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CLINICAL RESEARCH
Atrial fibrillation

Estimated incidence of previously undetected atrial fibrillation on a 14-day continuous electrocardiographic monitor and associated risk of stroke

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Aims There is uncertainty about whether and how to perform screening for atrial fibrillation (AF). To estimate the incidence of previously undetected AF that would be captured using a continuous 14-day ECG monitor and the associated risk of stroke.

Methods and results We analysed data from a cohort of patients >65 years old with hypertension and a pacemaker, but without known AF. For each participant, we simulated 1000 ECG monitors by randomly selecting 14-day windows in the 6 months following enrolment and calculated the average AF burden (total time in AF). We used Cox proportional hazards models adjusted for CHA_2DS_2-VASc score to estimate the risk of subsequent ischaemic stroke or systemic embolism (SSE) associated with burdens of AF > and <6 min. Among 2470 participants, the median CHA_2DS_2-VASc score was 4.0, and 44 patients experienced SSE after 6 months following enrolment. The proportion of participants with an AF burden >6 min was 3.10% (95% CI 2.53–3.72). This was consistent across strata of age and CHA_2DS_2-VASc scores. Over a mean follow-up of 2.4 years, the rate of SSE among patients with <6 min of AF was 0.70%/year, compared to 2.18%/year (adjusted HR 3.02; 95% CI 1.39–6.56) in those with >6 min of AF.

Conclusions Approximately 3% of individuals aged >65 years with hypertension may have more than 6 min of AF detected by a 14-day ECG monitor. This is associated with a stroke risk of over 2% per year. Whether oral anticoagulation will reduce stroke in these patients is unknown.

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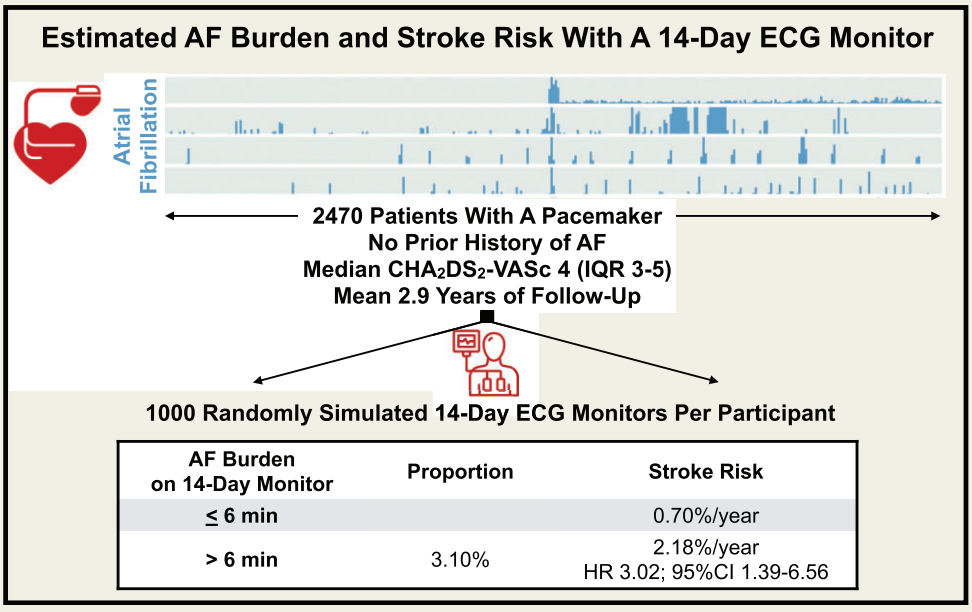
Graphical Abstract



Keywords Atrial fibrillation • Screening • Holter monitor • Stroke • Simulation • Oral anticoagulation

What's new?

- We used pacemaker data to simulate population-based screening for atrial fibrillation (AF) with a 14-day ECG monitor, estimating the incidence of AF episodes lasting at least 6 min and the associated risk of stroke.
- Among 2470 participants with a median CHA_2DS_2-VASc score of 4.0, the proportion with an AF burden >6 min on a simulated 14-day continuous ECG was 3.10% (95% CI 2.53–3.72%).
- Over a mean follow-up of 2.4 years, the rate of stroke or systemic embolism among patients with <6 min of AF was 0.70%/year, compared to 2.18%/year (adjusted HR 3.02; 95% CI 1.39–6.56) in those with >6 min of AF.
- Randomized controlled trials are needed to test the safety and efficacy of AF screening—a cut off of 6 min of AF on a 14-day Holter monitor is a promising strategy for such trials.

