ORIGINAL RESEARCH ARTICLE

Selective screening for atrial fibrillation using multivariable risk models

David T Linker,[1] Tasha B Murphy,[2] Ali H Mokdad[3]

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/heartjnl-2017-312686).

[1]Division of Cardiology, Department of Medicine, University of Washington, Seattle, Washington, USA
[2]School of Social Work, University of Washington, Seattle, Washington, USA
[3]Institute for Health Metrics and Evaluation, University of Washington, Seattle, Washington, USA

Correspondence to
Dr David T Linker, Division of Cardiology, Department of Medicine, University of Washington, Seattle, WA 98195, USA; dtlinker@uw.edu

Received 6 November 2017
Revised 30 January 2018
Accepted 2 February 2018
Published Online First 28 March 2018

Watch Video
www.goo.gl/7zUaoq

► http://dx.doi.org/10.1136/heartjnl-2018-313085

Check for updates

To cite: Linker DT, Murphy TB, Mokdad AH. *Heart* 2018;**104**:1492–1499.

ABSTRACT

Objective Atrial fibrillation can lead to stroke if untreated, and identifying those at higher risk is necessary for cost-effective screening for asymptomatic, paroxysmal atrial fibrillation. Age has been proposed to identify those at risk, but risk models may provide better discrimination. This study compares atrial fibrillation risk models with age for screening for atrial fibrillation.

Methods Nine atrial fibrillation risk models were compared using the Atherosclerosis Risk in Communities study (11 373 subjects, 60.0±5.7 years old). A new risk model (Screening for Asymptomatic Atrial Fibrillation Events—SAAFE) was created using data collected in the Monitoring Disparities in Chronic Conditions study (3790 subjects, 58.9±15.3 years old). The primary measure was the fraction of incident atrial fibrillation subjects who should receive treatment due to a high CHA_2DS_2-VASc score identified when screening a fixed number equivalent to the age criterion. Secondary measures were the C statistic and net benefit.

Results Five risk models were significantly better than age. Age identified 71 (61%) of the subjects at risk for stroke who subsequently developed atrial fibrillation, while the best risk model identified 96 (82%). The newly developed SAAFE model identified 95 (81%), primarily based on age, congestive heart failure and coronary artery disease.

Conclusions Use of a risk model increases identification of subjects at risk for atrial fibrillation. One of the best performing models (SAAFE) does not require an ECG for its application, so that it could be used instead of age as a screening criterion without adding to the cost.

INTRODUCTION

Atrial fibrillation is the most common rhythm disturbance of the heart requiring treatment, with a lifetime risk exceeding 20%.[1 2] Estimates of the prevalence of atrial fibrillation in the USA range from 2.2 to 5.1 million people[3 4] as of the year 2000. The incidence of atrial fibrillation increases with age,[5] and it has been estimated that as many as 12.1 million Americans will be diagnosed with atrial fibrillation by the year 2050.[4] Although many people experience symptoms when they develop atrial fibrillation, it can be asymptomatic.

The true prevalence of asymptomatic atrial fibrillation is unclear, but several studies provide some indication of the magnitude of the problem. In one study of paroxysmal atrial fibrillation, there were 12 times as many asymptomatic episodes as symptomatic episodes.[6] In another study using twice-weekly surveillance ECGs over 1 year, 42% of the atrial fibrillation that was discovered was asymptomatic.[7] Intermittent rhythm monitoring in higher risk populations has identified asymptomatic, undiagnosed atrial fibrillation in 3%–7% of those studied, and diagnosed four times more than a baseline ECG.[8 9]

All atrial fibrillation carries an increased risk of stroke, which can range from 0.4% to 15% per year depending on coexisting risk factors,[10] and is present even if the atrial fibrillation is asymptomatic.[11] If the patient is identified, treatment with anticoagulants can reduce that risk by as much as 62%.[11 12]

The clinical problem is how to practically identify people with asymptomatic, paroxysmal atrial fibrillation. This can be done with long-term rhythm monitoring or opportunistic ECG, with higher yields for longer durations of rhythm monitoring.[13] To be cost-effective, screening should be applied to specific groups that are at higher risk.[14]

Age over 65 has been adopted as a useful criterion for screening in the most recent European guidelines.[15] Alternatively, a number of risk models that have been created to predict the development of incident atrial fibrillation could be considered as an aid to screening.[16–21] We examined the ability of these models, and a new risk model based solely on historical information, to predict incident atrial fibrillation when compared with a simple age-based criterion.

METHODS

Derivation of the Screening for Asymptomatic Atrial Fibrillation Events risk model

The Screening for Asymptomatic Atrial Fibrillation Events (SAAFE) study is designed to prospectively determine the prevalence of asymptomatic, undiagnosed atrial fibrillation in subjects who are at increased risk relative to the general population. Potential subjects will be identified from a larger screening population based only on demographic and historical risk factors to reduce the screening cost. As part of the SAAFE study, a new risk model was created using only demographic and historical data.

The SAAFE risk model was derived from a subset of the data collected in the Monitoring Disparities in Chronic Conditions (MDCC) study,[22] which surveyed specific health conditions in King County, Washington. The MDCC study used two methods of data collection: a random, address-based sampling (ABS), and medical record review-based sampling (MRRBS). More details of MDCC data collection are available in the online supplementary material.

The data from both derivation cohorts were merged, with a variable identifying which cohort the subject was in, and if from the MRRBS cohort, the diagnosis that resulted in their inclusion. The variables tested for the risk model were age, sex, height, weight, body mass index (BMI), race, self-reported history of congestive heart failure, myocardial infarction, coronary artery disease, coronary artery stenting, diabetes mellitus, chronic obstructive lung disease, renal failure, kidney transplant, dialysis, cardiac arrest, hypercholesterolaemia, asthma, coronary artery bypass grafting, hypertension or stroke. In addition, for the MRRBS group, the reason for recruitment was included as a variable.

