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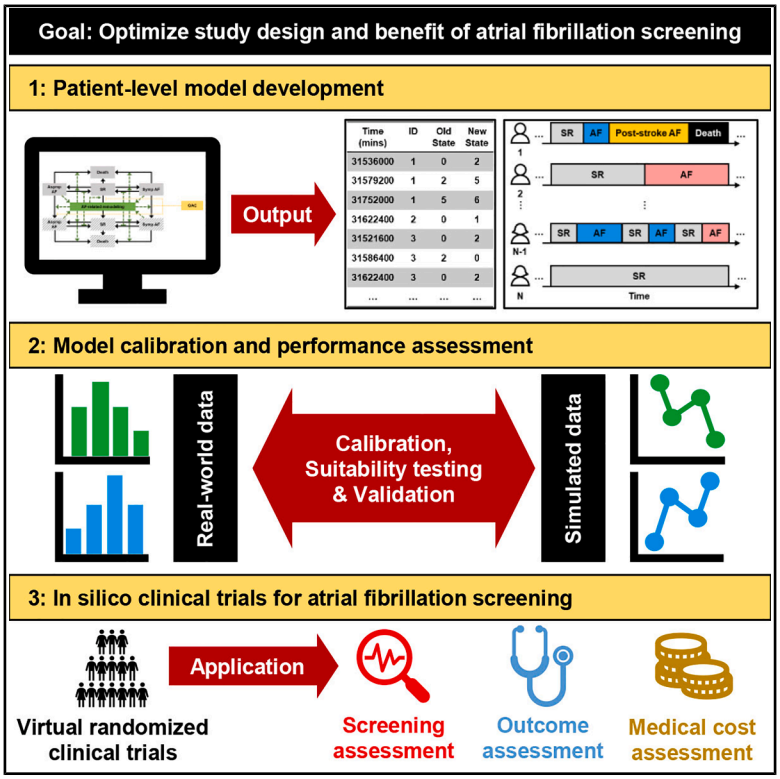
Optimizing atrial fibrillation management using a novel patient-level computational model

Graphical abstract



Highlights

- We present a novel computer model simulating atrial fibrillation patterns/outcomes
- The model captures episode- and population-level metrics of atrial fibrillation
- Screening improves atrial fibrillation detection, but stroke reduction is limited
- Stroke reduction from screening depends on disease and healthcare system factors

Authors

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In brief

Cai et al. present a novel patient-level computer model simulating atrial fibrillation (AF) episodes, progression, and clinical outcomes across a lifetime, reproducing numerous real-world studies. Virtual randomized trials show improved AF detection from screening, while stroke prevention is modest and depends on individual risk profiles, timely treatment, and anticoagulation efficacy.

Translation to Patients

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Optimizing atrial fibrillation management using a novel patient-level computational model

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CONTEXT AND SIGNIFICANCE Atrial fibrillation (AF) is the most common heart-rhythm disorder associated with higher stroke risks. Systematic screening aims for early AF detection and management; however, the best screening strategy and its benefits remain uncertain. This study presents a new computer model simulating how AF develops and progresses throughout life and tests different screening approaches in virtual randomized trials. The simulations suggest that while screening identifies more individuals with AF, the stroke reduction from simulated oral anticoagulation in the general population is modest. However, benefits are greater in people with higher stroke risks, limited access to medical care, or with more effective anticoagulants. This work provides new insights to guide the design of cost-effective screening strategies and personalized AF management.

SUMMARY

Background: The dynamic, heterogeneous nature of atrial fibrillation (AF) episodes and poor symptom-rhythm correlation make early AF detection challenging. The optimal screening strategy for early AF detection and its role in stroke prevention are unknown.

Methods: To analyze the impact of screening-mediated AF detection on stroke risk, a Markov-like computer model was created that captured seven clinical states. AF-related atrial remodeling was incorporated, which influenced the age-/sex-dependent transition probabilities between states. Model calibration/validation was performed by replicating clinical studies. The effect of screening strategies on early AF diagnosis and subsequent modulation of stroke rate by simulated oral anticoagulation were assessed.

Findings: The model simulates the entire lifetime of virtual patients with 30-min resolution and provides precise information on the occurrence of AF episodes and clinical outcomes. It replicates numerous age/sex-specific episode- and population-level AF metrics and clinical outcomes. The benefits of intermittent AF screening were frequency and duration dependent, with systematic thrice-daily single electrocardiogram providing the highest detection rates. Screening groups had comparable 5-year and lower 25-year stroke rates than the control group. These differences were increased by more effective anticoagulation therapy, in patients with higher baseline stroke risk, or with delayed clinical AF diagnosis.

Conclusions: We present a novel computational patient-level AF model consistent with a large body of real-world data, enabling for the first time the systematic assessment of AF-management strategies. More frequent and longer screening has higher AF-detection rates, but stroke reduction is highly dependent on patients' and healthcare-systems' characteristics.

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INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia[1,2] and is associated with higher risks of stroke/systemic embolism, heart failure, and mortality.[3–5] Early detection and treatment have been shown to improve outcomes[6] but remain challenging in clinical practice, due to the highly variable duration of AF episodes, heterogeneous dynamic AF progression, and poor symptom-rhythm correlation.[7,8] The optimal screening strategy to promote early AF detection and the benefits of anticoagulation therapy in patients with screening-detected AF remain a topic of debate[9,10] due to heterogeneous risk profiles in the target population, wide range of available monitoring devices, and heterogeneous AF patterns of patients. The high costs of clinical trials due to the low incidence of strokes preclude systematic analyses of these factors in clinical studies.

Computational modeling potentially offers significant advantages, including precise control over all parameters, the ability to track dynamic changes of all components, and the feasibility of comprehensively assessing various interventions. There is a long-standing history of computational modeling in cardiac electrophysiology with important real-world implications.[11,12] However, currently available mechanistic models have only been used for short-term simulations (seconds to minutes). Health-technology assessment models, on the other hand, are commonly used to assess cost effectiveness of therapies[13,14]; however, these have so far ignored disease pathophysiology, AF development, and progression. Here, we present and validate the first computational patient-level AF model able to simulate individual episode-level AF incidence and progression, population-level AF characteristics, key pathophysiological concepts, and relevant clinical outcomes during the entire lifetime of a virtual cohort. This approach is distinct from existing digital-twin approaches that aim to create a personalized model of a single patient (e.g., based on non-invasive imaging) to simulate local electrograms or body surface electrocardiograms (ECGs).[11,12] Instead, our model simulates stochastic changes in the clinical states (Figure S1) for each individual in a large virtual population during their entire (adult) lifetime. The model output comprises a list of transitions that can subsequently be analyzed to calculate, e.g., the prevalence of AF at a given age by counting which virtual individual is still alive at that age and had an AF-related state transition before this moment in time (Figure S2). In contrast to previous health-technology assessment models that also simulate the occurrence of clinical events, our novel approach also integrates key components of AF pathophysiology, including AF-related remodeling, enabling, e.g., the simulation of AF progression. We employ this model to identify effective AF-screening strategies, elucidate the impact of AF screening on clinical outcomes, and explore healthcare factors that can influence the effectiveness of AF screening in virtual randomized clinical trials (V-RCTs).

RESULTS

The patient-level model (Figure 1A) was able to simulate the entire lifetime of a virtual cohort of 10,000 individuals (50% female). During the 100-year follow up, the virtual patients showed various AF patterns and clinical outcomes including death and stroke (top panels in Figures 1B and 1C). All AF episodes were captured with 30-min resolution (bottom panels in Figures 1B and 1C) and in a subset of individuals showed the expected dynamic progression from paroxysmal AF (pAF) to persistent AF (Figure 1B).

Simulating key AF characteristics and clinical outcomes

Population-level AF metrics

Consistent with the known age dependence of AF risk, the AF prevalence (Figure 2A) and incidence (Figure 2B) in this virtual cohort were significantly higher in older age groups. AF incidence was numerically consistent with the range estimated from numerous studies,[15–28] while AF prevalence was slightly overestimated in the virtual cohort. Sex-specific AF prevalence and incidence were also calibrated and showed a similar age dependence, with both metrics significantly higher in males, especially in the older age groups (Figure S5A), consistent with clinical data.[18–22,24,26–29] The proportions of pAF (vs. non-pAF) patients (Figure 2C) and symptomatic (vs. asymptomatic) AF patients (Figure 2D) were also consistent with clinical data[30,31] and accounted for around 50% and 75% of total AF patients, respectively.

AF-episode and progression metrics

In pAF patients, the AF frequency, maximum duration of AF episodes, and AF burden during a 2-week period were assessed. Although the model slightly underestimates AF frequency (Figure 3A), the maximum duration of AF episodes (Figure 3B) and AF burden (Figure 3C) were in good agreement with the real data.[8] Consistent results were also obtained specifically for male and female patients (Figures S5B–S5D).

We subsequently reproduced the selection criteria for early pAF from the Reappraisal of Atrial fibrillation: interaction between hyperCoagulability, Electrical remodeling, and Vascular destabilisation in the progression of AF (RACE-V) study.[32] The median AF burden (Figure 3D) and age (Figure 3E) in patients with low, intermediate, and high AF burden according to the RACE-V definition were broadly consistent with the clinical data, with simulated median AF burden of 0.2%, 1.0%, and 7.8% vs. 0.2%, 1.3%, and 7.1% observed in the clinical study.[32] The proportion of symptomatic AF episodes was 45%, similar to the observed data (50%) in patients with continuous monitoring (Figure 3F).[33]

AF is known as a progressive disease. While the clinical AF progression rate from pAF to persistent AF was slightly overestimated at ~4.9%/year versus 3.8%/year (Figure 3G),[34] this factor can be quite variable depending on clinical characteristics and AF-detection parameters.[38] AF-burden progression rate is a more robust parameter and agreed well between simulated data (5.3%/year) and clinical data (5.5%/year; Figure 3H).[34]

AF recurrence after spontaneous cardioversion varies significantly between pAF patients with different baseline characteristics, ranging from 30% to 90%.[35–37] Therefore, the AF recurrence rate in the virtual cohort was calibrated by reproducing baseline characteristics (age, history of AF) in individual simulations for each clinical dataset. Different patterns of recurrent AF episodes during the 28-day follow up were documented for each virtual patient, with sparse and short episodes in patients with low AF recurrence rate (Figure S5E), but frequent and relatively longer episodes in patients with higher AF recurrence rate (Figure S5F).

