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ORIGINAL RESEARCH

Comparative Clinical Effectiveness of Population-Based Atrial Fibrillation Screening Using Contemporary Modalities: A Decision-Analytic Model

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BACKGROUND: Atrial fibrillation (AF) screening is endorsed by certain guidelines for individuals aged ≥65 years. Yet many AF screening strategies exist, including the use of wrist-worn wearable devices, and their comparative effectiveness is not well-understood.

METHODS AND RESULTS: We developed a decision-analytic model simulating 50 million individuals with an age, sex, and comorbidity profile matching the United States population aged ≥65 years (ie, with a guideline-based AF screening indication). We modeled no screening, in addition to 45 distinct AF screening strategies (comprising different modalities and screening intervals), each initiated at a clinical encounter. The primary effectiveness measure was quality-adjusted life-years, with incident stroke and major bleeding as secondary measures. We defined continuous or nearly continuous modalities as those capable of monitoring beyond a single time-point (eg, patch monitor), and discrete modalities as those capable of only instantaneous AF detection (eg, 12-lead ECG). In total, 10 AF screening strategies were effective compared with no screening (300–1500 quality-adjusted life-years gained/100 000 individuals screened). Nine (90%) effective strategies involved use of a continuous or nearly continuous modality such as patch monitor or wrist-worn wearable device, whereas 1 (10%) relied on discrete modalities alone. Effective strategies reduced stroke incidence (number needed to screen to prevent a stroke: 3087–4445) but increased major bleeding (number needed to screen to cause a major bleed: 1815–4049) and intracranial hemorrhage (number needed to screen to cause intracranial hemorrhage: 7693–16 950). The test specificity was a highly influential model parameter on screening effectiveness.

CONCLUSIONS: When modeled from a clinician-directed perspective, the comparative effectiveness of population-based AF screening varies substantially upon the specific strategy used. Future screening interventions and guidelines should consider the relative effectiveness of specific AF screening strategies.

Key Words: atrial fibrillation ■ cost-effectiveness ■ microsimulation ■ screening

Undetected atrial fibrillation (AF) may lead to increased stroke risk.[1] Since oral anticoagulation (OAC) can reduce risk of AF-related stroke,[2] AF screening may enable early diagnosis of AF and initiation of OAC to prevent strokes. However, concerns exist about the potential downstream complications

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CLINICAL PERSPECTIVE

What Is New?

- Using a comprehensive simulation model including 50 million individuals aged ≥65 years, we compared the clinical effectiveness of no screening versus 45 distinct atrial fibrillation screening strategies, including strategies using wearable devices.
- Strategies using a sensitive modality upfront (eg, single-lead ECG, wrist-worn wearable photoplethysmography), followed by a highly specific test to minimize false-positive diagnoses, were most effective.
- In our simulation, the majority of effective strategies included use of a wearable device in the screening pathway.

What Are the Clinical Implications?

- Minimizing false positives is critical for effective population-based atrial fibrillation screening. Wearable devices are likely to be important for clinician-directed atrial fibrillation screening.

Nonstandard Abbreviations and Acronyms

ICH	intracranial hemorrhage
OAC	oral anticoagulation
PM	patch monitor

of screening, such as OAC-related bleeding.[3] Multiple studies have demonstrated that AF screening is feasible and leads to increased AF diagnosis,[4] yet none have reported on whether screening prevents strokes or increases bleeding.

Recent technological advances have enabled a myriad of AF screening approaches, which have not been comprehensively compared. In addition to pulse palpation, 12-lead ECG, and patch monitoring, screening can now be conducted using handheld 1-lead ECG and wrist-worn wearable devices including smart watches or bands.[5,6] Wrist-worn wearables, in particular, can be used to ascertain cardiac rhythm in a frequent or nearly continuous manner using photoplethysmography or 1-lead ECG, thus offering the potential to detect episodes of paroxysmal AF otherwise eluding identification. Yet longer or more frequent screening may increase false positives or detect infrequent episodes of paroxysmal AF for which the degree of increased stroke risk is unclear.[7]

Studies testing whether AF screening reduces stroke are challenging to conduct because of sample size requirements and high costs. It therefore remains uncertain whether population-level AF screening is clinically effective. Consequently, consensus guidelines offer conflicting endorsements of population-based AF screening, with cardiology societies from Europe and Australia/New Zealand providing a class I recommendation for AF screening in individuals aged ≥65 years, and the United States Preventive Services Task Force concluding there is insufficient evidence for or against AF screening with electrocardiography.[8-10]

Given the prohibitive nature of conducting trials for each of the many potential AF screening methods, we used a comprehensive decision-analytic model to assess the long-term benefits and harms of clinician-directed AF screening using traditional and novel screening modalities incorporated into a wide range of potential screening strategies.

METHODS

Data Availability

The code underlying the simulation model described in the current study will be made available upon reasonable request to the corresponding author. Given that all data used in this study stem from previously published reports, and no new patient data were generated or used, the study did not require Institutional Review Board approval.

Model Structure

We constructed a microsimulation model recapitulating the clinical course of AF using an individual-level state-transition approach. The model was built using C++. The model simulated a 50-million person cohort with age and comorbidity distribution matching the 2019 US population aged ≥65 years—the age at which AF screening is guideline-recommended.[8,10] We assumed that only individuals at sufficient stroke risk to merit OAC based on the CHA_2DS_2-VASC score[11,12] in the presence of an AF diagnosis would be screened. The natural history (no screening) as well as 45 unique screening approaches were simulated. Health states in our model were characterized by the historical profile of clinical events that occurred in each simulated individual's life course up to that time (ie, acuteness, number of and types of events), the patient's demographics (eg, age and sex), AF status (including underlying presence, burden, whether symptomatic, and whether diagnosed), presence of CHA_2DS_2-VASC risk factors, and use of antithrombotic treatment, each of which governed transition probabilities into future states. The time between state transitions was 1 month. Given greater risk for recurrent events and mortality observed after more recent clinical events, we modeled recency of

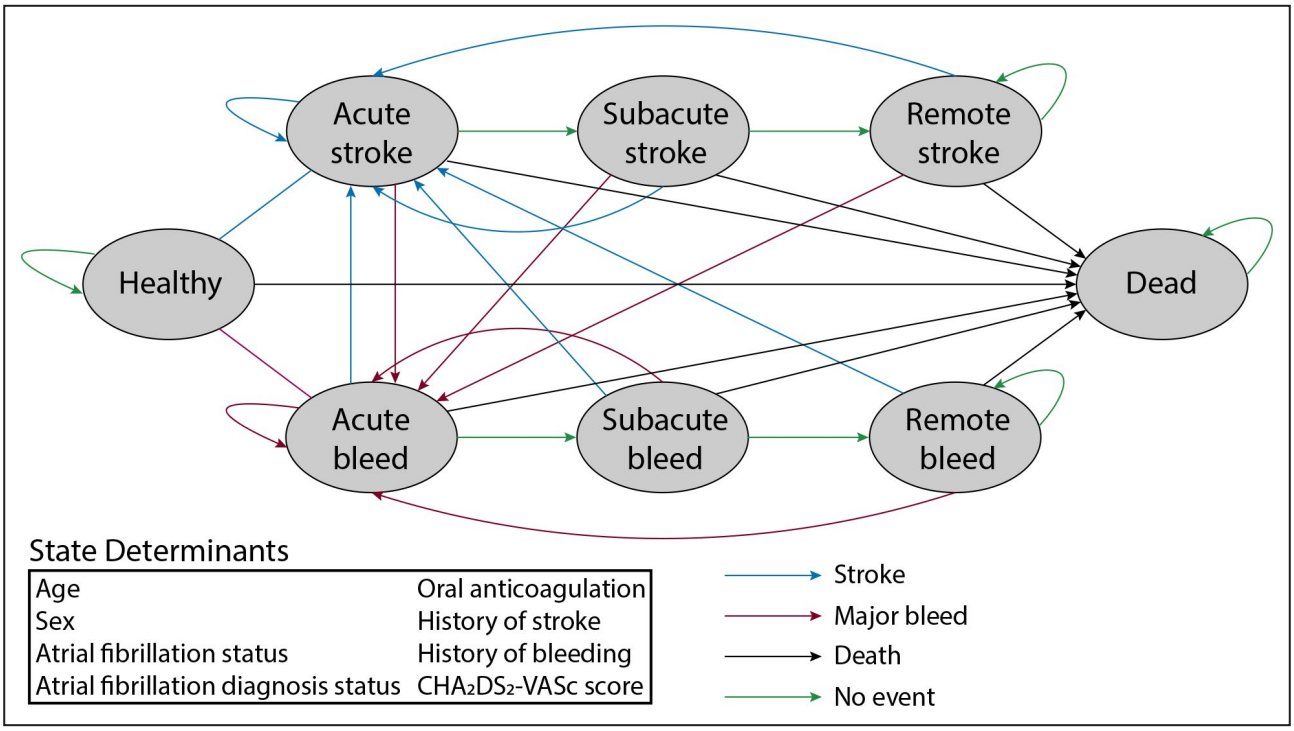

Figure 1. Model structure.
A state transition diagram is depicted summarizing the range of possible states occupied by simulated individuals. For stroke and bleeding events, post-event states (acute, subacute, remote) are used to capture the increased risk for morbidity and recurrent events observed in the period following these events. Medical comorbidities other than stroke or bleeding (eg, CHA_2DS_2-VASc[11] risk factors) could accrue across any transition period. In addition to the current state, other clinical factors (listed in the state determinants box) influenced transition probabilities to future states.

clinical events into 3 categories (ie, acute [0–30 days], subacute [31 days to 1 year], and remote [>1 year]). Figure 1 provides an overview of model structure. To fully encompass the potential long-term consequences of screening, we adopted a lifetime horizon, ending simulation at death or age 100. Further details of model structure and an overview of the sample size determination for the simulation are presented in Data S1.

AF Risk

Model input parameters were derived from published literature (Table S1), with studies selected systematically (Data S1). We modeled AF incidence using previously reported age- and sex-stratified estimates. AF could be detected in the context of routine care, screening, or a 2-week patch monitor (PM) deployed after every stroke (mirroring contemporary practice).[13,14]

Although the prevalence of undiagnosed AF is unknown, studies demonstrate that the proportion of additional cases detected using intermittent or short-term screening represents ≈24% of the underlying AF prevalence.[15-17] Therefore, we assumed that 24% of prevalent AF in the simulated population is undiagnosed. Individuals with undiagnosed AF could become diagnosed through AF screening, according to the test characteristics of the strategy applied. Since the underlying prevalence of undiagnosed AF is inherently uncertain, we varied the proportion of undiagnosed AF widely in sensitivity analyses.

