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CLINICAL RESEARCH
Atrial fibrillation

Stepwise mass screening for atrial fibrillation using N-terminal B-type natriuretic peptide: the STROKESTOP II study

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Aims To study the prevalence of unknown atrial fibrillation (AF) in a high-risk, 75/76-year-old, population using N-terminal B-type natriuretic peptide (NT-proBNP) and handheld electrocardiogram (ECG) recordings in a stepwise screening procedure.

Methods and results The STROKESTOP II study is a population-based cohort study in which all 75/76-year-old in the Stockholm region ($n = 28\,712$) were randomized 1:1 to be invited to an AF screening programme or to serve as the control group. Participants without known AF had NT-proBNP analysed and were stratified into low-risk (NT-proBNP <125 ng/L) and high-risk (NT-proBNP ≥125 ng/L) groups. The high-risk group was offered extended ECG-screening, whereas the low-risk group performed only one single-lead ECG recording. In total, 6868 individuals accepted the screening invitation of which 6315 (91.9%) did not have previously known AF. New AF was detected in 2.6% [95% confidence interval (CI) 2.2–3.0] of all participants without previous AF. In the high-risk group ($n = 3766/6315$, 59.6%), AF was diagnosed in 4.4% (95% CI 3.7–5.1) of the participants. Out of these, 18% had AF on their index-ECG. In the low-risk group, one participant was diagnosed with AF on index-ECG. The screening procedure resulted in an increase in known prevalence from 8.1% to 10.5% among participants. Oral anticoagulant treatment was initiated in 94.5% of the participants with newly diagnosed AF.

Conclusion N-terminal B-type natriuretic peptide-stratified systematic screening for AF identified 4.4% of the high-risk participants with new AF. Oral anticoagulant treatment initiation was well accepted in the group diagnosed with new AF.

Keywords Atrial fibrillation • N-terminal B-type natriuretic peptide • Screening • Stroke • Oral anticoagulants

Introduction

Atrial fibrillation (AF) is an important health problem that regardless of symptoms increases stroke risk.[1] A considerable share of patients have no symptoms from AF[2] and this poses a major difficulty when detecting new AF. Oral anticoagulant (OAC) treatment reduces stroke-risk by 60–70% in individuals at increased risk.[3]

Since AF is a common, chronic and progressive and commonly asymptomatic disease, with increased risk of serious but treatable complications it meets most of the World Health Organization's criteria for population screening as defined by the Wilson and Jungner in 1968.[4] However, there is yet no data on the long-term influence on hard endpoints from AF screening. The yield and feasibility of using intermittent handheld electrocardiogram (ECG) recordings in

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What's new?

- N-terminal B-type natriuretic peptide-stratified systematic screening for atrial fibrillation (AF) identified high-risk individuals with untreated AF.
- N-terminal B-type natriuretic peptide had better AF prediction performance than the CHA_2DS_2-VASc score.
- The implementation of an automated electrocardiogram (ECG) interpretation algorithm reduced ECG-related workload within the screening process.

population-based AF screening has previously been reported,[5] where screening with handheld ECG increased the prevalence of known AF by ~30%.

N-terminal B-type natriuretic peptide (NT-proBNP) levels are elevated in patients with AF, and previous studies have shown that NT-proBNP elevation can predict development of AF.[6] In patients with known AF, NT-proBNP levels are associated with risk of stroke.[7]

A previous study showed that using NT-proBNP 125 ng/L as cut-off showed a negative predictive value of 92%. Using this cut-off suggested that 35% fewer participants would have to undergo ECG monitoring,[8] while possibly still identifying those at highest risk for stroke. The STROKESTOP II trial was designed with the aim to study if NT-proBNP stratified AF screening will reduce stroke in the intervention group. The study design has previously been published.[9]

The aim of this analysis from the interventional arm of the STROKESTOP II trial is to report data regarding AF detection and prediction using NT-proBNP levels and initiation and 1-year adherence to OAC treatment. ClinicalTrials.gov identifier: NCT02743416.

Methods

Study population and invitation procedure

The study design has been previously reported.[9] In brief, all 75/76-year-old individuals ($n = 28\,712$) residing in the Stockholm region were identified using their personal identification number by Statistics Sweden. A stratified, gender- and aged-based 1:1 randomization provided a control and intervention group ($n = 14\,356$). No information or intervention was provided to the control group. After control of vital status, the intervention group was invited to screening via mail with a maximum of two reminders for non-responders. There were no inclusion criteria other than year of birth and residence in the Stockholm region for those in the intervention group and no exclusion criteria.

