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The SilenT AtRial FIBrillation (STAR-FIB) study programme – design and rationale

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Summary

AIMS OF THE STUDY: Anticoagulation of patients with screen-detected atrial fibrillation may prevent ischaemic strokes. The STAR-FIB study programme aims to determine the age- and sex-specific prevalence of silent atrial fibrillation and to develop a clinical prediction model to identify patients at risk of undiagnosed atrial fibrillation in a hospitalised patient population.

METHODS: The STAR-FIB study programme includes a prospective cohort study and a case-control study of hospitalised patients aged 65–84 years, evenly distributed for both age and sex. We recruited 795 patients without atrial fibrillation for the cohort study (49.2% females; median age 74.8 years). All patients had three serial 7-day Holter ECGs to screen for silent atrial fibrillation. The primary endpoint will be any episode of atrial fibrillation or atrial flutter of ≥30 seconds duration. The age- and sex-specific prevalence of newly diagnosed atrial fibrillation will be estimated. For the case-control study, 120 patients with paroxysmal atrial fibrillation were recruited as cases (41.7% females; median age 74.6 years); controls will be randomly selected from the cohort study in a 2:1 ratio. All participants in the cohort study and all cases were prospectively evaluated including clinical, laboratory, echocardiographic and electrical parameters. A clinical prediction model for undiagnosed atrial fibrillation will be derived in the case-control study and externally validated in the cohort study.

CONCLUSIONS: The STAR-FIB study programme will estimate the age- and sex-specific prevalence of silent atrial fibrillation in a hospitalised patient population, and develop and validate a clinical prediction model to identify patients at risk of silent atrial fibrillation.

Keywords: *atrial fibrillation, screening, gender, paroxysmal, subclinical, silent, prospective, cohort, case-control, hospitalised*

Introduction

Atrial fibrillation increases the risk of arterial thromboembolism and is associated with increased morbidity and mortality [1]. The guidelines of the European Society of Cardiology advise anticoagulation therapy in the presence of atrial fibrillation and a CHA_2DS_2-VASc score ≥1 in men and ≥2 in women [2]. The European guidelines and the AF-Screen International Collaboration recommend opportunistic screening by pulse taking or ECG strip for individuals aged ≥65 years, and systematic screening in patients aged ≥75 years or at high stroke risk [2, 3]. The incidence of screen-detected atrial fibrillation, i.e., atrial fibrillation diagnosed by specific screening efforts, is consistently higher with systematic screening than with opportunistic or no screening [4, 5]. Most patients with screen-detected atrial fibrillation by repeat patient-activated ECG or Holter-ECG have a clinically relevant atrial fibrillation burden [6]. Therefore, patients with screen-detected atrial fibrillation are likely to have the same benefit from anticoagulation therapy as those with incidentally detected atrial fibrillation and symptomatic atrial fibrillation, with significant reductions in stroke and death [3, 7].

Screen-detected atrial fibrillation has to be differentiated from atrial fibrillation detected by implantable devices such loop recorders, pacemakers and implantable cardioverter defibrillators (ICDs) [8–11]. These devices can record single atrial fibrillation episodes as short as 2 minutes and may detect atrial fibrillation in patients with a very low atrial fibrillation burden. The European guidelines recommend anticoagulation therapy in implanted device-detected atrial high-rate episodes only after ECG confirmation of atrial fibrillation. In the absence of further

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evidence, no clear recommendation for anticoagulation therapy is stated in the guidelines regarding atrial high-rate episodes without ECG confirmation of atrial fibrillation [2, 9]. Adequately powered, randomised, controlled trials of anticoagulation therapy in patients with both screen-detected [12–14] atrial fibrillation as well as implanted device-detected [15, 16] atrial high-rate episodes are underway and will ultimately settle the question.

The prevalence of silent atrial fibrillation, i.e., undiagnosed or subclinical atrial fibrillation, depends on the setting, screening method, population studied and individual patient characteristics [3, 17, 18]. Most atrial fibrillation screening studies have been carried out in primary care clinics, in pharmacies, by other non-medical healthcare practitioners or in the general population. Age, biomarkers and other patient characteristics have been included in various prediction models for screen-detected atrial fibrillation [8, 10, 11, 19–22]. These prediction models, together with the reported prevalence of screen-detected atrial fibrillation, form the basis for the design of large-scale, cost-efficient and successful screening programmes.

