Population screening of 75- and 76-year-old men and women for silent atrial fibrillation (STROKESTOP)

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Atrial fibrillation (AF) is important because it is common and is a major cause of stroke unless treated with oral anticoagulant. The prevalence of AF increases with age as does the risk of stroke. At 75 years the risk from age alone is so high that current guidelines recommend anticoagulation even in the absence of other risk factors. Atrial fibrillation is often asymptomatic and only discovered by chance or when a stroke already has occurred.

We have launched a major screening study for silent AF in which 25 000 Swedes aged 75 and 76 years are randomized to either participate in a screening programme using ambulant intermittent electrocardiogram (ECG) recording to detect silent AF, or act as a control group. Patients in whom AF is detected are offered cardiological examination and anticoagulant treatment according to current guidelines. The cohort and the controls will be followed prospectively for 5 years after the inclusion of the first participant. An interim analysis will be made after 3 years.

Our hypothesis is that screening for AF will reduce stroke incidence in the screened population, and that this screening will prove to be cost effective. Secondary endpoints are: any thromboembolic event, intracranial bleeding, other major bleeding, first ever diagnosis of dementia, death from any cause, and a composite of these endpoints.

Keywords
- Atrial fibrillation
- Silent atrial fibrillation
- Epidemiology
- Stroke
- Bleeding
- Anticoagulation
- Screening

Introduction

Atrial fibrillation (AF) is a common rhythm disorder and a major cause of stroke.1,2 It is associated with increased mortality,3,4 dementia,5,6 reduced quality of life,7,8 and considerable costs for society.9 Oral anticoagulation (OAC) with warfarin, or any of the new oral anticoagulants, is highly effective in reducing AF-related stroke10–13 but many of those who ought to have it14–16 do not receive it.17,18

Stroke risk is not related to whether AF is paroxysmal or permanent,19,20 or symptomatic or asymptomatic.21,22 Even brief, asymptomatic episodes of 5–6 min of AF are associated with increased stroke risk according to pacemaker studies.23,24 Other factors, of which the most important are included in the risk stratification schemes CHADS2 and CHA2DS2-VASc, decide stroke risk in AF.25,26

Silent paroxysmal AF is common but little is known about its prevalence. In a not-yet-completed pilot study in Halmstad in southwestern Sweden 1326 individuals aged 75 or 76 years were invited to participate in a screening study for AF. Of these 64% accepted the invitation. A history of already diagnosed AF was found in 9.4%. Screening with intermittent ambulant electrocardiogram (ECG) has (so far) increased the prevalence estimate to 13.6%. In other words; screening revealed 45% more AF than was previously known. The newly discovered AF in this study consisted mainly of silent paroxysmal AF.

We have therefore launched a mass screening study in order to find out whether it is feasible to identify and offer protection to individuals at high risk of AF-related stroke before it occurs. The World Health Organization lists 10 conditions that should be fulfilled in order to justify mass screening.27 Screening for AF in a...
population of aged 75 and 76 years satisfies most of these conditions (Table 1).

**Hypothesis**

We will test the hypothesis that screening 75- and 76-year-old individuals for AF will reduce stroke incidence cost effectively i.e. that the cost of the screening is either (i) lower than the cost for the avoided strokes, or else (ii) that the cost per quality adjusted life year gained by screening is low compared with other health care expenditures.

**Design**

Randomized, controlled, non-blinded cohort study using nationwide health registers for follow-up.

### Table 1 The Wilson–Jungner criteria for appraising the validity of a screening programme endorsed by World Health Organization 1968

<table>
<thead>
<tr>
<th>WHO criteria</th>
<th>Applicability for AF screening</th>
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<tbody>
<tr>
<td>1. The condition sought should be an important health problem</td>
<td>Yes, AF is a major cause for ischaemic stroke and is associated with increased mortality, morbidity, and reduced quality of life</td>
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<tr>
<td>2. There should be an accepted treatment for patients with recognized disease</td>
<td>Yes, all international guidelines agree that OAC should be given to patients at high risk of AF-related stroke unless the bleeding risk is very high</td>
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<tr>
<td>3. Facilities for diagnosis and treatment should be available</td>
<td>Yes, resources for diagnosis have been provided for the study. Treatment is part of the general health care system open for anyone living in Sweden</td>
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<tr>
<td>4. There should be a recognizable latent or early symptomatic stage</td>
<td>Yes, AF can be detected and prophylactic treatment given before there is a stroke</td>
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<tr>
<td>5. There should a suitable test or examination</td>
<td>Yes, permanent AF is easily detected with a single ECG recording. Intermittent AF requires prolonged ECG surveillance</td>
</tr>
<tr>
<td>6. The test should be acceptable to the population</td>
<td>Yes, ECG is non-invasive and without risk of bodily harm. The response to the invitation will tell if the population finds it acceptable or desirable to participate</td>
</tr>
<tr>
<td>7. The natural history of the condition, including development from latent to declared disease, should be adequately understood</td>
<td>Yes, the relationship between AF and stroke has been intensely studied and it is generally agreed that AF causes stroke</td>
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<tr>
<td>8. There should be an agreed policy on whom to treat as patients</td>
<td>Yes, international guideline documents are quite clear about which patients should be offered OAC</td>
</tr>
<tr>
<td>9. The cost of case finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole</td>
<td>This will be tested by current study</td>
</tr>
<tr>
<td>10. Case finding should be a continuing process and not a ‘once and for all’ project</td>
<td>Yes, if the main hypothesis of the study is confirmed, it will provide an argument for extending the screening both in time, and geographically</td>
</tr>
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</table>

**Ethics**

The study has been approved by the Ethics Committee of Stockholm (DNR 2011–1363–31/3).