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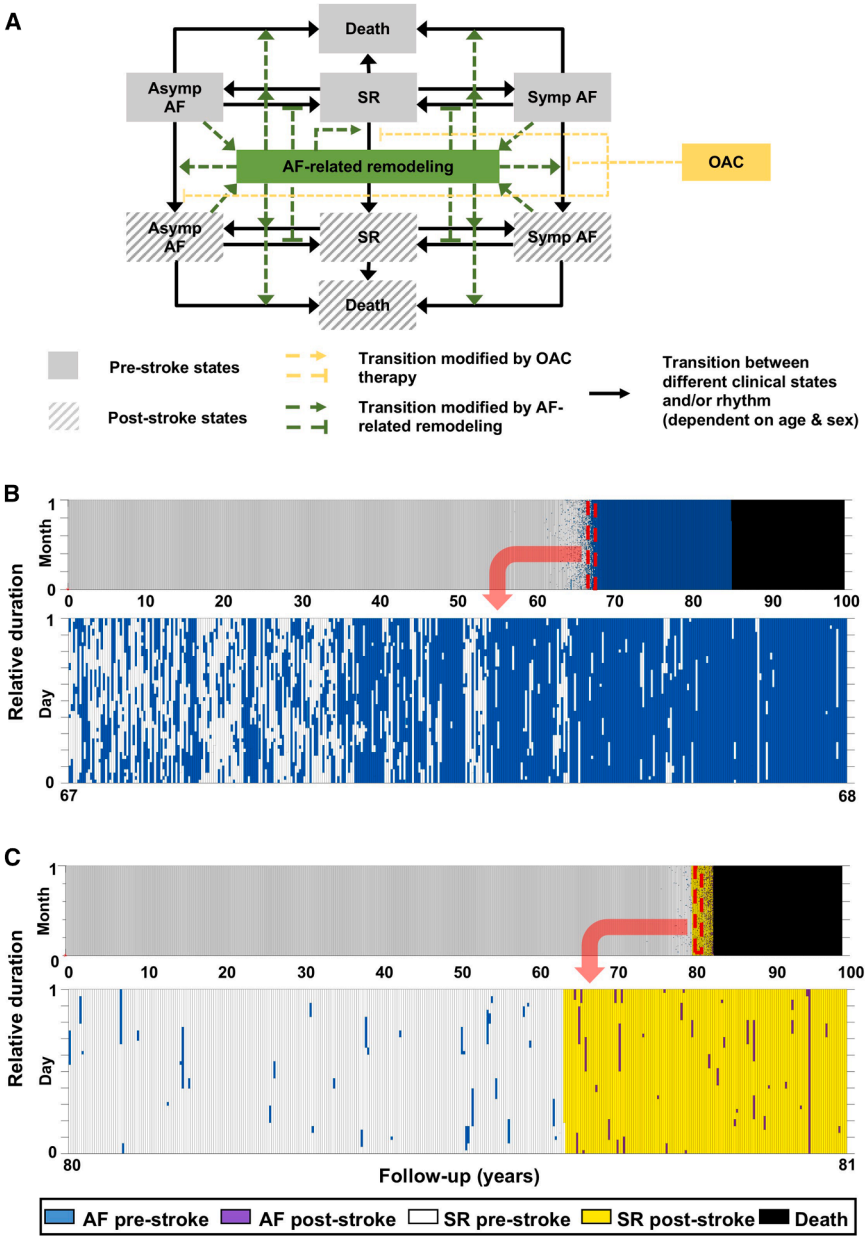

Figure 1. Schematic model overview and examples of AF episodes and clinical outcomes in virtual individuals simulated by the patient-level model

(A) Patient-level model with seven clinical states, including sinua rhythm (SR), symptomatic and asymptomatic AF (each with or without previous stroke), and death. Transition probabilities were age/sex dependent. AF-related remodeling was also incorporated in the model as function of the time in AF and modulated the likelihood of AF development, cardioversion, and the occurrence of stroke and death.

(B) Representative example of a patient with multiple AF episodes and AF progression during the 100-year follow up (top) and expanded view of the interval from 67 to 68 years of age during which paroxysmal AF progressed to persistent AF (bottom).

(C) Representative example of a patient with multiple AF episodes and incident stroke during the 100-year follow up (top) and expanded view from 80 to 81 years of age during which the stroke event occurred (yellow-shaded area). The *x* axis in (B) and (C) represents the follow-up time (i.e., the age of virtual individuals), which are divided into columns on the *y* axis. A single complete column represents 1 month and 1 day in the upper and lower panels, respectively. The columns provide detailed information on the events that occurred during that period of 1 month/1 day.

During the 28-day follow up, recurrent AF episodes were detected in 60%–90% of virtual patients with pAF (Figure 3I), which was in agreement with clinical data from some, but not all, randomized trials.[35–37] Together, these data confirm that the model can reproduce a wide range of AF characteristics occurring during the entire lifetime of a virtual population.

Clinical outcomes

The ultimate goal of AF management is to improve clinical outcomes. Accordingly, we assessed clinical outcomes in individuals with or without AF in our model. Mortality (Figure 4A), the percentage of deaths per age category (Figure S6B), stroke incidence (Figure 4B), and the percentage of strokes per age category (Figure S6D) in the virtual cohort were all consistent with age-dependent data from the literature.[39–41] A similar age dependence was present for both females and males, with higher risks of death and stroke in males (Figures S6E–S6L), consistent with clinical data. Furthermore, the acute, out-of-hospital death (≤24 h) and early-phase fatality (≤30 days and within 31–365 days) after stroke were reproduced for the total population as well as in female and male subpopulations (Figures S6M–S6O).[42,43]

Age- and sex-matched mortality at 15 years after AF diagnosis was approximately 25% higher in simulated AF patients than in simulated individuals with sinus rhythm (SR) (Figure 4C), which aligned well with clinical data.[44] Similarly, an almost 2-fold higher risk of stroke after AF diagnosis was observed in both simulated AF and clinical AF cohorts compared with those in SR over a 3-year follow-up period (Figure 4D).[45]

Model validation and suitability for screening

The model's suitability for evaluating AF screening was assessed by simulating the detection rates and benefits for stroke prevention of continuous rhythm monitoring (CRM) based on the Implantable Loop Recorder to Detect Atrial Fibrillation and Prevent Stroke (LOOP) study.[9] Cumulative stroke rates (Figure 4E) and AF-detection rates (Figure 4F) reproduced in

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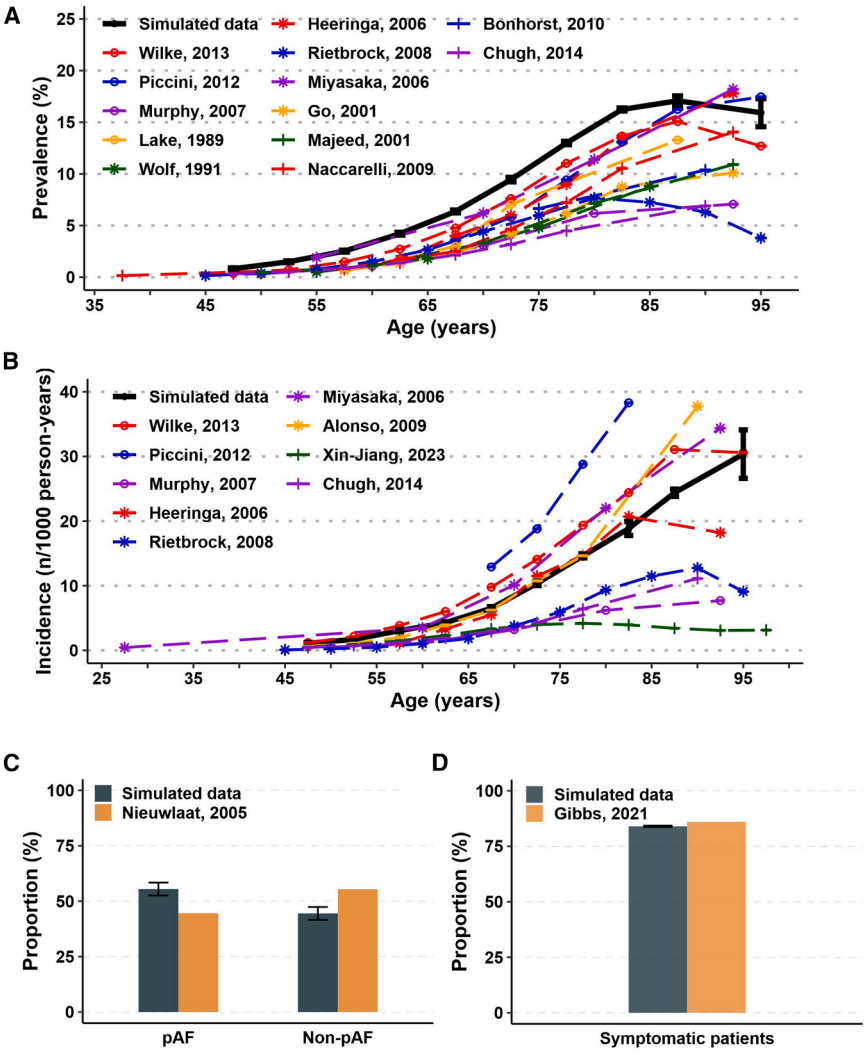

Figure 2. Comparison of population-level AF metrics in 10,000 virtual individuals to epidemiological data

(A and B) Age dependence of the prevalence (A) and incidence (B) of clinical AF in model (black line) and different clinical studies (colored lines).[15–28] Sex-specific AF prevalence and incidence are shown in Figure S5.

(C) The proportion of paroxysmal AF (pAF) and non-paroxysmal AF in virtual patients with a clinical diagnosis of AF compared to clinical data from Nieuwlaat et al.[30]

(D) The proportion of symptomatic AF patients in the model compared to Gibbs et al.[31]

Error bars in (A)–(D) represent mean ± standard deviation.

virtual CRM and control groups were highly similar to the clinical data, with 5.5-year stroke rates of 4.1% and 5%, and 5.5-year AF-detection rates of 29.5% and 16.5% in virtual CRM and control groups, respectively. These data confirm that the model can be used to assess the impact of screening on AF detection and stroke reduction.

