Screening for undiagnosed atrial fibrillation in the community

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Purpose of review
Recent years have seen significant advances in knowledge about the prevalence of ‘silent’ atrial fibrillation and the morbidity associated with this condition. Data are emerging on improved strategies for screening, and new technologies for detecting atrial fibrillation are becoming available, making a review of this field timely.

Recent findings
Studies suggest that, when screening is performed, undiagnosed atrial fibrillation is present in around 1% of the screened population, rising to 1.4% for those aged at least 65 years. The prevalence of silent atrial fibrillation is even higher in patients with additional risk factors (e.g. those aged 75 years, patients with heart failure). Prolonged monitoring of patients with hypertension and an implanted cardiac device showed subclinical atrial arrhythmias in at least 10% and these patients had a 2.5-fold increased risk of stroke or systemic embolism. The feasibility of screening for silent atrial fibrillation has been demonstrated in a number of populations and many new technologies for atrial fibrillation detection exist, which could improve the efficiency and cost-effectiveness of this process.

Summary
Increased attention is being directed towards screening for silent atrial fibrillation and our ‘toolbox’ for detecting it is expanding. Whether this will translate into improved outcomes for patients remains to be proven.

Keywords
ambulatory ECG, atrial fibrillation, screening, stroke, systemic embolism

INTRODUCTION
The prevalence of atrial fibrillation in the population is rising, and about one in four individuals over age 40 will develop this dysrhythmia [1]. Untreated atrial fibrillation carries on average a three to five-fold increase in the risk of stroke and is independently associated with a significant increase in congestive heart failure, cognitive impairment and mortality [2\textsuperscript{*},3\textsuperscript{*},4\textsuperscript{*},5\textsuperscript{*}]. Appropriate antithrombotic therapy can reduce the risk of stroke by around two-thirds and the risk of all-cause mortality by one-quarter [6]. Once atrial fibrillation is identified, there are well-validated risk scores to determine which patients merit anticoagulation (e.g. CHADS\textsubscript{2} and CHA\textsubscript{2}DS\textsubscript{2}-VASc scores) and clear guidelines to direct clinical care [3\textsuperscript{*},7\textsuperscript{*},8]. The first step in delivering evidence-based therapy is to identify those with the dysrhythmia, which may be hampered by the fact that at least 30–40% of those with atrial fibrillation may not be aware that they have it (‘silent AF’) [9\textsuperscript{*},10\textsuperscript{*}] and the first manifestation of atrial fibrillation may be an ischemic stroke.

DOES SILENT ATRIAL FIBRILLATION MATTER?
Patients with clinically undiagnosed atrial fibrillation are likely to carry a similar risk of stroke and thromboembolism as those with recognized atrial
fibrillation; indeed, their risk may be higher, as it is unlikely that they will take appropriate antithrombotic therapy. In a retrospective study in New Zealand of 1242 patients presenting with stroke where an ECG was available, 219 patients (21%) had atrial fibrillation recorded, and for 69 patients this was the first diagnosis of atrial fibrillation (6% of the total cohort, 32% of those with atrial fibrillation) [11]. Of the 150 patients with known atrial fibrillation, 29% were taking guideline-recommended antithrombotic therapy at the time of their stroke, whereas for those with previously undiagnosed atrial fibrillation, this figure was 6%.

Further insights into the risks of silent atrial fibrillation can be gleaned from patients with implanted pacemakers or defibrillators, in whom the burden of silent atrial arrhythmias can be determined. The Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and Their Atrial Pacing Trial (ASSERT) study followed 2580 patients with implanted pacemakers or defibrillators, in whom the mean CHADS2 score for those with previously undiagnosed atrial fibrillation would be 100 for the general population and 71 for those aged at least 65 years.