Screening protocol

Invitees in the intervention group were invited to the closest of three screening sites. All participants received oral and written information and signed informed consent documents. Participants were asked to self-report their medical history regarding prior AF diagnosis, OAC treatment, thromboembolic risk factors according to CHA_2DS_2-VASc, pacemaker treatment, palpitation symptoms, weight, and height. No further examination was performed in participants with known AF.

Using point-of-care analysis (Cobash 232, Roche diagnostics, Rotkreutz, Switzerland), NT-proBNP was analysed from venous blood samples in participants without known AF. Depending on NT-proBNP results participants were stratified into low-risk (NT-proBNP <125 ng/L) and high-risk (NT-proBNP ≥125 ng/L) groups. These cut-off values were predefined based on previous findings.[8]

All participants without known AF recorded an index-ECG consisting of a 30-s ECG using a handheld one-lead device (Zenicor 2 device, Zenicor Medical Systems, Stockholm, Sweden) regardless of NT-proBNP value. If AF was detected, participants were referred to a cardiologist. If index-ECG showed sinus rhythm, participants in the high-risk group were offered 2-week intermittent ambulatory handheld ECG recordings using the Zenicor II device and were instructed to perform ECG recordings four times daily, at morning, noon, afternoon, and evening. Participants in the low-risk group underwent no further investigation if their index ECG revealed sinus rhythm.

Participants with the following findings were also offered further investigations:

- N-terminal B-type natriuretic peptide ≥900 ng/L and without previously known heart failure were referred to a cardiologist in addition to the ECG screening.
- Individuals with known AF without OAC treatment were referred to cardiologist for assessment.
- In case of new AF diagnosis during the screening procedure, participants were referred to a cardiologist for a standard follow-up during which OAC treatment was initiated unless contraindicated.

Diagnostic modalities

The Zenicor II ECG device[10] records a 30-s ECG in lead I and automatically transmits the encrypted recording to a password protected database. The Zenicor device has been extensively validated and used in several previous AF screening studies.[11]

A computerized algorithm was used to identify ECG recordings with sinus rhythm or minor artefacts.[12] These were not manually interpreted systematically, only a random sample was scrutinized by cardiologists. All ECGs identified by the algorithm as abnormal were manually interpreted by specially trained nurses, and all pathological ECGs were scrutinized by a cardiologist. Participants with insufficient signal quality (less than 50% of recordings interpretable) on handheld ECG or possible positive finding like atrial flutter were offered a 5-day Holter recording. Participants with episodes of irregular supraventricular tachycardia—consisting of at least 5 b.p.m. with a heart rate of at least 100 b.p.m. suggestive of AF but with a duration less than 30 s—were followed-up in a sub-study using extended ECG recording with a continuous event recorder (R-test 4 evolution, Novacor, Rueil-Malmaison, France) for 14 days. The medical records of participants with pacemaker treatment were studied for atrial high rate episodes with a duration of at least 6 min and available device electrograms.

Outcome measures

Atrial fibrillation was defined as at least one episode of completely irregular rhythm with no organized or regular atrial activity and a duration of 30 s on one-lead ECG. Participants with AF diagnosed using handheld ECG did not undergo any additional ECG investigation. Initiation of OAC treatment was defined as an issued prescription after a cardiologist visit and adherence to treatment at 1-year follow-up.

Statistical methods

Baseline characteristics including age, sex, height, weight, and previous medical history according to CHA_2DS_2-VASc were summarized using frequencies for categorical variables and means with standard deviation (SD) for continuous variables. For CHA_2DS_2-VASc and NT-proBNP, both mean (SD) and median with 25th and 75th percentiles were calculated. The following tests were used for differences among groups: the χ^2 test was used for categorical variables, Student's *t*-test was used for height and weight, and Mann–Whitney *U* test was used for CHA_2DS_2-VASc and NT-proBNP, which showed a skewed distribution. The relations between clinical variables and logarithmically transformed NT-proBNP with new AF were investigated in the group with NT-proBNP ≥ 125 ng/L using multivariable logistic regression. A *P*-value of <0.05 was regarded as significant. Analyses were performed using STATA/MP 15.1 (StataCorp, College Station, TX, USA).

Ethics

The study complies with the Declaration of Helsinki, and the protocol was approved by the regional ethics committee in Stockholm (DNR 2015/2079-31/1). Written informed consent was obtained from all participants in the screening programme.

Results

Participation and patient characteristics

The number of inhabitants identified as eligible for participation in this screening study was 14 356. Excluded from analysis were 486 individuals that had died or migrated before receiving an invitation. In all, 6868 (6868/13870, 49.5%) individuals accepted the invitation. The cumulative response to the three invitations was 37%, 47%, and 49.5%. The consent to participate was later withdrawn by 27 individuals. The study flow chart is shown in *Figure 1*.