After calibrating the model to accurately reproduce these age- and sex-dependent clinical outcomes and assessing its suitability for screening, we independently validated the model by comparing stroke risks in patients with different durations of AF episodes to a clinical dataset that was not used for parameter estimation. The simulated stroke risks in patients with AF over a 3.5-year follow up resulted in hazard ratios (HRs) of 5.40 (95% confidence interval [CI], 3.38–8.63), 2.15 (95% CI, 1.40–3.30), and 1.31 (95% CI, 0.79–2.17) compared to individuals without AF for episodes of >24 h, 6–24 h, and 6 min to 6 h, respectively. These numbers were highly consistent with 5.73 (95% CI, 2.41–13.64), 1.79 (95% CI, 0.42–7.69), and 1.31 (95% CI, 0.89–5.02) observed in the Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT) study (Figure 4G).[46] These validation results highlight the model's accuracy and predictive abilities.

Impact of different screening strategies on AF detection and stroke reduction

AF screening has the potential to enable early AF detection and initiation of anticoagulation therapy to reduce stroke risk, but the optimal screening strategy and the benefit of anticoagulation for screening-detected AF remain uncertain.[9,10] We employed the model to evaluate self-defined systematic and symptom-based AF-screening protocols (Figures S7A–S7C). Generally, CRM and intermittent strategies with higher frequency and longer monitoring periods identified more AF cases from the total population. The top five screening protocols that patients with AF would benefit from (defined as percentage of AF patients with screening-detected AF before a clinical diagnosis) were systematic CRM (99.7%, 3,524/3,534), systematic daily three-time single ECG (64.6%, 2,268/3,511, representing a smart-watch-based approach), long-term (until death) symptom-based CRM (52.5%, 1,852/3,525), long-term symptom-based daily three-time single ECG (35.1%, 1,217/3,464), and systematic yearly 14-day Holter monitoring (23.3%, 818/3,517). AF could be detected earlier than the clinical diagnosis by 720 (interquartile range [IQR]: 140, 1,448), 301 (IQR: 9, 697), 390 (IQR: 94, 813), 204 (IQR: 11, 551), and 285 (IQR: 66, 718) days, respectively, in these protocols (Table 1).

Next, we assessed the impact of the five screening strategies on stroke rates in V-RCTs, comparing oral anticoagulation upon routine clinical AF diagnosis (control group) with oral anticoagulation upon screening-detected or clinical AF. At 5-year follow up, all strategies showed similar stroke rates to the control group (Figure 5A). However, at 25-year follow up, stroke rates were slightly reduced, with the lowest stroke rate (5% relative risk reduction) with systematic CRM (Figure 5B, top

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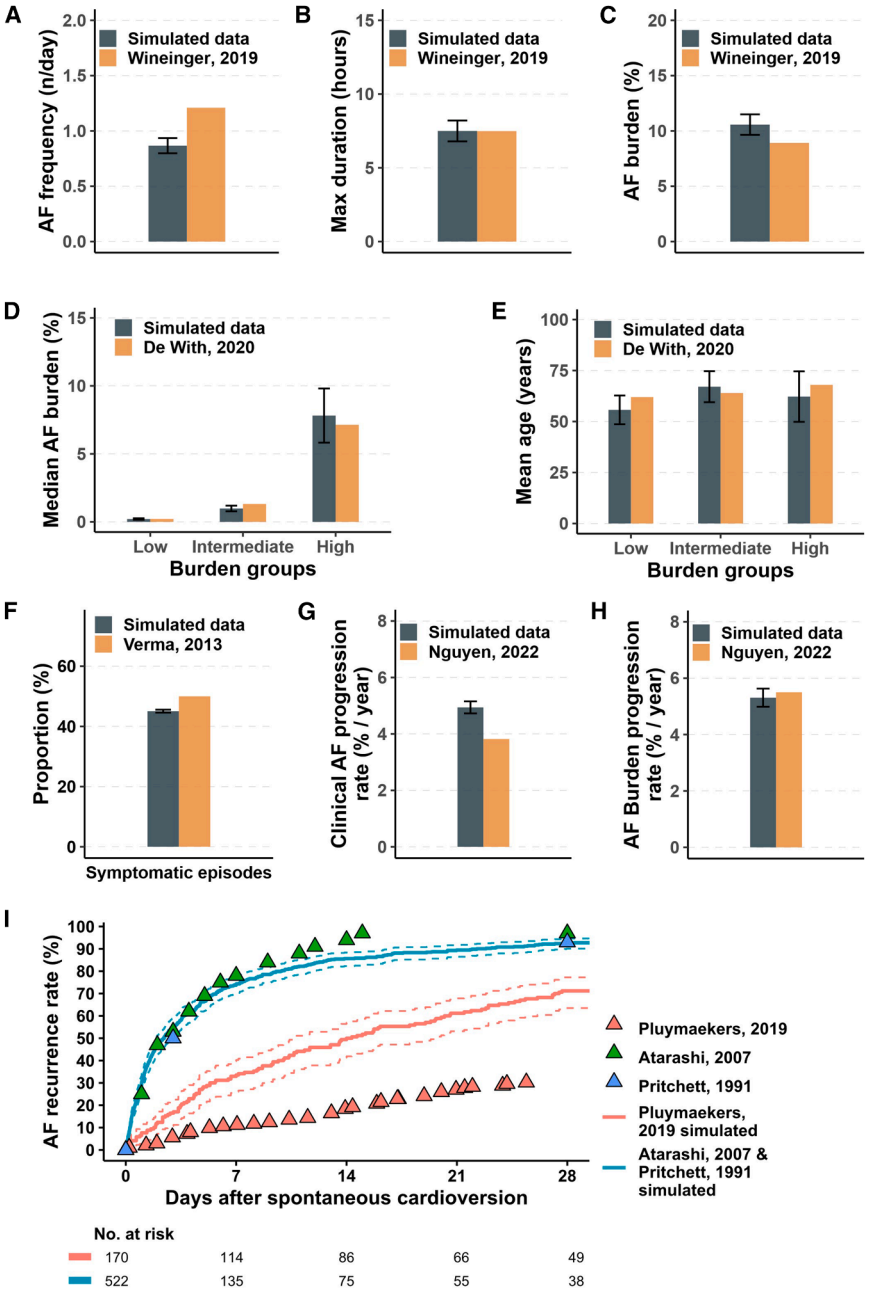

Figure 3. Comparison of episode-level AF metrics and AF progression in the patient-level model to rhythm-monitoring data in AF patients

(A–C) Frequency (A), maximum episode duration (B), and AF burden (C) during a 12-day follow-up period in virtual patients with paroxysmal AF compared to Wineinger et al.[8]

(D and E) Median AF burden (D) and mean age (E) in different AF-burden groups defined by the RACE-V study.[32]

(F) The proportion of symptomatic AF episodes from all virtual patients with AF compared to implantable cardiac monitor data.[33]

(G and H) Yearly progression rate from paroxysmal to non-paroxysmal AF (G) or AF-burden progression rate (H) compared to data from the RACE-V study.[34]

(I) AF-recurrence rate after spontaneous cardioversion in patients with early-phase AF, as defined by the different clinical trials.[35–37]

Error bars in (A)–(H) represent mean ± standard deviation. Kaplan-Meier curves with 95% confidence intervals in (I) are produced by R.

panel). On average, systematic CRM has the most expensive medical cost ($57,291 in total), followed by systematic yearly Holter ($28,820 in total), symptom-based CRM ($26,160 in total), systematic daily ECGs ($26,078 in total), and symptom-based daily ECGs ($24,933 in total) for each participant (Table S5).

Given the limited benefits from AF screening in an unselected population, we finally assessed the influences of the degree of AF progression, the moment of clinical AF diagnosis, the baseline stroke risk, and the efficacy of anticoagulation therapy. More pronounced AF progression rates reduced the time interval between screening-detected AF and clinical AF diagnosis (Table S6) but had minimal impact on the screening-induced stroke-risk reduction (Table S6). The 5-year stroke rates were similar in all groups and were not significantly reduced compared with the control group (all 95% CIs cross the zero-effect line). However, different AF-screening strategies showed distinct relative-stroke-risk reduction at 25-year follow up, the extent of which was sensitive to the efficacy of anticoagulation therapy, baseline stroke risk, and the latency for a clinical AF diagnosis (Figures 5B and S7D–S7F; Table 2). The largest effects were observed with systematic CRM, daily three times single ECG, and yearly 14-day Holter groups with significant 6%–12% reductions in stroke incidence (Figure 5B; Table 2).

DISCUSSION

We present a novel patient-level AF model that can simulate the entire lifetime of a virtual individual, capturing individual AF episodes, AF progression, and relevant clinical outcomes with 30-min resolution. The model incorporates key pathophysiological components, including "AF begets AF" and highlights the complex, heterogeneous, and dynamic development and progression of AF. It reproduces many important population-level and episode-level AF characteristics, including their age and sex dependence. The model enables, for the first time, a systematic evaluation of AF-screening strategies and their impact on clinical outcomes in V-RCTs, showing huge heterogeneity in AF-detection rates and identifying determinants of stroke reduction when anticoagulation therapy after clinical- or screening-detected AF was simulated,