All of the variables were self-reported except for the reason for inclusion in the MRRBS cohort. Also, the data were collected at a single point in time, and therefore reflect self-reported prevalence of atrial fibrillation rather than incidence. Based on prior risk models,[16 18] additional variables were included for age^2, age×congestive heart failure, age^2×sex, diabetes×age and coronary artery disease×age.

A binary logistic regression model was created and cross-validated using Weka (V.3.6.7, University of Waikato) using the SimpleLogistic algorithm for attribute selection, which employs an iterative cross-validation technique to choose variables that will significantly improve the model.

Prior atrial fibrillation risk scores

At least six other atrial fibrillation risk scores have been developed based on the Atherosclerosis Risk in Communities (ARIC) study,[18] the Framingham Heart Study,[16] the Euro Heart Survey on AF[17] (HATCH), the Women's Health Study[19] (WHS), a combination of studies including ARIC for the CHARGE-AF consortium[20] and a meta-analysis of risk factors[21] (Mayo). If a risk model had a version with full Cox regression coefficients, this was used in our analysis rather than a simplified points-based model. Two of the models included variations that either included or excluded some variables, so these variants were tested in our analysis as well.

Comparison of risk model performance

To compare the performance of the risk scores we used data collected as part of the ARIC study.[23] The variables required to calculate the risk for each of the models were collected from exam 3, along with telephone surveys and community surveillance prior to exam 3. Incident atrial fibrillation was determined as new atrial fibrillation noted at exam 4, or from the telephone or surveillance data between exams 3 and 4, in subjects who had not been identified as having atrial fibrillation by exam 3. An overview of the data collection and study design is in figure 1.

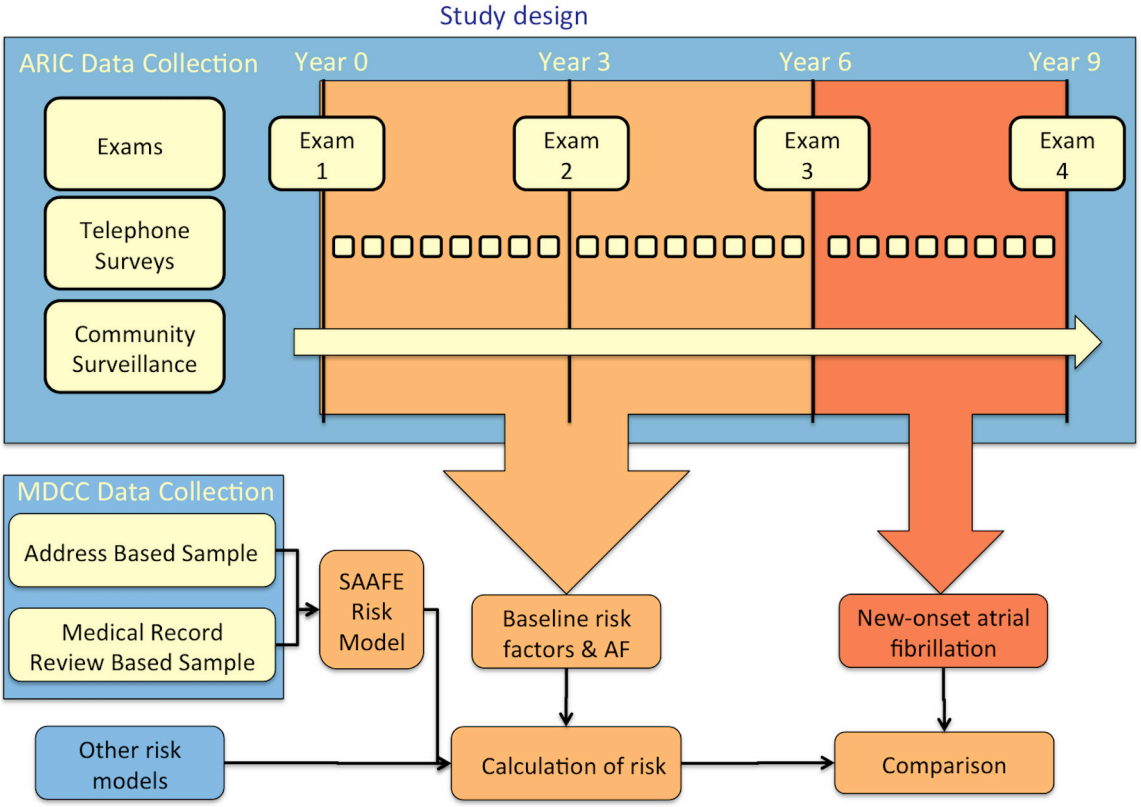

Figure 1 Overview of study design and data collection. The MDCC study consisted of two cohorts which were combined to derive the SAAFE risk model. The ARIC study collected data from exams every 3 years, from telephone surveys every 6 months and from community surveillance of healthcare records. All three sources were used in the current study. Data from the first 6 years of the ARIC study, including exam 3, were used as baseline risk data. These data were used to calculate risk of developing AF using the SAAFE risk model and the other models from the literature. Data from ARIC from exam 4, and the time period between exams 3 and 4 were used to determine new-onset AF, and compared with the results of the risk models. The light blue boxes represent prior studies. The yellow items represent data collection in those studies. The orange items represent the current study. AF, atrial fibrillation; ARIC, Atherosclerosis Risk in Communities; MDCC, Monitoring Disparities in Chronic Conditions; SAAFE, Screening for Asymptomatic Atrial Fibrillation Events.