Baseline characteristics for participants in the low-risk group and the high-risk group are shown in *Table 1*. Heart failure, hypertension, vascular disease, female gender, CHA_2DS_2-VASc, palpitations, and OAC use were more common in the high-risk group than in the low-risk group.

Electrocardiogram recordings

Compliance to ECG recordings was high with a mean of 49 recordings of the 56 (87.5%) instructed in high-risk participants. Only 137 participants of 3766 (3.6%) recorded less than 50% of the stipulated amount of ECG recordings. The total number of ECG recordings was 187 353. Of all the ECG recordings, 22 729 (12.1%) were interpreted as abnormal by the algorithm. Extended Holter monitoring was performed in 81 (2.2%) of the participants due to poor signal quality. No sustained ventricular arrhythmias were recorded on handheld ECG.

N-terminal B-type natriuretic peptide

N-terminal B-type natriuretic peptide was analysed in 6315 participant. Values ≥125 ng/L were found in 3766 (59.6%) of the participants. N-terminal B-type natriuretic peptide values ≥900 ng/L were found in 102 (1.6%) participants without previously known heart failure.

Atrial fibrillation detection

All but one of the participants with new AF were in the high-risk group, resulting in a detection rate of 164/3766 [4.4%, 95% confidence interval (CI) 3.7–5.1] in the high-risk group. In total, new AF was detected in 165/6315 (2.6%, 95% CI 2.2–3.0) participants without previously known AF.

A previous diagnosis of AF was present in 553 patients (8.1%). Baseline characteristics for participants with known AF, new AF, and no AF are shown in *Table 2*.

In 29 (29/165, 18%) participants, a new diagnosis of AF was made on the index-ECG. In addition, 136 more cases were identified during extended ECG screening.

The sensitivity and specificity for NT-proBNP 125 ng/L as cut-off for the index-ECG screening and for other clinically relevant cut-points recommended for heart failure diagnostics in acute and non-acute settings[13,14] are shown in *Table 3*.

The addition of screening four times a day compared to twice daily yielded 17 participants who had AF registered exclusively during mid-day recordings, i.e. at 9 am–6 pm. Extended ECG investigation was performed in 263 participants due to poor signal quality, possible atrial flutter, or shorter bursts of possible AF on handheld ECG. New AF was diagnosed in 30 (30/263, 11.4%) out of those cases. Scrutinizing the medical records of participants with pacemakers did not reveal any new or untreated AF. In total, the screening procedure resulted in an almost 30% increase in AF prevalence among participants, or an absolute increase in AF prevalence from 8.1% to 10.5%.

Use and initiation of oral anticoagulants

In the 165 participants with new AF, 156/165 (94.5%) were initiated on OAC treatment. A majority, 499 out of 553 (90.2%) of those with previously known AF were on OAC treatment. Of those not on OAC, 10 were not interested in referral for cardiologist assessment, but in those referred, 31/44 (70.5%) were initiated on OAC treatment. At 1-year follow-up, 96% of the patients initiated on OAC treatment were still adherent to the treatment. A detailed description of the 32 participants not receiving OAC treatment is found in a Supplementary material online, *Table S1*. In total, 219/6868 (3.2%) participants were diagnosed with new or previously untreated AF and thus eligible for OAC therapy.

None of the patients were referred for electrical cardioversion nor ablation after their initial cardiologist assessment. Pacemaker was implanted in six patients due to higher atrioventricular-block and two were referred for left atrial appendage occlusion because of OAC contraindication. Thus, only eight participants (0.1%) underwent invasive downstream therapy due to the screening procedure.

Risk factors—prediction of atrial fibrillation

The 29 participants diagnosed with new AF on their index-ECG had significantly higher NT-proBNP than those diagnosed with new AF during the following 2 weeks, with a median NT-proBNP levels of 1308 ng/L [interquartile range (IQR) 663–2180 ng/L] and 305 ng/L (IQR 199–522 ng/L), respectively, *Figure 2*.

The burden of AF represented by the number of AF episodes during the screening period did not have a linear association with NT-proBNP levels. In the highest quartile of NT-proBNP (NT-proBNP >353 ng/L), 25/945 (2.6%) participants had AF on the index-ECG and an additional 51/945 (5.4%) had AF diagnosed during prolonged screening. Of those diagnosed with AF on the index-ECG 25/29