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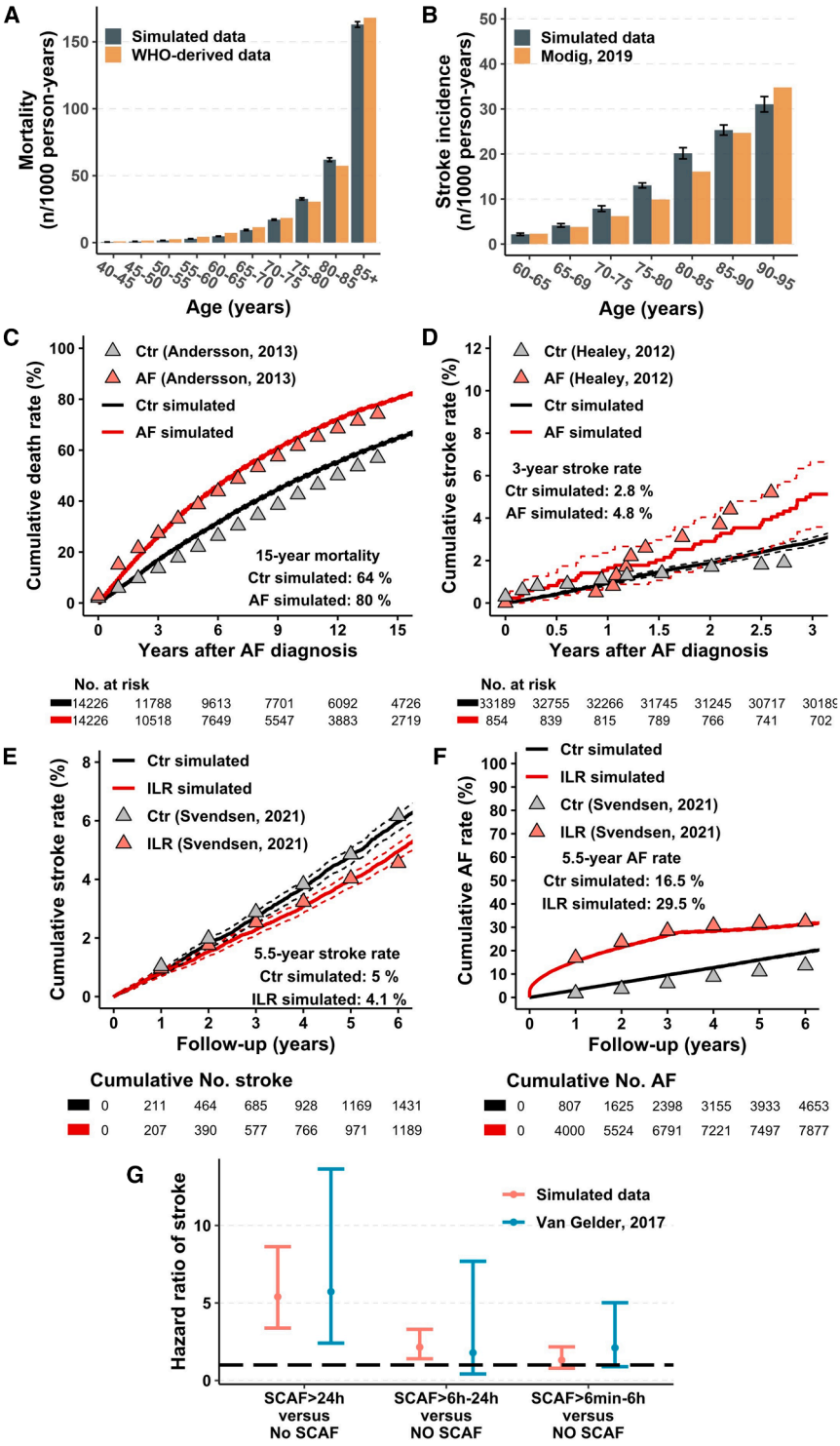

Figure 4. Comparison of clinical outcomes in virtual patients and epidemiological data and model validation

(A) Mortality across different age groups in the virtual cohort compared to data from the World Health Organization (WHO).[39]

(B) Stroke incidence across different age groups in the virtual cohort compared to data from Modig et al.[40]

(C) Mortality in patients with clinical atrial fibrillation (AF) compared to age- and sex-matched patients in model and data from Andersson et al.[44]

(D) Cumulative stroke rate in patients with or without any AF episodes compared to the continuous-monitoring data from the ASSERT study.[45]

(E and F) Cumulative-stroke rates (E) and AF-detection rates (F) with or without AF episodes in the virtual cohort compared to data from patients with implantable loop recorders (ILRs) from the LOOP trial.[9]

(G) Independent validation of stroke risks in patients with different durations of subclinical AF compared to individuals without any AF episodes during follow up in the model compared to data from the ASSERT study,[46] which were not used for model development and calibration.

Error bars in (A) and (B) represent mean ± standard deviation. Kaplan-Meier curves with 95% confidence intervals in (C)–(F) and hazard ratios with 95% confidence intervals in (G) are produced by R.

such as the efficacy of anticoagulation therapy, the baseline stroke risk profile, and the latency of clinical AF diagnoses.

Computational models of AF

Mechanistic modeling, data-driven modeling, and health-technology assessment modeling are different approaches for computational modeling of AF, each with a long history and several important real-world applications, including the guidance of AF ablation using digital twins, the prediction of a history of AF from an SR ECG, and the assessment of cost effectiveness of novel therapies.[11] However, none of these approaches have simulated AF development, progression, and its associated outcomes, making them unsuitable for assessing the benefit of AF screening. Chang et al. were the first to develop a patient-level Markov model for the simulation of AF progression during a person's lifetime.[47] However, this model did not include clinical outcomes and AF incidence, and its characteristics and progression were not calibrated based on real-world data (see Table S7 for a detailed comparison). Another study employed a patient-level Markov model to assess the effectiveness of 45 screening strategies by simulating bleeding and stroke risks in the general population. AF characteristics, common comorbidities, anticoagulation therapy, and screening specificity were considered. However, no individual AF episodes were simulated, and the progressive nature due to AF-induced remodeling was ignored

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Table 1. AF-detection rates of different screening protocols applied in the virtual cohort

Protocols applied (10,000 individuals)	% of patients benefiting from screening (*n*/AF cases possibly at benefit[a])	% of screening-detected AF[b] (*n*/AF cases possibly at benefit)	% of earlier –detected AF[c] (*n*/AF cases possibly at benefit)	# of days ahead of clinical AF diagnosis[d] for earlier-detected AF (*n*, IQR)
Continuous AF screening (systematic or long-term symptom based)				
Systematic continuous screen	99.7% (3,524/3,534)	31.6% (1,118/3,534)	68.1% (2,406/3,534)	720 (140, 1,448)
Symptom-based continuous screen	52.5% (1,852/3,525)	8.0% (281/3,525)	44.6% (1,571/3,525)	390 (94, 813)
Systematic AF screening (all participants from 65 years to death)				
Yearly 1-min ECG	4.7% (165/3,491)	4.7% (164/3,491)	0.03% (1/3,491)	516
Daily 3× 1-min ECG	64.6% (2,268/3,511)	17.2% (603/3,511)	47.4% (1,665/3,511)	301 (9, 697)
Yearly 7-day Holter	16.7% (588/3,514)	8.6% (301/3,514)	8.2% (287/3,514)	248 (53, 605)
Yearly 14-day Holter	23.3% (818/3,517)	10.4% (365/3,517)	12.9% (453/3,517)	285 (66, 718)
Short-term symptom-based AF screening (from the first symptomatic AF after 65 years, for 2 weeks)				
Daily 1-min ECG	0.2% (8/3,539)	0% (0/3,539)	0.2% (8/3,539)	428 (163, 558)
Daily 3× 1-min ECG	0.5% (26/3,517)	0% (0/3,517)	0.5% (26/3,517)	100 (36, 277)
Weekly 1-day Holter	0.6% (20/3,400)	0.06% (2/3,400)	0.5% (18/3,400)	218 (107, 647)
One-time 14-days Holter	2.7% (97/3,583)	0.4% (16/3,583)	2.3% (81/3,583)	279 (111, 610)
Long-term symptom-based AF screening (from the first symptomatic AF after 65 years, until death)				
Daily 1-min ECG	17.6% (623/3,530)	1.6% (58/3,530)	16.0% (565/3,530)	183 (17, 410)
Daily 3× 1-min ECG	35.1% (1217/3,464)	4.0% (139/3,464)	31.1% (1078/3,464)	204 (11, 551)
Yearly 1-day Holter	1.2% (29/3,558)	0.2% (1/3,558)	1.1% (28/3,558)	167 (46, 383)
Yearly 14-days Holter	12.0% (429/3,563)	1.2% (41/3,563)	10.9% (388/3,563)	229 (37, 507)

Results are presented as absolute numbers with percentage or median numbers with quartiles.
[a]AF cases possibly at benefit are those with *any* AF episodes during *lifetime* follow up and still alive at 65 years of age (i.e., start of screening) without clinical AF diagnosis (= the number of total AF cases within 100 years − AF cases died before 65 years − clinical AF cases before 65 years).
[b]Screening-detected AF are patients detected by screening protocols *only*.
[c]Earlier-detected AF are patients detected by screening protocols earlier than their clinical AF diagnosis.
[d]Clinical AF was diagnosed when the first symptomatic AF episode lasted ≥3 h.

in these simulations (see Table S7).[48] To the best of our knowledge, our model is the first to incorporate information about every single symptomatic or asymptomatic episode, together with electrical and structural remodeling of the atrium and clinical outcomes during the entire lifetime with 30-min resolution, providing all the components required for the systematic assessment of AF-screening strategies.

Model calibration

The model has been well calibrated and reproduced most epidemiological metrics in the virtual cohorts. However, some discrepancies still existed. Although the simulated AF incidence was numerically consistent with the range observed in clinical data, its prevalence was slightly overestimated. The calculation for incidence is based on the newly diagnosed AF cases rather than total number of diagnosed AF cases during the entire medical history used for prevalence calculation. It is likely that the historical overview in real-world studies of AF prevalence is incomplete, contributing to a relative underestimation of the true AF prevalence in these studies. Furthermore, different diagnostic criteria between the model and epidemiological studies might also contribute to the difference between computed and epidemiological AF prevalence. Additionally, prevalence is approximately equal to the product of disease incidence and disease duration, which means lower AF incidence at a given age can still cause higher AF prevalence if the disease duration is longer. All these factors may contribute to the mismatch of computed AF incidence and prevalence compared to epidemiological data (Figures 2A and 2B).

The current time resolution of the model is 30 min. Therefore, AF episodes shorter than 30 min will not be captured even after parameter optimization. This may explain the underestimation of AF-episode frequency in pAF patients (Figure 3A). As for the 28-day AF recurrence rate, computed data were overestimated in one randomized trial, possibly in part due to the declining patients' adherence to self-initiated rhythm monitoring during the follow up.[49] The reported AF recurrence rates ranged from 60% to 90% in different randomized trials, which could be explained by the heterogeneous baseline patient characteristics, including different AF history before randomization.