Statistics

All univariate HRs, the C statistic, also known as the area under the receiver operating characteristic curve (AUC), and 95% CIs of the AUC were calculated using SPSS (V.19, SPSS). Comparison between the AUC of pairs of risk models was performed using roccomp in Stata (V.14.1, StataCorp). The statistical significance of frequencies was calculated using the Fisher's exact test in R (V.3.2.2, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

SAAFE risk model

Data were analysed from a total of 3790 subjects, 1636 from the ABS cohort and 2154 from the MRRBS cohort. The mean age was 58.9 years for the entire sample, with the ABS cohort being younger on average than the MRRBS cohort (55.4 vs 61.6, $P<0.001$).

There were 2000 women representing 52.7% of the total sample, with 938 in the ABS cohort (57.3% of ABS cohort) and 1062 in the MRRBS cohort (49.3%). A total of 509 (13.4%) of subjects reported atrial fibrillation, with 130 (7.8%) in the ABS cohort and 379 (17.6%) in the MRRBS cohort. The univariate OR of atrial fibrillation as associated with variables in the two cohorts is summarised in online supplementary etable 1.

Univariate logistic regression was used to measure the association between prevalence of atrial fibrillation and each of the continuous variables including age, height and weight, as well as the calculated BMI and the product of height and weight. The results for each of the cohorts and the total sample are presented in online supplementary etable 2.

There was a significant association with age in both cohorts. Atrial fibrillation prevalence increased at a relative rate of 4.4% per year (figure 2). Associations for the other continuous variables were less consistent between cohorts, although all reached significance in the combined sample.

The continuous variables that remained in the multivariable logistic model were age, height and height×weight. Historical variables that remained in the multivariable model were congestive heart failure, coronary artery disease, chronic obstructive pulmonary disease, cardiac arrest, coronary artery stenting, stroke, diabetes and kidney transplant, as well as whether the subject was in the MRRBS cohort. The final ß coefficients of the multivariable SAAFE model are listed in online supplementary etable 3. The results on the combined cohorts yielded an AUC of 0.804 with a 95% CI of 0.785 to 0.826. Performance of 100-fold cross-validation resulted in an AUC of 0.785.

The prevalence of atrial fibrillation in the MDCC population increased monotonically from 2% to 66% with an increase in the SAAFE risk score (figure 3). The contribution of each variable to the total risk score in each group is illustrated in figure 4. For the lower risk scores, age was the primary factor, while at higher values comorbidities contributed increasing amounts of risk, especially congestive heart failure.

Comparison with prior risk models

The ARIC data set includes a very high percentage of African-American subjects (23.9% as of exam 3), and reported race is related to atrial fibrillation risk in many of the prior models. Since the MDCC sample had only 5.5% African-American subjects, and this was not sufficient to assess the relative risk of this population compared with Caucasians, the ß coefficient for race from the CHARGE-AF model was added to the SAAFE risk model. A comparison of the variables used for each of the risk score calculations is included in table 1.

The Framingham and CHARGE-AF risk models have versions with and without ECG variables, and both were tested. Since age has been recommended as a screening criterion,[15] age alone was also included as an independent risk model. The $CHADS_2$ and CHA_2DS_2-VASc scores were also included for comparison.

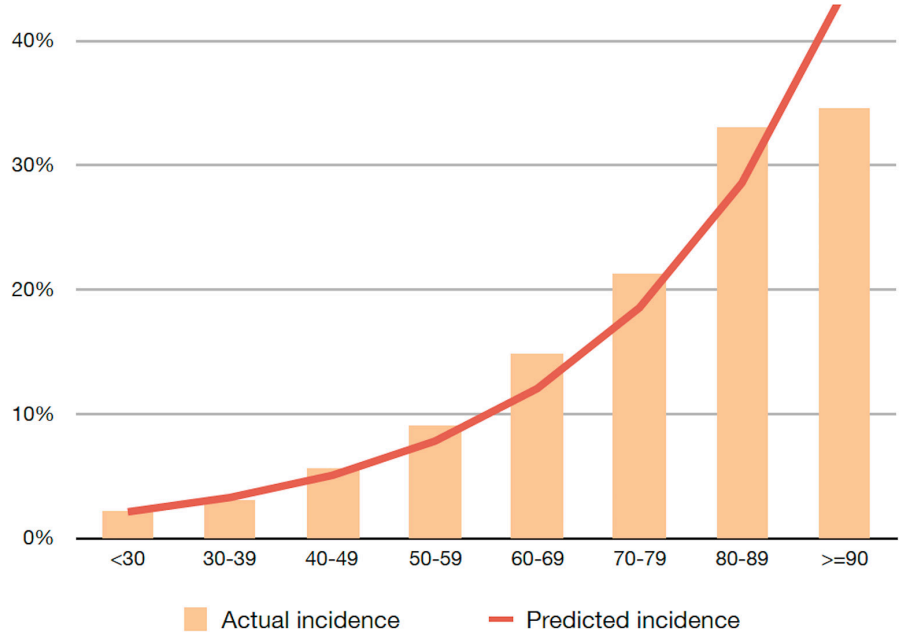

Figure 2 Prevalence of atrial fibrillation versus age: the columns show the percentage of the population with atrial fibrillation in the Monitoring Disparities in Chronic Conditions (MDCC) study as a function of age in decades for the entire sample. There was a continuous increase in prevalence of atrial fibrillation in all age groups, starting at 2.1% in the first group. The fitted line shows the predicted relative increase of 4.4% per year, as based on the regression equation using a compound model. Thus, after 10 years the prevalence would increase 1.044^{10} or 1.54 times to 1.54×2.8%=3.2% in the 30–39 age group.

