Stepwise Screening of Atrial Fibrillation in a 75-Year-Old Population
Implications for Stroke Prevention

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Background—Atrial fibrillation (AF) is a frequent source of cardiac emboli in patients with ischemic stroke. AF may be asymptomatic and therefore undiagnosed. Screening for silent AF seems suitable in risk populations, however little is known on the yield and cost-effectiveness of such screening.

Methods and Results—All inhabitants in the municipality of Halmstad, Sweden aged 75 to 76 years were invited to a stepwise screening program for AF. As a first step, participants recorded a 12-lead ECG and reported their relevant medical history. Those with sinus rhythm on 12-lead ECG, no history of AF, and ≥2 risk factors according to CHADS2 were invited to a 2-week recording period using a hand-held ECG and asked to record 20 or 30 seconds twice daily and if palpitations occurred. One thousand, three hundred thirty inhabitants were invited, of whom 848 (64%) participated. Previously undiagnosed silent AF was found in 10 (1%) among 848 individuals who recorded 12-lead ECG. Among 81 patients with known AF, 35 (43%) were not on oral anticoagulation treatment. Among 403 persons with ≥2 risk factors for stroke, who completed the hand-held ECG event recording, 30 (7.4%) were diagnosed with paroxysmal AF. Thus 75/848 (9%) of the screened population were candidates for new oral anticoagulation treatment, of those 57 actually started oral anticoagulation treatment.

Conclusions—Stepwise risk factor–stratified AF screening in a 75-year-old population yields a large share of candidates for oral anticoagulation treatment on AF indication. (Circulation. 2013;127:930-937.)

Key Words: atrial fibrillation ■ diagnosis ■ prevention and control ■ stroke
Table. Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Participating</th>
<th>Nonparticipating</th>
<th>P</th>
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<tbody>
<tr>
<td>Male sex</td>
<td>364 (43%)</td>
<td>149 (42%)</td>
<td></td>
</tr>
<tr>
<td>Previously diagnosed AF</td>
<td>81 (9%)</td>
<td>39 (11%)</td>
<td></td>
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<tr>
<td>Heart failure</td>
<td>30 (4%)</td>
<td>34 (10%)</td>
<td>&lt;0.001</td>
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<td>Hypertension</td>
<td>446 (53%)</td>
<td>185 (53%)</td>
<td></td>
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<tr>
<td>Diabetes mellitus</td>
<td>91 (11%)</td>
<td>60 (17%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Previous stroke/TIA</td>
<td>80 (10%)</td>
<td>49 (14%)</td>
<td>0.02</td>
</tr>
<tr>
<td>CHADS2 score (mean)*</td>
<td>1.85</td>
<td>2.08</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Values are listed as n (%). AF indicates atrial fibrillation; CHADS2, Congestive Heart Failure, Hypertension, Age>75, Diabetes, Stroke (Doubled); and TIA, transient ischemic attack.

*CHADS2 score was calculated regardless of diagnosis of AF.

The index visit also included recording of a 12-lead ECG. The first 100 12-lead ECGs were interpreted by a study nurse and a cardiologist; the following were interpreted by a study nurse who consulted a cardiologist on demand. The ECG interpretations were also checked by random samples viewed by a cardiologist. ECGs were interpreted only regarding rhythm and rate. Patients who had atrioventricular block grade II or III or a heart rate below 40/min or above 140/min were referred for further evaluation.

If the participant had a pacemaker or implantable cardioverter defibrillator implant, medical records were studied with regard to the presence of atrial high rate episodes (mode switch) caused by AF. If present and lasting more than 30 seconds, intracardiac electrograms recordings were studied.

If a 12-lead ECG revealed previously undiagnosed AF the patient was offered a work-up consisting of blood pressure measurement, blood samples of fasting plasma glucose and thyroid stimulating hormone at a study nurse visit, and an echocardiogram at a cardiologist visit. Serum glucose was not analyzed in previously known individuals with diabetes mellitus. Patients with a previously diagnosed AF without OAC treatment were offered this work-up if not previously performed. After this work-up, the patient was recommended anticoagulation treatment unless there were contraindications. OAC treatment was managed within routine health care and initiated in our OAC clinic.