Stroke Risk

We modeled the prevalence and incidence of stroke among individuals without AF using population-based estimates. Among individuals with AF, we varied stroke incidence in accordance with CHA_2DS_2VASc,[11] a widely used score for predicting stroke in AF. CHA_2DS_2VASc scores varied over time according to the incidence of component comorbidities. Since individuals with incident stroke are known to be at higher risk for recurrent events in a time-dependent manner, we also applied recurrence-specific stroke rates (Data S1).

Stroke severity was simulated by applying an expected distribution of the modified Rankin scale.[18] In accordance with published evidence, stroke mortality varied according to severity. We assumed that paroxysmal and persistent AF conferred similar stroke risk in the base case, but performed sensitivity analyses

in which we assumed that the stroke risk associated with paroxysmal AF was 75% of that associated with persistent AF.[7,19,20] We modeled the effect of antithrombotic therapy on stroke incidence and severity as a function of the presence or absence of AF.

Bleeding Risk

We modeled 2 classes of bleeding in accordance with International Society of Thrombosis and Hemostasis guidelines: major bleeding and clinically relevant nonmajor bleeding.[21,22] Accordingly, we treated intracranial hemorrhage (ICH) as a subset of major bleeding. We modeled the effect of antithrombotic therapy on bleeding incidence and mortality.

Antithrombotic Therapies

We modeled 3 forms of antithrombotic therapy: aspirin, warfarin, and direct-acting oral anticoagulant. We modeled aspirin use based on the presence of vascular disease, concurrent OAC administration, and contemporary primary prevention use patterns (Data S1). We assumed complete OAC usage at AF diagnosis but modeled real-world estimates of OAC discontinuation over time.[23,24] Frequency of warfarin versus direct-acting oral anticoagulant was based on contemporary use patterns.[25,26] We assumed permanent OAC discontinuation following major bleeds.

Screening Strategies

In addition to no screening, we evaluated 6 distinct AF screening modalities: pulse palpation, 1-lead handheld ECG, 12-lead ECG, PM, and wrist-worn wearables (smart watch/band photoplethysmography and smart watch/band ECG). We arranged screening modalities in pragmatic combinations including those evaluated in AF screening trials.[4,5,6,27,28,29,30,31] To facilitate comparison across strategies, we assumed a clinician-directed screening approach, in which screening would be initiated at a clinical encounter, and could be continued following the encounter based depending upon strategy used (eg, wrist-worn wearable). We defined continuous or nearly continuous modalities as those capable of monitoring beyond a single time-point (eg, PM, wrist-worn wearable photoplethysmography), and discrete modalities as those capable of only instantaneous AF detection (eg, pulse palpation, 12-lead ECG). We assumed that a continuous or nearly continuous modality would only be prescribed after a negative discrete modality. We defined confirmatory tests as those performed conditionally following an abnormal result on a preceding test (eg, confirmatory PM following abnormal wrist-worn wearable photoplethysmography). Mirroring previous interventions using confirmatory tests (eg, Screening for Atrial Fibrillation the Elderly [SAFE],[32] the VITAL-AF trial[29]), we assumed that confirmatory tests would be deployed immediately following the abnormal preceding test. Positive results on a confirmatory test, on the final test in the screening pathway, or on 12-lead ECG (even when not utilized as a confirmatory test) resulted in AF diagnosis and termination of screening. For each modality, we applied published test characteristics to determine the diagnostic result (eg, true positive, false positive). For strategies not using wrist-worn wearables, we also varied the screening interval (once, annually, every 5 years) to assess the effect of repeated screening. For strategies using wrist-worn wearables, to fully assess the potential effects of prolonged screening, we compared a 12-month versus lifetime screening duration. Although lifetime wearable use is an idealized scenario, we assumed this is plausible given the increasing availability of wrist-worn wearable devices. To mirror current technology, wrist-worn wearables with both photoplethysmography and ECG capability operated using photoplethysmography as the default function, with ECG triggered only after detection of abnormal photoplethysmography signals. Ultimately, our model compared 45 unique AF screening strategies (Figure 2). To facilitate reporting of results, strategies are reported by effectiveness rank, which corresponds to decreasing order of effectiveness (eg, *Strategy 1* is the most effective strategy and *Strategy 45* is the least effective strategy).

Utilities

We obtained long-term disutility values for chronic conditions (eg, AF, history of severe stroke) and exposures (eg, OAC use) from the previous literature. We also applied 1-time disutility penalties for short-lived adverse events (eg, major bleeding).

Outcomes

The primary outcome was quality-adjusted life-years (QALYs). Secondary outcomes included ischemic stroke, major bleeding, intracranial hemorrhage, and AF true-positive and false-positive rates. We calculated incidence rates by dividing incident events observed by the person-time accrued either before the event (events) or until death (non-events). We estimated the number needed to screen (NNS) to prevent a stroke or cause a bleed as the inverse of the absolute difference in the event rate compared with no screening.[33] We did not discount future QALYs. Based on our simulation size determinations (Data S1), QALY differences within 100 QALYs per 100 000 individuals may be attributable to simulation noise. Therefore, we defined effective strategies as only those providing an increase in QALYs of ≥200 per 100 000 individuals as compared with no screening.

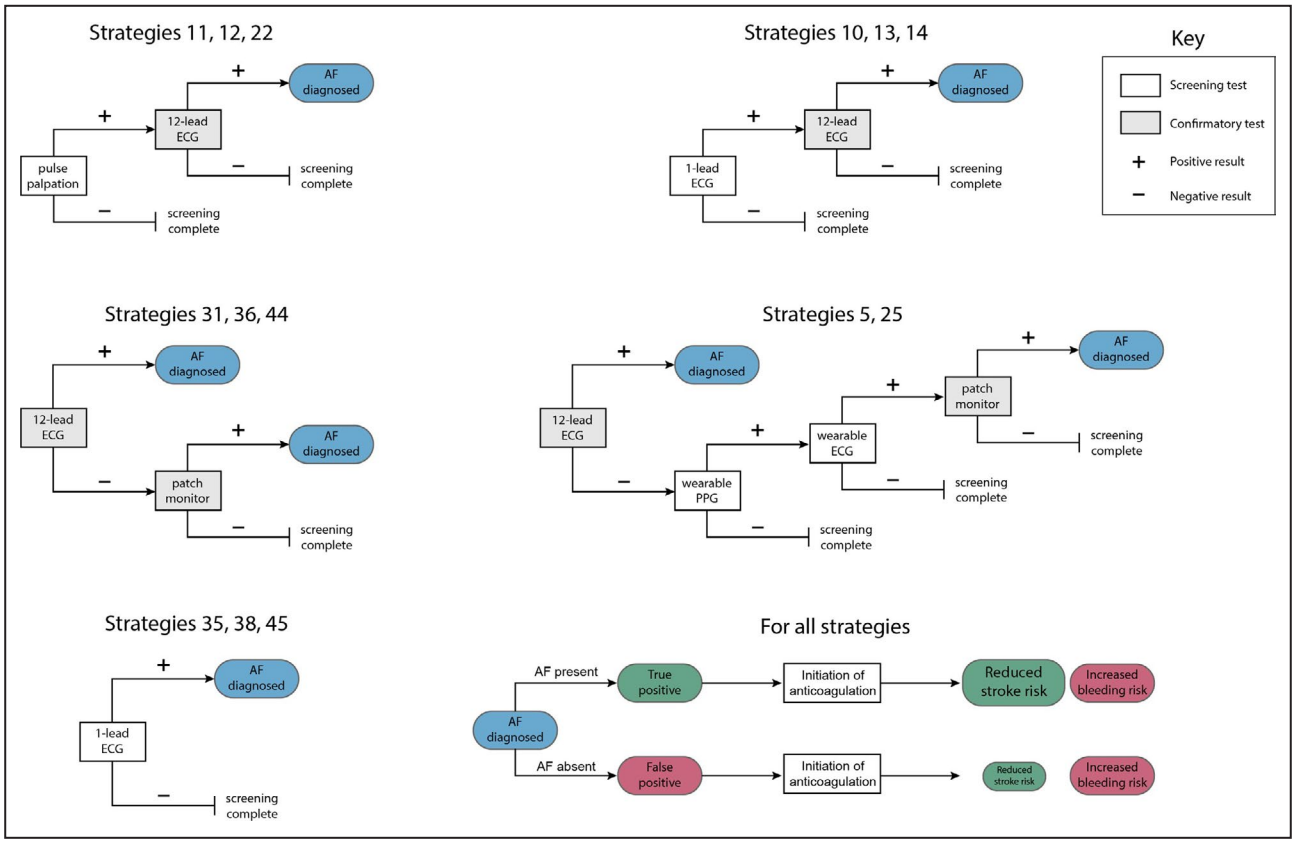

Figure 2. Screening strategies for population-based atrial fibrillation screening.
Diagrams depict selected population-based atrial fibrillation (AF) screening strategies evaluated. Strategies are labeled by rank order of decreasing effectiveness (see text). Diagrams correspond to multiple strategies since the same screening sequences were evaluated across varying durations and frequencies. *Strategies 11, 12, and 22* (top left) utilize pulse palpation followed by confirmatory 12-lead ECG if pulse palpation shows irregularity (analogous to the "opportunistic screening" strategy in the SAFE trial[31]). *Strategies 10, 13, and 14* (top right) utilize single-lead ECG followed by confirmatory 12-lead ECG if single-lead ECG suggests possible AF (analogous to SEARCH-AF[28] and VITAL-AF[29]). *Strategies 31, 36, and 44* (middle left) utilize 12-lead ECG followed by patch monitor if 12-lead ECG does not show AF (analogous to the mSToPS trial[30]). *Strategies 5 and 25* (middle right) use a novel strategy in which 12-lead ECG is followed by wrist-worn wearable-based photoplethysmography if 12-lead ECG is negative, then by wrist-worn wearable-based ECG if photoplethysmography is positive, then by confirmatory patch monitor if wrist-worn wearable-based ECG is positive. *Strategies 35, 38, and 45* (bottom left) utilize 1-lead ECG alone to diagnose AF. For all strategies, AF could be diagnosed by a positive result on a confirmatory test (gray box), on 12-lead ECG (even when not utilized as a confirmatory test) or on the final test in the screening pathway. An AF diagnosis could be made in an individual who truly has AF (true positive), or an individual who does not truly have AF (false positive). In either case, an AF diagnosis leads to initiation of anticoagulation (in the absence of major bleeding history, see text), which provides greater protection against stroke among individuals with AF versus those without and increases bleeding risk among all individuals. AF indicates atrial fibrillation.

Sensitivity Analyses

Although certain guidelines recommend AF screening in individuals aged ≥65 years, some studies have investigated screening older populations.[15] To assess the effect of varying age thresholds on screening effectiveness, we applied the base case model in simulated populations mirroring the US population aged ≥70 years, and aged ≥75 years.