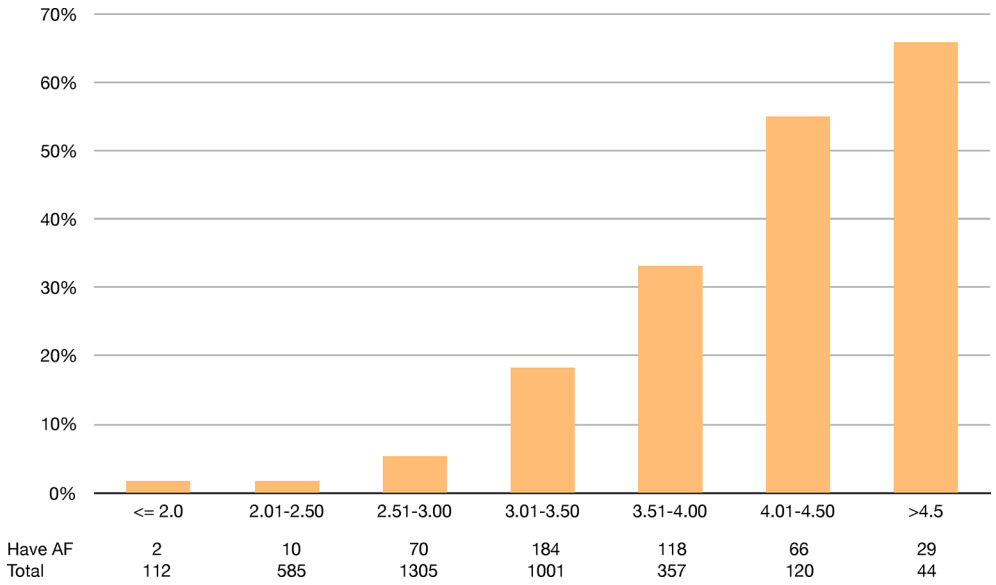

Figure 3 Prevalence of AF as a function of the Screening for Asymptomatic Atrial Fibrillation Events (SAAFE) risk score. The graph below shows the total number of subjects in the MDCC data set with each range of values, and the number within that group who have AF. AF, atrial fibrillation; MDCC, Monitoring Disparities in Chronic Conditions.

There was a total of 11 373 subjects with data available at exam 3. Over the next 3 years, 165 new cases of atrial fibrillation were diagnosed. Table 2 summarises the results for the various risk models as predictors of incident atrial fibrillation within 3 years of exam 3.

Treatment of patients with asymptomatic atrial fibrillation is primarily determined by their risk for stroke, which is usually estimated using the CHA_2DS_2-VASc score.[24] Anticoagulation with warfarin or direct oral anticoagulants is recommended for those with a CHA_2DS_2-VASc score of 2 or greater. For this

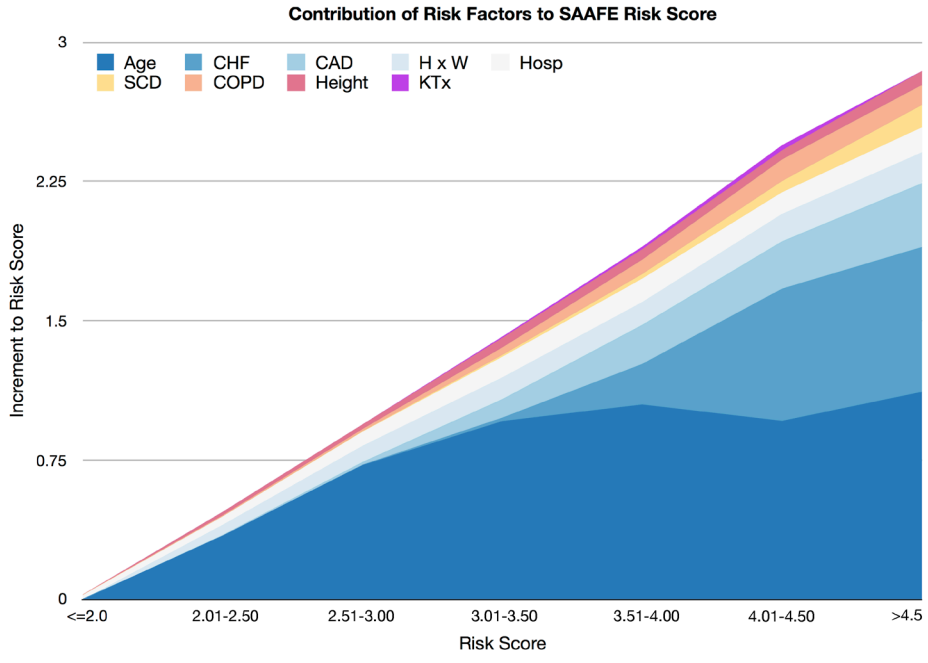

Figure 4 Contribution of risk factors to total Screening for Asymptomatic Atrial Fibrillation Events (SAAFE) risk score. The variables are age, CHF, CAD, H×W, recent hospitalisation for cardiopulmonary conditions (Hosp), cardiac arrest (SCD), chronic obstructive lung disease (COPD), height and KTx. Note that the first three variables have the greatest contribution to the total risk score. CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; H×W, height times weight; KTx, kidney transplant; SCD, sudden cardiac death.

Table 1 Variables used in the risk models

Study	Yr	Ht	Wt	CF	CD	MI	V	CPD	SD	Stnt	Str	DM	KTx	Hsp	M/F	HTN	Eth	BI	M	PR	BP	R	T	LAE	LVH
SAAFE	X	X	X	X	X	X		X	X	x	x	x	X	X								X			
CHARGE-AF-A	X	X	X	X		X						X								X	X	X	X		X
CHARGE-AF-S	X	X	X	X		X						X									X	X	X		
ARIC	X	X		X	X							X				X			X		X	X	X	X	X
WHS	X	X	X														X				X		X		
Framingham	X			X											X	X		X	X	X	X				
Framingham-PR	X			X											X	X		X	X		X				
Mayo	X			X	X		X					X			X	X									
HATCH	X			X				X			X					X									

