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Original research

Refined atrial fibrillation screening and cost-effectiveness in the German population

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ABSTRACT

Objective Little is known on optimal screening population for detecting new atrial fibrillation (AF) in the community. We describe characteristics and estimate cost-effectiveness for a single timepoint electrocardiographic screening.

Methods We performed a 12-lead ECG in the German population-based Gutenberg Health Study between 2007 and 2012 (n=15 010), mean age 55±11 years, 51% men and collected more than 120 clinical and biomarker variables, including N-terminal pro B-type natriuretic peptide (Nt-proBNP), risk factors, disease symptoms and echocardiographic variables.

Results Of 15 010 individuals, 466 (3.1%) had AF. New AF was found in 32 individuals, 0.2% of the total sample, 0.5% of individuals aged 65–74 years and predominantly men (86%). The classical risk factor burden was high in individuals with new AF. The median estimated stroke risk was 2.2%/year, while risk of developing heart failure was 21% over 10 years. In the 65–74 year age group, the cost per quality-adjusted life-year gained resulting from a single timepoint screening was €30 361. In simulations, the costs were highly sensitive to AF detection rates, proportion of treatment and type of oral anticoagulant. Prescreening by Nt-proBNP measurements was not cost-effective in the current setting.

Conclusions In our middle-aged population cohort, we identified 0.2% new AF by single timepoint screening. There was a significant estimated risk of stroke and heart failure in these individuals. Cost-effectiveness for screening may be reached in individuals aged 65 years and older. The simple age cut-off is not improved by using Nt-proBNP as a biomarker to guide a screening programme.

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia of clinical importance in the general population worldwide.¹ Its prevalence increases with age and is higher in men.² In contrast to the imminent AF epidemic in our society and costly treatments of the disease and its consequences, large-scale screening efforts have remained scant and the ideal target group in the general population is unknown.^{3,4}

In a recent study, we found that unknown AF was detected in 1.5% on a single screen using an

inexpensive rapid readout device, which was found likely to be cost-effective for stroke prevention in individuals aged 65 years or older (SEARCH-AF).⁵ An individual patient meta-analysis of more than 140 000 screened subjects suggested a detection rate of 1.4% in those aged ≥65 years, with a continuous gradation in detection rate with each 5 years of age.⁶ However, little is known on the screening effectiveness in the middle-aged general European population (35–74 years), where the prevalence of AF is about 2.5%.⁷

METHODS

Study participants

The population-based study cohort constitutes a random sample of individuals from the German region of Mainz and Mainz-Bingen (Gutenberg Health Study (GHS) cohort enrolled from 2007 to 2012). Study participants were aged 35–74 years at enrolment and invited by letter within 10-year age strata. Comprehensive information on cardiovascular risk factors were collected during a 5-hour study visit by standardised computer-assisted interview, anthropometric measurements, non-invasive cardiovascular function testing and transthoracic echocardiography (for further details, see the online supplemental methods). Medication information was collected from the packages brought by the participants.⁸ Exclusion of individuals based on the following conditions: (1) individuals with missing information on AF history and missing study ECG, (2) individuals with missing information on AF history and without AF in the baseline ECG and (3) individuals without AF history with missing ECG at baseline. N-terminal pro B-type natriuretic peptide (Nt-proBNP) was measured on the ELECSYS 2010 platform using an electrochemiluminescence immunoassay (Roche Diagnostics).

Outcome

A 10s 12-lead ECG was recorded for every participant (GE CardioSoft). We diagnosed AF based on a history of AF reported by the participant and/or the ECG documentation of AF or atrial flutter.⁹ AF was adjudicated by at least two physicians with cardiology training and experience in ECG reading. In difficult cases, a third opinion by an electrophysiologist was obtained. Screening-detected AF or new AF was defined as AF on the study ECG in



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individuals without a history of AF. Individuals with new AF on the study ECG were redefined as known AF if they were taking the following medications: oral anticoagulant (OAC), digoxin or Vaughan Williams class I or III antiarrhythmic drugs.¹⁰

Prior to enrolment, participants provided written, informed consent. All authors have read and approved the manuscript as written.