However, hospitalised patient populations have generally been exempt from screening studies, although they have a high prevalence of already known atrial fibrillation [23]. The prevalence of silent atrial fibrillation may be high in this patient population and justify intensified screening efforts. Prediction models for screen-detected atrial fibrillation developed and validated in other settings may need to be adapted for hospitalised patient populations.

Methods

The STAR-FIB study programme comprises a hospital-based, prospective cohort study and a hospital-based, case-control study. The programme has four aims:

1. To determine the age- and sex-specific, and overall prevalence of silent atrial fibrillation in the prospective cohort study.
2. To develop and internally validate a clinical prediction model based on clinical, laboratory, echocardiographic and electrical parameters in the case-control study to discriminate between cases with paroxysmal atrial fibrillation and controls without atrial fibrillation.
3. To validate the clinical prediction model in the prospective cohort study in predicting the detection of silent atrial fibrillation during the screening period.
4. To assess the long-term incidence of newly diagnosed atrial fibrillation in the prospective cohort study and validate the clinical prediction model in the extended follow-up of the prospective cohort study.

Between19 January 2015 and 26 June 2019, we recruited inpatients aged ≥65 to <85 years from the Departments of General Internal Medicine, Cardiology and Ophthalmology at our tertiary care hospital for both the prospective cohort and case-control study. The study was approved by the independent research ethics committee of the Canton of Bern (KEK-BE 257/14). All study participants provided written informed consent.

Prospective cohort study

Patients were eligible for the prospective cohort study if they were in sinus rhythm and did not have a previous diagnosis of atrial fibrillation (see table 1 for detailed eligibility criteria). Patients with repeat admissions were evaluated only during their first admission. During recruitment periods, all inpatients of a targeted sex- and age-specific subgroup were evaluated, with reasons for ineligibility for the cohort study and unwillingness to participate recorded in a recruitment log.

We intended to include 100 males and 100 females in each of four age bands of ≥65 to <70, ≥70 to <75, ≥75 to <80, and ≥80 to <85 years, corresponding to a total of 800 patients in the prospective cohort study. Recruitment of male participants aged <80 years was faster than recruitment of the remaining subgroups. We therefore randomly selected calendar weeks during which males aged <80 years would be recruited, whereas the remaining subgroups were continuously recruited. Recruitment was capped for each subgroup once the necessary number of participants was reached.

There were 44,636 hospital admissions during periods of study recruitment. Of these, we assessed 11,470 patients for eligibility for the cohort study (fig. 1). We excluded 2525 patients because of known atrial fibrillation (22.0%) and 3112 patients for other, prespecified exclusion criteria (27.1%; table 1). Of the remaining 5833 eligible patients, 2551 patients could not be approached for study participa-

Table 1: Overview of inclusion and exclusion criteria.

	Cohort study	Cases of case-control study
Inclusion criteria	Eight subgroups, stratified for age and gender (N=100 for each subgroup) – Males aged ≥65 and <70 years – Males aged ≥70 and <75 years – Males aged ≥75 and <80 years – Males aged ≥80 and <85 years – Females aged ≥65 and <70 years – Females aged ≥70 and <75 years – Females aged ≥75 and <80 years – Females aged ≥80 and <85 years	– Patients aged ≥65 and <85 years – Diagnosis of paroxysmal atrial fibrillation (not solely in the setting of thyrotoxicosis, severe systemic infection or after major cardiac surgery) – ECG documentation of atrial fibrillation – In sinus rhythm at baseline visit
Specific exclusion criteria	– Diagnosis of atrial fibrillation – Patients with an indication for long–term anticoagulation therapy	– History of catheter ablation of atrial fibrillation – Non-paroxysmal atrial fibrillation
General exclusion criteria	– History of acute coronary syndrome, percutaneous coronary revascularisation, transcutaneous aortic valve replacement, major cardiac or non-cardiac surgery or hospitalisation due to heart failure within the previous 3 months – Patients with planned percutaneous coronary revascularisation, transcutaneous aortic valve replacement, or major cardiac or non-cardiac surgery – Patients on class I or class III antiarrhythmic drugs – Patients with a projected life expectancy of less than 1 year – Patients incapable of providing written informed consent	