Determining optimal AF-screening strategies

The LOOP trial showed that CRM results in a >2-fold increase in AF detection.[9] However, AF screening with implantable CRM devices is not feasible in the general population. After successful replication of the results from the LOOP study, we therefore evaluated various self-designed AF-screening protocols. Our results suggest that systematic screening

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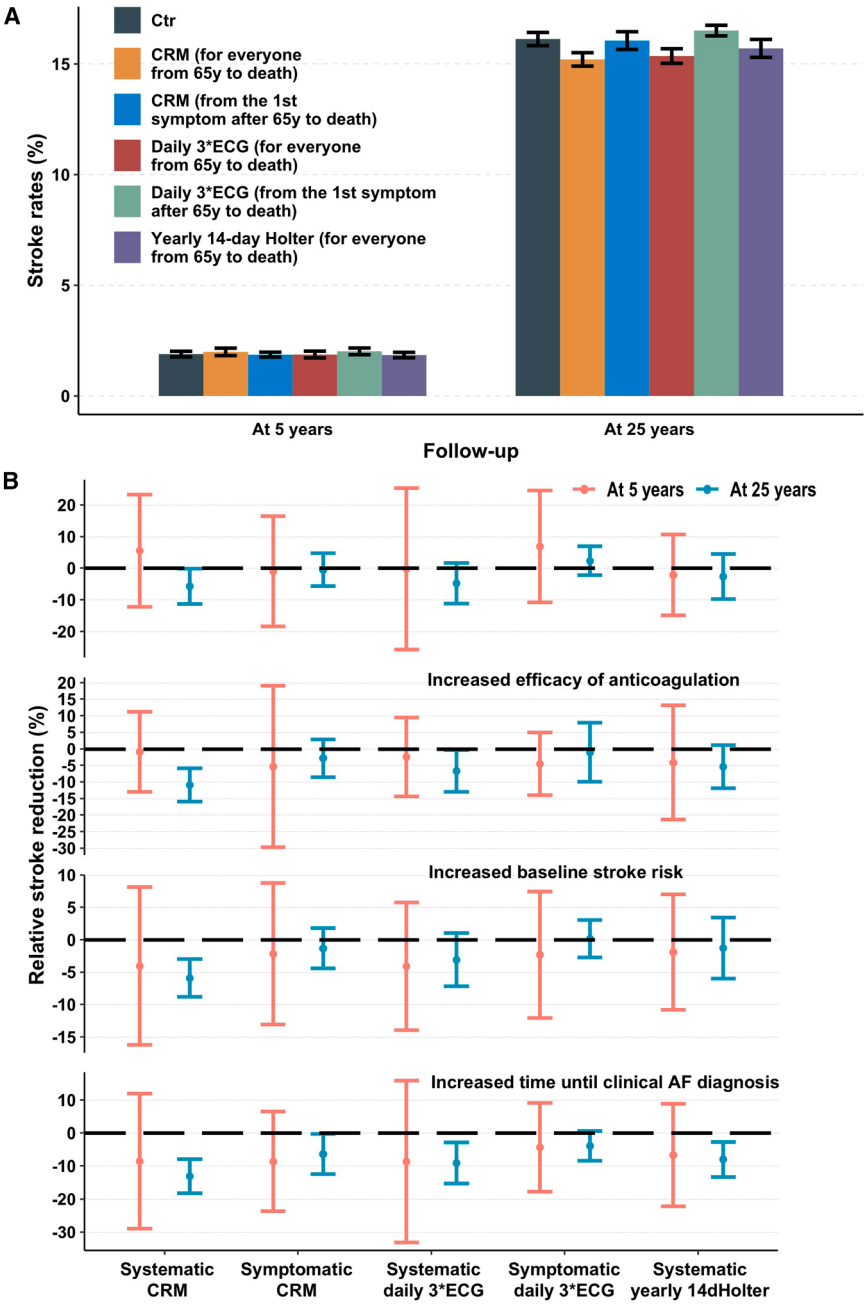

Figure 5. Stroke rates in populations with or without AF screening and assessment of impacts of different healthcare factors

(A) Comparison of 5- and 25-year stroke rates in populations with normal baseline stroke risk and different AF-screening strategies.

(B) The 5- and 25-year relative stroke reduction for AF-screening groups compared to the control group for, from top to bottom, normal baseline stroke risk, anticoagulation therapy with 70% efficacy, and a clinical diagnosis after 3 h of symptomatic AF; increased efficacy of anticoagulation therapy (90% less stroke versus the control group); 3-fold increase in baseline stroke risk; and increased time until clinical AF diagnosis (24 h symptomatic AF). Systematic screening means AF screening for everyone from 65 years to death, whereas symptomatic screening means AF screening initiated from the first symptomatic AF episode after 65 years to death. See STAR Methods for details.

Error bars in (A) represent mean ± standard deviation and in (B) represent 95% confidence intervals.

(assessing the whole population from a certain age onwards) outperforms symptom-based screening (only starting screening in individuals with suspected symptomatic AF episodes). This can be explained by the fact that one in four AF patients are totally asymptomatic and asymptomatic AF episodes account for 50% of total episodes in the virtual cohort, in line with clinical data.[31,33] On the other hand, the AF-detection rates of both systematic and symptom-based AF-screening strategies are frequency and duration dependent in the simulation, which is consistent with previous simulation data[50] and suggests a need for long-term monitoring for better AF diagnosis. This idea is supported by a recent randomized clinical trial (RCT) showing that one-time single-lead ECG screening at 65 years or older does not increase the rate of new AF diagnosis significantly in primary-care settings.[51] Of note, longer total screening time is not associated with higher AF-detection rates. For example, systematic daily three-times 1-min ECG (1,095 min per year) detects more AF patients than a systematic yearly 14-day Holter (20,160 min per year). This result is likely due to the typical patterns of AF development, often beginning with sporadic and short-lasting AF episodes and then progressing to more frequent and longer AF episodes during the follow up (Figures 1B and 1C). In the current simulations, AF screening was initiated at 65 years, when most virtual patients are most likely in the early phase of AF development. Thus, different screening strategies may capture this dynamic AF progression with heterogeneous sensitivity. Our results indicate that heterogeneous AF development and progression in the target population should be considered when choosing the best AF-screening strategy. Long-term short, frequent monitoring facilitated by developments in single-lead ECG hardware (e.g., in smartwatch devices) may be more sensitive to identify sparse AF episodes. The feasibility of AF screening with consumer devices has been validated in the general population, showing improved anticoagulation therapy, rate- or rhythm-control

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Table 2. Comparison of 5-/25-year stroke rates and relative stroke reduction in populations with or without AF screening for different characteristics of patients and healthcare systems

Groups	5-year stroke rates (%)	Relative reduction of 5-year stroke rates (%)	25-year stroke rates (%)	Relative reduction of 25-year stroke rates (%)
Efficacy of anticoagulation therapy increased to 90%, 3 h as diagnostic criterion for clinical AF, and normal baseline stroke rates				
Control	1.93 ± 0.12	–	15.18 ± 0.40	–
CRM (for everyone from 65years to death)	1.90 ± 0.08	−0.85 ± 6.18	13.53 ± 0.31	−10.85 ± 2.60
CRM (from the first symptom after 65years to death)	1.82 ± 0.19	−5.26 ± 12.46	14.75 ± 0.13	−2.77 ± 2.92
Daily 3× ECG (for everyone from 65 years to death)	1.88 ± 0.14	−2.38 ± 6.08	14.16 ± 0.28	−6.63 ± 3.22
Daily 3× ECG (from the first symptom after 65 years to death)	1.84 ± 0.07	−4.48 ± 4.85	15.01 ± 0.41	−1.00 ± 4.55
Yearly 14-day Holter (for everyone from 65 years to death)	1.84 ± 0.13	−4.06 ± 8.78	14.36 ± 0.36	−5.37 ± 3.31
Efficacy of anticoagulation therapy of 70%, 3 h as diagnostic criterion for clinical AF, and 3-fold increase in baseline stroke rate				
Control	5.64 ± 0.25	–	39.34 ± 0.62	–
CRM (for everyone from 65 years to death)	5.40 ± 0.20	−4.00 ± 6.22	37.02 ± 0.48	−5.88 ± 1.50
CRM (from the first symptom after 65 years to death)	5.51 ± 0.18	−2.15 ± 5.57	38.82 ± 0.39	−1.30 ± 1.58
Daily 3× ECG (for everyone from 65 years to death)	5.40 ± 0.18	−4.08 ± 5.02	38.13 ± 0.40	−3.05 ± 2.09
Daily 3× ECG (from the first symptom after 65 years to death)	5.50 ± 0.20	−2.28 ± 4.97	39.42 ± 0.39	0.21 ± 1.48
Yearly 14-day Holter (for everyone from 65 years to death)	5.53 ± 0.26	−1.86 ± 4.55	38.83 ± 0.58	−1.27 ± 2.40
Efficacy of anticoagulation therapy of 70%, diagnostic criterion for clinical AF increased to 24 h, and normal baseline stroke rates				
Control	2.00 ± 0.12	–	17.08 ± 0.34	–
CRM (for everyone from 65 years to death)	1.82 ± 0.17	−8.48 ± 10.45	14.85 ± 0.43	−13.06 ± 2.63
CRM (from the first symptom after 65 years to death)	1.82 ± 0.12	−8.55 ± 7.70	16.00 ± 0.46	−6.29 ± 3.13
Daily 3× ECG (for everyone from 65 years to death)	1.81 ± 0.17	−8.59 ± 12.51	15.53 ± 0.43	−9.03 ± 3.16
Daily 3× ECG (from the first symptom after 65 years to death)	1.91 ± 0.09	−4.27 ± 6.86	16.42 ± 0.17	−3.84 ± 2.31
Yearly 14-day Holter (for everyone from 65 years to death)	1.86 ± 0.11	−6.61 ± 7.95	15.72 ± 0.35	−7.91 ± 2.70

Numbers in the table are mean ± standard deviation. Three different cases were simulated in this sensitivity analysis, with efficacy of anticoagulation therapy increased to 90%, or 3-fold increase in baseline stroke rate, or diagnostic criterion for clinical AF increased to 24 h, respectively. Results are visualized in Figures S7D–S7F.

strategies, and risk-factor management in diagnosed AF patients.[52]

Potential benefits of AF screening and anticoagulation therapy

After evaluating AF-detection rates of different screening strategies, we evaluated the potential benefits of virtual anticoagulation therapy for screening-detected AF. The 5-year stroke rates are similar between control and screening groups, and only systematic CRM shows slight relative stroke-risk reduction during long-term (25-year) follow up in the unselected baseline population over 65 years of age. These results are consistent with recent RCTs that have shown small net reduction or no reduction in stroke despite increased AF diagnosis in individuals with extra stroke risks but without previous AF diagnosis undergoing intermittent screening or CRM during 5–7 years of follow up.[9,10] These results support the idea that, although AF screening will identify more AF cases and lead to earlier anticoagulation therapy, benefits of AF screening in terms of stroke reduction may still be limited, even when long-term CRM is used. Although systematic CRM is the most comprehensive strategy for stroke reduction, it is associated with the highest medical cost compared to other screening modes. Systematic yearly Holter-based screening and systematic daily ECGs have lower costs and slightly higher average quality-adjusted life years (QALYs). It should be noted that our economic analyses do not include costs related to bleeding or hospitalizations and ignore heterogeneous clinical practices and medical

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accessibility in different regions, which are beyond the scope of the current study. Considering the limited clinical benefit identified in our simulations, the significantly higher risk of major bleeding in patients with device-detected subclinical AF and anticoagulation therapy in clinical studies,[53] as well as the potential costs of such a screening strategy, it appears that screening for everyone is likely not the best choice. We therefore employed the model to evaluate parameters that may affect the benefits of AF screening.