Statistical methods

To assess disease risk, we used a published risk algorithm to estimate predicted AF risk in individuals with prevalent AF.¹¹ To understand stroke risk, we calculated the CHA₂DS₂-VASc (heart failure, hypertension, age ≥ 75 years (double score), diabetes, prior stroke or transient ischemic attack (TIA; double score), vascular disease, age 65–74 years, sex class (female)) score adding together the points for the following conditions: congestive heart failure/left ventricular dysfunction (1), high blood pressure (1), age > 75 years (2), diabetes (1), stroke/transient ischaemic attack/thromboembolism (2), vascular disease (coronary artery disease, myocardial infarction, peripheral artery disease and aortic plaque) (1), age 65–74 years (1) and sex category female (1). The estimated stroke risk was also adjusted for warfarin intake assuming that warfarin provides a reduction in thromboembolism events.² For the estimation of heart failure risk and risk of stroke or death, respective risk algorithms from the literature were applied.^{11 12}

In further analyses, we used random forest machine learning algorithms to identify clinical and biomarker variables most strongly related with AF among 121 variables available in the GHS.¹³ Least absolute shrinkage and selection operator (LASSO) and forward selection methods were applied to understand the validity of the results of the machine learning algorithm. We used all AF cases in order to increase the number of response variables with an expected relatively small number of cases in the cohort. Missing values were imputed as the weighted average of the non-missing observations using weights determined from random forests (for details, please see the online supplemental methods).¹⁴ If variable values were missing in more than 70% of individuals, the respective variable was not used for analyses. We used 70% as a cut-off in order to accommodate biomarker measurements which were available in a subgroup accepting the introduction of potential bias. For clinical variables, we assumed missingness at random.

The complete data sample was split into a training and a test (validation) data set before any statistical analysis was carried out. All individuals in the complete data sample were randomly allocated to the data sets using a ratio of 3:2 individuals. The fit of each statistical method (generated in the training data set) was validated by applying the fit to the test set. The performance of each method was presented by the C-statistic for the random forest method or area under curve (AUC) for the LASSO and forward selection method.^{15 16} Sensitivity and specificity analyses were performed for the best discriminator selected (Nt-proBNP), and the number needed to screen to find one new AF case depending on various Nt-proBNP cut-offs was calculated. The Nt-proBNP cut-off that maximised the sum of sensitivity and specificity, giving the sensitivity function a 20% higher weight, was identified.

Cost-effectiveness analyses

A cost-effectiveness analysis to understand the impact on health-care expenditure for a single timepoint electrocardiographic screening was performed, comparing the scenarios with and

without screening for AF in the German population aged 65–74 years based on Markov models that accounted for OAC treatment, incident strokes, major bleeds and all-cause mortality.⁵ The target variables of the cost-effectiveness analyses were costs per quality-adjusted life-year (QALY) gained and costs per stroke prevented.

In addition, refined screening scenarios (other than age cut-off (65 years) alone) were assessed by using an age cut-off plus clinical AF risk score based threshold of 5% and 10%, and age cut-off plus a point of care testing of Nt-proBNP to preselect individuals at higher risk of AF before performing a 12-lead ECG.

For cost-effectiveness analyses we used Stata MP V.14.2 (StataCorp LLC) and for all other analyses R V.3.4.1 (R Foundation for Statistical Computing).

Patients and public involvement

Patients and public were not involved in the design, conduct, reporting or dissemination plans of our research.

RESULTS

After excluding 72 (0.5%) individuals due to missing information on the history of AF from the overall GHS sample (n=15 010; 100%), we assessed 466 (3.1%) individuals with prevalent AF. New AF comprised 32 (0.2%) individuals. The GHS weighted (sex, age and region) prevalence of AF was 2.5% (n=380), including 0.2% (n=25) prevalence of new AF.

Table 1 and online supplemental table 1 summarise the characteristics of the study sample by AF status. The new AF group revealed the lowest proportion of women (14.1%). A high classical risk factor burden was seen in individuals with both new AF and known AF. Symptoms of dyspnoea and palpitations were about three times more common in known AF and almost twice as frequent in unknown AF, as in individuals without AF. The biomarker Nt-proBNP was about 14 times higher in the new AF group, and about four times higher in known AF compared with no AF.