We performed sensitivity analyses to assess the effect of parameter uncertainty. In probabilistic sensitivity analyses, we varied distribution parameters across plausible evidence-based ranges (Table S2). In 1-way sensitivity analyses, we assessed the effect of varying specific parameters chosen based on clinical importance or influence in previous models (Table S2).[17,28]

RESULTS

Base Case Results

Results of the base case analysis are depicted in Table S3 and summarized in Figures 3 and 4. With no screening, the average individual accrued 9.027 QALYs. Of the 45 strategies tested, only *Strategies 1–10* (22%) resulted in QALY gain (range 300–1500 QALYs gained/100 000 people screened) and were therefore considered effective. Among *Strategies*

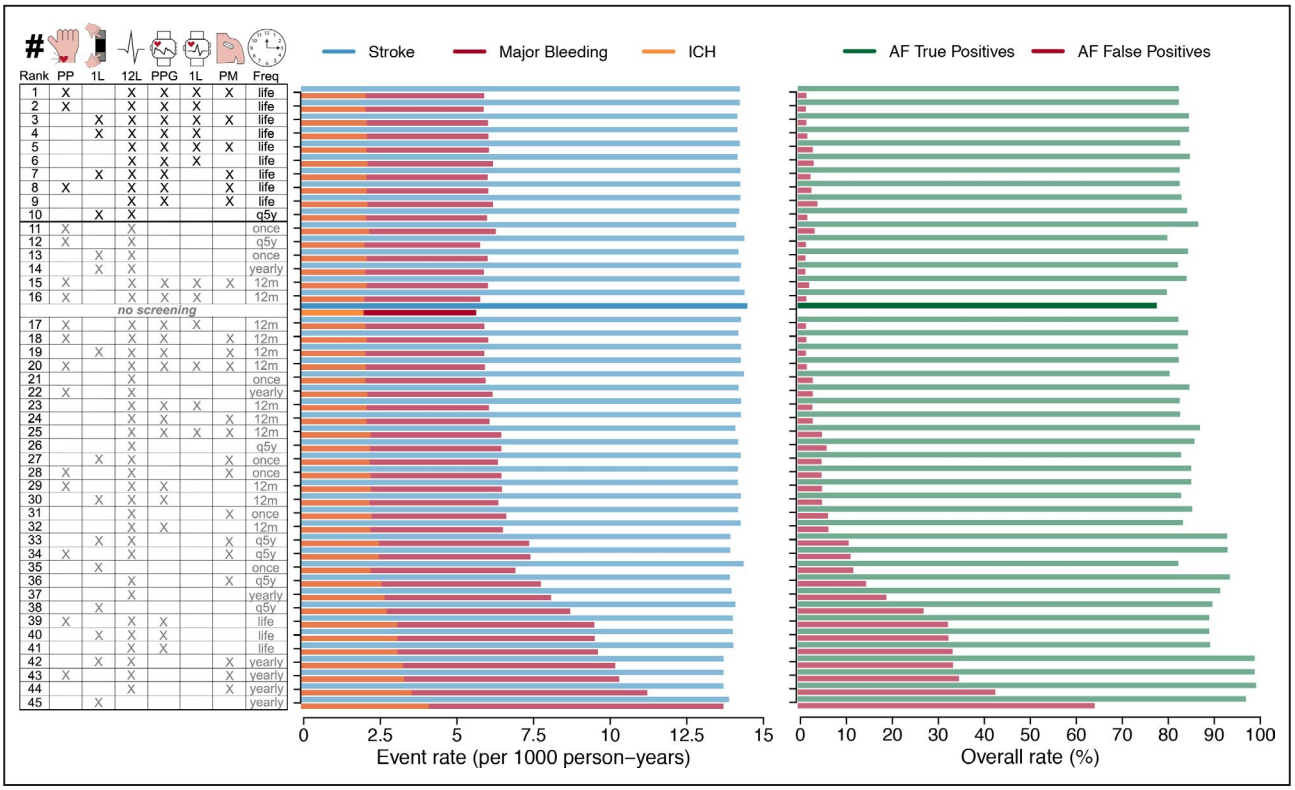

Figure 3. Clinical events by screening strategy.
Depicted are clinical effectiveness end points of interest according to atrial fibrillation screening strategy. The left panel depicts the incidence rates of ischemic stroke (blue), major bleeding (dark red), and intracranial hemorrhage (a subset of major bleeding, orange) according to atrial fibrillation screening strategy. The right panel depicts the overall atrial fibrillation true-positive rate (green) and false-positive rate (red). The strategies corresponding to each point are depicted by the table to the left of both graphs, corresponding to the icons above the table applied in sequence from left to right. The bars colored in darker shade depict relevant event rates with no screening. Strategies are numbered and sorted in rank order of decreasing effectiveness (ie, decreasing quality-adjusted life-years), starting with the most effective strategies at the top. Effective screening strategies (ie, providing an increase in quality-adjusted life-years of ≥200 per 100 000 individuals as compared with no screening), are depicted in black while all others are depicted in gray. A small false positive rate in the no screening condition (0.4%) is attributable to the application of a patch monitor following all stroke events (see text). 12L indicates 12-lead ECG; 12m, 12 months; 1L, 1-lead ECG; AF, atrial fibrillation; ICH, intracranial hemorrhage; PM, patch monitor; PP, pulse palpation; PPG, photoplethysmography; and q5y, every 5 years.

1–10, reduction in stroke ranged 0.23 to 0.32/1000 person-years (NNS to prevent stroke: 3087–4445), increase in major bleeding ranged 0.25 to 0.55/1000 person-years (NNS to cause major bleed: 1815–4049), and increase in ICH ranged 0.059 to 0.13/1000 person-years (NNS to cause ICH: 7693–16 950, Figure 3, Table S3).

Among *Strategies 1–10*, 9 (*Strategies 1–9*; 90%) involved use of a continuous or nearly continuous modality such as PM or wrist-worn wearable device, whereas 1 (*Strategy 10*; 10%) relied on discrete modalities alone. Wrist-worn wearables were included in 24 of 45 (53.3%) strategies modeled, but in 9 of 10 (90%) strategies identified as effective (*Strategies 1–9*). The most effective strategy comprised pulse palpation, confirmatory 12-lead ECG, and if necessary, wrist-worn wearable with photoplethysmography and single-lead ECG for lifetime duration, with confirmatory PM (*Strategy 1*: 1500 QALYs gained/100 000 people screened; NNS to prevent stroke: 4133; NNS to cause major bleed: 3847; NNS to cause ICH: 16 130). The only effective strategy not using a wrist-worn wearable was 1-lead ECG and confirmatory 12-lead ECG repeated every 5 years (*Strategy 10*: 300 QALYs gained/100 000 people screened; NNS to prevent stroke: 3862; NNS to cause major bleed: 2802; NNS to cause ICH: 11 112).

Compared with ineffective strategies, effective strategies generally demonstrated low AF false-positive rates with comparable AF true-positive rates (Figure 3, Table S3). Accordingly, although all screening strategies prevented strokes, effective strategies prevented strokes without inducing large increases in bleeding related to false positives. For example, *Strategy 9* (12-lead ECG, and if necessary, wrist-worn wearable photoplethysmography with confirmatory PM) detected roughly as many true AF cases as *Strategy 28* (pulse palpation with confirmatory 12-lead ECG and PM), but exhibited a lower bleeding rate (6.09 versus 6.26 per

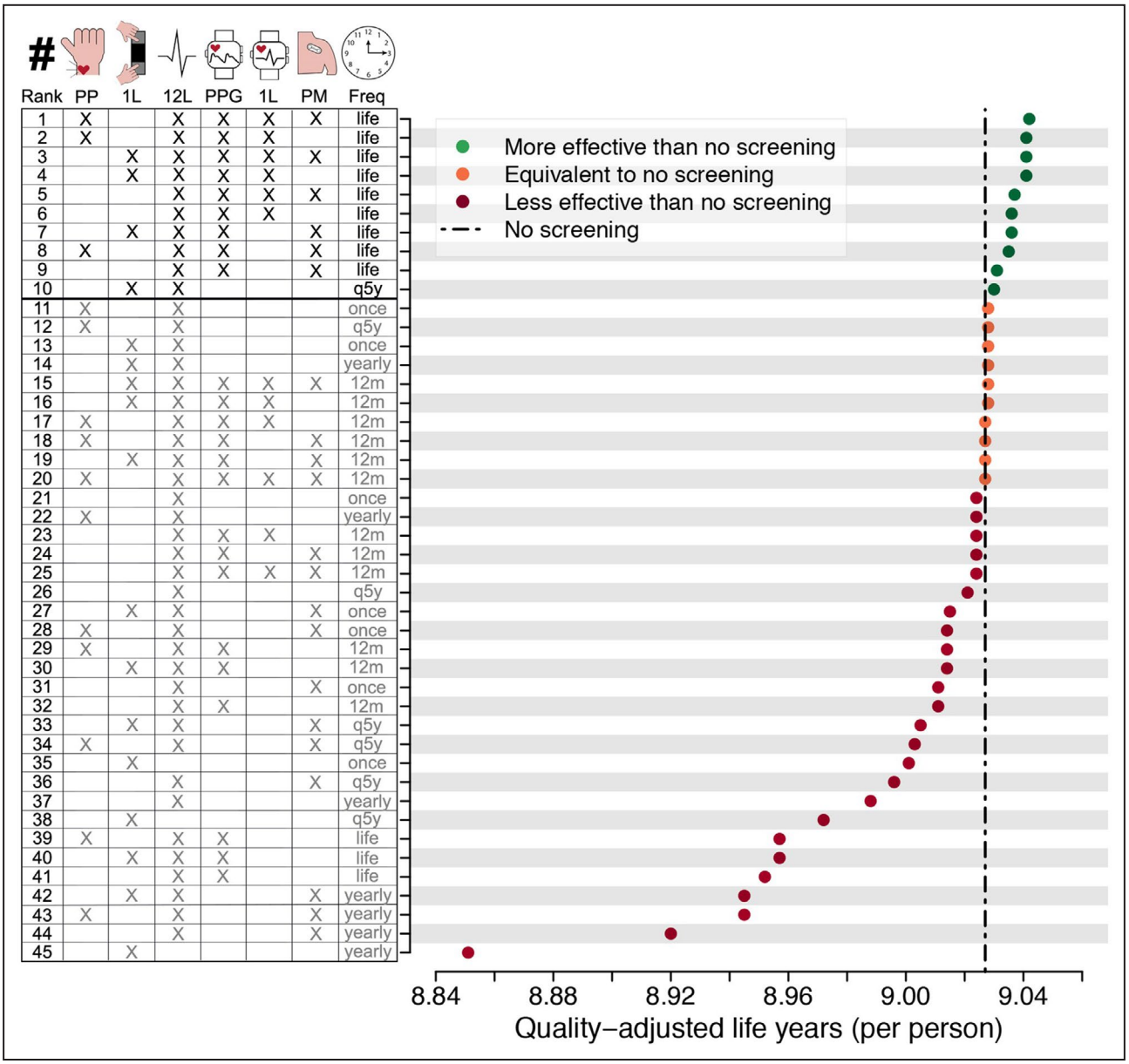

Figure 4. Screening effectiveness.
Depicted are the overall effectiveness results in the base case analysis assessing 45 unique strategies for atrial fibrillation screening. The strategies corresponding to each point are depicted by the table to the left of the graph, corresponding to the icons above the table. The vertical dashed line represents the expected quality-adjusted life-years lived without atrial fibrillation screening. Effective screening strategies (ie, providing an increase in quality-adjusted life-years of ≥200 per 100 000 individuals as compared with no screening) are depicted in green, ineffective screening strategies (ie, providing a decrease in quality-adjusted life-years of ≥200 per 100 000 individuals as compared with no screening), are depicted in red, while all others are considered equivalent to no screening and depicted in yellow. Strategies are numbered and sorted in rank order of decreasing effectiveness (ie, decreasing quality-adjusted life-years), starting with the most effective strategies at the top. 12L indicates 12-lead ECG; 12m, 12 months; 1L, 1-lead ECG; PM, patch monitor; PP, pulse palpation; PPG, photoplethysmography; and q5y, every 5 years.

