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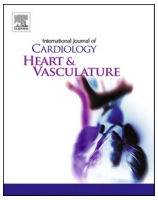

Towards improved detection of subclinical atrial fibrillation – Who could benefit from targeted screening?

Atrial fibrillation (AF) is the most common cardiac arrhythmia and a major cause of stroke. The intuitive goal of clinical management is early AF detection and initiation of anticoagulation for stroke prevention. This endeavour is hampered by the intermittent nature of AF, which makes it nearly undetectable on short single-point electrocardiogram (ECG), and its symptomatic spectrum. While some patients experience occasional palpitations, in others, the symptoms are strong and frequent enough to impact on quality of life. Others yet remain largely asymptomatic, and AF is only detected after an ischemic event has occurred.

Essentially, two important gaps need to be closed in order to improve the detection and management of AF: (i) better identification of those at risk who warrant closer monitoring, and (ii) advanced detection methods to capture silent AF despite apparent sinus rhythm on ECG. Machine-learning and advanced algorithms will undoubtedly aid at least in the second goal. For the first point, however, many unmet needs remain. Wholescale opportunistic population-based screening is not feasible, and willingness to participate is often a major hurdle [1]. Implantable loop recorders (ILR) are currently used mainly in patients with cryptogenic stroke, but are unsuitable for large-scale monitoring of all patients with a potential risk of AF. Possibly, longer monitoring by Holter ECG may be an alternative means to capture incidental arrhythmias in asymptomatic patients that will otherwise evade identification. Inarguably, optimised screening will improve timely detection and therapeutic managment of AF; but, which patients to screen? with which device?, and for how long, and how often? Up to 5 % of ischemic stroke patients are restrospectively diagnosed with AF, having previously been categorized as low-risk based on a relatively young age and a low CHA_2DS_2-VASc-Score [2]. Ideally, patients who will benefit from close monitoring could be identified based on specific risk-scores and/or non-invasive biomarkers that are easily measured in routine clinical practice.

Numerous risk factors associated with AF by retrospective analysis have been incorporated into adapted risk scores to improve AF risk prediction [3]. Several such trials are currently ongoing or still recruiting, including the CONSIDERING-AF (deteCtiON and Stroke preventIon by moDEl scRreenING for Atrial Fibrillation) study (NCT05838781) and the FIND-AF (Future Innovations in Novel Detection of Atrial Fibrillation) longitudinal cohort study (NCT05898165). FIND-AF will apply multimodal phenotyping, cardiac imaging and intermittent ECG monitoring to comprehensively characterise what drives AF and how to recognize it before it manifests. Of the recently published studies, the CHARGE-AF [4] score for example consolidates age, race, height, weight, systolic and diastolic blood pressure, current smoking, use of antihypertensive medication, diabetes mellitus, history of myocardial infarction and heart failure into a 5-year predictive model that appears to provide good discriminatory value in predicting incident AF. In the RITMO-Study [5], asymptomatic patients aged 65 and over, with either hypertension or heart failure plus a increased AF risk estimated with Stroke Risk Analysis algorithm, underwent home ECG monitoring for 7 days. Unknown AF was detected in 56 of the 408 included individuals (nearly 14 %). The ABC-Stroke score, incorporating Age, Biomarkers (N-terminal pro-B-type natriuretic peptide, NT-proBNP, and high-sensitivity troponins TnT or TnI), and Clinical history (prior stroke or transient ischaemic attack) was employed to distinguish low and high risk individuals in a cohort of 5,781 individuals enrolled in the LOOP (Atrial Fibrillation Detected by Continuous ECG Monitoring Using Implantable Loop Recorder to Prevent Stroke in High-Risk Individuals) study, and allocate them to receive either usual care or screening with an ILR. The close monitoring, however, provided no apparent improvement in terms of cardiovascular or thromboembolic events or mortality in any of the ABC risk groups, suggesting that this score may be less useful to pinpoint patients who will benefit from AF screening and subsequent anticoagulation [6].