Figure 1 demonstrates that among individuals with AF the relative proportion according to age decade in the subgroups of individuals with known and new AF was similar in both groups rising from less than 10% (35–44 years) to approximately 60% of those with AF in the latest age decade of 65–74 years. In online supplemental figure 1 and online supplemental table 2, the distribution of predicted risk of AF based on an AF risk algorithm is provided.¹⁷

The risk of adverse events in new AF cases is shown in figure 2A–C. The median CHA₂DS₂-VASc score was two with a median annual stroke risk of 2.2%. The distribution of stroke risk by CHA₂DS₂-VASc score in new AF cases is provided in online supplemental figure 2 and figure 2A. The 10-year risk of developing heart failure was 21% (25th/75th percentile 11/37%) shown in figure 2C, and the 5-year risk of stroke or death was 30% (25th/75th percentile 19/44%) for individuals with new AF (figure 2B).

In random forest selection, Nt-proBNP was the single variable most strongly related to prevalent AF validated by stepwise selection and LASSO methods (online supplemental figure 3). The model fit C-statistic was 0.829 for the random forest selection, the AUCs 0.802 for the stepwise selection and 0.834 for the LASSO methods. Evaluating different Nt-proBNP cut-offs with respect to sensitivity and specificity of high AF risk prediction revealed an optimal clinical threshold value of 120 ng/L, that is the 77th percentile of Nt-proBNP concentrations, with

Table 1 Characteristics of study participants by AF status weighted for age and sex of the population in Mainz and Mainz-Bingen area (weighted n=14937)

	No AF (n=14 557)	Known AF (n=355)	New AF (n=25)
Age, years	52.3±11.0	63.2±9.5	64.9±9.1
Female, %	50.6 (49.8–51.4)	34.4 (29.5–39.3)	14.1 (0.5–27.7)
Current smoking, %	20.9 (20.2–21.6)	13.4 (9.9–17.0)	24.7 (7.8–41.6)
Body mass index, kg/m ²	26.4 (23.7/29.8)	28.4 (25.9/32.0)	27.4 (26.1/33.4)
Systolic blood pressure, mm Hg	128 (118/139)	131 (120/142)	136 (120/147)
Diastolic blood pressure, mm Hg	82 (76/88)	80 (74/87)	84 (77/92)
Heart rate, bpm	69 (62/75)	67 (58/76)	77 (68/88)
Diabetes, %	6.0 (5.6–6.4)	14.5 (10.8–18.2)	23.6 (7.0–40.3)
Hypertension, %	44.5 (43.7–45.3)	70.1 (65.3–74.9)	66.7 (48.2–85.2)
Dyslipidaemia, %	27.7 (27.0–28.4)	43.7 (38.5–48.9)	30.5 (12.5–48.6)
Prevalent myocardial infarction, %	2.1 (1.9–2.3)	14.7 (11.0–18.4)	6.4 (0–16.0)
Prevalent stroke, %	1.4 (1.2–1.6)	8.7 (5.8–11.6)	0
Heart failure, %	16.4 (15.8–17.0)	44.3 (39.1–49.5)	41.7 (22.4–61.0)
Dyspnoea, %	10.7 (10.2–11.2)	30.8 (26.0–35.6)	22.1 (5.8–38.4)
Palpitations, %	15.2 (14.6–15.8)	46.5 (41.3–51.7)	25.9 (8.7–43.1)
NT-proBNP (pmol/L)*	61 (31/115)	261 (80/948)	868 (276/1951)
Thyroid-stimulating hormone (mU/L)	1.04 (0.73/1.47)	1.0 (0.7/1.4)	1.06 (0.64/1.28)
C reactive protein (mg/L)	1.5 (0.5/3.1)	2.1 (1.0/4.2)	2.9 (1.2/4.3)

Mean values and SD for continuous variables, median and 25th/75th percentiles for skewed continuous variables, or per cent and a 95% CI for categorical variables.
*Available for the first 5000 study participants.
AF, atrial fibrillation; NT-proBNP, N-terminal pro B-type natriuretic peptide.

a number needed to screen of 13, a test sensitivity of 0.68 and a test specificity of 0.78 (online supplemental table 3 and online supplemental figure 4).