**Method**

**Study population**

All individuals born in 1936 or 1937 and living in Stockholm County, or in the southwestern region of Halland, have been identified by means of the Swedish 10-digit personal identification number of which the first 6 digits provide the birth date (n = 25 415 at the end of 2010).

**Considerations regarding the optimal screening age**

Screening for silent AF is not practically feasible in an unselected population where the prevalence of AF is low. The ideal screening population would therefore be a group with high prevalence of AF, and at high risk of stroke unless given protective treatment. Screening of 75- and 76-year-olds satisfies these prerequisites in a way that few other groups do. Other groups may have similar stroke risk e.g. 65-year-olds with diabetes and hypertension, but the expected prevalence will be lower. Admittedly, both prevalence and stroke risk are higher in older age groups, but...
postponing detection of AF would also mean that some will suffer stroke that might have been averted by an earlier screening.

Another reason for choosing 75 years is that these patients have just reached the age when age alone, without other risk factors, is considered as sufficient cause for OAC treatment by the current European guidelines on the management of AF.\(^\text{15}\)

The 75 years age group is also much representative for AF patients in Sweden where the median age in the hospital-diagnosed AF is 76 years for men, and 81 years for women.\(^\text{28}\) At the age of 75 years the remaining life expectancy in Sweden is 11.0 years for men, and 13.1 years for women according to the most recent report from Statistics Sweden. The reason why we did not study a random sample of elderly patients of different ages is that we wanted to test a screening concept that could be repeated annually as an ongoing project if the screening should turn out to be successful. A random sample of elderly individuals would not suit that purpose.

Randomization

The populations in Stockholm (n = 21 060) and in Halland (n = 4 355) have been randomized into two groups of equal size in each region. One group serves as the intervention group, the other serves as the control group (Figure 1).

Sample size calculations

The sample size has been calculated on the following assumptions; the annual stroke risk with AF without OAC is 7% (5 year stroke risk 30%). The protective effect of oral anticoagulants is 70%, thus the expected annual stroke rate in treated patients is 2% (5 year stroke risk 10%). The annual stroke rate in this age group in the general population is 1.2% (5 year stroke rate 6%). Based on the response rate in the pilot study in Halland we expect that 55% of those invited will participate in the screening. In order to be able to detect a difference in stroke incidence after 5 years between the screened group and the controls at 5% two-sided significance level with 80% statistical power we need to include 11 397 in each study arm (Fisher’s approximation). The study has randomized 12 707 individuals into each arm, which should be sufficient.

Screening procedure

Subjects randomized to intervention are invited to a screening centre run by the Karolinska Trial Alliance (KTA) in central Stockholm, or to one of six local screening centres run by the regional hospital in Halland. Each week ~375 patients are invited to the screening in Stockholm and 25 patients to the same in Halland. Non-responders receive a second letter of invitation after a few weeks.

At the screening centre patients are informed about the study, both orally and in writing, and are asked to sign a document of informed consent before entering the study. Patients are asked if they have, or have had AF, stroke, transient ischaemic attack (TIA), systemic emboli, heart failure, hypertension, diabetes, or vascular disease. They are also asked if they are taking OAC. Those who already have a diagnosis of AF and are on OAC treatment will have no further investigations (Figure 2).

Electrocardiogram monitoring

Patients in sinus rhythm on the first visit, who have no previous history of AF, are equipped with a handheld device for intermittent ECG recordings during 2 weeks. We use a one-lead ECG recorder from Zenicor (www.zenicor.com) with an integrated mobile phone that automatically transmits the ECG to a database. The patient places his or her thumbs on the device twice daily or does so in the case of palpitations or symptoms suggestive of arrhythmia. Each ECG strip is 30 s. This device has been evaluated for AF screening and has shown higher sensitivity for detection of silent AF than conventional 24 h Holter recordings.\(^\text{29–31}\)

In the case of inconclusive ECG tracings, patients are offered an additional 24 h Holter recording. If no AF is detected during these procedures that individual is considered as free from AF.

Detection threshold

To be counted as AF there has to be at least one full 30 s recording with AF, or a minimum of two episodes with AF lasting 10–29 s during 2 weeks of intermittent recording corresponding to a total recording time for each patient of ~15 min. In the ASSERT trial 6 min of AF during 3 months of continuous recording was shown to be associated with increased stroke risk,\(^\text{23}\) which is an even lower AF burden than we are using for our study. In a recent substudy to ASSERT it has also been shown that increasing the minimum duration criterion did not increase the estimate of the relative risk of stroke or embolism.\(^\text{32}\)

However, we do not know if patients with such brief episodes benefit from anticoagulation, which is one of the questions that we hope our study will to be able to answer. In the analyses patients will be stratified according to the number of recordings showing AF during the screening period in order to decide the most appropriate detection threshold for future screening studies.