Extended ECG Recording

Participants with ≥1 additional risk factor beside their age (ie, CHADS2 ≥2), no history of AF, and sinus rhythm on the 12-lead ECG at the index visit were asked to make additional ECG recordings. These were made by a handheld unit, recording ECG via lead I by application of the users’ thumbs (Zenicor Medical Systems AB, Sweden. www.zenicor.se). Via an in-built mobile phone, the ECG is transmitted to a website. The participant was instructed to record 20 or 30 seconds of ECG twice daily during 2 weeks. The duration of the recording was decided by a study nurse who judged the participants ability to handle the ECG recorder. All handheld ECGs were interpreted by a cardiac research nurse and a cardiologist. AF was defined as 30 seconds or ≥2 separate recordings with ≥10 seconds each of irregular rhythm without visible p-waves. The Zenicor ECG system has been validated in previous reports.14,15 Patients with AF were offered a work-up and offered treatment as described above.

In cases were interpretation of handheld ECGs was hampered by poor signal quality, the participants were offered an additional 48-hour Holter recording. In participants who displayed runs of suspected AF on event recording not qualifying according to the definition above, another 2-week period of event recording was offered according to the judgment of the investigating cardiologist. A study flow chart is depicted in Figure 1.

Medical records from inhabitants who did not participate in the screening process were analyzed with respect to AF diagnosis, presence of anticoagulation treatment, and risk factors according to CHADS2. Both hospital and primary care records were studied.

Ethics

The study was approved by the regional health research ethics board at Lund University and conducted according to the declaration of Helsinki. Inhabitants who did not participate in the screening procedure were informed via letter and newspaper advertising that we intended to study their medical records in order to characterize this subgroup. They were given the possibility to withdraw their participation also in this part of the study.

Statistical Methods

Continuous variables are reported as mean and range. Selected proportions are reported with a 95% confidence interval (CI). For continuous variables, Student t test was used. For proportions, Fishers exact test was used. Two-tailed tests were applied. A probability value of < 0.05 was regarded as significant. In the tables, probability values of < 0.05 are listed.

Results

Of 1330 inhabitants invited to participation, 848 (64%) attended the index screening visit. The cardiac research nurse
spent 30 minutes at index visit per patient, including 12-lead ECG registration, and 40 minutes at handheld ECG recording, including ECG interpretation per patient. The cardiologist spent 5 to 10 minutes per patient for second opinion on handheld ECG recordings and 60 minutes per visit, including echocardiography among patients with newly diagnosed AF.

Characteristics including prevalence of AF among attending and not attending inhabitants are described in the Table. A previous diagnosis of AF was confirmed in 81/848 (9.6%; 95% CI, 7.8–11.7). In the group who did not attend the screening, the prevalence of AF was 39/352 (11.1%; 95% CI, 8.2–14.8; n.s.). Nonattendants had a higher prevalence of diabetes mellitus, heart failure, and previous stroke (Table).

Among the 81 patients who were previously diagnosed with AF in the screened group, 35 (43%) were not receiving anticoagulation treatment at study entry. The corresponding figure of the nonscreened group was 56% (n.s.). Of these 35 patients with previously known AF, 17/35 (52%) started anticoagulation treatment.

**ECG Recording – 12-Lead ECG**
Previously unknown AF was diagnosed in 10 patients (1.2%; 95% CI, 0.5–1.9) with a 12-lead ECG. The mean heart rate among these 10 patients was 83/min ranging from 64/min to 102/min. Their mean CHADS<sub>2</sub> score was 1.8.

One participant of 848 was diagnosed with newly detected AV block III on 12-lead ECG and received a pacemaker implant.

**Extended Handheld ECG Recording**
Among the 848 participants there were 419 (49%) with no previous AF, sinus rhythm on 12-lead ECG at index visit, and a CHADS<sub>2</sub> score of ≥2. Of these participants 16 declined further participation or deceased, leaving 403 who underwent ECG event recording with the hand-held ECG. These 403 participants in total recorded 12380 ECG tracings lasting 20 or 30 seconds. The mean number of recordings per patient was 31. Forty patients recorded <28 times, but only 6 patients recorded <20 times. All patients with ambulatory ECG recordings were included in the final analysis. Ten of the 403 recordings had to be completed with a 48-hour Holter recording as a result of difficulties in interpreting the handheld ECG recording and most often with a suspicion of AF. Six of these 10 recordings revealed paroxysmal AF. Because of short episodes of irregular heart rhythm on hand-held ECG raising suspicion of AF but not fulfilling our criteria, 4 participants undertook another period of 2 weeks ECG event recording. One of these 4 recordings revealed paroxysmal AF.

Thus, 30/403 (7.4%; 95% CI, 5.2–10.4) were diagnosed with AF previously unknown. The mean CHADS<sub>2</sub> score of these 30 patients was 2.5, including 6 patients with previous stroke. A description of patient flow and ECG diagnostics is shown in Figure 2.