1000 person-years) attributable to fewer false-positive AF diagnoses (Table S4).

Of 25 strategies demonstrating harm, 7 (*Strategies 23*, *29–30*, *32*, *39–41*; 28%) included use of a wrist-worn wearable without a confirmatory PM, and another 11 (*Strategy 22, 26, 33–34, 36–38, 41–45*; 44%) used discrete modalities repeated annually or every 5 years. Ineffective strategies tended to exhibit high false-positive rates, resulting in large increases in bleeding with small incremental reductions in stroke (Table S3, Figure 3). For example, the least effective strategy overall was annual 1-lead ECG (*Strategy 45*: 17 600 QALYs lost/100 000 people screened; NNS to prevent stroke: 1678; NNS to cause major bleed:

124; NNS to cause ICH: 470). When compared with *Strategy 1* (pulse palpation, confirmatory 12-lead ECG, and if necessary, wrist-worn wearable with photoplethysmography and single-lead ECG with confirmatory PM for lifetime duration), *Strategy 45* (annual 1-lead ECG) increased appropriate AF detection, yet AF was falsely diagnosed within an even greater number of individuals, leading to a substantially higher bleeding rate (13.61 versus 5.80 per 1000 person-years). In general, more frequent screening using discrete modalities reduced effectiveness because of accrual of false positives (Figure 5). Even strategies composed of highly specific modalities could exhibit considerable false-positive rates when performed annually (eg, false-positive rate increased from 5.5% for *Strategy 31* [12L and PM performed once] to 41.8% for *Strategy 44* [12L and PM performed annually]). In contrast, increasing the screening duration of wrist-worn wearables from 12 months to the lifespan generally resulted in greater benefit, as long as abnormal photoplethysmography signals were followed-up with either PM or wrist-worn single-lead ECG (Figure 5).

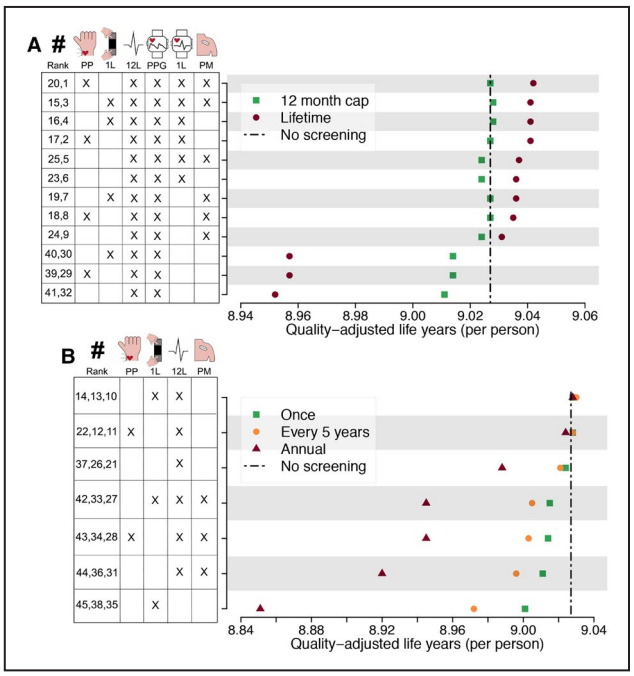

Figure 5. Screening effectiveness stratified by screening duration and interval.
Depicted are the results of analyses assessing the temporal effect of screening using (**A**) wrist-worn wearables, and (**B**) traditional screening modalities. The strategies corresponding to each point are depicted by the table to the left of the graph, corresponding to the icons above the table. The vertical dashed line represents the expected quality-adjusted life-years lived without atrial fibrillation screening. For strategies including wrist-worn wearables, temporal assessments compared use of the wearable for the lifespan (red) versus 12 months (green). For strategies not including wrist-worn wearables, temporal assessments compared screening once (green), every 5 years (yellow), and annually (red). 12L indicates 12-lead ECG; 12m, 12 months; 1L, 1-lead ECG; PM, patch monitor; PP, pulse palpation; PPG, photoplethysmography; and q5y, every 5 years.

Sensitivity Analyses

Models simulating more elderly populations demonstrated similar patterns of effectiveness with higher absolute event rates (individuals aged ≥70 years: QALYs gained 200–1600/100 000 people screened, NNS to prevent stroke: 1985–6061, NNS to cause major bleed: 1171–5320, Table S5, Figure S1) and individuals aged ≥75 years (QALYs gained 300–1000/100 000 people screened, NNS to prevent stroke: 1561–4525, NNS to cause major bleed: 965–3497, Table S6 and Figure S2). In 1-way sensitivity analyses, test specificity consistently emerged as highly influential (Figure S3). Other influential parameters included the treatment effect of OAC and aspirin on AF-related stroke and AF-related quality-of-life. Assuming a low estimate for the proportion of AF that is paroxysmal resulted in loss of effectiveness of 1 (10%) strategy, while assuming paroxysmal AF is associated with a lower risk of stroke than persistent AF did not result in loss of effectiveness of any strategy (Figure S3). In probabilistic sensitivity analyses, all effective strategies had a probability of effectiveness ≥50% (Figure S4).

DISCUSSION

Using a decision-analytic model to quantify the comparative effectiveness of 45 distinct AF screening strategies in individuals aged ≥65 years, we found that population-based AF screening can be effective within a clinician-directed context. Importantly, the comparative effectiveness of population-based AF screening varied substantially upon the specific strategy used, with less than one quarter of modeled strategies resulting in net benefit. Effective strategies were typically multimodal, and commonly included devices capable of prolonged continuous or nearly continuous cardiac rhythm assessment such as wrist-worn wearables. The most effective strategies resulted in 1500 QALYs gained/100 000 individuals screened, prevented 1 stroke for every 3087 to 4445 people screened, and caused 1 major bleed for every 1815 to 4049 people screened. Whereas all screening strategies reduced strokes, effective strategies characteristically had low false-positive rates and thereby resulted in only modest increases in bleeding.

In a previous model by Aronsson et al,[20] single time-point screening among individuals aged 75 to 76 years using 1-lead ECG, confirmed by cardiologist overread or short-term rhythm monitor, was clinically effective. We also found that 1-lead ECG with confirmatory 12-lead ECG performed once or every 5 years was effective, although we observed a more modest QALY gain.

Other studies have suggested both clinical and cost-effectiveness of AF screening using traditional modalities such as pulse palpation, 12-lead ECG, and patch monitoring.[32,34] In our analysis, we found that pulse palpation followed conditionally by 12-lead ECG resulted in similar QALY estimates as no screening, and screening using 12-lead ECG alone generally resulted in reduced QALYs. Given the multitude of possible AF screening approaches and the generally low stroke rates among individuals with detected AF, conducting well-powered randomized trials comparing each strategy is infeasible. Therefore, our simulation of 45 distinct strategies deployed within a unified screening context provides important comparative effectiveness data to guide future screening efforts and guidelines.

Our results demonstrate that application of screening strategies with low specificity or without inclusion of a confirmatory test may be ineffective and even harmful. All modeled strategies reduced stroke rates by a similar margin but increases in bleeding varied substantially. Effective strategies consistently demonstrated low false positive rates, whereas strategies utilizing repeated or prolonged application of less specific tests (eg, single-lead ECG, wrist-worn photoplethysmography) had higher false positive rates leading to excess bleeding. Therefore, our results indicate that abnormal findings using highly sensitive modalities with low specificity should be confirmed (eg, PM) before taking clinical action. For example, single-lead ECG or wrist-worn wearable-based photoplethysmography alone currently appear insufficient to reliably establish an AF diagnosis in the context of population-based AF screening. We also observed that strategies comprising discrete modalities repeated annually were universally ineffective. Repeating screening tests best equipped to detect persistent AF within a population in which undiagnosed AF is increasingly paroxysmal (as most individuals with persistent AF will have been diagnosed on previous screens) likely does not substantially increase AF yield yet increases exposure to potential false positives. Whether minimization of false positive results could be optimized by targeting AF screening towards individuals at highest AF risk[35] or utilizing emerging artificial technology-based methods for interpreting ECG waveforms[36] merits further study.

Our findings suggest that the high sensitivity afforded by wrist-worn wearables coupled with high specificity confirmatory testing may provide a favorable balance between detecting AF and avoiding erroneous diagnoses. Wrist-worn wearables are increasingly common,[37] and wearable-based AF screening is feasible.[5,6] Our model demonstrates that clinician-guided deployment of wrist-worn wearables for AF screening is effective, particularly when coupled with confirmatory testing. The best performing wrist-worn wearable strategy saved an additional 1200 QALYs/100 000 people screened when compared with the best strategy not using wrist-worn wearables. It is likely that a longer screen duration increases yield of low-burden paroxysmal AF that would otherwise go undetected even with repeated screening using discrete modalities, while confirmatory testing reduces false positive diagnoses potentially introduced by extended duration screening.[16,30] Our results indicate that reflexive single-lead ECGs following abnormal photoplethysmography signals may likewise offset false positives. Given the rapidly evolving field of consumer wearable technology, prospective study is warranted to confirm our findings.

Our results also identify key factors influencing AF screening effectiveness. Consistent with the importance of false positives, test specificity consistently emerged as highly influential. Furthermore, the treatment effect of OAC and aspirin on AF-related stroke, as well as the reduction in quality-of-life attributable to AF, also influenced QALY estimates. Future anticoagulants offering a more favorable balance of stroke protection versus bleeding risk may improve AF screening effectiveness.[38] Notably, even the most effective strategy modeled needed to be deployed in >4000 individuals to prevent 1 stroke. As a result, targeting additional potentially modifiable AF-related outcomes (eg, heart failure hospitalization[39]) may increase the effectiveness of future screening interventions. Similarly, given the observed influence of AF-related quality-of-life, integration of strategies known to improve AF symptoms (eg, weight loss,[40] alcohol cessation,[41] blood pressure management,[42] sleep apnea treatment[43]) with the screening intervention may increase net benefit.