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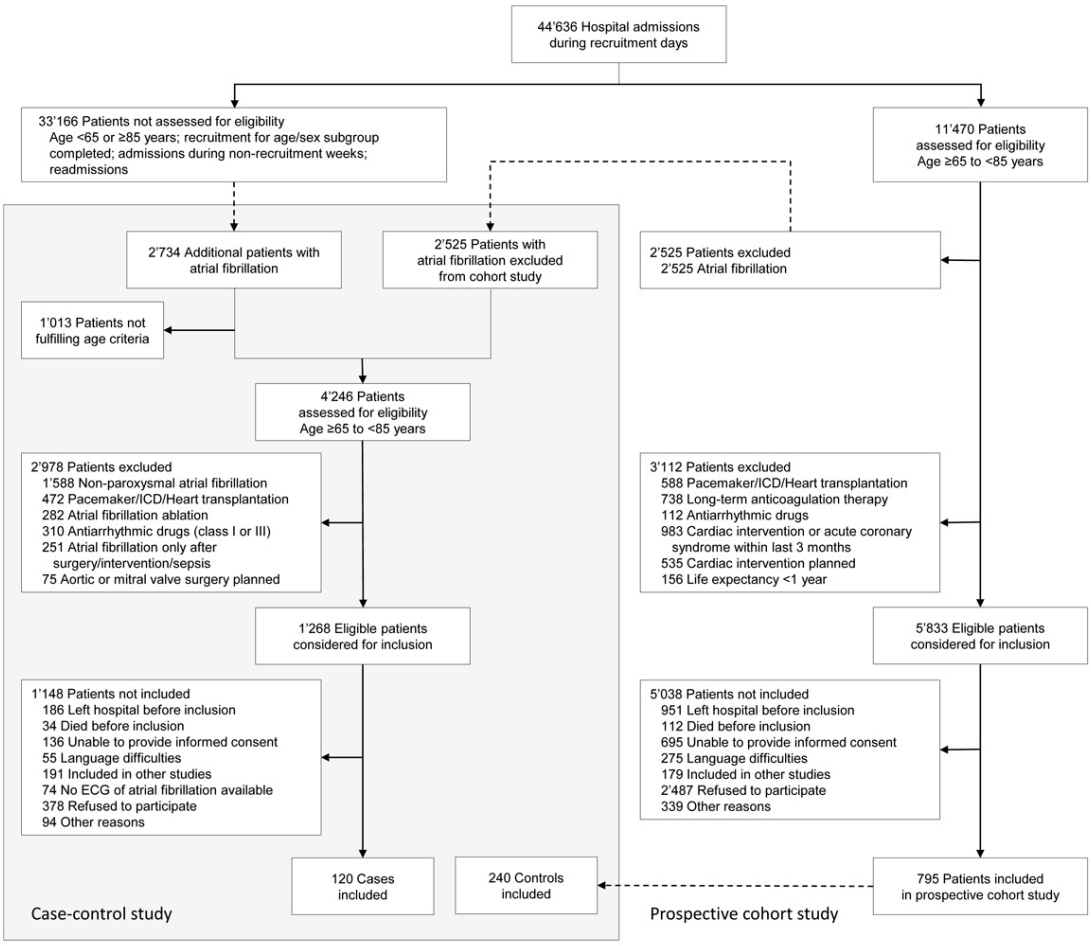
Figure 1: Flow chart showing recruitment of participants for the cohort study and for the case-control study (grey shaded area).

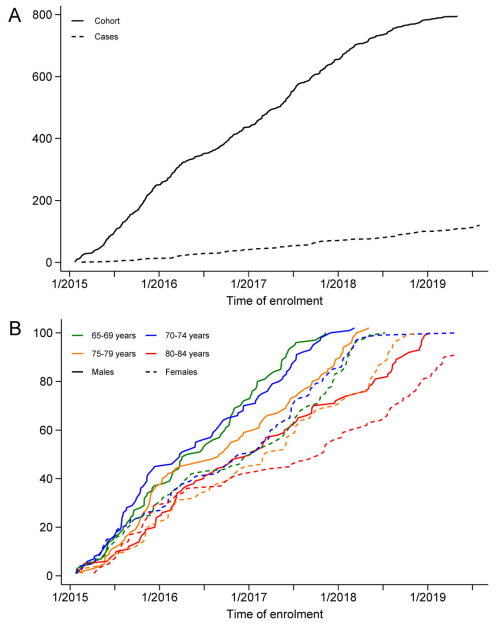


tion for various reasons (43.7%; fig. 1), 2487 refused to participate (42.6%) and 795 consented to inclusion in the prospective cohort study (13.6%).