Most patients with newly detected silent paroxysmal AF were diagnosed during the first days of their 2-week ECG registration period, and 22 of the 24 patient diagnosed with AF on handheld ECG had multiple recordings with AF runs. The duration of ECG recording necessary for detection of AF is shown in Figure 3.

The yield of different methods to identify patients with an indication for OAC treatment and the proportion actually starting OAC treatment is shown in Figure 4.

**Prevalence of AF**
At baseline, 81/848 (9.6%; 95% CI, 7.6–11.6) of participants had a previously confirmed diagnosis of AF. Another 10
patients with AF diagnosed with 12-lead ECG and 30 were diagnosed on handheld or Holter ECG, thus the total prevalence in the screened population was 121/848 (14.3%, 95 CI 12.1–16.8). Among participants without a previously known AF diagnose, 40/767 (5.2%; 95% CI, 3.8–7.7) were diagnosed with new AF. However, only 403 of these 767 participants were examined with extended handheld ECG recording.

Work-Up in Patients With Newly Diagnosed and Previously Diagnosed AF
Among the 40 patients with newly diagnosed AF, 38 underwent echocardiography. Left ventricular Ejection Fraction (LVEF) was slightly reduced (48%) in 1 patient and normal (> 50%) in the remaining patients. Mean LVEF was 60%. A majority (26/38) of these patients had enlarged left atria, defined as an area in apical four-chamber view of 24 cm² or larger. Mean left atrium area was 29 cm². None of these patients revealed significant valvular disease.

Among patients leaving blood samples for glucose, 7/41 (17%) displayed elevated fasting glucose levels, ranging from 6.4 to 7.4 mmol/L. No patients were diagnosed with previously unknown abnormal level of thyroid stimulating hormone.

Discussion
In this study, stepwise risk factor-stratified AF screening in a 75- to 76-year-old population identified a total prevalence of 14%, of which 62% had no OAC treatment. Among participants who were examined with extended handheld ECG recording, 30/403 were diagnosed with previously unknown paroxysmal AF. The amount of OAC treatment on AF indication more than doubled among the screened participants. Screening for AF might become an effective method to prevent stroke by initiation of OAC treatment.

Patient Demographics
More than 60% of our community’s inhabitants aged 75 and 76 participated in the study. Because our invitation process merely included an invitation by letter in combination with the fact that the study was not accompanied by a media campaign, we are pleased with the participation. In an AF prevalence study among 75-year-old persons by Tveit et al,16 82% of the population were examined. However, the Norwegian study used telephone reminders and even home visits for ECG recording.

Interestingly, inhabitants not attending the AF screening program had a higher burden of cardiovascular risk factors than those attending because they had higher mean CHADS² score, affected by higher prevalence of diabetes, heart failure, and stroke. There was no significant difference in baseline AF prevalence among participants and nonparticipants.

ECG Recording
A single 12-lead ECG-recording in a 75-year-old population revealed only 1% of newly diagnosed persistent or permanent AF; a figure also reported from Tveit et al.16 Fitzmaurice et al17 found 2% of new AF using this method.

Intermittent ECG recording yielded 7% new AF diagnoses in our study, comparable with the yield seen in extended ECG recordings in patients with ischemic stroke.18,19 This finding not only underlines the importance of age in AF prevalence, but also that most patients with AF have paroxysmal arrhythmia implicating that a single ECG recording with sinus rhythm has a low negative predictive value in excluding a diagnosis of AF. Hence, among the total of 121 patients with AF in this study, only 35 (29%) had persistent or permanent arrhythmia.

There are plenty of data on different methods of intermittent ECG-recording to detect paroxysmal AF, most of which is derived from studies on patients with cryptogenic ischemic stroke, on patients who underwent AF ablation, or from studies on antiarrhythmic drugs (ie, patient populations with previously diagnosed AF or patients with generally high cardiovascular risk). Studies on ambulant intermittent ECG recordings in the general population are scarce. Continuous ECG monitoring, which would be regarded as the gold standard for ECG screening, reveal previously undiagnosed paroxysmal AF in as much as 20% to 30% new AF diagnoses in populations with high cardiovascular risk.20,21 The evidence for the elevated risk of
ischemic stroke in connection with brief AF episodes is mainly derived from device studies. The AF episodes detected in this study are of larger recording proportion than the episodes detected in device studies. Because the stroke risk is similar in paroxysmal and in permanent or persistent AF, we hypothesize that patients diagnosed with silent paroxysmal AF in this study has a stroke risk similar to patients with clinical evident AF. Further long-term evaluation of our patients will reveal the clinical course of their AF disease.

