treatment of its clinically overt form. Indeed, we should start appropriate treatment(s) immediately when AF is identified. However, this when is a major concern, since AF may be asymptomatic in up to 30% of patients (13, 14) or may cause vague, atypical symptoms that could be easily ignored by both patient and physician (15). In such individuals, if lucky, AF may be accidentally diagnosed during medical examination for other reasons. Unfortunately, stroke risk is not mitigated by the absence of AF symptoms (16, 17) and a devastating stroke may be the very first clinical manifestation of AF. Indeed, every ischaemic stroke is directly attributable to AF and in 20-45% of such cases AF is first diagnosed at the time of stroke (9, 18). Needless to say, most of these strokes could have been prevented if AF had been diagnosed.

How about screening for asymptomatic or undiagnosed AF, then? The idea is not new (19-21), but the optimal AF screening strategy is still under investigation. In the June issue of *Thrombosis and Haemostasis*, Lowres, et al. reported the results of their elegant SEARCH-AF study on feasibility and cost effectiveness of opportunistic, community-based screening in Australia for previously unknown AF in individuals aged ≥65 years, conducted in 10 local pharmacies, using a structured screening method with a brief medical history, pulse palpation and a handheld iPhone-based single lead iECG recording, which was first interpreted by the pharmacist and then by a cardiologist (22).

Generally, screening study designs are largely influenced by their goals and cost effectiveness (23). The current gold standard diagnostic test for AF is a 12-lead ECG interpreted by a cardiologist (9-11). Pulse palpation itself is not conclusive if not followed by ECG confirmation (23) [23], and a number of screening tests such as a single-lead ECG, finger probes and home blood pressure monitors with in-built AF algorithm detection have reported promising results (24-26). Recently, a smartphone-based ECG technology emerged as an attractive AF screening tool (27). Diagnostic tests may be used for opportunistic screening (i.e. during a routine medical consultation), targeted screening (in a pre-selected group of patients), or population-based screening (when a diagnostic test is offered to everyone who has not already been diagnosed with AF) (23). Whilst similar numbers of patients with previously unknown AF can be detected by opportunistic and systematic screening, the former was shown to be more cost-effective (28).

Using an innovative combined screening strategy, Lowres, et al. identified previously unknown AF in 1.5% of screened individuals, in line with data from their earlier meta-analysis showing that single time-point screening in individuals aged ≥65 years identified previously unknown AF in 1.4% of patients, regardless of the screening setting (that is, general practice/outpatient clinic or community) (15). However, Lowres, et al. addressed individuals who were less likely to be medically examined compared to opportunistic screening for AF in the general practice or...
outpatient clinic, and yet this community based screening in the SEARCH-AF was cost effective. Of course, a stepwise risk-stratified population-based screening with prolonged intermittent ECG recording captured more individuals with previously unknown paroxysmal AF (7.4%), but the data on the cost effectiveness were not reported in that study (29). Nonetheless, it should be kept in mind that short paroxysms of AF are very common in patients with cryptogenic stroke (30), and no ‘safe’ daily amount of AF has yet been identified. Indeed, studies of patients with cardiac implantable electrical devices reported that even a 6-minute device-detected asymptomatic AF episode in patients without known AF (and not taking oral anticoagulation) was associated with a 2.5-fold increased risk of subsequent stroke (31-33).

Importantly, all individuals with newly detected AF in the SEARCH-AF study were at increased risk of stroke, as measured by a CHA2DS2-VASc score of ≥2, hence all were candidates for oral anticoagulation (9, 22). However, only 53% of them were eventually prescribed an oral anticoagulant. In addition to the well-known gap in adherence to AF guidelines, the SEARCH-AF study highlighted another well-recognised issue of poor patient knowledge and awareness of AF (<50% of patients already taking oral anticoagulant therapy for AF were aware of the diagnosis) (34). Both improved education and availability of the NOACs should facilitate adequate stroke prevention in AF patients, and increasing experience with these drugs will soon overcome the existing gaps in translation from trials to clinical practice, thus increasing the overall use of oral anticoagulant therapy for stroke prevention in AF (35, 36).

Which population(s) should screening target for the primary prevention of AF-related stroke?

The prevalence of AF increases with age (1), and the lifetime incidence of stroke in AF patients rises sharply from age of 55 (for a decade, the risk increases from 3.0-5.9% to 7.2-11.0%), reaching the threshold for oral anticoagulation therapy at age of ≥65 even in the absence of other stroke risk factors (9, 37). Hence, screening for AF is clearly justified in individuals aged 65 or older (and younger AF patients with ≥2 stroke risk factors).

Which diagnostic test should we use?

Most probably, any test (pulse palpation, single-lead ECG, finger probes, home blood pressure monitors with in-built AF algorithm detection, etc.) is preferable to no screening. However, findings from the SEARCH-AF study suggest that with new, smartphone-based automated ECG algorithm (98.5% sensitivity and 91.4% specificity for AF diagnosis) trained health workers of various profiles (such as pharmacists) could successfully perform screening for AF; thus contributing to the widespread stroke prevention through detection of AF.

There is still a lot to be learned about most appropriate screening strategies for AF. Perhaps some more subtle screening tools (such as biomarkers, for example) will enable a reliable, quick identification of previously unknown AF in the future. Until that time, let’s do our best to get to the foot of the ‘AF iceberg’ with the equipment we have available.

Conflicts of interest
None declared.

References