We included 391 females (49.2%) and 404 males. We were unable to reach the necessary target number of females aged ≥80 years during the recruitment period; only 91 participants were recruited (fig. 2). Conversely, 102 males were recruited in age groups ≥70 to <75 and ≥75 to <80 years. The median age of the entire cohort was 74.8 years (interquartile range 69.9 to 79.7). Figure 2 shows the cumulative recruitment over time overall (top) and by age and sex (bottom).

The primary endpoint of the cohort study is a diagnosis of atrial fibrillation or atrial flutter of more than 30 seconds duration during a 7-day Holter ECG, on a rhythm strip or on any conventional 12-lead ECG up to the last follow-up visit, according to the definition of the European atrial fibrillation guidelines [2]. All primary endpoints are adjudicated by two experienced electrophysiologists. Included participants underwent three 7-day Holter ECGs to screen for silent atrial fibrillation. The first 7-day Holter ECG was recorded upon hospital discharge. The second and third 7-day Holter ECGs were recorded during two further study visits 2 and 4 months after hospital discharge – the first 24 hours of the second 7-day Holter ECG were analysed separately as a 24-hour Holter ECG to calculate premature atrial complex count and number, and the longest du-

Figure 2: Cumulative recruitment over time overall for the cohort study and for the cases of the case-control study (top) and by age and sex subgroups for the cohort study (bottom).



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ration of atrial tachycardias. If atrial fibrillation was diagnosed, the subsequent 7-day Holter ECGs were cancelled, except for the 24-hour Holter ECG during the 2-month visit. In the case of an incidental finding during a 7-day Holter ECG, the patients were notified and offered specialist evaluation. Complete recordings of all 7-day Holter ECGs were analysed using the Pathfinder SL® software (Spacelabs Healthcare, Issaquah, WA, USA) with additional manual confirmatory analysis by experienced study staff, as previously described [24]. Specificity and sensitivity of the software were 80.2% and 98.5%, respectively, in previous analyses by our group [24]. All software-detected episodes of atrial fibrillation were manually confirmed or rejected by experienced study staff supervised by a board-certified electrophysiologist. To further improve sensitivity, all Holter recordings were additionally analysed manually to identify episodes of atrial fibrillation missed by the software. The number and duration of atrial fibrillation episodes, as well as the number and duration of non-sustained and sustained atrial tachycardias, were assessed manually. Premature atrial complexes were defined as a reduction of the RR interval of ≥25% compared with the previous normal RR interval and with normal or aberrant QRS morphology. Premature atrial complex count was assessed automatically after manual confirmation of normal or aberrant QRS morphology. For logistical reasons, study staff could not be blinded to baseline characteristics, including age and sex.

During the 2-month study visit, a 12-lead ECG, a signal-averaged ECG, measurement of blood pressure and heart rate, advanced echocardiography and blood sampling were performed. Examinations were only performed if participants were in stable condition, without intercurrent illness (table 2). Appendix 1 describes all study procedures in detail. All cohort participants and/or their physicians will subsequently be contacted after 30 and 60 months during an extended follow-up to ascertain the following clinical endpoints: diagnosis of atrial fibrillation and/or atrial flutter; death; anticoagulation therapy; acute ischaemic stroke and/or transient ischemic attack; pacemaker or ICD implantation.

Case-control study

Cases were included from the same source population as the participants in the prospective cohort study. To be eligible as cases, participants had to have ECG-documented paroxysmal atrial fibrillation but be in sinus rhythm at the time of inclusion (see table 1 for inclusion and exclusion criteria). We assessed 5259 patients with atrial fibrillation according to medical records for eligibility as cases for the case-control study; 2525 of these had been excluded from the cohort study (48.0%) and 2734 were directly recruited from the remainder of the source population (52.0%; fig. 1). We excluded 1013 patients because they did not fulfil age criteria (19.3%) and 2978 because they fulfilled other, prespecified exclusion criteria (56.6%; table 1). Of the remaining 1268 eligible patients, 770 patients could not be approached for study participation for various reasons (60.7%; fig. 1), 378 refused to participate (29.8%), and 120 consented to be included as cases for the case-control study (9.5%). Of these, 50 were females (41.7%), and the median age was 74.6 years (interquartile range 69.3 to 79.2). All cases were in sinus rhythm at inclusion and an ECG with documented atrial fibrillation available. Figure 2 shows the cumulative recruitment over time for the cases of the case-control study (top).