Limited data are available concerning the stroke risk of those with silent atrial fibrillation. Deif et al. [14] reviewed the ECGs of 1459 ambulatory patients aged more than 65 years presenting for elective surgery and found previously undiagnosed atrial fibrillation in 10 (0.7%). The mean CHADS2 score of these patients was 2.2 (standard deviation 1.5) and none with a CHADS2 score more than 1 were anticoagulated (compared with 65% of patients with known atrial fibrillation and a CHADS2 score >1). In a study by Engdahl et al. (see below) [15], the mean CHADS2 score for those with previously undiagnosed atrial fibrillation detected on a 12-lead ECG was 1.8 and none of these patients were on anticoagulation. Thus, a high proportion of those with silent atrial fibrillation in these studies were eligible for anticoagulation.

RECENT STUDIES OF PROLONGED MONITORING FOR ATRIAL FIBRILLATION IN THE COMMUNITY

Screening methods relying on a single assessment for atrial fibrillation will miss many patients with paroxysmal atrial fibrillation. These patients have a similar risk of stroke to those with persistent atrial fibrillation [16,17] and screening strategies should take this into account. Engdahl et al. [15] reported the results of an elegant study of stratified screening in a community of 92000 inhabitants in Sweden. All individuals aged 75 or 76 years were invited to screening and a 64% response rate was achieved (848 individuals). Initial screening was
with a 12-lead ECG; then those with sinus rhythm on ECG, no prior history of atrial fibrillation and at least two CHADS2 risk factors were given a hand-held ECG device (Zenicor Medical Systems AB, Stockholm, Sweden) and made recordings twice per day (or if they had symptoms) over a 2-week period. Eighty-one patients had known atrial fibrillation (9.6% of those screened) and 35 of these patients were not on oral anticoagulation. New atrial fibrillation was diagnosed on the initial ECG in 10 patients (1.2% of those screened). Home ECG recordings were obtained on 403 individuals with a CHADS 2 score of at least 2, and 30 of these patients were found to have atrial fibrillation (see Fig. 1 for an illustration of the time required to detect these cases). Thus, silent or undiagnosed atrial fibrillation was present in a total of 40 individuals (4.7% of the screened cohort) and the screening programme identified 75 patients with atrial fibrillation (known or undiagnosed) who would merit anticoagulation. Fifty-seven of these patients did start anticoagulation. This study is commendable for several reasons: it was conducted in an unselected general population, screening was stratified by baseline risk, the screening protocol was simple, acceptable and feasible, the strategy picked up a significant number of patients with atrial fibrillation in whom anticoagulation would be recommended and this was converted into a change in therapy in the majority.

**ROLE OF NEW TECHNOLOGIES IN SCREENING FOR ATRIAL FIBRILLATION**

There has been a proliferation of new technologies and devices promising simple and accurate detection of atrial fibrillation, with some examples summarized in Table 1 [15**,18,19,20*,21,22,23,24*,25] and reviewed by Harris et al. [26**]. Most have only been validated in select populations enriched for the presence of atrial fibrillation (e.g. cardiology outpatients, patients before and after cardioversion), so accurate data on their ‘real-world’ sensitivity and specificity are lacking. Nonetheless, they may herald a new era of home rhythm monitoring and may simplify screening for atrial fibrillation in other settings.

With an ageing population becoming more technologically advanced [27], it is likely that manufacturers of smartphones and other portable electronic equipment will start to incorporate biological sensors into their devices. Several applications already exist to determine the heart rate using the inbuilt camera on a number of smartphones. An application to detect atrial fibrillation by this method is in development [20*], but has not yet been tested in a general population. Phone cases now exist with dry electrodes for recording single-lead ECG tracings (e.g. AliveCor Heart Monitor, AliveCor Inc., San Francisco, California, USA; ECG Check, CardiacDesigns, Park City, Utah, USA). The AliveCor/iPhone system was studied by Lau et al. [21*]. A Lead I rhythm strip was obtained, which was read by two cardiologists and later compared with the gold standard of a 12-lead ECG. Sensitivity for atrial fibrillation detection was 95–100%, with a specificity of 90–94%, giving an overall accuracy of 94–95%. The authors also developed and optimized an automated algorithm for atrial fibrillation detection, and, in a validation set of patients, this had a sensitivity, specificity and overall accuracy of 98, 97 and 97%, respectively. A study using this technology to screen for atrial fibrillation in community pharmacies is currently underway [22].