Introduction

Undiagnosed, atrial fibrillation (AF) is believed to account for a large number of preventable ischaemic strokes.[1–4] There is global interest in evaluating the feasibility and efficacy of using ambulatory electrocardiogram (ECG) technologies to screen at-risk patients for undiagnosed AF to prevent strokes.[4,5] This interest is driven by the practicality and ubiquity of modern ambulatory ECG technologies, the potentially disabling impact of stroke and the convenience, safety and efficacy of contemporary oral anticoagulation (OAC).[4,6–12] Recently, the United States Preventative Services Task Force concluded that there is presently insufficient evidence to recommend for or against AF screening.[13] Similarly, the European Society of Cardiology (ESC) has recommended further research into systematic AF-screening programmes.[14]

Central to the problem of population-based AF screening is the uncertainty that surrounds the minimum duration of AF associated with a stroke risk high enough to justify the use of OAC.[15–17] Stroke risk increases proportionally with AF burden, yet there is no consensus on the minimum duration or burden of AF that should prompt initiation of OAC.[17,18] Several publications have proposed a 'cut-off' point of 6 min, but the practicality of this threshold remains unclear.[19–23]

We randomly sampled continuous heart rhythm data from patients without a history of clinical AF to estimate the proportion of patients that would have a burden of AF >6 min detected by a single continuous 14-day ECG monitor. We estimated the associated risk of ischaemic stroke or systemic embolism (SSE) above and below this threshold.

Methods

For this study, we used data collected in the Stroke Evaluation in pacemaker patients and the atrial fibrillation Reduction atrial pacing Trial (ASSERT). The methods, rationale, and primary results of ASSERT have

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Table 1 Baseline characteristics of the population used for simulated screening

	Overall (*N* = 2470)
Age (year), mean±SD	76.2 ± 6.6
Sex (male), *n* (%)	1431 (57.9)
BMI (kg/m^2), mean±SD	27.4 ± 4.9
History of heart failure, *n* (%)	357 (14.5)
Hypertension, *n* (%)	2469 (100)
Diabetes mellitus, *n* (%)	693 (28.1)
Prior stroke, *n* (%)	173 (7.0)
Prior TIA, *n* (%)	116 (4.7)
Prior myocardial infarction, *n* (%)	432 (17.5)
CHA_2DS_2-VASc score, median (IQR)	4.0 (3.0–5.0)
Time from implantation of pacemaker/ICD to enrolment (days), median (IQR)	28.0 (8.0–42.0)

BMI, body mass index; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; SD, standard deviation.

been published previously.[20,24] The study enrolled 2580 patients, aged ≥65 years and with a history of hypertension who underwent *de novo* implantation of a St Jude Medical (St Paul, MN, USA) dual-chamber pacemaker or implantable cardioverter-defibrillator (ICD). ASSERT excluded patients with a history of clinical AF or atrial flutter lasting >5 min and those that were taking OAC therapy for any indication. In this study, we analysed study participants with at least 6 months of follow-up. An ethics committee at each participating centre reviewed and approved the original trial and all patients provided written informed consent. There was central adjudication of all electrograms showing device-detected AF (defined as atrial rate >190 b.p.m.) for >6 min and 50% of electrograms showing device-detected AF <6 min.

For this current, *post hoc* analysis, we examined the date and duration of all episodes of device-detected AF occurring over the entire follow-up period.[25] Over a mean follow-up of 2.5 years, at least one episode of device-detected AF of >6 min in duration was documented in 34.7% of participants.[20,24] The rate of false positives was inversely associated with episode duration: episodes lasting ≥6 min had a positive predictive value of 83%, while those lasting <6 min had a positive predictive value of only 48%.[26] Therefore, we chose a total AF burden threshold of 6 min to be consistent with the primary analysis of ASSERT. We chose a 14-day monitoring period for our primary analysis 14 days due to the widespread availability of this technology and its established efficacy in detecting AF.[9,11,27,28] We performed sensitivity analyses using continuous 7- and 30-day monitoring periods.

Statistical analysis

Baseline characteristics are summarized with frequency/percentage for categorical variables and mean/standard deviation (SD) for continuous variables. For each participant, we simulated a continuous 14-day ECG monitor by randomly selecting a 14-day window in the first 6 months following enrolment. We measured the total cumulative time in AF during that 14-day window, defined as the AF burden. We repeated random sampling 1000 times for each participant to ensure a robust estimate of the likelihood of capturing AF on a single monitor. In order to test the generalizability of our results, we estimated the AF burden that would be detected by simulated monitors performed across strata of age and CHA_2DS_2-VASc score and at different time points over the total follow-up period.