Intervention

All individuals with newly detected AF are offered individualized follow-up by a cardiologist to assure that adequate treatment, according to current European guideline recommendations.
Follow-up includes echocardiography, assessment of blood pressure, renal function, and evaluation of individual net benefit from OAC treatment. Individuals with previously known AF, who are not taking OAC, are also referred to a cardiologist for evaluation and appropriate treatment. In the case the recordings show potentially dangerous arrhythmias, these patients will promptly be taken care of by cardiologists.

Inclusion period
Screening started in Stockholm on 5 March 2012 and in Halland on 12 March 2012. Most of the screening will take place during 2012, but will continue into 2013 until all randomized individuals have received invitations and have had an opportunity to participate.

Duration of follow-up
The screened population, the invited non-responders, and the controls will be followed prospectively for 5 years after the inclusion of the first participant. An interim analysis will be made after 3 years in order to make it possible to terminate the study early if the results indicate a clear benefit from screening, or if there is an unacceptable increase of serious bleeding events in the screened population.

Endpoints
Our main endpoint is ischaemic stroke. Pre-specified secondary endpoints are: any thromboembolic event, intracranial bleeding, other major bleeding, death from any cause, and a composite of these. Furthermore, we will study whether OAC treatment is protective against AF-associated dementia. There are indications that this may be the case, but this has never before been studied in a randomized controlled trial. Analyses will be made on intention to treat.

Health economy
Time in hospital during follow-up will be studied for screened patients, for non-responders, and for the control group. A health economic assessment will be made using information from previous studies of the cost of stroke in Sweden. This assessment will combine the within trial results concerning health effects and resource consumption with long-term (20-year) costs and effects of screening estimated within a previously presented decision analytic model.

Detection of events and comorbidity
Information about events during follow-up, as well as information about comorbidities and previous diseases, will be identified through the National Patient Register using appropriate codes in the International Classification Diseases, 10th revision (ICD-10). The codes that will be used are shown in Table 2. This information will also be used for the calculation of individual risk scores for stroke and bleedings according to the risk stratification schemes CHADS2, CHA2DS2-VASc, and HAS-BLED (REF). Information about deaths occurring during the study period will be obtained from the Swedish population register.

Validity of the patient register
The Swedish patient register includes information about diagnoses and procedures, and dates of admission, and discharge, for all inpatient care in Sweden since 1987. From 2001, the register comprises outpatient visits from both private and public specialist care, and from 2005 also comprises diagnoses in primary care, although this has not yet been fully implemented.

The patient register misses information about principal diagnosis in 0.5–0.9% of hospitalizations in somatic care. A diagnosis of AF or flutter in the register has a positive predictive value in 97% of the cases. A diagnosis of stroke or TIA is correct in 98.6% of the cases and the proportion of stroke events correctly identified (sensitivity) ranges from 84 to 98% in validation studies.
Information about medication during follow-up will be obtained from the National Prescription Drugs register. All pharmacies in the country are linked to this register which automatically collects information about date, dosage, and quantity for all dispensed prescriptions. This information will be available for all individuals, screened, non-responders, and controls alike, and will make it possible to include exposure to anticoagulant drugs as covariates in the analyses.

Exposure to warfarin

New oral anticoagulants have fixed dosages, which makes it easy to determine drug exposure from the dispensed quantities in drug register. Determining exposure to warfarin is much more complicated since dosages vary both between individuals and over time. Warfarin exposure will therefore be approximated in the following way: each prescription is assumed to cover the consumption for 3 months (Swedish regulations state that each prescription should be for the estimated consumption during no > 3 months). If a new purchase of warfarin is made within 90 days of the foregoing, treatment is considered as continuous. If the purchase occurs after 90 days, but before 180 days a grace period will be applied (e.g. the patient may have a very low dose) and treatment will be considered as continuous. If there is no purchase within 180 days, warfarin exposure will be considered as terminated 90 days after the previous purchase. If there is another purchase after day 180, a new exposure period will start.

Clinical relevance

Atrial fibrillation may be an even more important cause of stroke than previously assumed, due to silent AF. It could be argued that permanent screening programmes should be initiated if the study shows cost-effectiveness and health benefits for 75- and 76-year-old who participate. In this project lies, in our opinion, a potential for a major reduction of stroke in the elderly population.

Conflict of interest: LF is a consultant for sanofi-aventis, Boehringer Ingelheim, and Bristol-Myers Squibb. JE has received lecture fees from AstraZeneca and Boehringer Ingelheim, and consultant fees from sanofi-aventis. LL is a consultant for Boehringer Ingelheim. MR is a consultant to Sanofi-Aventis and Nycomed, Sweden. He has also been National Coordinator for the RECORD, REALISE, and ARISTOTLE study. ES and VF declare no conflict of interest.

Funding

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