Cases were scheduled for a single study visit within 3 months after hospital discharge, if in stable condition without intercurrent illness. During this visit, a 12-lead ECG, a signal-averaged ECG, measurement of blood pressure and heart rate, advanced echocardiography, blood sampling and a 24-hour Holter ECG were performed (table 2). Appendix 1 describes all study procedures in detail.

Participants in the prospective cohort study will serve as controls. Within each sex and age subgroup and clinical department (internal medicine, ophthalmology and cardiology), cases and controls will be randomly selected in a 1:2 ratio. To minimise spectrum bias [25, 26], participants in the prospective cohort study will be eligible as controls irrespective of the presence or absence of atrial fibrillation found during follow-up.

Sample size considerations

For the prospective cohort study, we assumed an incident diagnosis of silent atrial fibrillation in 5% of participants, based on the study by Engdahl et al. [27], with a strong positive association with age. With 200 patients included in each age subgroup (100 males and 100 females each), we will be able to estimate the frequency of incident diagnoses of atrial fibrillation in each age subgroup with sufficiently narrow 95% confidence intervals (CIs). The anticipated frequency will increase from 1.0% in participants aged 65 to 69 years (95% CI 0.3 to 3.6%) to 10.0% in participants aged 80 to 84 years (95% CI 6.6% to 14.9%).

Table 2: Overview of study procedures.

	Cohort study	Cases of case-control study
Baseline visit	– Informed consent – Baseline case report form	– Informed consent – Baseline case report form – Blood samples – Advanced echocardiography – ECG and signal-averaged ECG – 24-hour Holter ECG
Hospital discharge	– First 7-day Holter ECG	– n/a
2-month visit	– Second 7-day Holter ECG – Blood samples – Advanced echocardiography – ECG and signal-averaged ECG	– n/a
4-month visit	– Third 7-day Holter ECG	– n/a
30 months follow-up	– Telephone interview	– n/a
60 months follow-up	– Telephone interview	– n/a

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For the case-control study, the analysis of 120 cases and 240 controls, using analytical weights to achieve independence of the age/sex distribution from the recruitment strategy (see below), will afford more than 80% power to detect an odds ratio of 1.8 for the association of paroxysmal atrial fibrillation with a dichotomous risk factor, which has a prevalence of 40%, at a two-sided alpha of 5%.

Statistical analyses

Using data from the recruitment log, we will estimate the age- and sex-specific, and overall prevalence of any type of atrial fibrillation and of paroxysmal atrial fibrillation with 95% CIs for the source population of inpatients aged ≥65 to <85 years hospitalised at the participating departments between 19 January 2015 and 26 June 2019. To derive these estimates, we will use extrapolations based on age/sex-specific recruitment fractions, assuming that those assessed for eligibility and those not assessed were similar in terms of baseline characteristics and consent rates. We will consider only the first hospital admission per patient during the study period. For each age/sex subgroup, the variances of prevalence estimates will be obtained as the sum of the relevant variances of estimates used to derive prevalence [28]. Then, we will use fixed-effect linear regression with the inverse of the variance as analytical weights to derive p-values for difference in prevalence between males and females, and p-values for trend across age subgroups.

For the prospective cohort study, we will estimate the age- and sex-specific prevalence of newly diagnosed atrial fibrillation and corresponding 95% CIs based on the number of participants in the prospective cohort study diagnosed with atrial fibrillation up to the last follow-up visit. To derive the age/sex-specific prevalence, and the overall prevalence of newly diagnosed atrial fibrillation, reflecting the true age and sex distribution of potentially eligible inpatients hospitalised during the entire recruitment period, we will use the svy family of commands in Stata that take the complex recruitment strategy into account based on appropriate analytical weights [29]. The use of analytical weights will result in independence of estimates from the age/sex distribution targeted during recruitment. Weights will be calculated separately for each age-, sex- and department-specific subgroup, dividing the total number of 1620 possible recruitment days during the study by the number of days used to recruit participants in the respective subgroup. A hypothetical participant of a specific subgroup, who we recruited during a cumulative period of 600 days, would therefore receive twice the analytical weight of a hypothetical participant in another subgroup, who we recruited during a cumulative period of 1200 days.