We used Cox proportional hazards models adjusted for CHA_2DS_2-VASc score to estimate the subsequent risk of ischaemic stroke or SSE associated with AF burdens < and >6 min in a randomly selected 14-day window in the first 6 months following enrolment, repeating random sampling 1000 times. We derived the standard error of the log hazard ratio (HR) from its sample SD over the 1000 replicates and constructed a 95% confidence interval (95% CI) assuming a normal distribution. We performed sensitivity analyses using 500 and 2000 simulations and using continuous 7- and 30-day windows. We considered a two-sided *P*-value <0.05 to be statistically significant. All analyses were conducted using SAS 9.4 software (SAS Institute, Inc., Cary, NC, USA).

Results

Among 2470 participants with at least 6 months of follow-up, 57.9% were men and the median CHA_2DS_2-VASc score was 4.0 [interquartile range (IQR) 3.0–5.0]. *Table 1* displays characteristics of the study population.

The proportion of participants with a burden of >6 min of AF on a single 14-day monitor within 6 months after enrolment was estimated as 3.1%, this proportion was consistent when we tested time periods other than the first 6 months following enrolment (*Table 2*). Among ECG monitors with >6 min of AF, the average burden of AF was 55.3 ± 104.7 h in 14 days and the median burden was 6.1 (IQR 1.1–38.3) hours in 14 days. Crude rates of AF detection remained similar across strata of age, CHA_2DS_2-VASc score, and sex (*Table 3*).

Over a mean follow-up of 2.4 years (beginning 6 months following enrolment), 44 patients had a first ischaemic stroke or SSE. The event rate among patients with total AF burden <6 min was 0.70%/year (*Table 4*). An AF burden >6 min was associated with a significant increase in the risk of stroke or SSE (2.18%/year; adjusted HR 3.02; 95% CI 1.39–6.56). In sensitivity analyses, we obtained similar results for AF detection and associated stroke risk when we performed 500 and 2000 simulations (Supplementary material online, *Appendix Tables S1–S4*). Sensitivity analyses testing a 7-day monitoring showed a slightly lower yield of AF detection and a higher hazard for stroke among participants in whom AF was detected (Supplementary material online, *Appendix Tables S5* and *S6*). In contrast, Sensitivity analyses testing a 30-day monitoring showed a slightly higher yield of AF detection and a lower hazard for stroke among participants in whom AF was detected (Supplementary material online, *Appendix Tables S7* and *S8*).

Discussion

Main findings

In this study, we estimated the rate of AF detection with a single 14-day ECG monitor in hypertensive patients aged 65 and older, without a history of clinical AF. We found that the proportion of study participants with an AF burden of more than 6 min on a simulated 14-day continuous ECG monitor was ~3%. The burden of AF remained similar with increasing age and CHA_2DS_2-VASc score. Detection of more than 6 min of AF was associated with an absolute risk of subsequent ischaemic stroke or SSE of 2.18% per year, a risk that was three

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Table 2 Proportion of patients with AF burden >6 min detected within randomly selected 2-week window[a] in different time periods during follow-up

Time period of simulated 14-day window following enrolment into ASSERT							
0–6 months (*N* = 2470)		6–12 months (*N* = 2378)		1–2 years (*N* = 1949)		2–3 years (*N* = 1126)	
n	%	*n*	%	*n*	%	*n*	%
	(95% CI)		(95% CI)		(95% CI)		(95% CI)
77	3.10 (2.53–3.72)	64	2.70 (2.19–3.24)	58	2.97 (2.41–3.59)	41	3.63 (2.75–4.53)

ASSERT, atrial fibrillation Reduction atrial pacing Trial.
[a]Random selection was repeated 1000 times. The 95% confidence interval was constructed using percentile approach.

Table 3 Proportion of patients with AF burden >6 min detected within randomly selected 2-week window[a] in the first 6 months after enrolment by age groups, CHA_2DS_2-VASc score, and sex

Age in years									
<70 (*N* = 455)			70–75 (*N* = 682)			>75 (*N* = 1333)			
n	% (95% CI)		*n*	% (95% CI)		n	% (95% CI)		
13	2.90 (1.54–4.40)		19	2.79 (1.76–3.81)		44	3.33 (2.55–4.20)		
CHA_2DS_2-VASc score									
2 (*N* = 259)		3 (*N* = 691)		4 (*N* = 756)		5 (*N* = 457)		≥6 (*N* = 295)	
n	%	*n*	%	*n*	%	*n*	%	*n*	%
	(95% CI)		(95% CI)		(95% CI)		(95% CI)		(95% CI)
9	3.47 (1.54–5.41)	20	2.90 (1.88–4.05)	26	3.50 (2.38–4.63)	12	2.53 (1.53–3.94)	9	3.13 (1.69–4.75)