In patients with more effective anticoagulation therapy, higher baseline stroke risk, and higher likelihood of delayed clinical AF diagnosis, e.g., due to poor *ad hoc* accessibility to cardiology care (simulated by prolonged AF-duration criteria for clinical AF diagnosis), the reduction of 25-year stroke rates was more significant, particularly in CRM and systematic screening groups (Figures 5 and S7D–S7F; Table 2). Thus, our approach suggests that tailored systematic screening approaches in selected settings could be beneficial. One recent population-level simulation has indicated that AF screening can result in QALY gains and a reduction in stroke risk, which varies significantly and is highly dependent on specific combinations of strategies used.[48] Of note, most current AF-screening studies, including our simulations, have only evaluated the screening-enabled benefits of anticoagulation therapy, whereas a systematic evaluation of the combined effects with other interventions, such as rhythm control and upstream treatments, has not been performed. Importantly, our model can help identify populations who may truly benefit from AF screening while minimizing harms, and it can be accessed freely by anyone in any country. As shown by our preliminary economic analysis, the model can also be used to compare the costs associated with different screening strategies. These advantages may limit some of the screening-related challenges related to anxiety and may help direct medical resources to a more targeted population. Finally, although privacy and data protection will need to be considered for future patient-specific applications (patient-specific risk assessment, etc.), they are not an issue for the current model, which is based on population-level data and provides information for subgroups of individuals without using any identifying information.

Future perspectives

We developed a novel patient-level AF model that captures the individual dynamic AF development and progression in a virtual patient. The model reproduces many important clinical characteristics and population-level metrics of AF in virtual cohorts. V-RCTs simulated by the model revealed that CRM and intermittent strategies with higher frequency and longer monitoring periods identified more AF cases. However, AF screening and screening-triggered anticoagulation therapy caused only slight long-term stroke reduction, even in populations with CRM and intensive intermittent screening. Sensitivity analyses highlighted potential benefits of AF screening combined with anticoagulation therapy in populations suspected of delayed AF diagnosis, with higher baseline stroke risk or taking anticoagulation therapy with better efficacy. These findings need to be validated in future clinical studies.

The current computational patient-level AF model provides precise control over every component responsible for AF development, progression, and relevant clinical outcomes and can reproduce numerous population-level metrics and essential clinical characteristics of AF during the entire lifetime of a virtual patient. As such, the model is expected to be helpful for future mechanistic studies on AF development. Furthermore, it provides a foundation for follow-up studies into the role of different risk factors, making it a valuable tool to analyze personalized holistic AF management without any costs. For example, heterogeneous genetic background and AF-specific biomarkers could be incorporated in the model to simulate individual natural history of AF more accurately. Moreover, AF-episode-level data from wearable ECG devices can be used for model validation and could potentially be combined with data-driven artificial intelligence algorithms to identify those patients who can benefit the most from early AF detection and subsequent AF management. Together with additional personalized clinical data (e.g., on atrial size and fibrosis), our approach could provide a digital-twin approach to simulate the potential future health trajectories of an individual patient and analyze long-term effects of rhythm control, upstream treatment, and anticoagulation therapy.

Finally, the model's ability to evaluate AF patterns and progression, predict long-term prognosis, and assess efficacies of interventions may provide valuable information for the design and statistical power estimation of future RCTs, potentially helping to overcome gender disparities by explicitly addressing sex differences and enabling studies with equal representation of men and women.

Limitations of the study

Although age, the most important risk factor for AF development, and sex have been explicitly included in the model, other known AF risk factors, such as hypertension and heart failure, are only incorporated implicitly by reproducing epidemiological datasets. In particular, the model captures the age dependence of AF development and mortality. Virtual individuals that develop AF or die at a younger age likely implicitly represent individuals with a higher burden of risk factors and comorbidities, such as genetic background, obesity, hypertension, and heart failure, even though these are not modeled explicitly. The current baseline model mainly focuses on capturing population-level characteristics rather than individual heterogeneity of AF; therefore, we aggregated the effects of multiple risk factors and comorbidities on AF as an implicit part in the model. Nevertheless, the absence of these components can make the exact replication of inclusion criteria in different studies challenging. We have tried to simulate the study-specific patient selection as much as possible based on age, sex, AF history, and clinical priors (Table S3). While the model is generally consistent with a wide range of clinical data, some quantitative differences exist and may be due to this patient selection. On the other hand, results from clinical studies may also be biased due to various practical issues during the implementation. For example, a lack of patients' adherence to full monitoring during the 4-week follow up after spontaneous cardioversion was reported,[49] but without sufficient detail to reproduce in the model, potentially contributing to the mismatch between simulated and observed AF recurrence rates (red line and triangles in Figure 3I).

Although the entire lifetime of virtual individuals has been successfully simulated in the model, metrics during childhood in virtual cohorts are not calibrated and validated due to the lack of available data. Thus, simulation results for children should be interpreted with caution. In addition, the model uses a temporal resolution of 30 min for computational efficiency. As such, short episodes of micro-AF cannot be simulated, potentially contributing to the underestimation of the AF frequency (Figure 3A). However, the clinical relevance of such short-lived episodes remains uncertain at present. Moreover, the dynamic risks of stroke and death are assumed to be irreversible in the current model, which may not be true in reality. For example, lifestyle modification and comorbidity management for AF patients can decrease those risks during the lifetime follow up. Finally, only stroke and death were incorporated as clinical outcomes in our model. Other prognostic outcomes, such as heart failure, changes in quality of life, altered cognitive function, and bleeding risk, are also ignored in the current model, which limits its clinical applicability. In particular, without simulation of bleeding events, safety analyses (e.g., in terms of bleeding risk after starting anticoagulation in screening-detected AF[53]), and risk-benefit assessment cannot be performed in the current V-RCTs and should be considered in future research. Nevertheless, our simulation results are consistent with the limited short-term efficacy of oral anticoagulation therapy for screening-detected AF reported in recent trials. They also help to identify conditions in which AF screening may benefit long-term outcomes, which will ultimately need to be validated in a real-world RCT.

RESOURCE AVAILABILITY

Lead contact

Requests for further information and resources should be directed to and will be fulfilled by the lead contact, Jordi Heijman (jordi.heijman@medunigraz.at).

Materials availability

This study did not generate new unique reagents.

Data and code availability

- This paper analyzes existing, publicly available data. Researchers can get the data used for model calibration and validation as listed in the key resources table.
- The model and all original code will be deposited at https://github.com/HeijmanLab/at the date of publication to allow others to use and expand this novel approach.
- Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

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AUTHOR CONTRIBUTIONS

M.R., H.J.G.M.C., U.S., and J.H. conceptualized the project. M.C., C.B.-E., and J.H. built the model and ran the simulations. M.C. and J.H. had unrestricted access to all data. M.C. performed the statistical analyses. M.C. wrote the first draft of the manuscript. All authors reviewed and edited the manuscript. All authors agreed to submit the manuscript, read and approved the final draft, and take responsibility for its content, including the accuracy of the data and their statistical analysis.

DECLARATION OF INTERESTS

U.S. received consultancy fees or honoraria from Università della Svizzera Italiana (USI, Switzerland), Roche Diagnostics (Switzerland), EP Solutions Inc. (Switzerland), Johnson & Johnson Medical Limited (United Kingdom), and Bayer Healthcare (Germany). U.S. is co-founder and shareholder of YourRhythmics BV, a spin-off company of the University Maastricht.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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SUPPLEMENTAL INFORMATION

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Software and algorithms		
R version 4.3.0	R Software Foundation	https://www.r-project.org/
MATLAB 2024a	The MathWorks, Inc.	https://nl.mathworks.com/products/matlab.html
C++ code of the Markov-like model	This paper	https://github.com/HeijmanLab/

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

Development of a dynamic patient-level Markov model

It should be noted that the current model is distinct from digital twin models. A digital twin is a virtual model of a dynamic biological system that reflects its structure, function, and behavior change, typically using multiscale patient-specific data. Instead, the model presented here represents a novel approach combining elements from mechanistic models and Markov-based health economy models. It simulates the dynamic changes between clinical states (e.g., cardiac rhythms SR/AF and clinical outcomes) during the life time of a virtual individual, determined by a set of predefined parameters controlling the probabilistic transition among states together with random numbers generated during each time step (Figure S1). As such, the primary model output is a large dataset with the state transitions for all virtual patients. Subsequently, this dataset is post-processed to quantify clinically relevant population-level quantities such as AF incidence or age-dependent mortality (Figure S2).

The Markov-like model comprised 7 different clinical states: sinus rhythm (SR), symptomatic and asymptomatic AF (sAF and aAF, respectively), each with or without a previous stroke, as well as death (Figure 1A). States were connected through age-dependent and sex-specific transition probabilities for AF development, conversion, incident stroke, and death. All virtual patients started in the SR state at birth. During each subsequent time step (30 min, unless specified otherwise), the transition probabilities toward every neighboring state were calculated. Subsequently, the state for the next time step was obtained by a stochastic process in which every state was chosen with likelihood corresponding to these probabilities (Figure S1). Proarrhythmic AF-related atrial remodeling was incorporated through changes in three components conceptually representing effective refractory period (ERP), atrial fibrosis, and atrial enlargement, which was determined by the time spent in AF states and age. Being in AF states decreased the value of ERP and increased the production rates of atrial fibrosis and atrial enlargement, whereas being in SR states selectively reversed the ERP variable back to normal, capturing the concept of 'AF-begets-AF'. The relative values of the three components were used to modify the probability of AF development and cardioversion. Similarly, the non-reversible probabilities of stroke and death were modulated by vulnerability factors that increased when the virtual patient was in AF states and continued to modulate stroke/death risks after returning to sinus rhythm. A detailed model description is provided below and in Table S1, Figures S1 and S2.