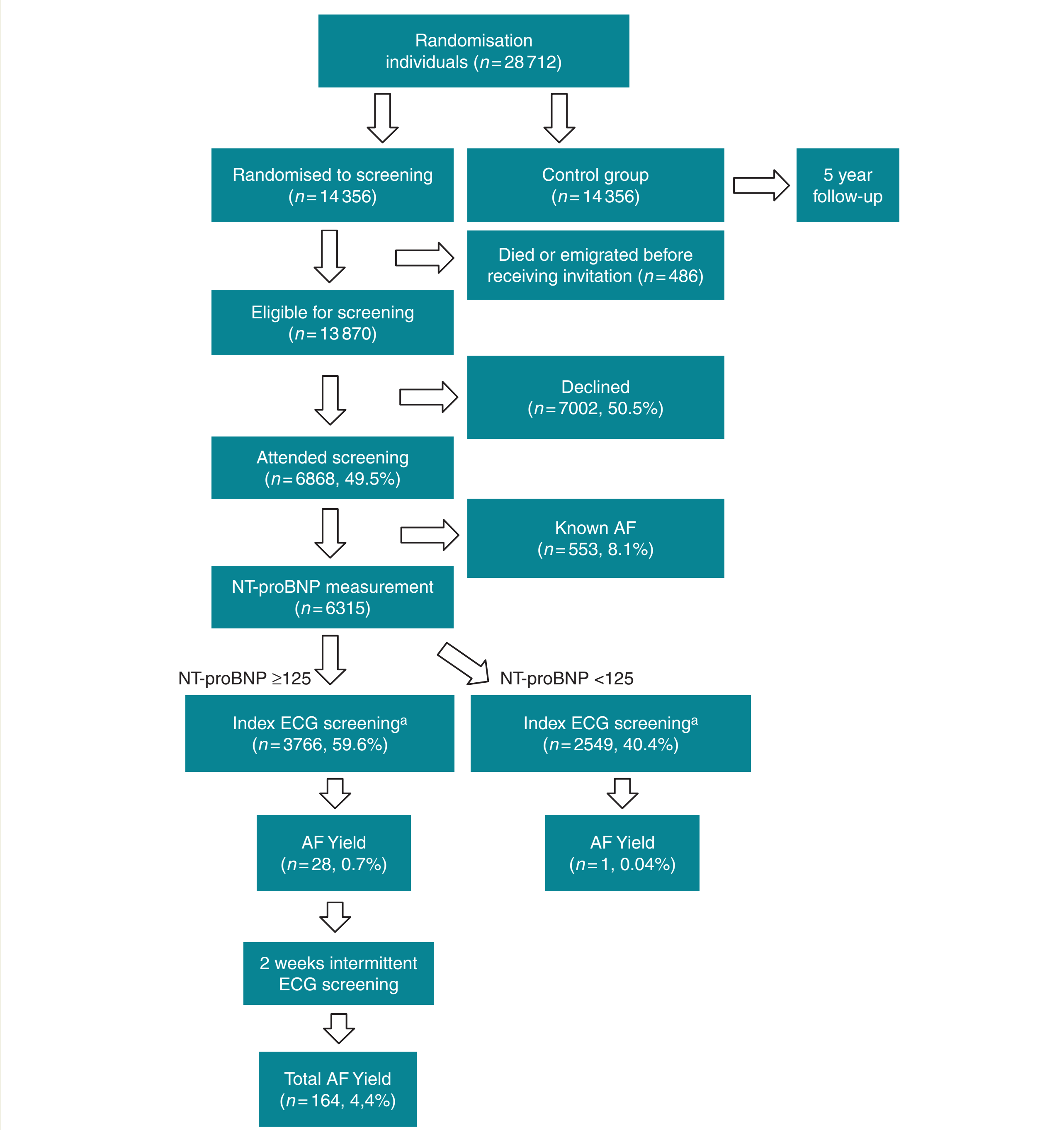

Figure 1 Study flow chart. [a]Regardless of NT-proBNP level participants without known AF recorded a 30-s ECG using a handheld one-lead device (Zenicor II device, Zenicor Medical Systems, Stockholm, Sweden). AF, atrial fibrillation; ECG, electrocardiogram; NT-proBNP, N-terminal B-type natriuretic peptide.

(86%) were in the highest NT-proBNP quartile as well as 51/136 (38%) participants with AF diagnosed during screening. *Figure 3* shows the predicted probability of having a new AF for each NT-proBNP quartile in the high-risk group.

The distribution of new AF in relation to NT-proBNP levels and CHA_2DS_2-VASc scores is depicted in *Figure 4*. The interquartile odds ratio from NT-proBNP quartile 1 to 4 was 4.19 (95% CI 2.54–6.93).

The strongest predictor in the high-risk group for new AF was NT-proBNP as shown in *Table 4*.