Cost-effectiveness

We estimated costs per QALY gained by single timepoint AF screening in those aged 65–74 years of €30 361 for a prevalence of new AF of 0.5% and VKA prescriptions in 58% of cases. The costs per stroke prevented were inversely related to the prevalence of new AF (figure 3). Thus screening in a younger age group with both a lower prevalence of new AF and a lower estimated stroke risk would not be cost-effective. A higher proportion taking OAC therapy reduced the costs per stroke prevented. With a higher proportion of OAC uptake, the distance between the curves for different proportions of AF prevalence declined and the additional decrease in costs was less pronounced (figure 3). A sensitivity analysis demonstrated that a higher

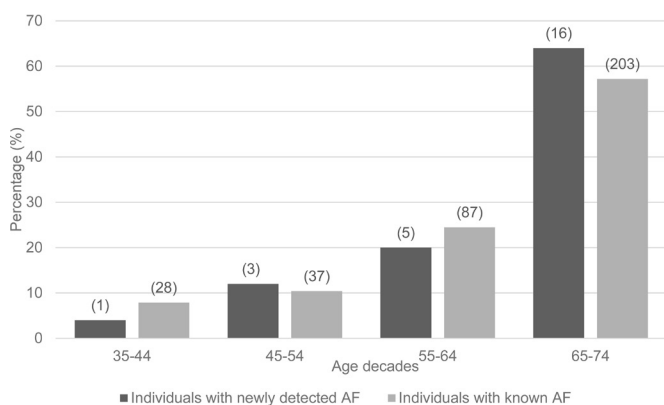


Figure 1 Distribution of individuals with known AF (n=355) and newly detected AF (n=25) by age decades, weighted for residence, age and sex of the population in Mainz and Mainz-Bingen area (n=14937). AF, atrial fibrillation.

proportion of non-vitamin K oral anticoagulant (NOAC) intake compared with VKA increased the costs per prevented stroke (figure 4).

The number of strokes avoided and costs per QALY gained using a stepwise screening approach including Nt-proBNP prescreening tests are provided in online supplemental table 4 and online supplemental figures 5,6. As an example, using an Nt-proBNP threshold of 120 ng/L, 23% of the prescreened individuals get a positive AF test result and hence a subsequent ECG. In the German population, this would lead to 17 499 individuals with newly identified AF and subsequently 763 strokes avoided according to OAC treatment. The costs per stroke prevented would be €140 800 and the costs per QALY gained €36 382. Independent of the threshold value, Nt-proBNP prescreening was less cost-effective for stroke prevention or QALYs gained than the ECG screening using age alone. When using a clinical risk score guided screening using a 5% or 10% risk cut-off, n=972 (sensitivity 86.7% (online supplemental table 5)) and n=539 (sensitivity 48.1%) strokes would have been avoided, respectively.

DISCUSSION

In a large, middle-aged to older population-based cohort of 15 010 individuals, we identified 32 (0.2%) new AF cases by a single ECG. The yield of newly identified AF increased with age and risk factor burden.

The definition of the most efficient method of screening for AF in the ageing population is an urgent research and health economics question.⁴ In our study, undiagnosed AF was not necessarily silent. One quarter of new AF individuals indicated that they had the typical symptom of palpitations and one-fifth had dyspnoea, but despite that, patients had not been diagnosed. The heart rate of participants with new AF has shown a broad range.^{4,5} In our sample, mean heart rate was higher compared with individuals with known disease or participants without AF but was still below 80, which may mean that symptoms were less