Inter-patient variability was simulated by setting the baseline risk of AF development and the probability of converting to sinus rhythm to a different value for each patient at the start of the simulation based on a normal distribution centered around the default parameter value, reflecting a heterogeneous genetic background in the population (Table S1). In addition, virtual patients were randomly assigned a male or female biological sex at the beginning of the simulation, which modulated transition probabilities throughout the simulation (Table S1).

Time resolution and clinical factors

The time resolution is 30 min in the simulation:

$$dt = 30 \text{ minutes}$$

The sex of virtual patients is defined as:

$$sex = \begin{cases} 1, \text{if female} \\ 0, \text{if male} \end{cases}$$

The age of virtual patients is determined by time elapsed in the simulation, denoted as t in units of minutes.

Probability of AF development

The probability of AF development is dependent on the baseline risk of AF development (p[2]), the relative change in baseline AF risk in women (p[3] * sex), aging (t), and atrial remodeling caused by AF episodes ($F_{remodeling}(t)$). The probabilities from SR to sAF episodes and from SR to aAF episodes are assumed to be equal to half of the total probability of AF development.

$$P_{SR\rightarrow AF}(t) = dt * p[2] * (1 + p[3] * sex) * \left(\frac{p[40]}{1 + \exp\left(\frac{-t + p[4] + p[6] * sex}{p[5]} \right)} + F_{remodeling}(t) \right), \quad \text{(Equation 1)}$$

$$P_{SR\rightarrow sAF}(t) = P_{SR\rightarrow aAF}(t) = 0.5 * P_{SR\rightarrow AF}(t) \quad \text{(Equation 2)}$$

Combined atrial remodeling

The atrial remodeling at time t ($F_{remodeling}(t)$) includes three components: electrical remodeling ($F_{ERP}(t)$) determined by ERP shortening, atrial enlargement ($F_{Enlargement}(t)$), and fibrosis ($F_{Fibrosis}(t)$). The impact of $F_{ERP}(t)$ and $F_{Fibrosis}(t)$ are dependent on the patient's age (t).

$$F_{remodeling}(t) = (F_{ERP}(t) + F_{Fibrosis}(t)) * \frac{1}{1 + \exp\left(\frac{-t + p[44]}{p[45]} \right)} + F_{Enlargement}(t), \quad \text{(Equation 3)}$$

$$F_{ERP}(t) = p[7] * (1 - ERP(t)) * 100, \quad \text{(Equation 4)}$$

$$F_{Fibrosis}(t) = p[8] * Fibrosis(t), \quad \text{(Equation 5)}$$

$$F_{Enlargement}(t) = p[9] * Enlargement(t) \quad \text{(Equation 6)}$$

Dynamic changes in electrical remodeling, atrial fibrosis, and atrial enlargement

(1) The arial electrical remodeling in patients with AF is phenomenologically modeled as a change in relative ERP level. It is assumed to be a reversible process. The values of ERP in our model are between 0 and 1, representing the relative ERP duration compared with the normal duration in SR, which will increase during SR and decrease during AF, controlled by a fixed time constant (p[28]) of 24 h (1440 min) based on animal studies suggesting that electrical remodeling is a rapid process occurring within hours.[54]

$$\frac{dERP}{dt} = \frac{SS_{ERP} - ERP(t)}{p[28]},$$

$$SS_{ERP} = \begin{cases} 1, \text{when patient is in SR} \\ 0, \text{when patient is in AF} \end{cases} \quad \text{(Equation 7)}$$

(1) Fibrosis accumulation is assumed to be an irreversible process, with fibrosis production (controlled by R_Fibrosis) occurring when AF episodes are present, developing with a fixed time constant (p[29]) of 14 days, in line with experimental data. The total fibrosis in our model is defined between 0 and 100, representing the percentage of atrial tissue that has become fibrotic, which is determined by p[31] controlling the rate of fibrosis accumulation, and the R_Fibrosis factors.

$$\frac{dFibrosis}{dt} = p[31] * R\_Fibrosis(t) * (100 - Fibrosis(t)), \quad \text{(Equation 8)}$$

$$\frac{dR\_Fibrosis}{dt} = \frac{SS_{Fibrosis} - R\_Fibrosis(t)}{p[29]},$$

$$SS_{Fibrosis} = \begin{cases} 1, \text{when patient is in AF} \\ 0, \text{when patient is in SR} \end{cases} \quad \text{(Equation 9)}$$

(1) Atrial enlargement represents the second important component of atrial structural remodeling in patients with AF. Similar to fibrosis, it is assumed to be an irreversible process. It will increase with aging or during AF episodes. The values of atrial enlargement in our model are between 0 and 100, meaning the current percentage of maximum atrial enlargement, which will be determined by a factor controlling the relative dilatation increase (R_Enlargement) and age (t). Like R_Fibrosis, the R_Enlargement factor activates with a fixed time constant of 14 days when a patient is in AF.

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$$\frac{dEnlargement}{dt} = \left(p[32] * R_{Enlargement(t)} + p[46] * \left(\frac{1}{1+\exp\left(- \frac{t - p[47]}{p[48]} \right)} \right) \right) * (100 - Enlargement(t)), \quad \text{(Equation 10)}$$

$$\frac{dR\_Enlargement}{dt} = \frac{SS_{Enlargement} - R\_Enlargement(t)}{p[30]},$$

$$SS_{Enlargement} = \begin{cases} 1, \text{when patient is in AF} \\ 0, \text{when patient is in SR} \end{cases} \quad \text{(Equation 11)}$$

Probability of conversion to sinus rhythm:

The probability of conversion from AF to SR is determined by the integrated effects of ERP, Fibrosis and atrial enlargement on cardioversion and were assumed to be equal for aAF and sAF.

$$P_{AF \to SR}(t) = dt * p[10] * C_{ERP}(t) * C_{Fibrosis}(t) * C_{Enlargement}(t), \quad \text{(Equation 12)}$$

$$C_{ERP}(t) = \frac{p[42]}{1+\exp\left(\frac{-ERP(t)+p[13]}{p[14]} \right)}, \quad \text{(Equation 13)}$$

$$C_{Fibrosis}(t) = \frac{p[41]}{1+\exp\left(\frac{Fibrosis(t) - p[11]}{p[12]} \right)}, \quad \text{(Equation 14)}$$

$$C_{Enlargement}(t) = \frac{p[43]}{1+\exp\left(\frac{Enlargement(t) - p[15]}{p[16]} \right)}, \quad \text{(Equation 15)}$$

$$P_{sAF \to SR}(t) = P_{aAF \to SR}(t) = P_{AF \to SR}(t) \quad \text{(Equation 16)}$$

AF-dependent changes in stroke vulnerability:

The stroke vulnerability represents the accumulation of stroke risk during a patient's lifetime, which is assumed to be an irreversible process and will increase when AF episodes are present. The values of stroke vulnerability are between 0 and 100, meaning the current percentage of maximum stroke risk, which is determined by a factor controlling relative stroke risk increasement (R_StrokeV). Of note, although this vulnerability is implemented in the model as a direct AF-dependent effect, it in reality reflects both direct AF-dependent and indirect AF-associated effects, e.g., implicitly reflecting the burden of cardiovascular disease for which AF is used as a proxy.

$$\frac{dStrokeV}{dt} = p[34] * R\_StrokeV(t) * (100 - StrokeV(t)), \quad \text{(Equation 17)}$$

$$\frac{dR\_StrokeV}{dt} = \frac{SS_{StrokeV} - R\_StrokeV(t)}{p[33]},$$

$$SS_{StrokeV} = \begin{cases} 1, \text{when patient is in AF} \\ 0, \text{when patient is in SR} \end{cases} \quad \text{(Equation 18)}$$

Probability of first stroke

The probability of stroke is dependent on the baseline risk of stroke (p[17]), its relative change in women (p[18] * sex), aging (t), the stroke vulnerability that is promoted by AF episodes (StrokeV * p[21]), and any interventions (e.g., anticoagulation therapy). The probabilities from SR to stroke, from aAF to stroke, and from sAF to stroke are assumed to be equal.

$$P_{Stroke}(t) = dt * Intervention\_stroke * p[17] * (1 + p[18] * sex) * (1 + StrokeV(t) * p[21]) * \left(\frac{1}{1+\exp\left(\frac{-t+p[19]}{p[20]} \right)} \right),$$

$$\text{Intervention\_stroke} = \begin{cases} 1, \text{if AF not diagnosed} \\ p[49], \text{if AF diagnosed} \end{cases} \quad \text{(Equation 19)}$$

$$P_{SR\rightarrow SRStroke}(t) = P_{aAF\rightarrow aAFStroke}(t) = P_{sAF\rightarrow sAFStroke}(t) = P_{Stroke}(t) \quad \text{(Equation 20)}$$

AF-dependent changes in death vulnerability:

The death vulnerability represents the accumulation of death risk during a patient's lifetime, which is assumed to be an irreversible process and will increase during AF episodes. The values of the death vulnerability variable are between 0 and 100, meaning the current percentage of maximum death risk, which will be determined by a factor controlling the relative death risk increase (R_DeathV). Like stroke vulnerability, this vulnerability is implemented in the model as a direct AF-dependent effect, although it in reality reflects both direct AF-dependent and indirect AF-associated effects, e.g., implicitly reflecting the burden of cardiovascular disease for which AF is used as a proxy.

$$\frac{dDeathV}{dt} = p[36] * R\_DeathV(t) * (100 - DeathV(t)), \quad \text{(Equation 21)}$$

$$\frac{dR\_DeathV}{dt} = \frac{SS_{DeathV} - R\_DeathV(t)}{p[35]},$$

$$SS_{DeathV} = \begin{cases} 1, \text{when patients in AF} \\ 0, \text{when patients in SR} \end{cases} \quad \text{(Equation 22)}$$

Probability of death:

The probability of death is dependent on the baseline risk of death (p[22]), relative change in females (p[23] * sex), aging (t), and the death vulnerability variable (DeathV * p[26]). The probabilities from SR to death, from aAF to death, and from sAF to death are assumed to be equal, and have the same relative increase after the occurrence of stroke.

$$P_{Death}(t) = dt * p[22] * (1 + p[23] * sex) * (1 + DeathV(t) * p[26]) * \exp\left(\frac{t - p[24]}{p[25]}\right), \quad \text{(Equation 23)}$$

$$P_{SR\rightarrow death}(t) = P_{aAF\rightarrow death}(t) = P_{sAF\rightarrow death}(t) = P_{Death}(t) \quad \text{(Equation 24)}$$

$$P_{SRStroke\rightarrow death}(t) = (1 + p[27]) * P_{Death}(t) \quad \text{(Equation 25)}$$

$$P_{aAFStroke\rightarrow death}(t) = P_{sAFStroke\rightarrow death}(t) = P_{SRStroke\rightarrow death}(t) \quad \text{(Equation 26)}$$

METHOD DETAILS

Model calibration and validation

A general overview of the model calibration strategy is depicted in Figure S3. Population-level AF metrics, episode-level AF metrics, clinical outcomes, and the effects of continuous AF monitoring were calibrated by reproducing study-specific patient selection criteria (e.g., matching age/sex distribution, history/type of AF, etc., see Table S2) and optimizing parameters to reproduce the clinical outcomes. Suitability of the model for AF screening evaluation was validated by simulating the protocol of the LOOP study.[9] Subsequently, model validation with independent data not used for calibration was implemented by simulating a landmark analysis of stroke risks in patients with different durations of subclinical AF by a sub-study of ASSERT[46] using the final optimized parameters. The detailed definitions and calculation of different metrics for model calibration, parameter optimization, suitability evaluation, model validation, and corresponding parameters are described below and in Tables S1–S4.