Our study should be interpreted in the context of design. First, evidence to support certain model inputs was limited. For example, AF disutility was based on relatively dated surveys and varies substantially across studies. Since AF-related quality-of-life may have changed with contemporary therapies,[44] future studies are needed to better quantify the disutility associated with AF and related outcomes. Second, we assumed that the stroke risk of screen-detected AF was similar to that of clinically detected AF. Screen-detected AF likely reflects a lower burden of disease, and AF burden may be associated with stroke risk.[45,46] We observed that assuming lower stroke risk in the setting of paroxysmal AF had little impact on screening effectiveness, though further data are needed.[7] Third, although we used a systematic approach to selecting studies to inform model inputs, we did not incorporate study heterogeneity when combining estimates across multiple studies. Fourth, we estimated AF-related stroke risk using the CHA_2DS_2-VASc score[11] given widespread use in clinical practice and endorsement by consensus guidelines.[12] The score has limited predictive utility, does not consider differences in risk associated with

specific combinations of risk factors, and does not incorporate additional variables likely exerting some influence on risk of stroke in AF (eg, smoking,[47] obesity[48]). Fifth, our models focused on stroke (and bleeding) since this is a major irreversible hazard that may present as the initial manifestation of AF. Future models are warranted to assess the effectiveness of AF screening for additional end points including heart failure[49] and cognitive decline.[50] Sixth, we did not simulate screening using implantable loop recorders, or the impacts of pacemakers or defibrillators given our focus on population-based screening. Seventh, to estimate the maximum plausible effectiveness of contemporary AF screening, we modeled complete OAC use. Future analyses are warranted to examine the impact of initial OAC use on screening effectiveness.

CONCLUSIONS

Using a decision-analytic model comparing 45 contemporary strategies deployed within a clinician-directed context to perform population-based AF screening, we found that roughly one quarter were clinically effective. Strategies using a sensitive modality upfront (eg, single-lead ECG, wrist-worn wearable photoplethysmography), followed by a highly specific test to minimize false-positive diagnoses, tended to be most effective. Future screening interventions and clinical guidelines should consider the relative effectiveness of specific screening approaches.

ARTICLE INFORMATION

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Supplementary Material

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Supplemental Material

Data S1.

Supplemental Methods

A. Study selection

The majority of model inputs were derived directly from published literature sources. Detailed model inputs with corresponding lower and upper bounds and their sources are listed in **Table 1**. Published studies were identified using PubMed queries (https://pubmed.ncbi.nlm.nih.gov/), with search terms corresponding to inputs of interest. Studies were included if they met the following criteria: 1) provided relevant information regarding the input of interest and 2) had adequately described methods to ascertain that the information reported corresponded to the input of interest and was estimated in a manner free from excessive bias. All potentially relevant literature sources were reviewed by at least one study author for potential inclusion. Studies passing the initial screen were reviewed by at least one additional study author and included on the basis of consensus between reviewing authors that the study met criteria for inclusion. In cases where parameters could be estimated from multiple eligible sources, summary estimates were obtained by taking means weighted by study sample size. In cases where point estimates were highly variable, priority for calculating the summary estimate was placed on studies with the following features (in order of importance): a) a meta-analysis, b) prospective and/or randomized, c) multi-center, and d) larger in size. All relevant studies contributed to selection of parameter bounds.

For a minority of input parameters, published literature was insufficient to obtain accurate estimates. In these cases, we assumed values after achievement of consensus between two clinical cardiologists. All assumed values are indicated in **Table 1**.

B. Competing event rates

In cases in which a simulated individual has multiple competing candidate rates for an outcome event, we applied the highest of the relevant rates.

For example, an individual with AF and a CHA_2DS_2VASc score of 5 is estimated to have a 8.4% yearly risk of stroke without treatment. An individual with an incident stroke has a 13.0% risk of a recurrent stroke in the first year, after which the risk decreases to 4.1% per year. If this simulated individual has an incident stroke, then their risk of a recurrent stroke in the year following that stroke event will be 13.0% (the highest of 13.0% and 8.4%). Following the first year, their yearly risk of a recurrent stroke will be 8.4% (the highest of 4.1% and 8.4%). Note, probabilities in this particular example assume no anticoagulation therapy.

C. Aspirin use

An individual was assumed to be taking aspirin in the setting of the following:

If on OAC:

1) History of myocardial infarction

If not on OAC:

1) History of vascular disease
2) No history of myocardial infarction and age ≥ 50 years with probability 0.43[51]

D. Integration of paroxysmal AF

Given lack of reliable data regarding the test characteristics of wearable devices for detecting paroxysmal AF over longer durations of monitoring (i.e., months to years), we modeled the temporal effect of screening via a wearable device as follows:

We applied literature-based values for the estimated prevalence of paroxysmal AF among individuals with screen-detected AF (59%). We then utilized estimates of the average AF burden among individuals with paroxysmal AF (4.5%). We assumed that the average AF burden follows a uniform distribution on the order of days (i.e., an individual with an AF burden of 4.5% would be expected, on average, to spend 4.5% of each day in AF).

Then, the probability that an individual will not experience a single AF episode over *t* days is $(1-0.045)^t$. The probability that an individual will experience at least one AF episode over *t* days is the complement, or $1-(1-0.045)^t$. We then applied the known static test characteristics of the wearable device to the probability of observing AF with each cycle of simulation (i.e., one month or 30 days).

For example, an individual with AF wearing a watch for 3 months would have a probability of the device being exposed to an AF episode after one cycle of $1-(1-0.045)^{30}$, or 0.749. If this individual is wearing a W-PPG (sensitivity 95.3, specificity 99.7), they will be diagnosed with AF with probability 0.749 * 0.953, or 0.714 after one cycle. As with other screening modalities, if a diagnosis of AF is not made, and the screening strategy under evaluation includes continued screening, then the screening process will repeat as dictated by the length of the screening interval being evaluated. In this case of 3-month screening, screening would continue for three cycles, with a probability of being diagnosed with AF of 0.714 after each cycle, and the overall probability of being diagnosed with AF of $1-(1-0.714)^3$ or 0.977.

Although the data provided by a recent study by Diedrichsen et al. is insufficient to primarily inform test characteristics over the necessary durations required to model wearable screening approaches, we were able to validate that our approach described above resulted in comparable estimates of sensitivity for paroxysmal AF at 30 days, after allowance for the uncertainty in AF burden, which we modeled in probabilistic sensitivity analyses.[52]

Methods Table 1. Probability of AF episode with 30 days of monitoring

Method	AF burden value	Probability
AF model (lower bound)	0.011	0.282
AF model (base)	0.045	0.749
AF model (upper bound)	0.17	0.996
Diedrichsen et al.[52]	-	0.34

E. Sensitivity analysis assumptions

In cases where estimates of uncertainty in model parameters was unavailable in the literature, we varied point estimates by +/- 20% when performing both one-way and probabilistic sensitivity analyses. In cases for which certain parameters serve as subsets of other parameters (e.g., intracranial hemorrhage as a subset of major hemorrhage), we modeled uncertainty in the parameter for which the uncertainty was most clearly defined in the literature, then applied base case ratios to derive values for other members of the set, therefore avoiding clinically implausible scenarios (e.g., a higher rate of intracranial hemorrhage than that of major hemorrhage).

F. Transformation of various effect sizes to monthly transition probabilities

In multiple scenarios, incidence/recurrence rates from the literature were used to derive monthly transition probabilities of events. For example, the annual recurrence probability of ischemic stroke with no treatment is 0.13.[53] Thus, the annual recurrence rate (number of recurrent ischemic strokes per person-year) is $-\ln(1-0.13)=0.139$. Using this value, we estimated the monthly recurrence rate as $\frac{0.139}{12}=0.0116$. Finally, we converted the monthly recurrence rate to a monthly probability of recurrent ischemic stroke: $1-\exp(-0.0116)=0.0115$.

In various cases, relative risks from the literature were used to derive monthly transition probabilities of events with different risk factors in place. For example, to obtain the monthly probability of recurrent ischemic stroke with aspirin, we applied the relative risk of aspirin vs. placebo (0.78[54]) to the monthly recurrence rate of ischemic stroke (0.0116 as above) to obtain the monthly recurrence rate with aspirin as $0.0116\times 0.78=0.009$. Using this value, we can calculate the monthly probability of recurrent ischemic stroke with aspirin as $1-\exp(-0.009)=0.009$.

G. Modeling interactions between prevalent vascular comorbidities

In our model, we incorporated the effects of clinical risk factors on outcomes (e.g., increased risk of stroke in AF given the presence of CHA_2DS_2VASc conditions) by allowing the presence of risk factors to influence transition probabilities. The three specific comorbidities comprising the "Vascular" component of the CHA_2DS_2VASc score: PAD (peripheral artery disease), MI (myocardial infarction), and non-MI CAD (coronary artery disease) are known to frequently coexist. Therefore, we used literature estimates indicating the conditional and marginal distributions of these conditions (see **Table I** for values and sources). At the beginning of the simulation we used Baye's conditional probability theorem, i.e., $P(A\ \&\ B)\ =\ P(A)\times P(B|A)\ =\ P(B)\times P(A|B)$, to derive the joint distributions of the prevalence of multiple vascular comorbidities, where *A* and *B* are notations indicating any one of three vascular conditions: non-MI CAD, MI, and PAD.

More specifically, there are six possible combinations of vascular diseases: non-MI CAD only, MI only, PAD only, non-MI CAD and PAD, MI and PAD, and none of these.

$P(non-MI\ CAD\ only)\ =\ P(non-MI\ CAD)\times(1-P(PAD\mid non-MI\ CAD))$, where both $P(non-MI\ CAD)$ indicates the prevalence of non-MI CAD and $P(PAD\mid non-MI\ CAD)$ indicates the probability of having coexisting PAD given that one already has non-MI CAD. Both were found in the literature. Likewise for the other combinations:

$P(MI\ only)\ =\ P(MI)*(1-P(PAD\mid MI))$

$P(PAD\ only)\ =\ P(PAD)*(1-P(non-MI\ CAD\mid PAD)-P(MI\mid PAD))$

$P(non-MI\ CAD\ \&\ PAD)\ =\ P(non-MI\ CAD)*P(PAD\mid non-MI\ CAD)$

$P(MI\ \&\ PAD)\ =\ P(MI)*P(PAD\mid MI)$

$P(no\ vascular\ conditions)\ =\ 1-P(non-MI\ CAD\ only)-P(MI\ only)-P(PAD\ only)-P(non-MI\ CAD\ \&\ PAD)-P(MI\ \&\ PAD)$

H. Simulation size determination

To determine sufficient cohort size for base case simulation taking into account first-order uncertainty (i.e., Monte Carlo error), we followed the guidelines provided by the ISPOR-SMDM Modeling Good Research Practices Task Force.[55] Specifically, we tested results at increasing sample size from from 1 million to 65 million and noted the comparative clinical effectiveness of all 45 screening strategies with respect to no screening, i.e., d(QALY). We report these values in the table below. At a precision of 0.001

(i.e., 100 QALYs per 100,000 persons), one can see that d(QALY) is well-stabilized at simulation sizes at or above 50 million. As a result, we utilized a simulation size of 50 million for the base case analysis.