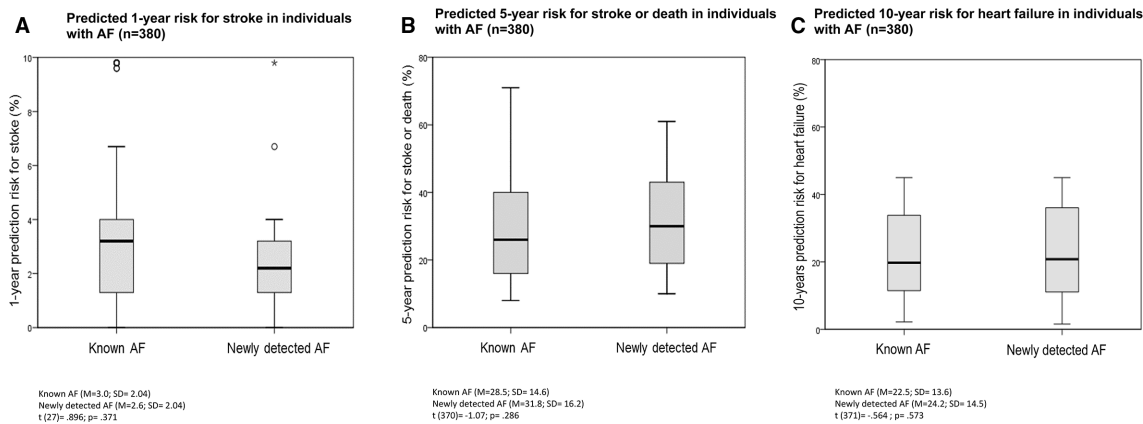


Figure 2 Boxplots of predicted risk of stroke (A), stroke or death (B) and heart failure (C) in individuals with known and newly detected AF. Risk algorithms for annual stroke risk (CHA₂DS₂-VASC score),¹¹ 10-year heart failure risk³⁰ and 5-year risk of stroke or death¹² were used. Heart failure risk scores were truncated at the upper risk estimate of ≥45% to avoid inaccuracies due to extreme observations. Stroke risk assessed by CHA₂DS₂-VASC score is adjusted for warfarin intake. Cardiac murmur is not available in the Gutenberg Health Study and is left out of the calculation of heart failure risk. Data are weighted for residence, age and sex of the population in Mainz and in Mainz-Bingen area. AF, atrial fibrillation.

notable, and consistent with not seeking medical attention for the symptom. These signs and symptoms are not specific for AF, for example, 15% of individuals without diagnosed AF reported palpitations but may be sensitive and thus help to guide a closer look and possibly more intensified diagnostics based on symptoms alone.

Classical AF risk factors were more common in individuals with new AF. Strikingly, about 40% of new AF participants had heart failure based on symptoms and echocardiographic findings. Echocardiography certainly is not a screening tool at the population level; however, our data confirm the importance of heart failure as a risk factor for AF not only in the clinical setting.¹⁸ When applying a recent risk prediction algorithm,¹¹ the median risk of AF in individuals with incidentally diagnosed AF was highest; however, with a median of 6.7%, predicted 10-year risk was still comparatively low and therefore may not be expected to be a very useful guide to screening. The calculated risk in participants without AF was negligible. These findings indicate the remaining limitation of the scoring system to accurately identify individuals at risk of AF and call for improvement of prediction tools.

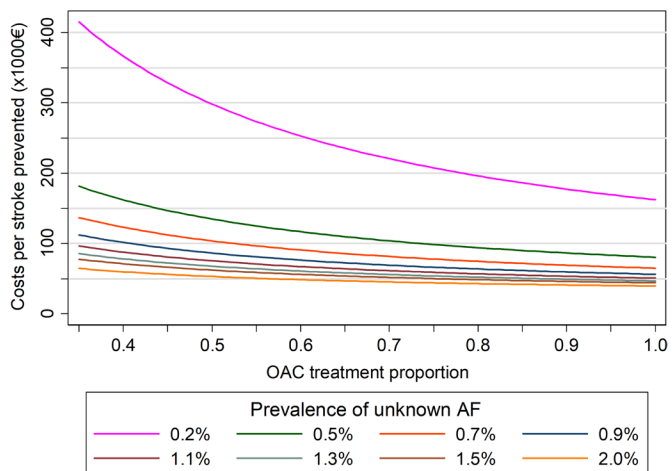


Figure 3 Costs per stroke prevented by OAC intake stratified by the prevalence of unknown AF. AF, atrial fibrillation; OAC, oral anticoagulant.