Technical development has provided several ways of ambulatory ECG recording. Short-term Holter recordings of 24 to 48 h was previously the standard method but is hampered by low diagnostic yield, particularly when looking for paroxysmal AF. In addition, Holter monitoring most often generates a large share of ECG information without diagnostic interest. The efficacy of detecting silent paroxysmal AF by different ambulant ECG monitoring strategies has been outlined by Kirchhof and colleagues. Event recorders and loop recorders, on the other hand, are activated by the patient when symptoms occur. They can also detect and store asymptomatic arrhythmias, particularly when the recorder is continuously monitoring, which in turn requires continuous attachment of the recorder to the patient, which might affect patient compliance during longer recordings. Event recorders not continuously attached to the patient, like the ones used in this study, must be activated and attached by the patient. Event and loop recorders with intermittent and continuously ambulatory ECG recording have demonstrated a better diagnostic yield in comparison with Holter recordings when it comes to detecting paroxysmal AF in stroke patients. Rizos et al reported that automated analysis of continuous ECG recorded in a stroke unit among patients with ischemic stroke or TIA almost tripled the diagnostic yield with regard to detection of silent paroxysmal AF in comparison with 24-hour Holter recording. High diagnostic yield is demonstrated by Mobile Cardiac Outpatient Telemetry (MCOT) and implantable loop recorders in preliminary reports. These 2 modalities are, however, expensive, and implantable loop recorder requires minor surgery. The optimal ambulatory ECG method is yet to be defined; the choice of this study is directed by patient compliance and cost effectiveness. Further screening studies will reveal whether there are more suitable ambulatory ECG modalities.

**Work-Up**

Work-up in patients with newly detected AF yielded a low prevalence of pathological findings, with the exception of 12% elevated fasting glucose levels. No patient had newly detected thyroid disease or structural heart disease besides the more or less expected finding of enlarged left atria. Because we only measured blood pressure at 1 visit, no patient was diagnosed with hypertension in the work up.

**Initiation of OAC**

Patients with a newly diagnosed AF were more inclined to initiate OAC treatment than patients with a known diagnosis of AF. Some of the patients with known AF without OAC treatment had previously been treated with OAC in connection to a cardioversion, after which the OAC treatment was withheld if sinus rhythm seemingly persisted. Patients with known AF without symptoms seemed less declined to restart OAC treatment after its termination. The change in 2010 AF guidelines to recommend long-term OAC after cardioversion if there are thromboembolic risk factors present was not always applied in patients treated according to previous recommendations. Patients with newly diagnosed AF were, on the other hand, easily motivated to commence OAC treatment, despite that most of them were without symptoms.

Undertreatment with OAC in patients with AF and thromboembolic risk factors is very common. Among patients with known AF in our study, 43% were not receiving OAC at study entry. According to nationwide Swedish inpatient statistics, half of patients with AF are never treated with OAC. Similar figures are reported from Go et al and Waldo et al. A markedly better guideline adherence with 85% of patients with AF and risk factors treated with OAC was reported from Tveit et al. Thus, the widespread OAC undertreatment in patients with AF contributes to an unnecessary high stroke incidence.
AF Prevalence

The baseline prevalence of AF in the 75-year-old population in this study (9.6%) is higher than reported from most other studies. A prevalence of 6% to 8% is often reported in this age group, but higher prevalence figures are reported from Nordic countries and from the UK. After including the share of patients who underwent extended ECG recording, the prevalence of AF rose to 14% in our study. Because only half of the screened population was examined with handheld ECG recorder, it is not controversial to speculate that such ECG recording in the entire screened population would have further increased the prevalence.

Screening programs for AF, mainly in the primary care setting, have been reported from the UK. In a large randomised UK study in patients aged >65 years, primary care centers were randomized to systematic or opportunistic screening, which was compared with routine care. In patients invited to systematic screening, 53% registered ECG, and a new AF diagnosis was noted in 52/2357 (2%). The UK study from Fitzmaurice et al lacks data on OAC treatment, both in patients with known AF and in patients newly diagnosed with AF. Data on OAC is of importance for calculations of cost-effectiveness because the majority of costs for AF stem from stroke care. Furthermore, single recordings of 12-lead ECG, as used in the UK study, have severe limitations in detecting paroxysmal AF.