Methods Table 2. Simulation size determination

#								Simulation size						
								65 million	50 million	25 million	20 million	15 million	10 million	5 million	1 million
Rank	PP	1L	12L	PPG	1L	PM	Freq								
1	X		X	X	X	X	life	0.015	0.015	0.016	0.016	0.018	0.018	0.016	0.015
2	X		X	X	X		life	0.014	0.014	0.016	0.016	0.017	0.017	0.015	0.015
3		X	X	X	X	X	life	0.015	0.014	0.016	0.016	0.018	0.018	0.016	0.015
4		X	X	X	X		life	0.015	0.014	0.016	0.016	0.017	0.017	0.015	0.015
5			X	X	X	X	life	0.011	0.010	0.011	0.010	0.011	0.011	0.009	0.008
6			X	X	X		life	0.010	0.009	0.011	0.009	0.009	0.009	0.007	0.003
7		X	X	X		X	life	0.009	0.009	0.011	0.011	0.012	0.012	0.009	0.006
8	X		X	X		X	life	0.009	0.008	0.010	0.009	0.011	0.011	0.009	0.009
9			X	X		X	life	0.004	0.004	0.006	0.005	0.006	0.006	0.003	-0.003
10		X	X				q5y	0.003	0.003	0.004	0.004	0.003	0.003	0.004	0.005
11	X		X				once	0.001	0.001	0.002	0.002	0.002	0.002	0.000	0.000
12	X		X				q5y	0.001	0.001	0.002	0.002	0.003	0.003	0.002	0.004
13		X	X				once	0.002	0.001	0.003	0.003	0.003	0.003	0.002	0.001
14		X	X				yearly	0.001	0.001	0.002	0.001	0.003	0.003	0.001	0.003
15		X	X	X	X	X	12m	0.000	0.001	0.001	0.001	0.001	0.001	-0.003	-0.005
16		X	X	X	X		12m	0.001	0.001	0.001	0.002	0.001	0.001	-0.003	-0.004
17	X		X	X	X		12m	0.000	0.000	0.000	0.001	0.003	0.003	-0.002	-0.005
18	X		X	X		X	12m	0.000	0.000	0.000	0.000	0.003	0.003	-0.001	-0.004
19		X	X	X		X	12m	0.000	0.000	0.000	0.001	0.002	0.002	-0.002	-0.003
20	X		X	X	X	X	12m	0.000	0.000	0.000	0.000	0.001	0.001	-0.003	-0.006
21			X				once	-0.002	-0.003	-0.001	-0.001	-0.001	-0.001	-0.003	-0.003

22	X		X				yearly	-0.002	-0.003	-0.002	-0.002	-0.001	-0.001	-0.001	-0.003
23			X	X	X		12m	-0.003	-0.003	-0.004	-0.003	-0.002	-0.002	-0.006	-0.007
24			X	X		X	12m	-0.004	-0.003	-0.004	-0.003	-0.001	-0.001	-0.005	-0.005
25			X	X	X	X	12m	-0.003	-0.003	-0.004	-0.003	-0.003	-0.003	-0.006	-0.008
26			X				q5y	-0.006	-0.006	-0.005	-0.005	-0.006	-0.006	-0.008	-0.003
27		X	X			X	once	-0.012	-0.012	-0.012	-0.012	-0.011	-0.011	-0.012	-0.009
28	X		X			X	once	-0.012	-0.013	-0.013	-0.012	-0.011	-0.011	-0.013	-0.011
29	X		X	X			12m	-0.013	-0.013	-0.013	-0.013	-0.012	-0.012	-0.017	-0.022
30		X	X	X			12m	-0.013	-0.013	-0.013	-0.012	-0.012	-0.012	-0.017	-0.019
31			X			X	once	-0.016	-0.016	-0.015	-0.015	-0.014	-0.014	-0.017	-0.016
32			X	X			12m	-0.016	-0.016	-0.017	-0.016	-0.015	-0.015	-0.019	-0.021
33		X	X			X	q5y	-0.022	-0.022	-0.021	-0.021	-0.019	-0.019	-0.023	-0.024
34	X		X			X	q5y	-0.023	-0.024	-0.022	-0.022	-0.020	-0.020	-0.023	-0.022
35		X					once	-0.026	-0.026	-0.026	-0.025	-0.026	-0.026	-0.027	-0.035
36			X			X	q5y	-0.031	-0.031	-0.030	-0.030	-0.028	-0.028	-0.029	-0.029
37			X				yearly	-0.039	-0.039	-0.038	-0.039	-0.036	-0.036	-0.039	-0.035
38		X					q5y	-0.055	-0.055	-0.055	-0.056	-0.055	-0.055	-0.059	-0.057
39	X		X	X			life	-0.071	-0.070	-0.069	-0.068	-0.066	-0.066	-0.064	-0.067
40		X	X	X			life	-0.070	-0.070	-0.068	-0.068	-0.066	-0.066	-0.065	-0.073
41			X	X			life	-0.075	-0.075	-0.074	-0.075	-0.073	-0.073	-0.072	-0.075
42		X	X			X	yearly	-0.082	-0.082	-0.081	-0.082	-0.077	-0.077	-0.082	-0.081
43	X		X			X	yearly	-0.081	-0.082	-0.080	-0.081	-0.075	-0.075	-0.080	-0.083
44			X			X	yearly	-0.107	-0.107	-0.106	-0.106	-0.103	-0.103	-0.103	-0.103
45		X					yearly	-0.176	-0.176	-0.174	-0.175	-0.170	-0.170	-0.170	-0.164

Table S1. Model inputs.

Outcome Incidence (per 1000 person-years)

Clinically recognized AF

	< 55 years	55 to 64 years	65 to 74 years	75 to 84 years	≥ 85 years	References
Male	0.62 (0.62-0.76)	4.34 (4.31-4.56)	12.91 (9.24-14.33)	24.52 (19.80-26.31)	39.66 (15.6[56]-46.81)	56,57
Female	0.19 (0.19-0.21)	2.16 (1.10-3.70[56])	6.79 (5.91-7.65[56])	17.14 (14.40[56]-17.69)	27.69 (11.9[56]-28.67)	

All stroke (for no AF and no treatment group)

	< 35 years	35 to 44 years	45 to 54 years	55 to 64 years	65 to 74 years	75 to 84 years	≥ 85 years	References
Male	0.03 (0-0.19)	0.27 (0.07-0.81)	0.73 (0.33-1.38)	1.77 (1.03-2.84)	6.46 (4.70-8.68)	9.42 (6.56-13.10)	19.72 (11.49-31.58)	58
Female	0.06 (0-0.25)	0.16 (0.02-0.57)	0.54 (0.05-1.17)	1.75 (1.00-2.84)	4.08 (2.71-5.89)	10.51 (7.89-13.71)	15.08 (10.17-21.52)	

Intracranial hemorrhage

	Base	Lower	Upper	References
No treatment (converted from probability at 7.4y)	0.81			59
Aspirin	0.95	0.95[59]	4	59,60
Warfarin	7.8 (WA)	3.3[61]	8.5[62]	61–64
DOAC	3.99 (WA)	3.3[61]	5.0[64]	61–64
OAC+aspirin	16.0			65

Major hemorrhage

	Base	Lower	Upper	References
No treatment	1.64[66]	0.467	1.64	66,67
Aspirin	2.31[66]	1.92[66]	8.0[68]	66,68
Warfarin	31.2 (WA)	16.9[61]	34.3[62]	61–64
DOAC	29.0 (WA)	9.6[61]	36.0[64]	61–64
OAC+aspirin	43.0			65

Clinically relevant non-major hemorrhage

	Base	Lower	Upper	References
No treatment	2.9 (A)	2.2[69]	3.6[70]	[69,70]
Aspirin (converted from probability at 2.3y)	5.61			[71]
Warfarin	107.1 (WA)	101.5[62]	114.0[64]	[62,64]
DOAC	102.2 (WA)	86.7	118.0	[62,64]
OAC+aspirin (HR versus warfarin)	1.19	0.36	4.17	[65]

Comorbidity Incidence/Prevalence

Heart failure

Incidence

	55-64 years	65-69 years	70-74 years	75-79 years	80-84 years	≥85 years	References
Male	3.9 (3.9-11.2)[72]	7.4 (6.4-8.5)	10.8 (9.2-12.5)	16.9 (14.3-19.5)	29.4 (24.1-34.8)	45.6 (35.3-55.8)	[72,73]
Female	2.7 (2.7-8.2)[72]	5.1 (4.3-5.9)	10.2 (8.8-11.6)	14.4 (12.3-16.5)	23.2 (19.5-26.8)	41.1 (34.8-47.4)	
Defined using presence of Framingham heart failure criteria[74]							

Prevalence

	20-39 years	40-59 years	60-79 years	≥80 years	References
Male	0.3	1.2	6.9	12.8	[72]
Female	0.2	1.7	4.8	12.0	
Defined using NHANES 2013-2016 health interviews. Heart failure was considered present if a person reported "yes" to being told by a healthcare professional that he or she had heart failure.					

Hypertension

Incidence

	20-29 years	30-39 years	40-49 years	50-59 years	60-69 years	70-79 years	References
Male	8.15 (5.5-10.0)	16.6 (1.3-75.0)	21.9 (3.9-71.0)	23.6 (8.7-91.0)	28.0 (10.2-88.6)	31.1	[75]
Female	3.3 (2.0-4.6)	7.7 (6.8-33.0)	18.0 (16.1-57.0)	24.9 (32.4-66.0)	34.7 (42.6-95.8)	42.8	
Defined using systolic blood pressure ≥ 160mmHg or diastolic blood pressure ≥ 95mmHg on two consecutive measurements, or use of anti-hypertensive medication							

Prevalence

	20-34 years	35-44 years	45-54 years	55-64 years	65-74 years	≥75 years	References
Male	25.7	42.5	56.3	66.4	70.8	80.0	[72]
Female	13.0	31.6	49.7	64.9	77.8	85.6	
Defined using NHANES 2013-2016 blood pressure measurements and health interviews. Hypertension was considered present if a person had systolic blood pressure ≥ 130mmHg or diastolic blood pressure ≥ 80mmHg, reported "yes" to taking anti-hypertensive medication, or reported "yes" to being told by a healthcare professional that he or she had hypertension on at least two occasions.							