Discussion

In this prospective cohort study, we found a high proportion of screening-detected AF in participants with increased NT-proBNP

Table 1 Baseline characteristics at study entry in all participants, low- and high-risk groups

	All participants	Low-risk group NT-proBNP < 125 ng/L (n = 2549)	High-risk group NT-proBNP ≥ 125 ng/L (n = 3766)	P-value low risk vs. high risk
Congestive heart failure, n (%)	168 (2.4)	9 (0.4)	69 (1.8)	<0.001
Hypertension, n (%)	3548 (51.7)	1251 (49.1)	1975 (52.4)	0.009
Diabetes mellitus, n (%)	785 (11.4)	280 (11.0)	412 (10.9)	
Prior stroke/TIA, n (%)	556 (8.1)	180 (7.1)	278 (7.4)	
Vascular disease, n (%)	474 (6.9)	95 (3.7)	297 (7.9)	<0.001
Female gender, n (%)	3708 (54.0)	1260 (49.4)	2247 (59.7)	<0.001
CHA_2DS_2-VASc				
Mean ± SD	3.4 ± 1.0	3.3 ± 1.0	3.5 ± 1.0	<0.001
Median (IQR)	3 (1)	3 (1)	3 (1)	
OAC treatment, n (%)	602 (8.8)	27 (1.1)	76 (2.0)	0.003
Systolic BP, mean ± SD		138 ± 17.2	140 ± 19.1	<0.001
Diastolic BP, mean ± SD		82 ± 9.6	81 ± 10.7	<0.001
Height (cm), mean ± SD				
All		170 ± 9.0	170 ± 9.1	
Women		164 ± 6.1	164 ± 6.1	
Men		177 ± 6.4	178 ± 6.6	<0.001
Weight (kg), mean ± SD				
All		76 ± 13.1	73 ± 13.7	<0.001
Women		70 ± 12.0	68 ± 12.2	<0.001
Men		81 ± 11.5	81 ± 12.0	
BMI (kg/m^2), mean ± SD				
All		26 ± 3.8	25 ± 4.0	<0.001
Women		26 ± 4.2	25 ± 4.4	<0.001
Men		26 ± 3.3	26 ± 3.4	

BMI, body mass index; BP, blood pressure; IQR, interquartile range; NT-proBNP, N-terminal B-type natriuretic peptide; OAC, oral anticoagulation; SD, standard deviation; TIA, transient ischaemic attack.

levels. In our analysis, NT-proBNP was the strongest independent predictor for new AF diagnosis. N-terminal B-type natriuretic peptide could hence be useful as a stratifying tool for AF screening.

Using NT-proBNP for risk-stratification led to a similar proportion of new AF being detected with only 59% of the participants recording ECG's for 2 weeks, as compared to our previous trial, STROKESTOP I,[11] in which all the participants underwent the 2-week extended ECG screening procedure. Participants in the high-risk group had significantly higher stroke risk according to the CHA_2DS_2-VASc score. Initiation of oral anticoagulation treatment was well accepted among participants with newly diagnosed AF.

Participation and patient characteristics

Screening uptake in this study was moderate. Using the experience from our previous trial,[15] several measures were taken that aimed to increase uptake. A website (www.strokestop2.se) was launched with general information about AF, information on the screening procedure in the nine most common languages in Sweden and information about the study team. We used three different screening sites in order to shorten travel distance for participants. Despite these measures uptake was lower than we had anticipated although it was significantly higher compared to the uptake within the Stockholm site in STROKESTOP I.[15]

Only 27 participants (0.4%) withdrew from the current study after the initial visit, indicating that this screening procedure is highly acceptable to participants.

Electrocardiogram recordings

In comparison to our previous AF screening trial, STROKESTOP I,[11] we doubled the ECG-recording frequency from twice daily to four times daily. This resulted in 17 cases of new AF that would not have been diagnosed using twice-daily recordings. There was high adherence to the ECG recording protocol, with a mean of 87.5% of the stipulated recordings per participant compared to 75% of the participants in the REHEARSE-AF trial.[16] The amount of new AF was also similar in the studies and one might argue that frequent handheld ECG-recordings during a limited time results in higher compliance compared to infrequent long-term handheld ECG-recordings with no difference in AF detection.

The number of participants referred for Holter recording because of poor signal quality was modest and similar to prior studies with the same device. A similarly low proportion of unreadable recordings was reported from the REHEARSE-AF trial.[16] Using the validated ECG-interpreting algorithm,[12] the ECG-interpreting workload was reduced by over 85% compared to the STROKESTOP I trial.[11]

Table 2 Baseline characteristics at study entry in the groups with known AF, new AF, and no AF