Overall, age remained the major determinant of risk of unknown AF and is certainly the easiest variable to select patients for screening. This is the basis of guideline recommendation for opportunistic screening for AF in individuals aged ≥65 years.^{19 20} The risk of adverse events in individuals with first detected AF was not negligible: the median CHA₂DS₂-VASC score was 2, only 31% had a score of <2. Respectively, 69% of individuals with new AF had a score of ≥2 and would be eligible for an OAC prescription according to guidelines.²⁰ Among individuals with known AF, 75% had a CHA₂DS₂-VASC score of ≥2; however, only 35% were taking an OAC. A CHA₂DS₂-VASC score that requires the evaluation of therapeutic anticoagulation in individuals with first detected AF in community screening has been reported earlier.^{4 17 21}

Our data further support the need to raise the awareness for AF. We and others have shown that a relevant proportion of individuals did not know their very likely diagnosis of AF.^{5 22} They were older, more often men, had diabetes and present

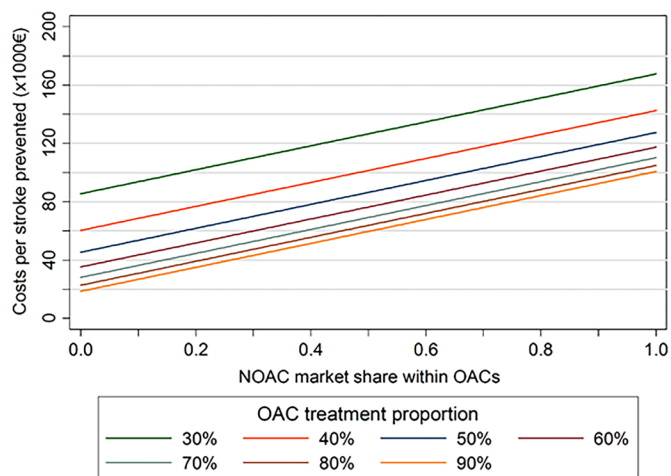


Figure 4 Costs per stroke prevented in relation to the proportion of NOAC versus VKA stratified by the proportion of OAC intake. AF, atrial fibrillation; NOAC, non-vitamin K oral anticoagulant; OAC, oral anticoagulant.

higher values of NT-proBNP, thyroid-stimulating hormone and C reactive protein.

Cost-effectiveness

The proportion of known and new AF cases increased similarly with age, while the absolute numbers in the first two age decades in both groups remained small. The proportion of OAC uptake affects cost-effectiveness especially for the OAC proportion band below 65%. Another cost driver was NOAC treatment compared with VKA. For an OAC uptake of more than 90%, which has been shown in the STROKESTOP study,²³ treatment with NOAC only compared with VKA only revealed a fivefold increase in costs per stroke prevented, from about €20 000 to €100 000. These differences may become less pronounced once NOAC patents run out. Overall, cost-effectiveness for a single timepoint screening appears to be given in age groups 65 years and older.⁵

We restricted cost-effectiveness analyses to participants 65 years or older due to the screening yield of unknown AF in the sample and risk factor burden that warrants anticoagulation. However, the prevalence of new AF of 0.5% after the age of 65 years in this German cohort with an upper age limit of 74 years at enrolment remained low. In other screening studies such as SEARCH-AF,⁵ which also included individuals aged 65 years and older (mean age 79±6 years) the AF detection rate was 1.4%. A meta-analysis of single timepoint screening confirmed a detection rate of 1.4% in individuals ≥65 years.²⁴ As shown by our simulations, cost-effectiveness is highly dependent on the prevalence of undetected or undertreated AF in the screened population.

The search for more specific and sensitive biomarkers for AF in addition to the CHARGE-AF equation was one of the motivations for the GHS. We assumed that elevated natriuretic peptide concentrations mirror underlying cardiac stress as a predisposition to the arrhythmia or episodes of the AF, which increase biomarker secretion and confirmed that Nt-proBNP was the best biomarker. This assumption has also been the rationale for the use of this biomarker in STROKESTOP-2 study, as it was hypothesised the biomarker would be more cost-effective than a simple age criterion as in the STROKESTOP-1 study and in most other current and proposed screening studies. A similar biomarker threshold of Nt-proBNP (125 pmol/L) identified fewer individuals with AF in the STROKESTOP-2 study, which may be explained by an older study cohort with possibly more comorbidities, overall higher Nt-proBNP concentrations and a lower discriminatory ability.²² In our cohort, we found that the strategy of refined screening by upfront application of current clinical risk scores or Nt-proBNP measurement was unlikely to be more cost-effective for a single timepoint screening at present. Cost-effectiveness requires more specific markers than Nt-proBNP and/or lower costs for the test to be applied at scale. In our sample, the costs per QALY achieved using Nt-proBNP prescreening would have been equal to the ECG screening only if the test itself cost €6.23. Lower costs, which are likely in the future, could render biomarker-guided prescreening cost-effective.