Yr=age, Ht=height, Wt=weight, CF=congestive heart failure, CD=coronary artery disease, MI=myocardial infarction, V=valvular heart disease, CPD=chronic obstructive pulmonary disease, SD=cardiac arrest, Stnt=coronary stent, Str=stroke, DM=diabetes mellitus, KTx=kidney transplant, Hsp=hospitalisation within 2 years for specified cardiovascular and pulmonary conditions, M/F=sex, HTN=medication use for hypertension, Eth=ethanol use, BI=body mass index, M=heart murmur, PR=PR interval on ECG, BP=blood pressure, R=reported race, T=tobacco/smoking status, LAE=left atrial enlargement, LVH=left ventricular hypertrophy.
ARIC, Atherosclerosis Risk in Communities; CHARGE-AF-A, 'Augmented' CHARGE-AF model with ECG variables; CHARGE-AF-S, 'Simple' CHARGE-AF model excluding ECG variables; SAAFE, Screening for Asymptomatic Atrial Fibrillation Events; WHS, Women's Health Study.

reason, a repeat analysis was limited to subjects in ARIC who at exam 3 had a CHA_2DS_2-VASc score of 2 or greater. The results are shown in the right half of table 2 and the receiver operating characteristic curves are shown in online supplementary efigure 1. A total of 5723 subjects had a CHA_2DS_2-VASc score of ≥2 at exam 3, and of those, 117 were diagnosed with atrial fibrillation over the next 3 years. Neither the Framingham or HATCH models nor $CHADS_2$ or CHA_2DS_2-VASc were significantly better than age alone (Framingham P=0.52 and 0.71 with and without ECG variables, respectively; HATCH P=0.55, $CHADS_2$ P=0.31, CHA_2DS_2-VASc P=0.70), while all other models were significantly better than age (P=0.021 for WHS, P=0.01 for Mayo and P<0.001 for all others). There was no significant difference between the best performing risk score (CHARGE-AF-A, with ECG variables) and either ARIC or SAAFE (P=0.15 and P=0.45, respectively). All other comparisons with CHARGE-AF-A were significantly worse (P=0.004 for CHARGE-AF without ECG variables and Mayo, and P<0.001 for all others).

To estimate the effectiveness in identifying subjects at risk, several screening strategies were compared. The baseline strategy was to screen all subjects aged 65 or greater, as has been recommended.[15] There were 2548 subjects that met this criterion and had a CHA_2DS_2-VASc score of 2 or greater. The alternative strategies were to use the WHS, ARIC, Mayo, HATCH, SAAFE, and both CHARGE-AF and Framingham models on all subjects with a CHA_2DS_2-VASc score of 2 or greater, with the threshold for each model adjusted so that 2548 subjects would be screened. The results are shown in table 3. The ARIC, CHARGE and SAAFE models all identified significantly more of the subjects who subsequently developed atrial fibrillation than the baseline strategy.

Decision curve analysis[25] plots the net benefit of a strategy versus the threshold probability of finding a treatable condition. Figure 5 shows the net benefit for the top four models compared with age alone. All of the models outperform age, and in the range 4%–12%, the SAAFE model is generally superior. At threshold probabilities of 2%–4%, the CHARGE-AF model with ECG was superior. If the cost of added ECG was included as 'harm', the net benefit of CHARGE-AF-A and ARIC curves would be reduced, moving those curves downward, while the other curves would be unchanged.

Table 2 Comparison of predictors for incident atrial fibrillation in ARIC over 3 years

	All		CHA_2DS_2-VASc≥2	
Risk model	**AUC (95% CI)**	**P value**	**AUC (95% CI)**	**P value**
Age	0.678 (0.639 to 0.717)	–	0.614 (0.565 to 0.662)	–
SAAFE	0.766 (0.732 to 0.800)	<0.001	0.745 (0.701 to 0.789)	<0.001
CHARGE-AF-A	0.785 (0.750 to 0.819)	<0.001	0.759 (0.715 to 0.803)	<0.001
CHARGE-AF-S	0.775 (0.741 to 0.810)	<0.001	0.742 (0.698 to 0.787)	<0.001
ARIC	0.762 (0.727 to 0.797)	<0.001	0.734 (0.689 to 0.780)	<0.001
WHS	0.725 (0.688 to 0.762)	0.006	0.671 (0.623 to 0.719)	0.02
Framingham	0.626 (0.578 to 0.673)	0.07	0.597 (0.539 to 0.656)	0.52
Framingham-PR	0.639 (0.587 to 0.690)	0.18	0.597 (0.534 to 0.660)	0.71
Mayo	0.721 (0.683 to 0.759)	0.05	0.700 (0.651 to 0.749)	0.01
HATCH	0.659 (0.615 to 0.703)	0.48	0.644 (0.592 to 0.697)	0.55
$CHADS_2$	0.658 (0.613 to 0.702)	0.47	0.639 (0.587 to 0.690)	0.31
CHA_2DS_2-VASc	0.660 (0.615 to 0.706)	0.49	0.654 (0.602 to 0.705)	0.70
Total subjects	11 373		5723	
AF incidence	165		117	

The P values are comparing the C statistic to age alone.
AF, atrial fibrillation; ARIC, Atherosclerosis Risk in Communities; AUC, area under the receiver operating characteristic curve; CHARGE-AF-A, 'Augmented' CHARGE-AF model with ECG variables; CHARGE-AF-S, 'Simple' CHARGE-AF model excluding ECG variables; Framingham PR, Framingham risk model excluding PR interval; SAAFE, Screening for Asymptomatic Atrial Fibrillation Events; WHS, Women's Health Study.