The case-control study will be analysed using a weighted logistic regression model based on an analogous approach [29] to achieve independence of the age/sex distribution from the recruitment strategy of controls and from the matching strategy. We will perform univariate analyses to examine associations between clinical, laboratory, echocardiographic and electrical parameters and atrial fibrillation. The final multivariable model intended for clinical prediction will be based on stepwise backward selection using the Akaike Information Criterion to eliminate variables, irrespective of significance levels of the observed association [30]. Discrimination of the final clinical prediction model will be internally validated based on a minimum of 200 bootstrap samples with replacement [30], and externally validated based on the primary endpoint of the prospective cohort study. Participants of the prospective cohort study will be eligible as controls in the case-control study irrespective of the presence or absence of atrial fibrillation found during follow-up, therefore incorporation bias should not occur [31]. External validation will subsequently be repeated using data from the extended follow-up of the prospective cohort study. Parameters in the case-control study will be ranked based on univariate analyses, using the absolute magnitude of the log odds ratio comparing the presence or absence of a dichotomous parameter, or the log odds ratio for two standard deviations increase of a continuous parameter to ensure comparability of scales [32]. We will account for missing data in the baseline covariates using multiple imputation to create 20 imputed datasets, with baseline characteristics and presence or absence of screen-detected atrial fibrillation as variables in the imputation model. All associations will be reported as odds ratios with corresponding two-sided 95% CIs and two-sided p-values. All statistical analyses will be performed using Stata 15.1 (StataCorp, College Station, TX, United States).

Discussion

Strategies to diagnose silent atrial fibrillation and initiation of anticoagulation therapy are essential for stroke prevention. European and international guidelines advocate systematic screening in patients at high stroke risk [3, 33]. The screening yield depends on the prevalence of silent atrial fibrillation in the screened population and the diagnostic performance of the test [34]. Single time-point screening by ECG recording is the most widely used screening tool for silent atrial fibrillation, with a screening yield of 1% overall and 1.4% in subjects aged >65 years [35]. With more advanced screening strategies, using Holter monitoring, ECG patches [5, 36], repeat ECG self-recording with dedicated devices [27, 37] or smartphone-based gadgets [38, 39], the screening yield increases to 5% and higher, depending on the population studied, monitoring duration and frequency. With implanted cardiac monitors, typically used in populations at high risk of stroke, screening yield reaches 20–30% if monitoring is continued for 2–3 years [8, 10, 11, 40, 41]. Atrial fibrillation screening studies have mostly been performed in larger communities [27, 36, 37], primary care [4], outpatient clinics [9], pharmacies [42] or consumer volunteers [38, 39]. No screening study in hospitalised patient populations has been reported, except for one study of single time-point screening comparing two handheld ECG devices [43]. In this study, atrial fibrillation was detected in one of 206 patients without previously known atrial fibrillation on a cardiology ward and in two of 80 patients on a geriatric ward.

The STAR-FIB study will be the first study to report the prevalence of silent atrial fibrillation in a hospitalised patient population aged ≥65 years using a more advanced screening strategy. Although implantable cardiac monitors may be able to more precisely estimate the prevalence of silent atrial fibrillation, they are invasive and costly. Repeat 7-day Holter ECGs are a noninvasive, affordable and widely available alternative, providing continuous record-

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ings of two ECG channels for 7 days. According to data from implanted cardiac monitors, the sensitivity to diagnose silent atrial fibrillation with three repeat 7-day Holter ECGs is about 33%, whereas the sensitivity is only about 8% with twice daily recordings of a 30 seconds ECG strip for 2 weeks [17]. A screening strategy of three repeat 7-day Holter ECGs within 4 months therefore represents a reasonable balance between sensitivity and costs.