	Known AF ($n = 553$)	*P*-value known vs. new AF	New AF ($n = 165$)	*P*-value new vs. no AF	No AF ($n = 6150$)
Congestive heart failure, *n* (%)	90 (16.2)	<0.001	7 (4.2)	<0.001	71 (1.2)
Hypertension, *n* (%)	322 (58.2)		90 (54.5)		3136 (51.0)
Diabetes mellitus, *n* (%)	93 (16.8)	0.015	15 (9.1)		677 (11.0)
Prior stroke/TIA, *n* (%)	98 (17.7)	0.001	11 (6.7)		447 (7.3)
Vascular disease, *n* (%)	82 (14.8)	0.012	12 (7.3)		380 (6.2)
Female gender, *n* (%)	201 (36.3)	0.012	78 (47.3)	0.038	3429 (55.7)
CHA_2DS_2-VASc					
Mean ± SD	3.8 ± 1.3	<0.001	3.4 ± 1.1		3.4 ± 1.0
Median (IQR)	4 (2)		3 (1)		3 (1)
OAC treatment, *n* (%)	499 (90.2)	<0.001	4 (2.4)		99 (1.6)
Systolic BP, mean ± SD			136 ± 19.2	0.039	139 ± 18.3
Diastolic BP, mean ± SD			81 ± 11.5		81 ± 10.2
NT-proBNP					
Mean ± SD			657 ± 843	<0.001	212 ± 317
Median (IQR)			325 (495)		149 (173)
Height (cm), mean ± SD					
All			172 ± 9.1	0.005	170 ± 9.
Women			165 ± 6.4	0.036	164 ± 6.1
Men			178 ± 6.8	0.050	177 ± 6.5
Weight (kg), mean ± SD					
All			77 ± 14.9	0.005	74 ± 13.5
Women			71 ± 15.7	0.036	69 ± 12.1
Men			82 ± 12.3		81 ± 11.8
BMI (kg/m^2), mean ± SD					
All			25.9 ± 4.5		25.6 ± 3.9
Women			26.2 ± 5.5	0.018	25.4 ± 4.3
Men			25.7 ± 3.4		25.8 ± 3.4

AF, atrial fibrillation; BP, blood pressure; BMI, body mass index; IQR, interquartile range; NT-proBNP, N-terminal B-type natriuretic peptide; OAC, oral anticoagulation; SD, standard deviation; TIA, transient ischaemic attack.

Table 3 Sensitivity and specificity for detecting AF on index-ECG for NT-proBNP levels 125 ng/L, 300 ng/L, 450 ng/L, 900 ng/L, and 1800 ng/L

Level of NT-proBNP cut-point (ng/L)	Sensitivity (%)	Specificity (%)
125	97	41
300	86	80
450	86	91
900	59	98
1800	34	100

AF, atrial fibrillation; ECG, electrocardiogram; NT-proBNP, N-terminal B-type natriuretic peptide.

N-terminal B-type natriuretic peptide and atrial fibrillation detection

The number of participants who had to undergo intermittent 2-week ECG recordings was reduced by 41% by the use of NT-proBNP pre-test but the overall proportion of newly diagnosed AF was still similar to the STROKESTOP I[11] trial, where all participants underwent 2-week intermittent ECG recordings, even when correcting for the 17 cases found during the mid-day recordings. Both studies resulted in an increase of AF prevalence of ∼30%. This agreed with the pilot trial[8] preceding this study. Previously undiagnosed AF was found in 2.6% of the participants without previous AF, suggesting that the number needed to screen in this population to diagnose one new case of AF would be 38 (1/0.026). Our findings support prior reports[17] on the association between NT-proBNP and incident AF. Although the low-risk group was not investigated with repeated ECG recordings and hence there is risk of undetected AF in that group, the proportion of participants diagnosed with AF on index ECG was markedly higher in the high-risk group, suggesting the discriminative performance of NT-proBNP.

N-terminal B-type natriuretic peptide has repeatedly been shown to be one of the strongest predictors for AF development.[6] When adding NT-proBNP to the multivariable analyses, heart failure became an insignificant factor for AF prediction. This finding is similar to findings in other studies by Hijazi *et al.*,[18] in which clinical factors such

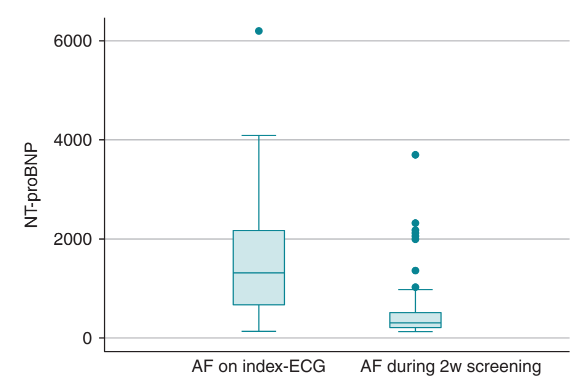

Figure 2 NT-proBNP levels in participants with new AF on index-ECG vs. 2 weeks screening. The 29 participants diagnosed with new AF on the index-ECG had a median NT-proBNP level of 1308 ng/L (IQR 663–2180 ng/L) and those with new AF during the following 2 weeks 305 ng/L (IQR 199–522 ng/L). AF, atrial fibrillation; ECG, electrocardiogram; IQR, interquartile range; NT-proBNP, N-terminal B-type natriuretic peptide.