Population-level metrics

Age/sex-specific AF incidence was calculated as the number of newly diagnosed AF patients divided by the number of person-years of the total population within the age interval and sex category. Age/sex-specific AF prevalence was calculated as the number of AF patients alive at the midpoint of an age interval divided by the total number of individuals alive at this moment, for men and women. The proportion of patients with paroxysmal AF (pAF) was assessed by generating a random detection timepoint. Anyone with a clinical diagnosis of paroxysmal (but not persistent) AF before this timepoint would count towards the proportion of pAF. These population-level metrics were calculated based on a virtual diagnosis of clinical AF, consistent with the epidemiological origin of the clinical data. A virtual patient received a clinical AF diagnosis in our model whenever a symptomatic AF episode reached a duration of 3 h for the first time, reflecting a lower bound on the time needed to receive medical care. The impact of this healthcare system-related parameter was subsequently investigated (see manuscript). The proportion of symptomatic AF patients was calculated as the number of patients with any symptomatic episodes divided by the total number of AF patients.

Episode-level metrics and progression

The average number of AF episodes per day (AF frequency), the maximum duration among AF episodes (maximum duration), and the percentage of the time in AF (AF burden) were calculated.[8] Low/intermediate/high burden groups were defined as AF burden <0.5%, 0.5%–2.5%, and ≥2.5% based on the RACE-V study.[32] Clinical AF progression rate was defined as the yearly percentage of pAF patients developing persistent or permanent AF. while AF burden progression rate was defined as the yearly percentage of patients with an increase in AF burden >3%, based on the RACE-V study.[34] AF recurrence rate after spontaneous cardioversion was assessed using Kaplan-Meier (K-M) curves.[36] All metrics were calibrated in virtual patients with a clinical diagnosis of pAF selected to match the characteristics of the clinical studies. The proportion of symptomatic AF episodes was calculated among all AF episodes of all virtual AF patients and compared to clinical data from patients with CRM.[33]

Clinical outcome metrics

Age/sex-specific all-cause mortality was calculated as the number of new deaths divided by the number of person-years of the total population during the age range in men and women. The percentage of deaths was calculated as the number of deaths within the age interval divided by the total number of deaths. Similar definitions applied for age/sex-specific stroke incidence and percentage of strokes. Mortality and stroke rates for specific time frames were calculated as the total number of deaths and strokes during the follow-up period divided by the total population at the start of follow-up. Cumulative death and stroke rates were estimated by K-M curves.

Parameter optimization

Fifty-eight parameters were included in the current model (Table S1, including ones for the sex of the virtual patient and screening characteristics such as frequency and duration of screening). Initial values were manually chosen based on the clinical data for the aforementioned metrics and a sensitivity analysis (see below) was implemented for 47 AF- and outcome-relevant parameters in order to show their impact on model calibration (Figure S4). Subsequently, 17 parameters were selected for further optimization using the Nelder-Mead Simplex algorithm in MATLAB R2024a (Mathworks, Natick, MA) using the difference between the metrics calculated based on model output and the clinical data. The initial parameters were manually selected allowing a step change of 15% for each parameter at 1 iteration. The maximum number of iterations is 300. The termination tolerance on the function value and parameters are both 0.0001. Of note, the optimization was limited by the time required for the evaluation of a single parameter set, as the generation of the data required for all analyses required several hours. As such, we cannot guarantee that the identified parameters are unique, nor that a true minimum in the parameter space has been obtained. However, these aspects should not hinder the reproducibility of the research since the code and parameter values used for all simulations have been provided.

AF detection rate and incident strokes with continuous monitoring

The optimized model was verified by simulating the LOOP study.[9] Based on the inclusion criteria in the LOOP study, several parameters were changed to simulate the 3.25-year continuous screening (the average duration of screening) in individuals >70 years with at least one additional stroke/AF risk factor but without previous stroke and clinical AF, and the effect of anticoagulation therapy that could decrease the stroke probability by 70% (footnote of Table S1).[55,56] Next, AF detection rates for specific time frames with or without CRM were calculated as the total number of patients with AF episodes detected (with CRM) or newly diagnosed clinical AF (for patients with/without CRM) during the monitoring time, divided by the total population at the start of follow-up. Cumulative AF detection rates were estimated by K-M curves.

QUANTIFICATION AND STATISTICAL ANALYSIS

Parameter sensitivity analysis

We employed a one-factor-at-a-time sensitivity analysis to determine the impact of the model parameters on the different outcome variables to facilitate the calibration process. This analysis was performed as follows.

Step 1: Calculate the baseline relative error between simulated data and clinical data for different metrics based on the dataset produced by baseline parameters.

$$\text{baseline\_error}_x = \frac{|\text{simulated\_data}_x - \text{clinical\_data}_x|}{\text{clinical\_data}_x}, \quad \text{(Equation 27)}$$

X represents different metrics of model calibration, including AF prevalence, AF incidence, the proportion of pAF, the proportion of symptomatic AF patients, AF frequency, the maximum AF duration, AF burden, age and median AF burden of low, intermediate and high AF burden groups, the proportion of asymptomatic AF episodes, clinical AF progression rate, AF burden progression rate, AF recurrence rate, mortality, stroke incidence, AF-related mortality, and AF-related stroke.

Step 2: Increase the value of a single parameter y by 50% and simulate a new dataset. Then, repeat Step 1 and obtain the new relative error.

Step 3: Calculate the absolute difference between the two relative errors.

$$\text{absolute\_error}_{x,y} = \left|\text{baseline\_error}_{x} - \text{new\_error}_{x,y}\right|, \quad \text{(Equation 28)}$$

X represents different metrics of model calibration and y the parameter that was changed

Step 4: Repeat Steps 1–3 five times and calculate the mean value and standard deviation of the corresponding five absolute errors for a given parameter. Then, the signal-to-noise (SNR) indicator of all calibration metrics for a given parameter y can be calculated as the following.

$$\text{SNR}_{x,y} = \frac{\text{mean\_absolute\_error}_{x,y}}{\text{SD\_absolute\_error}_{x,y}}, \quad \text{(Equation 29)}$$

Step 5: Repeat Steps 1–4 for all parameters and transform the SNRs of different parameters into logarithmic scale.
Step 6: Map the logarithmic values on a heatmap to show how sensitive model calibration metrics are to the 50% increase in a given parameter.

Assessment of different AF screening strategies and their impacts on stroke

Systematic screening protocols with different frequency and duration were designed and were applied to all virtual individuals from 65 years old to death, while symptom-based strategies were initiated after the first symptomatic AF episode after 65 years of age (independent of its duration) for 2 weeks (short-term symptom-based strategies) or until death (long-term symptom-based strategies) (Table S4). Whenever clinical AF was diagnosed before or during follow-up, screening protocols for the virtual individual were stopped. Screening-detected AF was defined as patients without clinical AF but with at least one AF episode detected by the screening. Earlier-detected AF was defined as patients with screening-detected AF who also met the criteria for a subsequent clinical AF diagnosis. In all analyses, virtual anticoagulation therapy was initiated as soon as AF was detected by implementing a 70% reduction in the probability of stroke (i.e., parameter[51] set to 0.3). Subsequently, 5- or 25-year stroke rates after the initiation of AF screening were compared among different strategies. The effect of screening was assessed for baseline stroke risk and 3 times baseline stroke risk (controlled by parameter[17]). Additional analyses were conducted by changing the cutoff value for a clinical AF diagnosis from 3 h to 24 h of continuous symptomatic AF, by increasing the efficacy of anticoagulation therapy from 70% to 90% lower stroke incidence, reflecting potential future advances in anticoagulation therapy, and by simulating 1.5-fold more aggressive AF progression in virtual patients.

Economic analysis of AF screening

To support clinical decision-making on AF screening, an economic analysis was conducted for 5 screening strategies with the highest AF detection rates. Medical costs for monitoring devices, oral anticoagulation therapy, and stroke treatment were estimated. Similarly, survived life years and quality-adjusted life years (QALYs) were calculated accounting for the utilities of symptomatic/asymptomatic AF, stroke, and oral anticoagulation therapy during the same period. Total medical cost of control and screening groups in the unselected population was estimated. Inserted rhythm monitors and ECG-enabled wearable watches were assumed to be replaced every 5 years and continuous anticoagulation was initiated after AF detection or clinical diagnosis until death. Screening would cease upon AF detection or clinical diagnosis. All the data about medical cost and utilities are presented in Table S5.

Statistical analysis

Five independent datasets were simulated using the optimized parameters to produce calibration bar plots with error bars (mean ± standard deviation) for all metrics. Cost metrics (mean ± standard deviation) were calculated from 10 simulated datasets due to the stochastic nature of our model. For K-M curves, all datasets were combined together and plotted with 95% confidence intervals (95% CIs) calculated by Greenwood's method. Hazard ratios (HRs) with 95%CIs in model validation were estimated by Cox regression. Mean relative reduction of stroke for each AF screening strategy compared with the control group was estimated with 95% CIs using 10 simulated datasets due to the limited number of strokes at 5-year follow-up. All K-M plots and survival analysis were conducted in RStudio v2023.06.1 and statistical software R v4.3.0 (R core team, 2023).