Despite this outcome, one of the components of the ABC-score, NT-proBNP, has yet moved into the spotlight as a potential predictor of incident AF. The natriuretic peptides classically used to indicate hypertension, hypertrophic cardiomyopathy and heart failure [7,8], but may serve equally well as biomarkers of AF. NT-proBNP is elevated in patients with both established AF [7,9], and those with so-called „micro-AF," defined as short episodes of irregular supraventricular ectopic beats [10], with each 1 pg/mL increase in NT-proBNP equating to a 1.8 % higher rate of micro-AF. A recent sub-analysis of the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial revealed that in patients with established heart failure with preserved ejection fraction, but no AF at baseline, an incrementally elevated NT-proBNP level correlated with a respective increase in the incidence of new-onset AF [11]. Similarly, NT-proBNP may be used to forecast new-onset AF after cardiac surgery [12,13] as well as recurrence after AF ablation [14,15]. As a side-note, NT-proBNP may also explain racial differences in AF susceptibility. Black cohorts generally habour a greater cardiovascular risk factors than whites, yet incident AF is lower. In the Cardiovascular Health Study and the ARIC (Atherosclerosis Risk in Communities) studies, NT-proBNP levels were 40 % higher in white individuals, correlating with increased AF hazard ratio

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of 1.6–1.9 compared to black cohorts. Curiously, no such NT-proBNP-dependent relationship was found between race and heart failure [16].

In this issue of the *International Journal of Cardiology Heart & Vasculature*, Sado et al. [17] highlight NT-proBNP as a candidate discriminator to identify patients who will likely benefit from intensified monitoring for AF. The STROKESTOP II trial was a randomized controlled study in which participants were stratified as low- or high-risk according to NT-proBNP levels, based upon which the high-risk participants were randomized for invitation to undergo screening for AF or not. The study design saw the low-risk group (NT-proBNP $<$ 125 ng/mL) to be screened once, while the high-risk group (NT-proBNP $>$ 125 ng/mL) underwent AF monitoring by hand-held single-lead ECG 4x/day for 2 weeks, or no screening. Although the mass screening for AF did not lower the rate of thromboembolic endpoints over the 5-year follow-up, the study importantly identified elevated NT-proBNP as a predictor of undetected AF in an apparently low-risk group. A high NT-proBNP doubled risk of having silent AF and raised the risk of an ischemic event by nearly 60 % [18]. The key take home message is that high NT-proBNP equals high risk of AF, identifying a patient cohort that warrants intensified monitoring.

In the sub-study presented here, Sado et al. [17] additionally stratified according to the presence of hypertension. Hypertension and AF are linked in an intricate and likely bi-directional manner, with a high prevalence of hypertension noted in patients with AF, and an elevated risk for developing AF in those with hypertension [19]. The precise nature of the interaction between the two disease entities is poorly understood. Generally, hypertension can develop in younger individuals while AF tends to manifest with older age. It known if hypertension in the young differs qualitatively from hypertension that develops in older individuals. In the present study, the lowest risk group was accordingly defined by no hypertension and low NT-proBNP levels, the highest risk group by combined hypertension and high NT-proBNP levels. In this latter cohort, screening-detected AF was notably more common, with an incidence of 3.7 % compared to 0.1 %. The study essentially verifies that NT-proBNP increases with concomitant hypertension, and importantly, can robustly discriminate between low and high risk of undiagnosed AF, regardless of hypertension status. Implicit in this finding is that low blood pressure and low NT-proBNP associate with a very low risk of undetected AF.

Accordingly, stratification of elderly patients based on hypertension and NT-proBNP may identify those who will benefit from intensified AF monitoring. This will ideally narrow down the cohort warranting prolonged AF screening, which is not feasible on a large scale, but many aspects remain uncertain. For instance, the cut-off values for risk stratification need to be harmonized, as should the assay platforms. Concomitant conditions that either falsely overestimate (e.g. renal dysfunction, age, female sex, inflammation, hyperthyroidism, AF) or underestimate (e.g. obesity, acute coronary syndrome, pericardial effusion) NT-proBNP levels also provide pitfalls to interpretation [20,21]. Will the predictive value of NT-proBNP remain constant with advanced age for example, or will it vary? Or will cut-off values need to be adapted with age, comorbidity constellations or medications such as neprilysin inhibitors? Finally, the consequences of a positive screen for silent AF need to be clarified. Optimal AF management remains problematic, regarding when and how to treat the disease – rate or rhythm control, antiarrythmic drugs or ablation? - and prevent its consequences [22–24]. How great is the risk of ischaemic stroke in subclincial AF detected by intensified and improved approaches, compared to manifest AF? The risk may likely be lower in this specific cohort, warranting a careful balancing of thromboembolic versus bleeding risk associated with anticoagulation, perhaps by specialised risk scores.

In conclusion, NT-proBNP provides an incremental advancement towards refined identification and management of patients with subclinical AF, but many gaps and pitfalls still need to be considered for optimal implementtaion.

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Disclosures

None.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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