Automated blood pressure machines are now available with algorithms to detect atrial fibrillation on the basis of pulse irregularity (e.g. WatchBP, Microlife AG, Widnau, Switzerland; Omron M6, Omron Corp., Kyoto, Japan), with reasonable diagnostic accuracy [23,24*,25], although it is likely that most physicians would want ECG confirmation of atrial fibrillation before initiating therapy.
**Table 1. Performance of novel technologies for atrial fibrillation detection**

<table>
<thead>
<tr>
<th>Type of device</th>
<th>Company</th>
<th>Device</th>
<th>Reference standard</th>
<th>Population studied</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>Reference</th>
<th>Notes</th>
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<tr>
<td>Hand-held single-lead ECG with dry electrodes</td>
<td>Zenicor Medical Systems AB</td>
<td>Zenicor-EKG</td>
<td>12-lead ECG interpreted by cardiologist</td>
<td>100 patients with AF, atrial flutter or sinus rhythm from cardiology outpatient clinic</td>
<td>92&lt;sup&gt;a&lt;/sup&gt;</td>
<td>96&lt;sup&gt;a&lt;/sup&gt;</td>
<td>96&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Doliwa et al. [18]</td>
<td>Used for AF screening by Engdahl et al. [15]&lt;sup&gt;a&lt;/sup&gt;. Sensitivity and specificity recalculated for identification of AF. Latest device can send data via GSM/GPRS network.</td>
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<tr>
<td></td>
<td>Omron Healthcare</td>
<td>HeartScan HCG-801</td>
<td>12-lead ECG interpreted by cardiologist</td>
<td>508 cardiology clinic patients</td>
<td>99</td>
<td>96</td>
<td>92</td>
<td>Kaleschke et al. [19]</td>
<td>Tracings in study taken with electrodes in contact with right index finger and chest (close to V4 position).</td>
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<td>iPhone 4S application</td>
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<td></td>
<td>96.2</td>
<td>97.5</td>
<td>McManus et al. [20]&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Uses iPhone light and camera to obtain pulsatile signals. Specificity will be overestimated, as all patients had AF prior to cardioversion.</td>
<td></td>
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<tr>
<td>Smartphone case with dry electrodes</td>
<td>AliveCor Inc.</td>
<td>Heart Monitor</td>
<td>12-lead ECG interpreted by cardiologist</td>
<td>109 patients (39 in AF): learning cohort; 204 patients (48 in AF): validation cohort</td>
<td>95–100% (Cardiologist interpretation of single-lead ECG); 98% (Automated algorithm)</td>
<td>90–94% (Cardiologist interpretation of single-lead ECG); 97% (Automated algorithm)</td>
<td>Lau et al. [21]&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Being used for AF screening in SEARCH-AF trial [22]. Requires iPhone.</td>
<td></td>
</tr>
<tr>
<td>Automated BP machine with AF detection algorithm</td>
<td>MicroLife</td>
<td>BP A200 Plus</td>
<td>12-lead ECG interpreted by cardiologist</td>
<td>503 patients referred to hypertension clinic</td>
<td>92&lt;sup&gt;a&lt;/sup&gt;</td>
<td>95&lt;sup&gt;a&lt;/sup&gt;</td>
<td>83&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Marazzi et al. [23]</td>
<td>Based on three consecutive measurements</td>
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</table>
There have also been rapid advances in devices for continuous ambulatory ECG monitoring, either using skin electrodes (e.g. CardioNet MCOT, CardioNet, Conshohocken, Pennsylvania, USA) or completely enclosed in one or more adhesive patches (e.g. ZioPatch, iRhythm Technologies, Inc., San Francisco, California, USA; Nuvant MCT System, Corventis, San Jose, California, USA). Some devices store data and are returned for later analysis, while some allow real-time transmission of data to a central monitoring station over the cellphone network. No clinical trials have yet reported data using such devices for atrial fibrillation screening in the general community.