Diabetes

Incidence

	≥20 years	References
Male	4.15 (4.15-6.15)	[76]
Female	2.70 (2.70-6.79)	
Defined as fasting glucose ≥ 126 mg/dL, 2 hour post-challenge glucose ≥ 200 mg/dL, random glucose ≥ 200 mg/dL with presence of hyperglycemia symptoms, hemoglobin a1c ≥ 6.5%		

Prevalence

	≥20 years	References
Male	15.5	[72]
Female	11.7	
Defined as fasting glucose ≥ 126 mg/dL, 2 hour post-challenge glucose ≥ 200 mg/dL, hemoglobin a1c ≥ 6.5%, or use of anti-glycemic medications		

Coronary disease (including both MI and non-MI CAD)

Incidence

	35-54 years	55-69 years	≥70 years	References
Male	2.06	6.33	15.5	[77]
Female	0.57	2.82	9.52	
Defined using International Classification of Diseases, 9th revision (ICD-9) and ICD, 10th revision (ICD-10) codes: 410-414, I21-I25 applied to hospital admission data and cause of death register				

Prevalence

	20-39 years	40-59 years	60-79 years	≥ 80 years	References
Male	0.5	6.1	19.7	31.0	[72]
Female	1.0	6.2	12.6	25.4	
Defined using NHANES 2013-2016 health interviews. Coronary heart disease was considered present if a person reported “yes” to being told by a healthcare professional that he or she had coronary heart disease, angina or angina pectoris, heart attack, or myocardial infarction. Those who answered “no” but were diagnosed with angina based on the Rose questionnaire were also included.					

Myocardial infarction (MI)

Incidence

	35-44 years	45-54 years	55-64 years	65-74 years	≥ 75 years	References
Male	0.79 (0.79-2.35)	2.14 (2.14-4.01)	3.82 (3.82-7.05)	7.26 (7.26-10.67)	9.39 (9.39-15.9)	[72]
Female	0.27 (0.27-1.05)	0.99 (0.99-2.70)	2.10 (2.10-4.35)	3.69 (3.69-7.70)	8.53 (8.53-12.0)	
Defined using the Atherosclerosis Risk in Communities Study acute myocardial infarction surveillance definition[78]						

Prevalence

	20-39 years	40-59 years	60-79 years	≥ 80 years	References
Male	0.1	2.8	11.5	17.3	[72]
Female	0.4	2.1	4.2	12.7	
Defined using NHANES 2013-2016 health interviews. Myocardial infarction was considered present if a person reported “yes” to being told by a healthcare professional that he or she ever had a heart attack or myocardial infarction.					

Peripheral arterial disease (PAD)

Incidence

	50-59 years	60-69 years	70-79 years	≥ 80 years	References
Overall	1.0	2.0	2.8	3.5	[79]
Female (vs. Male)	Relative risk/incidence ratio: 0.538				
Defined using presence of Read diagnosis codes indicative of a symptomatic PAD diagnosis or related revascularization procedures					

Prevalence

	40-49 years	50-59 years	60-69 years	70-79 years	≥ 80 years	References
Male	1.4 (0.2-2.6)	1.9 (0.9-5.0)	5.4 (3.5-13.2)	9.2 (9.2-24.4)	22.6 (21.5-59.0)	[72]
Female	1.9 (0-3.0)	4.3 (0.4-4.3)	5.1 (0.7-8.9)	7.9 (6.9-20.0)	18.2 (18.2-35.1)	
Defined using ankle-brachial index < 0.9 or previous revascularization for PAD						

Conditional Prevalence

Condition	Value	References
Prevalence (PAD | non-MI CAD)	0.141	[80]
Prevalence (PAD | MI)	0.048	[81–83]
Prevalence (PAD | no CAD)	0.0090	[84]
Prevalence (non-MI CAD | PAD)	0.109	[85]
Prevalence (MI | PAD)	0.182	[85]

Stroke incidence in AF (by CHA_2DS_2VASc score, per 100 person-years)

CHA_2DS_2-VASc Score	Base	Lower	Upper	References
0	0.2			[86]
1	0.6			
2	2.5			
3	3.7			
4	5.5			
5	8.4			
6	11.4			
7	13.1			
8	12.6			
9	14.4			

Recurrence (Monthly Probabilities)

	Base	Lower	Upper	References
Ischemic stroke				
No treatment				
First year	0.0115	0.00874	0.0144	[53]
Subsequent years	0.00348	0.00141	0.00668	[53]
Aspirin				
First year	0.009			Use RR
Subsequent years	0.003			Use RR
OAC (with or without aspirin)				
First year	0.004			Use RR
Subsequent years	0.001			Use RR
Intracranial hemorrhage				
First year	0.0135			[87]
Subsequent years	Baseline incidence			

Mortality (Monthly Probabilities)

	Base	Lower	Upper	References
Ischemic stroke (30-day, AF)				
Mild	0.01			[88]
Moderate	0.13			[88]
Severe	0.39			[88]
Ischemic stroke (first year among 30-day survivors, no AF)				
Mild	0			Assumption
Moderate-severe	Use RR			
Ischemic stroke (first year among 30-day survivors, AF)				
Mild	0			Assumption
Moderate-severe	0.026			[89]
Ischemic stroke (subsequent years among 1-year survivors, no AF)				

	Base	Lower	Upper	References
Mild	0			Assumption
Moderate-severe	Use RR			
Ischemic stroke (subsequent years among 1-year survivors, AF)				
Mild	0			Assumption
Moderate-severe	0.0077			[89]
Relative risk of ischemic stroke mortality (AF versus no AF)	1.63	1.25	2.00	[89,90]
Intracranial hemorrhage (disabling)				
30-day probability of death (aspirin or no treatment)	0.35	0.332	0.374	[91]
Odds ratio for death at 30 days (OAC or OAC+aspirin)	3	1.9	4.7	[92]
First and Subsequent years among 30-day survivors	0.01575			[93]
Major hemorrhage				
No treatment	0.091			[94]
Aspirin	0.078			[94]
Warfarin	0.14	0.112	0.206	[95]
DOAC	0.082	0.068	0.104	[61,62,64]
OAC+Aspirin	0.11			Assumption

Severity measures

	Base	Lower	Upper	References
Ischemic Stroke				
No AF, No Treatment				
Proportion of ischemic strokes that are mild (mRS 0-2)	0.47	0.375	0.575	[96]
Proportion of ischemic strokes that are moderate (mRS 3-4)	0.405	0.3	0.5	[96]
Proportion of ischemic strokes that are severe or fatal (mRS 5-6)	0.125	0.07	0.16	[96]
AF, No Treatment				

	Base	Lower	Upper	References
Proportion of ischemic strokes that are mild (mRS 0-2)	0.363	0.3	0.45	[96]
Proportion of ischemic strokes that are moderate (mRS 3-4)	0.364			[96]
Proportion of ischemic strokes that are severe or fatal (mRS 5-6)	0.273			[96]
AF, on OAC				
Proportion of ischemic strokes that are mild (mRS 0-2)	0.47			[88]
Proportion of ischemic strokes that are moderate (mRS 3-4)	0.42			[88]
Proportion of ischemic strokes that are severe or fatal (mRS 5-6)	0.11			[88]
Intracranial hemorrhage				
Proportion of intracranial hemorrhages that are nondisabling	0.26	0.12	0.39	[91]

Additional clinical factors

	Base	Lower	Upper	References
Atrial Fibrillation				
Proportion of AF that is undiagnosed	0.24	0.22	0.28	[15,16]
Proportion of AF that is asymptomatic	0.12			[97]
Proportion of undiagnosed AF that is persistent	0.41	0.04	0.66	[16,30,31,98]
Average AF burden in individuals with paroxysmal AF (%)	0.045	0.011	0.17	[7,16,45]
Risk of ischemic stroke for parosxymal screen-detected AF (vs persistent AF)	1	0.75		Assumption[28]
Patient Factors				
Proportion of OAC that is NOAC (vs. warfarin)	0.33	.10	.50	[25,26]
Yearly probability of warfarin discontinuation	0.101		0.40	[23,24]
RR of NOAC discontinuation (vs. warfarin)	0.69 (WA)	0.57	0.84	[23]
Initial uptake of follow-up patch monitoring	1	0.62	1	Assumption[5,6]
Ischemic Stroke				
Proportion of strokes that are ischemic	0.87	0.83	0.88	[72]

	Base	Lower	Upper	References
RR of ischemic stroke (aspirin vs. placebo, AF)	0.78	0.65	0.94	54
RR of ischemic stroke (warfarin vs. placebo, AF)	0.33	0.23	0.46	54
RR of ischemic stroke (OAC vs. placebo, no AF)	0.58	0.44	0.76	99
RR of ischemic stroke (NOAC vs. warfarin)	1	0.83	1.02	2
RR of ischemic stroke (OAC+aspirin vs. OAC alone)	1	0.44	2.22	65
Screening methods				
Sensitivity (single time point)				
Pulse palpation	89.0	16	100	32,100,101
Single-lead handheld ECG	96.9	36.8	100	102,103
Patch monitor	100		100	104
12-lead ECG	90.0	52.0	100	105
Smart watch/band (PPG)	95.3	92.0	97.4	106,107
Smart watch/band (ECG)	85.2		0.983	unpublished data
Specificity (single time point)				
Pulse palpation	81.0	65	91	32,100,101
Single-lead handheld ECG	89.6	71.0	100	102
Patch monitor	96.6			104
12-lead ECG	98.3	55.0	100	105
Smart watch/band (PPG)	99.7	98.1	99.9	106,107
Smart watch/band (ECG)	99.6			unpublished data

Utilities

	Base	Lower	Upper	References
Atrial Fibrillation				
Asymptomatic	0.954			108
Symptomatic	0.81	0.68	0.91	109
Ischemic stroke				

	Base	Lower	Upper	References
Mild stroke (mRS 0-2)	0.89	0.80	0.93	[96]
Moderate stroke (mRS 3-4, first year)	0.67	0.56	0.71	[96]
Moderate stroke (mRS 3-4, subsequent years)	0.71	0.67	0.80	[96]
Severe or fatal stroke (mRS 5-6, first year)	0.30	0.20	0.40	[96]
Severe stroke (mRS 5, subsequent years)	0.48	0.30	0.60	[96]
Intracranial hemorrhage				
Nondisabling	0.89			[96]
Disabling (first year)	0.42			[96]
Disabling (subsequent years)	0.55			[96]
Major bleeding				
1 month	0.8			[96]
Therapeutics (while receiving)				
Warfarin	0.987	0.953	1.0	[110]
Novel oral anticoagulants	0.994	0.993	0.996	[111]
Aspirin	0.998	0.994	1	[110]

Table S2. Summary of parameters included in sensitivity analyses.