Table 3 Prediction of incident AF in ARIC for CHA_2DS_2-VASc≥2

Risk model	Cases included (%) n=117	Proportion P value	Event NRI	Sum NRI	NRI P value
Age ≥65	71 (61)				
SAAFE	95 (81)	0.001	0.205	0.209	<0.001
CHARGE-AF-A	96 (82)	<0.001	0.214	0.217	<0.001
CHARGE-AF-S	94 (80)	0.002	0.197	0.200	<0.001
ARIC	90 (77)	0.011	0.171	0.174	0.002
WHS	85 (73)	0.071	0.119	0.113	0.016
Framingham	70 (60)	>0.999	−0.009	−0.009	0.878
Framingham-PR	73 (62)	0.893	0.017	0.017	0.770
Mayo	85 (73)*	0.071	0.119	0.113	0.043
CHA_2DS_2-VASc	84 (72)*	0.097	0.111	0.09	0.14
HATCH	NA*				

Thresholds were adjusted so that all strategies would screen the same number of subjects (2548) as age ≥65. Number in parentheses is the percentage of the total incident AF in subjects with CHA_2DS_2-VASc ≥2.
Proportion P value: Fisher's exact two-sided P values, compared with the base frequency for the age criterion (71/117).
Event NRI: net reclassification improvement for subjects who had incident AF.
Sum NRI: sum of event and non-event net reclassification improvement compared with age ≥65.
NRI P value: P value calculated for the sum of net reclassification improvement based on the z-statistic. Note that the P values for all non-event NRIs (not shown) were not significant with the exception of CHA_2DS_2-VASc which was P=0.003, and the P values for the event NRI were similar to those shown.
*For the Mayo score, the closest cut point was for screening 2595 subjects. For CHA_2DS_2-VASc, the nearest cut point was at 2678 subjects, with a transition from 2 to >3. For HATCH, the nearest cut points were at screening 962 subjects or 4574 subjects, so that the comparison is not applicable.
AF, atrial fibrillation; ARIC, Atherosclerosis Risk in Communities; CHARGE-AF-A, 'Augmented' CHARGE-AF model with ECG variables; CHARGE-AF-S, 'Simple' CHARGE-AF model excluding ECG variables; Framingham PR, Framingham risk model excluding PR interval; NA, not applicable; SAAFE, Screening for Asymptomatic Atrial Fibrillation Events; WHS, Women's Health Study.

DISCUSSION

Detection of asymptomatic atrial fibrillation requires evaluation of the cardiac rhythm, and longer periods of rhythm monitoring increase the yield.[13] Any rhythm monitoring can be expensive, and we should try to limit it to those who are most likely to benefit. Our results suggest that a strategy of screening those with CHA_2DS_2-VASc≥2 and a high risk score using the ARIC, SAAFE or either CHARGE-AF model would select a larger proportion of those at risk for further testing than using the age criterion alone, while excluding most of those who would not need treatment if diagnosed, or are at lower risk. The actual yield of a screening programme is likely to be higher than in the current study, since diagnosis in ARIC was using traditional methods, without screening of asymptomatic individuals.

The time frame for prediction of atrial fibrillation for the risk models was extremely variable. SAAFE was a prevalence model, while HATCH is 1-year incidence, CHARGE-AF is 5 years, the Mayo model a mean of 8.5 years and all others 10 years (online supplementary etable 4). Longer time frames can be challenging, since risk factors may change during the observation time, and it seems unlikely that atrial fibrillation risk would only be assessed at such infrequent intervals in practice. Very short time frames may not allow sufficient cases for analysis. We chose 3 years as a compromise since it was a reasonably short time period, and allowed inclusion of the subsequent exam data in the ARIC data set. Clinically, the shorter time frame would allow earlier identification and treatment to reduce stroke risk.

There are a number of differences between the SAAFE model and previous models. The SAAFE model relies almost exclusively on subject-reported demographic and historical data, while many other models include ECG parameters. In spite of derivation based on self-reported prevalence, it showed excellent predictive power for incident atrial fibrillation, performing as well as the best model (CHARGE-AF-A), and better than all other models which do not include the ECG. Of note, the only two models that had comparable performance used ARIC for derivation, either alone or in combination with other data sets.

Age has long been known to be a risk factor for atrial fibrillation,[5 26 27] and our results underscore its importance. The univariate prevalence followed a compound model, with a relative increase in prevalence of 4.4% per year. In the final multivariable model, the effect of age alone was reduced to 2.2% per year due to including the effect of comorbidities, which are covariates with age.

Sex has been considered a risk, however its association in our study was not significant when height was also included, as was reported previously in the ARIC cohort. This effect of inclusion of height-eliminating sex has been noted in the Cardiovascular Health Study as well.[28] Similarly, weight[29 30] and BMI,[4 16] which have been cited as risk factors for atrial fibrillation, were also eliminated once height was included. The reasons for this strong association with height are unclear, although correlation with the size of the atrium, or growth pathway genes that are also associated with atrial fibrillation risk have been proposed.[28]

There are a number of uncertainties that should be addressed before any of these risk models can be put into practice to guide a screening programme for asymptomatic atrial fibrillation. The first is that the threshold probability has yet to be determined, since it is a choice based on a subjective assessment of the relative benefit as a function of the potential yield. As noted above, that relative benefit would also be influenced by the assessment of 'harm' associated with the cost of additional testing, such as ECG.

The current study adjusted the thresholds of each model so that the same number of subjects was screened as with the recommended age criterion, but it is not clear that this is optimal. None of these models have been calibrated to predict absolute risk of developing atrial fibrillation over a shorter, clinically relevant time frame, and ARIC most likely underestimates the true burden of atrial fibrillation that would be found if a screening programme were implemented. The choice of threshold value should also be influenced by the method of screening contemplated. Lower cost screening methods could be applied to a larger, lower risk population without incurring excessive expenditures.

There is also a question about application to different populations. Two of the best performing models (ARIC and CHARGE-AF) were totally or partially derived from the ARIC data set, and therefore may be overfitted to it. The effect of ethnicity is most probably more complicated than used in the current models. The classification of race in ARIC was limited to Caucasian and African American, and the reason for the differences in incident atrial fibrillation in these groups is unclear. Finally, the importance of other risk factors such as presence of valvular heart disease or implantable pacemaker was not assessed.