Most screening studies are not able to adequately describe the prevalence of already known atrial fibrillation in the screened population, because of a selection bias [27, 37]. However, the prevalence of known atrial fibrillation is important, as it may also influence the prevalence of silent atrial fibrillation. The prevalence of atrial fibrillation increases with age and several studies have reported an association of age with prevalence of silent atrial fibrillation. However, no study has investigated in detail the interplay of age with the prevalence of known atrial fibrillation and prevalence of silent atrial fibrillation. Through the recruitment log of the STAR-FIB cohort study we will be able to precisely estimate the age- and sex-specific prevalence of known atrial fibrillation in the source population of the cohort study, to which the prevalence of silent atrial fibrillation will add.

Prediction models may be useful to increase the yield of a screening programme and to improve its cost-efficiency by devoting screening efforts to subpopulations at higher risk of silent atrial fibrillation [34]. Existing prediction models mostly use age, biomarkers and other, widely available clinical patient characteristics [8, 10, 11, 19–22, 44, 45]. The STAR-FIB study will expand these prediction models to a hospitalised patient population. In addition to clinical patient characteristics and biomarkers, the STAR-FIB study will explore other advanced echocardiographic and electrical markers, such as atrial electromechanical delay [46], excessive atrial ectopy [47], or signal-averaged P-wave duration [48], as risk factors for the detection of undiagnosed atrial fibrillation.

The STAR-FIB study programme aimed at simultaneously recruiting participants for a hospital-based prospective cohort study and a case-control study. For the cohort study, we included 795 patients, using a complex recruitment strategy that ensured approximately equal numbers of males and females, and even age distributions between 65 and 84 years. The representation of octogenarians and females is one of the unique features of STAR-FIB. The 120 cases for the case-control study originate from the same source population as the cohort study and are representative of patients with undiagnosed atrial fibrillation, as they all had paroxysmal atrial fibrillation, were not on antiarrhythmic drugs, without previous ablation procedures and in sinus rhythm when undergoing assessments. Controls will be participants of the cohort study, randomly selected on a 2:1 basis with cases. Incorporation bias [31] will be avoided by considering participants of the prospective cohort study as controls, irrespective of the subsequent detection of atrial fibrillation during follow-up. The complex recruitment strategy will be taken into account by applying an appropriate weighting scheme for the analysis of the case-control study to achieve independence of the age/sex distribution from recruitment and matching strategies.

The STAR-FIB study programme has several limitations. First, it is a single centre study. Second, results will only be applicable to a hospitalised patient population aged between 65 and 84 years. Third, additional, external validation of the results will be necessary in independent patient populations. Fourth, the implantation of a loop recorder would be the gold standard to screen for silent atrial fibrillation and with repeat 7-day Holter ECGs the prevalence of silent atrial fibrillation will be underestimated.

In conclusion, the STAR-FIB study programme will clarify the prevalence of silent atrial fibrillation in a hospitalised patient population aged 65 to 84 years. It will thoroughly investigate various clinical, electrical, laboratory and echocardiographic parameters of atrial function and develop a clinical prediction model for hospitalised patients at risk of undiagnosed atrial fibrillation.

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Potential competing interests

Fabian Noti has received speaker honoraria from Abbott/SJM and Medtronic, consulting honoraria from Medtronic, travel grants from Abbott/SJM, Medtronic, Boston Scientific and Spectranetix, and educational grants from Spectranetix. The spouse of Jens Seiler is an employee of Boston Scientific. Samuel Baldinger has received research support from Biosense-Webster and travel grants from Biosense Webster and Boston-Scientific. Andreas Haeberlin has received travel grants from Medtronic. He is a consultant for Cairdac, co-founder and head of Act-Inno, and has received research funding from Novartis. Drahomir Aujesky has received consulting honoraria from Bayer AG and Sanofi. Hildegard Tanner has received travel support/educational grants from Abbott/SJM and Biosense-Webster. Tobias Reichlin has received speaker/consulting honoraria or travel support from Abbott/SJM, Astra Zeneca, Brahms, Bayer, Biosense-Webster, Biotronik, Boston-Scientific, Daiichi Sankyo, Medtronic, Pfizer-BMS and Roche, all for work outside the submitted study. He has received support for his institution's fellowship program from Abbott/SJM, Biosense-Webster, Biotronik, Boston-Scientific and Medtronic for work outside the submitted study. Peter Jüni serves as unpaid member of steering group or executive committee of trials funded by Abbott Vascular, Astra Zeneca, Biotronik, Biosensors, St. Jude Medical, Terumo and The Medicines Company, has received research grants to the institution from Appili Therapeutics, Astra Zeneca, Biotronik, Biosensors International, Eli Lilly, The Medicines Company, and honoraria to the institution for participation in advisory boards and/or consulting from Amgen, Ava and Fresenius, but has not received personal payments by any pharmaceutical company or device manufacturer. Laurent Roten has received speaker honoraria from Abbott/SJM and consulting honoraria from Medtronic.