Limitations

Despite the large cohort size, the number of new AF cases was small and may result in unstable estimates. An older cohort over 75 years, such as in the STROKESTOP studies, might have had a higher yield for screen-detected AF and cost-effectiveness as AF incidence increases with age.

A single 12-lead ECG is not sufficient to rule out prevalent AF, and we underestimate the true disease burden and capture more persistent forms of AF.²⁵ However, longer term monitoring or repeat ECG registration may be less feasible at a large scale for screening in the general population and may find AF with a lower stroke risk as seen in implanted device-detected AF.²⁶ More intensified screening is efficient in predefined subgroups at increased risk. Such groups could be defined by age⁴ or by risk factor burden, in particular heart failure, which will increase the yield of new AF. Elevated biomarkers may help guide screening and may reduce the number needed to screen.²⁷

Furthermore, the proportion of individuals with known AF on OAC would most likely be higher today since the change of recommendations for anticoagulation towards a lower CHA₂DS₂-VASc score, which would render screening more effective.⁹ Furthermore, current guidelines more strongly recommend screening and explicitly recommend screening in patients with hypertension or obstructive sleep apnoea, which may impact screening efficiency.²⁰

A limitation of any cost-effectiveness analysis to date is that the results strongly depend on assumed input parameters and outcome information from external studies not designed for screening purposes. Therefore, we investigated the effect of a change in input parameters on the costs per QALY gained and costs per stroke prevented across a range of inputs. Furthermore, the cost-effectiveness analysis included simplifications, for example, NOACs were assumed to have the same characteristics as VKAs with respect to treatment persistence and to the incidence of stroke, mortality and major bleeds during treatment, although in practice, NOACs are likely related to a lower risk of stroke, major bleeds and mortality.²⁸ These simplifications may have to be revised once more robust real-life data become available.

We conclude that screening for AF by 12-lead ECG in individuals from the general population aged <65 years yields a low proportion of new AF cases and is therefore not cost-effective. The cost-effectiveness of single timepoint screening improves with increasing age and risk factor burden and when simpler methods for detection are used, such as handheld devices or repeat ECGs as available from smart watches.²⁹ At present, a simple age cut-off appeared to be the most effective selection criterion for screening. Our results

Key messages

What is already known on this subject?

⇒ Individuals with atrial fibrillation (AF) have a high risk of stroke, and opportunistic screening for AF is recommended in patients aged 65 years or older. Data on screening yield and cost-effectiveness are limited.

What might this study add?

⇒ This population-based study of middle-aged to older individuals shows that cost-effectiveness may be achieved with single time point screening in older individuals with age as the strongest predictor, possibly optimised by clinical risk factors. Prescreening by B-type natriuretic peptide measurement at current costs and precision is not efficient.

How might this impact on clinical practice?

⇒ Age remains the major determinant of screen-detected AF in the population and is easily available. Cost-effectiveness of AF screening may be reached in people 65 years and older for single timepoint screening, especially if the 12-lead ECG could be replaced by, for example, handheld devices.

may spur future investigations of the characteristics of individuals who are at increased risk of developing AF such as classical risk factors combined in more accurate risk scores and biomarkers, for example, Nt-proBNP and in whom simple screening efforts may be more efficient to detect AF. Such data are needed to implement large-scale screening at the population level and inform public health programmes.

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Contributors RS and BF developed the conceptual framework and the design of the study. CW and CM conducted the economic analysis. NAS and DE calculated the epidemiological analysis. RS, BF, CW, CM, NAS and DE interpreted the data. RS and BF drafted the manuscript, and CW, CM and DE revised the manuscript critically. SB, TM, PSW, NP, MB and MM commented and approved the version of the manuscript to be published.

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Patient consent for publication Not required.

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Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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