All of the best performing models were computed using the full coefficients, rather than simple point systems. Although this means that the calculation is more complicated, web and smartphone tools could be developed to perform the calculations, as they have for other models.

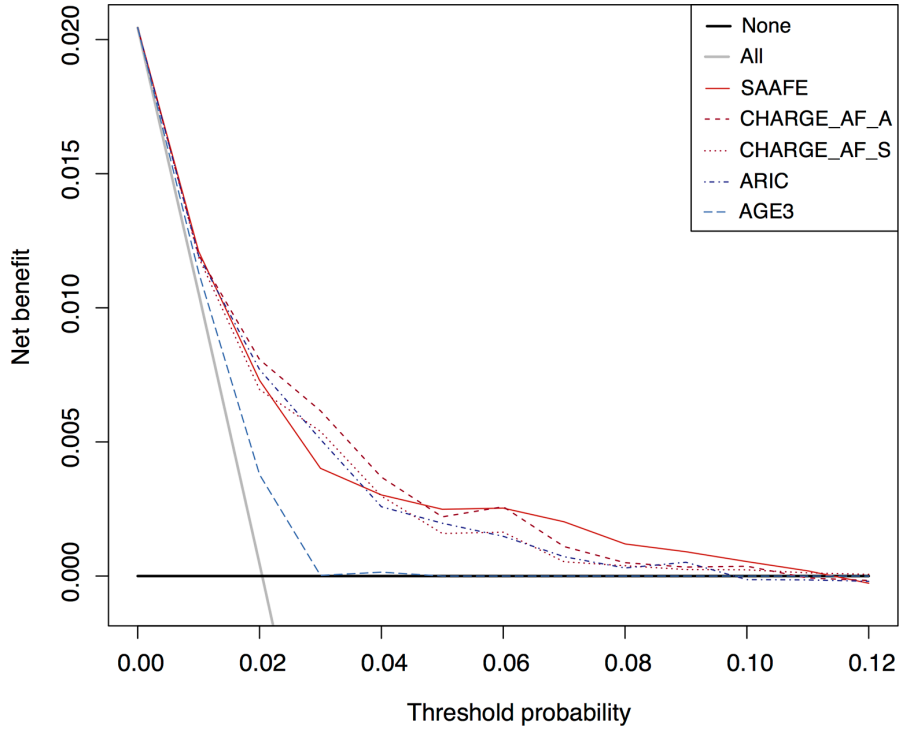

Figure 5 Decision curve for predicting incident atrial fibrillation in ARIC over 3 years in subjects with CHA_2DS_2-VASc≥2 in ARIC. The two best performing models with and without ECG, and age alone were included. All of the models show superior net benefit compared with the simple age criterion. AGE3, age at exam 3; ARIC, Atherosclerosis Risk in Communities; CHARGE-AF-A, 'Augmented' CHARGE-AF model with ECG variables; CHARGE-AF-S, 'Simple' CHARGE-AF model excluding ECG variables; SAAFE, Screening for Asymptomatic Atrial Fibrillation Events (model developed in the current study).

CONCLUSIONS

This study revealed that multivariable risk models performed better than an age criterion for identifying subjects at risk for developing atrial fibrillation and therefore stroke. It also showed that a prevalence risk model for atrial fibrillation using self-reported data with no need for medical tests or examination performed comparably to other existing risk models at predicting incident atrial fibrillation over a 3-year period. A strategy of screening subjects based on CHA_2DS_2-VASc and the SAAFE risk model could provide more effective screening for atrial fibrillation than simple age-based screening.

Our model could be easily incorporated by physicians as a screening tool used in a medical setting to identify patients who could benefit from rhythm monitoring to diagnose asymptomatic atrial fibrillation, and thereby potentially reduce the burden of stroke.

Key messages

What is already known on this subject?
Asymptomatic atrial fibrillation is a risk factor for stroke, and treatment can reduce that risk. Screening for paroxysmal asymptomatic atrial fibrillation should be targeted at those at higher risk to be cost-effective, and age has been proposed as a criterion for screening.

What might this study add?
Some clinical risk models performed better than age alone in predicting those likely to be diagnosed with atrial fibrillation, while others were worse. One of the best models did not require any additional testing, meaning that it would not add to the cost of screening.

How might this impact on clinical practice?
The use of clinical risk models could increase the yield of a screening programme for asymptomatic paroxysmal atrial fibrillation, while not adding to the cost.

Acknowledgements ARIC data came from the NHLBI Biologic Specimen and Data Repository Information Coordinating Center. The authors acknowledge and thank Sarah L Mikhitarian for managing the databases and queries for analysis of MDCC. These healthcare entities reviewed the medical records for participants in MDCC: Auburn Regional Medical Center, Group Health Cooperative, Harborview Medical Center, HealthPoint, Northwest Medical Center, Overlake Hospital Medical Center, Snoqualmie Valley Hospital, University of Washington Medical Center, University of Washington Comprehensive Stroke Center, Emergency Medical Services at Seattle and King County Public Health.

Contributors AHM conceived and designed the MDCC study and critically revised the current manuscript. TBM acquired the data in the MDCC study and critically revised the current manuscript. DTL conceived and designed the SAAFE study, conceived and designed the current study, performed the statistical analysis and drafted the manuscript.

Funding Life Sciences Discovery Fund of Washington State, Seattle, WA (Grant 5628758) and National Heart, Lung and Blood Institute of the NIH, Bethesda, MD (Grant RC2HL101759).

Disclaimer This paper does not necessarily reflect the opinions or views of ARIC or the NHLBI.

Competing interests DTL reports stock ownership in Cardiac Insight, a company developing new ambulatory cardiac monitoring solutions, and patents related to automated detection of atrial fibrillation.