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Appendix 1

Study procedures

Baseline case report form

The following clinical parameters will be assessed: age; gender; hypertension; diabetes mellitus; history of ischaemic stroke or transient ischaemic attack; coronary artery disease (defined as ≥50% coronary artery stenosis; previous myocardial infarction; previous coronary artery bypass grafting or coronary angioplasty); peripheral arterial disease; history of congestive heart failure; weight; height; body mass index; CHADS score; CHA_2DS_2-VASc score.

Blood sampling

The following laboratory parameters will be assessed: creatinine; haemoglobin; high-sensitivity C-reactive protein (hsCRP); brain natriuretic peptide (BNP); high-sensitivity troponin T (hsTnT). In the cohort study the fibrin D-dimer levels will additionally be assessed.

Electrocardiography

A standard 12-lead ECG will be recorded with assessment of the RR, PR and QT interval, QRS width, presence of left or right bundle branch block. The QTc interval will be calculated using the Bazett formula.

Signal-averaged ECG (SAECG)

A signal-averaged ECG of the P-wave will be recorded by averaging 250 sinus rhythm P-waves. The total duration of the signal-averaged P-wave will be measured.

A signal-averaged ECG of the QRS-complex will be recorded by averaging 150 sinus rhythm QRS complexes. The total duration of the signal-averaged QRS complex will be measured.

Clinical parameters

Blood pressure and resting heart rate will be measured.

Echocardiography

The left ventricular dimensions and wall thickness will be determined in the parasternal long-axis view, as well as left atrial diameter and 2D- and 3D-volume from the parasternal long-axis view, 4- and 2-chamber view. The left ventricular ejection fraction will be assessed from the apical 4- and 2-chamber views using Simpson's rule. The mitral valve inflow pattern will be visualised by pulsed-wave Doppler (E/A ratio; deceleration time). Myocardial velocities obtained with tissue Doppler will be recorded using a standard pulsed-wave Doppler technique with the sample volume placed at the junction of the left ventricular lateral wall with the mitral lateral annulus in the 4-chamber view. The time interval from the onset of the P-wave in lead II to the peak of the atrial systole (A') at the lateral side of the left atrium will be measured (electromechanical delay; PA-TDI).

7-day Holter ECG

Seven-day continuous ECGs will be recorded with the Lifecard CF® (Spacelabs Healthcare, Issaquah, WA, United States). This recording system allows the continuous recording of two ECG channels for up to 7 days. Complete recordings will be analysed with the Pathfinder SL® software (Spacelabs Healthcare, Issaquah, WA, USA) with additional manual confirmatory analysis. The main endpoint will be a diagnosis of atrial fibrillation with a duration of ≥30 seconds.

24-hour Holter ECG

The same recording system as for the 7-day Holter ECG will be used (see above). In the 24-hour Holter ECG, the number of atrial premature complexes will be counted. Atrial premature complexes are defined as a reduction of the RR interval of ≥25% compared with the previous normal RR interval and with normal or aberrant QRS morphology. The minimum RR coupling interval as well as the relative reduction in the coupling interval from the previous normal RR interval (coupling interval index [CI-index]) will be calculated. The presence of non-sustained or sustained atrial tachycardia will be noted and, if present, the number of atrial tachycardias and longest duration in seconds counted. Non-sustained atrial tachycardia will be any supraventricular tachycardia of ≥3 beats up to 30 seconds duration and sustained atrial tachycardia will be any supraventricular tachycardia of ≥30 seconds duration.

30- and 60-month follow-up

The following clinical endpoints will be assessed during follow-up by a telephone interview with all cohort patients and/or their physicians: diagnosis of atrial fibrillation and/or atrial flutter; death; anticoagulation therapy; acute ischaemic stroke or transient ischaemic attack; pacemaker or ICD implantation.

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