	Sex			
	Male (*N* = 1431)		Female (*N* = 1039)	
	n	%	*n*	%
		(95% CI)		(95% CI)
AF burden >6 min	46	3.18 (2.45–3.98)	31	2.99 (2.21–3.85)

AF, atrial fibrillation; 95% CI, 95% confidence interval.
[a]Random selection was repeated 1000 times. The 95% confidence interval was constructed using percentile approach.

times higher than in patients who had 6 min or less of AF. This absolute risk is the same as for a woman with established AF and a CHA_2DS_2-VASc score of three or a man with established AF and a CHA_2DS_2-VASc score of two in the Swedish Atrial Fibrillation cohort.[29] Both the ESC and the American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines recommend OAC for these patients. Thus, a total burden of more than 6 min of AF on a single 14-day ECG monitor may be a practical cut-off point above which the risk of stroke is high enough to justify OAC.

Interpretation of results

This study suggests that a significant proportion of older hypertensive adults could have previously undiagnosed AF detected by a screening 14-day continuous ECG monitor. Importantly, both the relative and

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Table 4 Risk of ischaemic stroke or SSE according to the presence of absence of an AF burden >6 min in a randomly selected 2-week window[a]

AF burden detected		AF burden not detected		Unadjusted		Adjusted[b]	
Events/patients (*n*/*N*)	Rate (%/year)	Events/patients (*n*/*N*)	Rate (%/year)	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
4/77	2.18	40/2393	0.70	2.94 (1.34–6.45)	0.007	3.02 (1.39–6.56)	0.005

AF, atrial fibrillation; 95% CI, 95% confidence interval; HR, hazard ratio.
[a]Window selected in the first 6 months following enrolment, random selection was repeated 1000 times.
[b]Adjusted for CHA_2DS_2-VASc score.

absolute risk of stroke associated with these episodes was high. Interestingly, the yield of AF detection did not vary with age or CHA_2D_2S-VASc score. This suggests that such an approach could be implemented and tested in a relatively unselected population. The small variability when the simulated monitors were repeated at different times during follow-up suggests a high likelihood of reproducibility of these results.

Our findings may inform efforts for population-based AF screening. For at-risk patients to benefit from AF screening, two important assumptions must hold true. The first is that patients with screening-detected AF will initiate OAC. However, published cohort studies of AF screening show variable uptake of OAC.[30,31] The second assumption is that they will derive the same benefit as patients in previous studies.[4] Observational studies suggest that low-burden AF detected by screening may confer relatively lower risks of stroke, and that patients with screen-detected AF may not derive the same benefit from OAC as those who were studied in landmark OAC trials.[16,17,32–35] Thus, definitive evidence from randomized controlled trials is required to assess this problem.[36,37] This study sets the basis for a pragmatic approach for randomized studies testing AF screening.

Previous studies

This study is novel because it uses simulated continuous ECG monitoring in a population of patients without a history of AF monitors, and with <2% use of OAC during follow-up to estimate both AF yield from screening and the associated stroke risk.[38–44] Several previous studies have simulated shorter-duration ECG monitors from implanted loop recorder (ILR) or pacemaker data.[38–44] These studies were limited in that they were performed on patients with known history of AF,[38–40] only assessed a subset of screened patients in whom AF was found,[41,42] or were conducted in the cryptogenic stroke population.[39,43]

The rate of AF detection in this study [3.1% (95% CI 2.53–3.72) with an AF burden >6 min on a single simulated 14-day continuous ECG monitor] is consistent with several previously published screening studies using both implantable monitors and surface ECGs.[45–51] A series of observational studies using ILRs detected >5 min of previously unrecognized AF in 6.1–12% of participants within 30–90 days of monitoring.[45–47] The rate of AF in our study is comparable to that found in 14-day patch ECG studies.[49–51] In the mHealth Screening to Prevent Strokes (mSTOPS) study, among 1366 individuals (mean age 73.7 + 7 years, median CHA_2DS_2-VaSC 3.0), the proportion of participants with AF ≥30 s was 3.9%.[49] In the Multi-Ethnic Study of Atherosclerosis (MESA), among 804 participants (mean age 75 + 8 years, 54% HTN, 18% DM) AF ≥30 s was detected in 4.0%.[50] In the Atherosclerotic Risk in Communities (ARIC) study, among 2616 participants (mean age 79 ± 5 years, mean CHA_2DS_2-VaSC 3.9 ± 1.2) the overall rate of AF >30 s was 2.2%.[51] Among 434 participants aged 75 years or older with hypertension and without known AF who wore a 14-day ECG monitor in the SCREEN-AF RCT, AF was detected in 5.3%.[52] The median burden of AF in SCREEN AF [6.3 h (IQR 4.2–14.0 h)] was similar to what we found in this study. The REVEAL AF investigators simulated 14-day monitoring in 385 patients without AF who had an ILR. Among adults aged 71.5 ± 9.9 years and with a mean CHADS2 score 3.0 ± 1.0, the rate of AF ≥6 min with a single simulated 14-day monitor was 3.1% (95% CI 1.4–4.8%).[44] The consistency of our findings with those of prior studies supports both the validity and generalizability of our results.