Ethics approval Institutional Review Board of the University of Washington.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No new data were collected in this study. The ARIC data set is available from the NHLBI Biologic Specimen and Data Repository Information Coordinating Center. The MDCC data will be available as soon as it has been deidentified.

REFERENCES

1 Lloyd-Jones DM, Wang TJ, Leip EP, *et al*. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. *Circulation* 2004;110:1042–6.
2 Heeringa J, van der Kuip DA, Hofman A, *et al*. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. *Eur Heart J* 2006;27:949–53.
3 AS G, Hylek EM, Phillips KA, *et al*. Prevalence of diagnosed atrial fibrillation in adults: National implications for rhythm management and stroke prevention: The anticoagulation and risk factors in atrial fibrillation (ATRIA) study. *JAMA* 2001;285:2370–5.
4 Miyasaka Y, Barnes ME, Gersh BJ, *et al*. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation* 2006;114:119–25.
5 Feinberg WM. Prevalence, Age Distribution, and Gender of Patients With Atrial Fibrillation. *Arch Intern Med* 1995;155:469–73.
6 Page RL, Wilkinson WE, Clair WK, *et al*. Asymptomatic arrhythmias in patients with symptomatic paroxysmal atrial fibrillation and paroxysmal supraventricular tachycardia. *Circulation* 1994;89:224–7.
7 Halcox JPJ, Wareham K, Cardew A, *et al*. Assessment of remote heart rhythm sampling using the alivecor heart monitor to screen for atrial fibrillation: the REHEARSE-AF study. *Circulation* 2017;136:1784–94.
8 Engdahl J, Andersson L, Mirskaya M, *et al*. Stepwise screening of atrial fibrillation in a 75-year-old population: implications for stroke prevention. *Circulation* 2013;127:930–7.
9 Svennberg E, Engdahl J, Al-Khalili F, *et al*. Mass screening for untreated atrial fibrillation: the STROKESTOP study. *Circulation* 2015;131:2176–84.
10 van den Ham HA, Klungel OH, Singer DE, *et al*. Comparative performance of ATRIA, CHADS2, and CHA2DS2 VASC risk scores predicting stroke in patients with atrial fibrillation: results from a national primary care database. *J Am Coll Cardiol* 2015;66:1851–9.
11 Martinez C, Katholing A, Freedman SB. Adverse prognosis of incidentally detected ambulatory atrial fibrillation. A cohort study. *Thromb Haemost* 2014;112:276–86.
12 Hart RG, Halperin JL. Atrial fibrillation and thromboembolism: a decade of progress in stroke prevention. *Ann Intern Med* 1999;131:688–95.
13 Botto GL, Padeletti L, Santini M, *et al*. Presence and duration of atrial fibrillation detected by continuous monitoring: crucial implications for the risk of thromboembolic events. *J Cardiovasc Electrophysiol* 2009;20:241–8.
14 Ben Freedman S, Lowres N. Asymptomatic atrial fibrillation: the case for screening to prevent stroke. *JAMA* 2015;314:1911–2.
15 Kirchhof P, Benussi S, Kotecha D, *et al*. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur J Cardiothorac Surg* 2016;50:e1–e88.
16 Schnabel RB, Sullivan LM, Levy D, *et al*. Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. *Lancet* 2009;373:739–45.
17 de Vos CB, Pisters R, Nieuwlaat R, *et al*. Progression from paroxysmal to persistent atrial fibrillation clinical correlates and prognosis. *J Am Coll Cardiol* 2010;55:725–31.
18 Chamberlain AM, Agarwal SK, Folsom AR, *et al*. A clinical risk score for atrial fibrillation in a biracial prospective cohort (from the Atherosclerosis Risk in Communities [ARIC] study). *Am J Cardiol* 2011;107:85–91.
19 Everett BM, Cook NR, Conen D, *et al*. Novel genetic markers improve measures of atrial fibrillation risk prediction. *Eur Heart J* 2013;34:2243–51.
20 Alonso A, Krijthe BP, Aspelund T, *et al*. Simple risk model predicts incidence of atrial fibrillation in a racially and geographically diverse population: the CHARGE-AF consortium. *J Am Heart Assoc* 2013;2:e000102.
21 Brunner KJ, Bunch TJ, Mullin CM, *et al*. Clinical predictors of risk for atrial fibrillation: implications for diagnosis and monitoring. *Mayo Clin Proc* 2014;89:1498–505.
22 Roth GA, Gillespie CW, Mokdad AA, *et al*. Aspirin use and knowledge in the community: a population- and health facility based survey for measuring local health system performance. *BMC Cardiovasc Disord* 2014;14:16.
23 The atherosclerosis risk in communities (ARIC) study: Design and objectives. The ARIC investigators. *Am J Epidemiol* 1989;129:687–702.
24 January CT, Wann LS, Alpert JS, *et al*. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 20142014;64:e1–e76.
25 Vickers AJ. Decision analysis for the evaluation of diagnostic tests, prediction models and molecular markers. *Am Stat* 2008;62:314–20.
26 Benjamin EJ, Levy D, Vaziri SM, *et al*. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *JAMA* 1994;271:840–4.
27 Krahn AD, Manfreda J, Tate RB, *et al*. The natural history of atrial fibrillation: Incidence, risk factors, and prognosis in the manitoba follow-up study. *Am J Med* 1995;98:476–84.
28 Rosenberg MA, Patton KK, Sotoodehnia N, *et al*. The impact of height on the risk of atrial fibrillation: the Cardiovascular Health Study. *Eur Heart J* 2012;33:2709–17.
29 Wang TJ, Parise H, Levy D, *et al*. Obesity and the risk of new-onset atrial fibrillation. *JAMA* 2004;292:2471–7.
30 Frost L, Hune LJ, Vestergaard P. Overweight and obesity as risk factors for atrial fibrillation or flutter: the Danish diet, cancer, and health study. *Am J Med* 2005;118:489–95.