Whether screening for AF in patients with risk factors and initiation of OAC treatment will significantly reduce the incidence of stroke and be cost effective remains to be shown in further studies. However, based on the study from the UK, both American Heart Association and American Stroke Association Primary Prevention of Stroke Guidelines from 2011 and the 2012 Focused Update of AF Guidelines from the European Society of Cardiology recommend opportunistic screening of AF in individuals ≥65 years of age in the primary care setting by pulse palpation followed by ECG recording in case of irregular pulse.

As proposed by our study, systematic screening with extended ECG recording in a 75-year-old population detect a considerable share of high-risk patients with untreated silent AF, partly as a result of the higher prevalence of AF at age 75 years rather than 65 years and partly as a result of the extended ECG recording. The most favorable and cost-effective method for screening of AF is subject to further studies.

Limitations

This study has several limitations. Because our study was carried out in a single community, the results are probably not reproducible in all populations. The generalizability to individuals of other ages and races/ethnicity is uncertain.

The benefit from OAC treatment in patients with AF is so far studied among patients diagnosed on standard (ie, 12-lead) ECG recordings, and the benefit in patients diagnosed with shorter episodes of AF in single-lead ECG recordings remains less studied. However, the following data suggest that these short AF episodes carry a risk similar to permanent and persistent AF:

- short episodes of AF is a common finding in patients suffering from cryptogenic stroke.

Because handheld ECG recording was intermittent, episodes of AF may have remained undiagnosed. Data on risk factors according to CHADS, were self-reported in participants without a diagnosis of AF and collected from medical records in nonparticipants. Both methods of data collection have limitations.

A more comprehensive invitation procedure might have increased participation further. Persons might have been more willing to take part in an established and routinely performed screening program rather than taking part in a clinical study. For instance, 83% of invited 65-year-old men accepted to participate in aortic abdominal aneurysm screening in the Uppland region in Sweden.

Implications

Undiagnosed AF is often the cause behind cryptogenic stroke. It is a challenge of considerable proportions to diagnose patients with silent AF and offer them OAC treatment. Unfortunately, OAC is withheld among half of patients with already known AF and risk factors. This study implies than patients with previously diagnosed and not yet diagnosed AF can get better stroke prevention within a screening program.

Conclusion

Stepwise risk factor-stratified AF screening in a 75-year-old population yields a large share of candidates for OAC treatment on AF indication. Persons not participating had more cardiovascular risk factors than those participating. Patients with paroxysmal AF constitute the majority of the AF population. Repeated handheld ECG recording detected new AF in 7% of participants, and the total prevalence of AF was 14% in the population who participated in the screening program. Most patients with newly diagnosed AF were willing to commence OAC treatment.

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Disclosures

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author). Dr Engdahl has received lecture fees from AstraZeneca and Boehringer Ingelheim and consultant fees from Sanofi Aventis. Dr Rosenqvist has received lecture fees from Sanofi Aventis, Merck Sharpe & Dome, Bayer, Boehringer Ingelheim, Pfizer, and Medtronic, consultant fees from Sanofi Aventis, Merck Sharpe & Dome, Nycomed, Bristol Meyers Squibb, Bayer, and Medtronic, and research grants from Sanofi Aventis, Merck Sharpe & Dome, and boehringer Ingelheim.
References


**CLINICAL PERSPECTIVE**

Atrial Fibrillation (AF) is the most frequently encountered clinical arrhythmia and also a frequent source of cardiac emboli in stroke patients. AF will in some cases be present without any symptoms, often denoted “silent” AF. The prevalence of silent AF in the general population is not known. Silent AF seems to confer a stroke risk similar to symptomatic AF. Oral anticoagulation therapy (OAC) reduces the risk of stroke by 60–65% among patients with AF and thromboembolic risk factors. Unfortunately, approximately half of all patients with clinical apparent AF and risk factors are not treated with OAC, for various reasons. We conducted a screening study in which we invited all inhabitants 75 and 76 years old in the community of Halmstad, Sweden (n=1330). Of the 848 (64%) individuals who responded and recorded a 12-lead ECG, 1% was diagnosed with newly detected persistent or permanent AF. Among the 403 individuals with a CHADS2-score of at least 2 who made an additional intermittent ambulant ECG recording over two weeks, 7% were diagnosed with paroxysmal AF. Among patients with known AF, 35/81 were not on OAC treatment. After screening, 9% of the participants were new candidates for OAC treatment. As a result of the screening intervention, the frequency of OAC treatment more than doubled among the participants.
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