Two ongoing randomized control trials (ARTESiA and NOAH-AFNET 6) are assessing the role of OAC in patients with a least 6-min device-detected AF.[36,53] The results of these trials may inform further efforts for AF screening.

Strengths and limitations

The strengths of our analysis are the inclusion of stroke outcomes and the low rate of OAC initiation in this population (<2%). The latter mitigates much of the potential confounding in our findings.

The most important limitation of this *post hoc* study is its simulated observational design. Although this is the first study of its kind to include thromboembolic outcomes, the total number of patients with a stroke or SSE was small. This study cohort is comprised of hypertensive patients aged at least 65 years implanted with a pacemaker or an implantable ICD. Thus, participants in this study could have a higher likelihood of underlying heart disease than similarly aged patients without a cardiac implantable electronic device; however, consistency of our AF detection rates with those from ILR and ambulatory ECG studies suggests that our findings could be generalizable.

Our study used an AF burden cut off of 6 min, based on the positive predictive value of AF detected by automatic algorithms in pacemakers and ICDs.[26] Thus, the risk associated with lower burdens of AF is unclear and we had limited power to examine the risk of stroke associated with longer AF durations (e.g. 6 and 24 h). We do not take into account different patterns of AF burden (e.g. frequent short episodes vs. infrequent longer episodes) although stroke risk could vary according to these phenotypes.[54] It is also not certain that

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ambulatory ECG would capture all episodes of device-detected AF, although the overall sensitivity of Holter monitoring for capturing AF that occurs during the monitoring period is likely to be high.[7,11] Finally, it remains unproven whether the bleeding risks conferred by OAC are outweighed by the stroke prevention benefit in patients with device-detected AF. Randomized clinical trials are required to definitively assess the impact of AF screening on stroke prevention in the general population.

Conclusions

Approximately 3% of individuals aged >65 years with hypertension and a pacemaker may have a burden of more than 6 min of AF detected by a single 14-day continuous ECG monitor; this burden is associated with a three-fold increased risk of stroke, and an absolute risk exceeding the conventional thresholds for OAC. These data were simulated from patients with a pacemaker or ICD and whether or not they would apply to patients without a device is unclear. Whether or not these patients will derive net benefit from treatment with OAC is currently unknown.

Supplementary material

Supplementary material is available at *Europace* online.

Funding

The ASSERT trial was supported by St. Jude Medical. They had no role in this *post hoc* sub-study.

Conflict of interest: W.F.M. is supported by a fellowship awards from the Canadian Institutes of Health Research and the Canadian Stroke Prevention Intervention Network. He has received speaking fees from Bayer and Servier. S.J.C. has received grant support and consulting fees from Abbott. R.D.L. reports receiving grant support, paid to his institution, and consulting fees from Bayer, Bristol Myers Squibb, GlaxoSmithKline, Medtronic, Pfizer, and Sanofi and consulting fees from Boehringer Ingelheim, Daiichi Sankyo, Merck, and Portola. M.R.G. is on the steering committee for Boston Scientific Corporation, Medtronic, and St Jude; and has received consulting and lecture fees from Medtronic and Boston Scientific Corporation. S.H.H. has received consulting fees from Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Johnson & Johnson, Pfizer, Medtronic, and St Jude Medical; and lecture fees from Boehringer Ingelheim, Bayer, Bristol-Myers Squibb, Pfizer, and Abbott. C.W.I. has received honoraria for presentations, reimbursement of travel costs, and congress fees from Abbott and St Jude Medical. D.C. holds a McMaster University Department of Medicine Mid-Career Research Award and is supported by the Hamilton Health Sciences RFA Strategic Initiative Program. J.S.H. is supported by the Population Health Research Institute Stuart Connolly Chair in Cardiology Research at McMaster University; has received research grants from St Jude Medical, Boehringer Ingelheim, Medtronic, Bristol-Myers Squibb/Pfizer, and Boston Scientific; and speaking fees from St Jude Medical, Boston Scientific, and Medtronic. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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