TARGETED SCREENING IN HIGHER-RISK POPULATIONS

Unselected screening for atrial fibrillation across the general population is unlikely to be feasible, acceptable or cost-effective. It makes sense to target screening strategies to patient groups with a higher baseline prevalence of atrial fibrillation (thus reducing the number needed to screen to detect one case of atrial fibrillation) and/or to patient groups wherein detection of atrial fibrillation would be likely to lead to a change in therapy (e.g. commencing anticoagulation). The intensity of screening (on-off versus more prolonged monitoring) can also be varied depending on the patient's baseline stroke risk; the more it matters that atrial fibrillation is detected, the harder you should look. This was the approach taken by Engdahl et al. [15], wherein those with at least two CHADS2 risk factors underwent additional 2-week ambulatory monitoring, with a significant pick-up rate for atrial fibrillation in this high-risk group (7.4%).

Age is perhaps the simplest variable that can aid in targeting screening; with each decade of advancing age, prevalence roughly doubles [4**] and the risk of stroke in the presence of atrial fibrillation increases by around 1.5 to two-fold [28,29]. There is consensus in the guidelines that most patients aged 75 years and over with atrial fibrillation should be anticoagulated, and, in the European and Canadian guidelines, the age cut-off where anticoagulation is recommended is 65 [3**,7**]. Current European guidelines suggest that opportunistic screening for atrial fibrillation with a pulse check, followed by an ECG if irregularity is detected, should be performed for patients aged at least 65 years (Class 1 recommendation) [3**].

Contemporary data from the UK on the prevalence of atrial fibrillation in patients with certain risk factors were reported by Davis et al. [4**]. Atrial

<table>
<thead>
<tr>
<th>Table 1 (Continued)</th>
<th>Type of device</th>
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<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>Notes</th>
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<tbody>
<tr>
<td>BP3MQ1-2D 60-s event recorder ECG, repeated if BP machine suggested AF</td>
<td>BPM BP3MQ1-2D</td>
<td>139 ambulatory ECG patients from internists' offices, who had a history of hypertension or left ventricular hypertrophy</td>
<td>90</td>
<td>52° based on logistic regression model.</td>
<td>Wiesel et al. [24]</td>
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<tr>
<td>12-lead ECG interpreted by cardiologist</td>
<td>BPM BP3MQ1-2D</td>
<td>405 general cardiology outpatients</td>
<td>97</td>
<td>94</td>
<td>Wiesel et al. [25]</td>
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<tr>
<td>12-lead ECG interpreted by cardiologist</td>
<td>Omron Healthcare M6</td>
<td>503 patients referred to hypertension clinic</td>
<td>100</td>
<td></td>
<td>Marazzi et al. [23]</td>
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</table>

Information is presented on selected devices with published data regarding AF detection. See text for further discussion. AF, atrial fibrillation; CHADS2, Cardiovascular Health and Disability Scale 2; GPRS, General Packet Radio Service; GSM, Global System for Mobile Communications; PPV, positive predictive value; SEARCH-AF, Screening Education And Recognition in Community Pharmacies of Atrial Fibrillation. Recalculated from original manuscript.
fibrillation was found in 2% of a cohort of 3960 patients aged 45 years and older randomly selected from the general population. Of 782 patients with a prior clinical diagnosis of heart failure, 22.4% were in atrial fibrillation (around half of these patients had normal left ventricular systolic function). In 1161 patients with other risk factors for atrial fibrillation (prior myocardial infarction, hypertension, angina, diabetes), the dysrhythmia was found in around 5%. Targeting screening strategies to such patient groups could be an effective means of reducing the number needed to screen to detect a case of silent atrial fibrillation.

A further population with a high burden of undiagnosed atrial fibrillation are those who have suffered a cryptogenic stroke. Methods for detecting silent atrial fibrillation in this ‘secondary prevention’ population have been reviewed elsewhere [26**,30] and are beyond the scope of the current review.

WHAT DO WE DO WITH THE RESULTS OF SCREENING? HOW MUCH ATRIAL FIBRILLATION IS TOO MUCH ATRIAL FIBRILLATION?