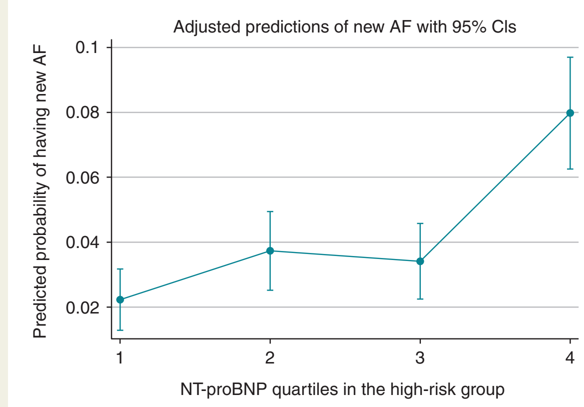

Figure 3 Predicted probability of new AF diagnosis in relation to NT-proBNP quartiles in the high-risk group. 1, quartile 1 (NT-proBNP 125–171 ng/L); 2, quartile 2 (NT-proBNP 171–236 ng/L); 3, quartile 3 (NT-proBNP 237–352 ng/L); and 4, quartile 4 (NT-proBNP 353–9000 ng/L). AF, atrial fibrillation; NT-proBNP, N-terminal B-type natriuretic peptide.

as heart failure, diabetes, hypertension, other cardiovascular diseases, or gender no longer added prognostic value after adding biomarkers to models concerning risk of stroke, such as the age, biomarkers, clinical history (ABC)-stroke risk score.[18] Our results extend these findings and highlight the important addition of biomarkers such as NT-proBNP for improved AF screening.

Use and initiation of oral anticoagulants

Among patients diagnosed with new AF, almost 95% accepted initiation of OAC and of those 96% were still adherent to the treatment at 1-year follow-up. This is in accordance with our previous results from AF screening trials.[11] This high acceptance was probably due to a predefined care pathway within the trial. Referring the patient outside the screening context has been associated with lower OAC initiation rates.[19] A dedicated research team taking responsibility for the entire screening process could of course affect the participants' willingness to accept OAC therapy. Participants with previously known AF were OAC treated to a higher extent than in our previous trials,[5,11] which is in line with considerable increase in OAC use on AF indication in Sweden during the last 5 years.[20] Patients with previously known AF who were not on OAC treatment accepted the initiation of OAC in lower amounts. Very few participants were referred for invasive downstream therapies due to screening findings.

Study limitations

This is the first trial evaluating biomarker enrichment in systematic AF screening. Participation in the study was slightly lower than expected, and the mean CHA_2DS_2-VASc score in the participants was relatively low at 3.4 considering that all participants were awarded 2 points for age alone. In our study, only 2.4% of the participants had previously known heart failure, which suggests that our participants represented a low-risk selection of the population. It is a known problem in medical screening studies that individuals with the highest risk of disease are often those less likely to attend, which could introduce selection bias among participants and possibly lead to fewer AF cases found. The limited participation, in addition to the prespecified age of 75/76 years reduces the generalizability of this study. However, the invitation by mail, and the lack of exclusion criteria in the trial mimics the reality of screening programmes hence our results are likely representative of those that would occur if screening for AF using NT-proBNP enrichment was used in clinical practice.

Medical history was self-reported and collected from a questionnaire without confirmation from medical records. This could have affected validity of medical history data. Regarding predictors for AF, we were restricted to the variables collected within the trial so there is risk for unknown residual confounding.

N-terminal B-type natriuretic peptide level of 125 ng/L as a first-step screening tool is more sensitive than specific, and as such we consider the number of participants (59.6%) having to go on with more intensified screening to be acceptable.

The low-risk group was only screened with one ECG recording and AF might be underdiagnosed in this group but based on current data we presume that those individuals have a lower risk for stroke as they have lower NT-proBNP.[7] This hypothesis will be evaluated in our final analysis of the STROKESTOP II study in a 5 years' time, where we will compare the outcomes in the intervention group to the control group.