A crucial unanswered question remains whether patients with very brief episodes of atrial fibrillation detected on prolonged monitoring merit anticoagulation. Studies have shown that patients with paroxysmal atrial fibrillation share a similar risk of stroke as persistent atrial fibrillation and derive similar benefit from anticoagulation [16,17]. Patients in such studies generally required documentation of atrial fibrillation on at least two 12-lead ECGs as well as periods of sinus rhythm to be classified as paroxysmal atrial fibrillation, that is, the atrial fibrillation episodes had to be sustained enough to be recorded on a standard ECG. Studies in patients with implanted devices have given more information on the clinical impact of shorter episodes of atrial fibrillation, although it should be remembered that these patients may not be representative of the general population. As mentioned earlier, the TRENDS study found that more than 5.5 h of atrial fibrillation in a single day increased the risk of thromboembolism [12]. In the ASSERT study, the minimum duration of AHRE stored by the implanted devices was 6 min and the median duration of the longest AHRE was around 3.6 h [9**]. The presence of any recorded AHRE (i.e. >6 min) was associated with an increased risk of ischemic stroke or systemic embolism (hazard ratio 2.5), but the study was not powered to determine whether there was a ‘dose–response’ effect for AHRE duration.

One way to stratify further patients with device-detected episodes of atrial fibrillation is to combine information on the duration of AHRE with the CHADS2 score. Botto et al. [31] obtained data from 568 patients with pacemakers and a history of atrial fibrillation and divided AHRE episodes on a given day into those less than 5 min, between 5 min and 24 h and more than 24 h. Patients with a CHADS2 score of 0 had a low risk of thromboembolism, irrespective of the duration of atrial fibrillation, whereas those with a CHADS2 score of 3 or more had a high risk, even if no atrial fibrillation was detected. The risk of thromboembolism for patients with a CHADS2 score of 1 or 2 could be stratified by the duration of atrial fibrillation detected, and, for the overall cohort, this could be used to dichotomize patients into those with low risk (0.8% annual risk) versus high risk (5.0% annual risk). However, no trial has yet determined whether anticoagulation patients with device-detected atrial fibrillation impacts clinical outcomes.

BEYOND SILENT ATRIAL FIBRILLATION: OTHER ADVANTAGES OF SCREENING PROGRAMMES

As well as detecting silent atrial fibrillation, instituting systems approaches for atrial fibrillation screening will also pick up those with known atrial fibrillation, a population in which rates of anticoagulation in those at moderate or high stroke risk have remained stubbornly around 50% [32*]. Identifying these patients may present a point of contact with the healthcare system wherein their medication can be reviewed to ensure that it is consistent with current guidelines. In addition, a broader consideration than just anticoagulation is required when atrial fibrillation is detected in any patient; it should be ensured that appropriate investigations are carried out into possible underlying causes (e.g. hypertension, cardiomyopathy, valvular heart disease), and management of the dysrhythmia should also be addressed (rate-control or rhythm-control) to minimize the chance of future complications.

CONCLUSION

There is a growing body of data demonstrating that significant morbidity is associated with silent atrial fibrillation. Recent studies have shown us which populations carry a high burden of this disease and advancing technology is giving us new tools to detect it. Further trials are required to demonstrate the utility, acceptability and cost-effectiveness of these approaches in ‘real-world’ settings. With
increasing data from prolonged patient monitoring (including pacemakers and other implanted devices), it is still not clear which patients with brief episodes of atrial fibrillation merit anticoagulation; clinical trials in this realm are eagerly awaited.

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Conflicts of interest
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REFERENCES AND RECOMMENDED READING
Papers of particular interest, published within the annual period of review, have been highlighted as:
■ of special interest
★★ of outstanding interest
8. This guideline highlights important changes in the recommendations for anticoagulation of patients with atrial fibrillation, based on more accurate determination of those who are truly low risk. Most other patients are recommended to be anticoagulated with warfarin or one of the novel anticoagulant agents.
11. A landmark study demonstrating that ‘silent’ atrial arrhythmias are common in patients with pacemakers or defibrillators and are associated with significant morbidity. Strategies to detect asymptomatic atrial fibrillation could therefore be an important step towards prevention of stroke, although trials to prove this have not yet been performed.
This study demonstrates the utility of large patient databases for deriving data on anticoagulant use. It also highlights the underutilization of anticoagulation in eligible patients.