Conclusions

N-terminal B-type natriuretic peptide-stratified systematic screening for AF identified 4.4% of the high-risk group with new AF. Oral anticoagulation treatment was well accepted in the group diagnosed with

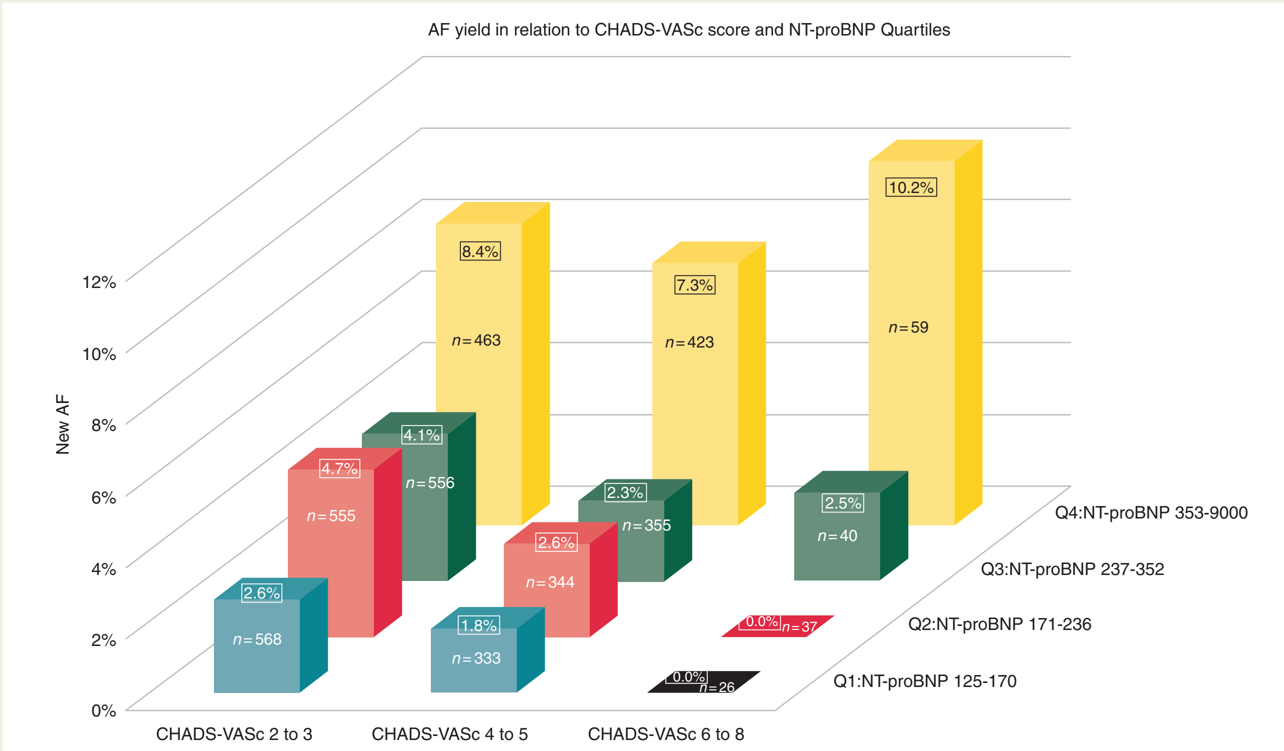

Figure 4 AF screening yield in relation to CHA_2DS_2-VASc and NT-proBNP quartiles. Interquartile odds ratio from Q1 to Q4, NT-proBNP was 4.19 (95% CI 2.54–6.93). The AF detection yield comparing CHA_2DS_2-VASc scores within NT-proBNP quartiles was not significant. AF, atrial fibrillation; CI, confidence interval; NT-proBNP, N-terminal B-type natriuretic peptide; Q1, first quartile of NT-proBNP; Q2, second quartile of NT-proBNP; Q3, third quartile of NT-proBNP; Q4, fourth quartile of NT-proBNP.

Table 4 Multivariable analysis for AF detection in the high-risk group

Variables	OR (95 % CI)	*P*-value
Congestive heart failure (yes)	0.85 (0.31–2.33)	
Hypertension (yes)	0.97 (0.70–1.36)	
Diabetes mellitus (yes)	0.65 (0.37–1.15)	
Prior stroke/TIA (yes)	0.83 (0.59–1.16)	
Vascular disease (yes)	0.52 (0.27–0.99)	0.047
Gender (female)	0.53 (0.38–0.74)	<0.001
BMI (kg/m^2)	1.05 (1.01–1.10)	0.011
Log NT-proBNP	3.06 (2.39–3.75)	<0.001

The low-risk group was not included in the multivariable analysis, as they only performed an index-ECG and there was no further attempt to diagnose AF.
AF, atrial fibrillation; BMI, body mass index; CI, confidence interval; ECG, electrocardiogram; NT-proBNP, N-terminal B-type natriuretic peptide; OR, odds ratio; TIA, transient ischaemic attack.

AF. Our results support the use of NT-proBNP-enriched screening for AF detection.

Supplementary material

Supplementary material is available at *Europace* online.

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