Parameter	Included in one-way sensitivity analysis	Included in probabilistic sensitivity analysis (PSA)	Distribution(s) utilized in PSA
Incidence rates			
Atrial fibrillation		X	Log-normal, beta
Ischemic stroke (AF)	X	X	Log-normal, beta
Ischemic stroke (non-AF)		X	Log-normal, beta
Intracranial hemorrhage	X	X	Log-normal, beta
Major hemorrhage	X	X	Log-normal, beta
Recurrent stroke		X	Log-normal, beta
Mortality			
Ischemic stroke	X	X	Beta
Intracranial hemorrhage	X	X	Beta
Major hemorrhage		X	Beta
Severity			
Ischemic stroke		X	Beta
Intracranial hemorrhage		X	Beta
Other clinical factors			
Proportion of AF that is undiagnosed	X	X	Beta
Proportion of AF that is persistent	X	X	Beta
Average AF burden in paroxysmal AF	X	X	Beta
Proportion of OAC that is DOAC	X	X	Beta
OAC discontinuation rate	X	X	Beta
Patch monitor adherence	X	X	Triangular
Effect of OAC on ischemic stroke	X	X	Beta
Test characteristics			
Pulse palpation	X	X	Beta
Single-lead ECG	X	X	Beta
Patch monitor			Beta, Triangular
12-lead ECG			Beta
Smart watch/band PPG			Beta
Smart watch/band ECG			Beta
Utilities			
AF	X	X	Beta
Ischemic stroke		X	Beta
OAC		X	Beta
Aspirin		X	Beta

Table S3. Clinical effectiveness of atrial fibrillation screening by strategy.

#								Life expectancy (yr)	Quality-adjusted life expectancy (yr)	Ischemic stroke (per 1,000 person-yr)	Major bleed (per 1,000 person-yr)	Intracranial Bleed (per 1,000 person-yr)	AF true positive rate (%)	AF false positive rate (%)
Rank	PP	1L	12L	PPG	1L	PM	Freq							
1	X		X	X	X	X	life	12.543	9.042	14.142	5.798	1.928	81.7	0.7
2	X		X	X	X		life	12.542	9.041	14.060	5.938	1.971	83.9	0.9
3		X	X	X	X	X	life	12.542	9.041	14.140	5.785	1.925	81.7	0.6
4		X	X	X	X		life	12.541	9.041	14.060	5.925	1.968	83.9	0.7
5			X	X	X	X	life	12.537	9.037	14.142	5.956	1.956	82.0	2.1
6			X	X	X		life	12.536	9.036	14.066	6.089	1.996	84.1	2.3
7		X	X	X		X	life	12.538	9.036	14.158	5.917	1.963	81.9	1.6
8	X		X	X		X	life	12.537	9.035	14.157	5.935	1.967	81.9	1.8
9			X	X		X	life	12.532	9.031	14.159	6.087	1.992	82.3	3.1
10		X	X				q5y	12.531	9.030	14.125	5.895	1.956	83.5	0.9
11	X		X				once	12.528	9.028	14.295	5.673	1.890	79.1	0.7
12	X		X				q5y	12.528	9.028	14.133	5.923	1.964	83.4	1.3
13		X	X				once	12.529	9.028	14.289	5.667	1.889	79.2	0.6
14		X	X				yearly	12.527	9.028	14.016	6.180	2.039	85.9	2.5
15		X	X	X	X	X	12m	12.525	9.028	14.181	5.788	1.926	81.5	0.5
16		X	X	X	X		12m	12.525	9.028	14.098	5.914	1.964	83.7	0.5
			no screening					12.528	9.027	14.384	5.538	1.866	76.9	0.4*
17	X		X	X	X		12m	12.525	9.027	14.095	5.931	1.970	83.7	0.7
18	X		X	X		X	12m	12.525	9.027	14.175	5.824	1.938	81.7	0.8
19		X	X	X		X	12m	12.525	9.027	14.178	5.808	1.932	81.6	0.6
20	X		X	X	X	X	12m	12.525	9.027	14.179	5.804	1.931	81.5	0.6
21			X				once	12.524	9.024	14.276	5.845	1.923	79.7	2.1
22	X		X				yearly	12.522	9.024	13.995	6.358	2.090	86.3	4.1

23			X	X	X		12m	12.521	9.024	14.102	6.076	1.993	84.0	2.1
24			X	X		X	12m	12.521	9.024	14.178	5.973	1.962	82.0	2.1
25			X	X	X	X	12m	12.521	9.024	14.181	5.955	1.957	81.9	2.0
26			X				q5y	12.521	9.021	14.085	6.361	2.074	85.1	5.1
27		X	X			X	once	12.512	9.015	14.172	6.246	2.059	82.2	4.0
28	X		X			X	once	12.511	9.014	14.174	6.263	2.063	82.2	4.1
29	X		X	X			12m	12.508	9.014	14.078	6.380	2.100	84.4	4.1
30		X	X	X			12m	12.509	9.014	14.079	6.364	2.095	84.4	4.0
31			X			X	once	12.508	9.011	14.171	6.410	2.087	82.6	5.5
32			X	X			12m	12.505	9.011	14.083	6.522	2.122	84.6	5.4
33		X	X			X	q5y	12.499	9.005	13.831	7.266	2.359	92.2	9.9
34	X		X			X	q5y	12.498	9.003	13.827	7.309	2.370	92.3	10.3
35		X					once	12.496	9.001	14.268	6.820	2.098	81.6	10.9
36			X			X	q5y	12.490	8.996	13.820	7.651	2.452	92.8	13.7
37			X				yearly	12.481	8.988	13.871	7.981	2.546	90.7	18.1
38		X					q5y	12.462	8.972	13.996	8.608	2.617	89.0	26.2
39	X		X	X			life	12.443	8.957	13.912	9.406	2.965	88.3	31.6
40		X	X	X			life	12.444	8.957	13.913	9.393	2.961	88.3	31.5
41			X	X			life	12.438	8.952	13.930	9.513	2.975	88.5	32.5
42		X	X			X	yearly	12.429	8.945	13.611	10.075	3.152	98.2	32.6
43	X		X			X	yearly	12.429	8.945	13.609	10.205	3.189	98.2	33.9
44			X			X	yearly	12.398	8.920	13.607	11.122	3.427	98.5	41.8
45		X					yearly	12.318	8.851	13.788	13.606	3.994	96.3	63.4

*False positive rate in no screening condition attributable to application of patch monitor following stroke events

Effective strategies (defined as improvement in QALYs of ≥ 200 per 100,000 individuals versus no screening) highlighted in gray

Table S4. AF screening diagnostic results by strategy.

#								Total number of individuals with AF (millions)	True AF cases detected (millions)	False AF diagnoses made (millions)	Total AF diagnoses made (millions)	AF incidence rate (per 1,000 person-yr)	AF true positive rate (%)	AF false positive rate (%)
Rank	PP	1L	12L	PPG	1L	PM	Freq							
1	X		X	X	X	X	life	17.937	14.654	0.232	14.886	25.589	81.7	0.7
2	X		X	X	X		life	17.936	15.046	0.282	15.328	25.593	83.9	0.9
3		X	X	X	X	X	life	17.943	14.655	0.184	14.839	25.591	81.7	0.6
4		X	X	X	X		life	17.941	15.049	0.234	15.283	25.594	83.9	0.7
5			X	X	X	X	life	17.941	14.716	0.676	15.392	25.585	82.0	2.1
6			X	X	X		life	17.939	15.093	0.725	15.818	25.583	84.1	2.3
7		X	X	X		X	life	17.978	14.727	0.517	15.244	25.569	81.9	1.6
8	X		X	X		X	life	17.975	14.728	0.563	15.291	25.572	81.9	1.8
9			X	X		X	life	17.978	14.791	1.003	15.795	25.569	82.3	3.1
10		X	X				q5y	17.996	15.027	0.282	15.309	25.592	83.5	0.9
11	X		X				once	17.990	14.222	0.226	14.448	25.590	79.1	0.7
12	X		X				q5y	17.994	15.000	0.415	15.415	25.593	83.4	1.3
13		X	X				once	17.993	14.249	0.178	14.427	25.592	79.2	0.6
14		X	X				yearly	17.982	15.443	0.786	16.229	25.592	85.9	2.5
15		X	X	X	X	X	12m	17.959	14.639	0.160	14.799	25.590	81.5	0.5
16		X	X	X	X		12m	17.957	15.036	0.164	15.201	25.589	83.7	0.5
			no screening					17.993	13.831	0.121	13.952	25.593	76.9	0.4*
17	X		X	X	X		12m	17.954	15.036	0.212	15.248	25.591	83.7	0.7
18	X		X	X		X	12m	17.956	14.661	0.243	14.904	25.590	81.7	0.8
19		X	X	X		X	12m	17.960	14.659	0.195	14.854	25.590	81.6	0.6
20	X		X	X	X	X	12m	17.955	14.640	0.208	14.848	25.591	81.5	0.6
21			X				once	17.987	14.339	0.670	15.009	25.599	79.7	2.1
22	X		X				yearly	17.951	15.491	1.322	16.813	25.590	86.3	4.1

23			X	X	X		12m	17.955	15.081	0.657	15.738	25.582	84.0	2.1
24			X	X		X	12m	17.957	14.723	0.687	15.410	25.583	82.0	2.1
25			X	X	X	X	12m	17.958	14.705	0.654	15.358	25.586	81.9	2.0
26			X				q5y	17.977	15.300	1.636	16.937	25.592	85.1	5.1
27		X	X			X	once	17.966	14.770	1.276	16.046	25.589	82.2	4.0
28	X		X			X	once	17.964	14.775	1.322	16.097	25.584	82.2	4.1
29	X		X	X			12m	17.932	15.137	1.314	16.451	25.590	84.4	4.1
30		X	X	X			12m	17.937	15.139	1.269	16.407	25.589	84.4	4.0
31			X			X	once	17.960	14.829	1.751	16.580	25.587	82.6	5.5
32			X	X			12m	17.935	15.181	1.745	16.926	25.586	84.6	5.4
33		X	X			X	q5y	17.943	16.552	3.186	19.737	25.582	92.2	9.9
34	X		X			X	q5y	17.943	16.559	3.304	19.863	25.585	92.3	10.3
35		X					once	17.940	14.646	3.491	18.137	25.590	81.6	10.9
36			X			X	q5y	17.927	16.632	4.391	21.023	25.579	92.8	13.7
37			X				yearly	17.921	16.255	5.799	22.054	25.566	90.7	18.1
38		X					q5y	17.878	15.909	8.413	24.322	25.555	89.0	26.2
39	X		X	X			life	17.823	15.737	10.156	25.893	25.548	88.3	31.6
40		X	X	X			life	17.825	15.737	10.125	25.862	25.545	88.3	31.5
41			X	X			life	17.829	15.773	10.457	26.230	25.550	88.5	32.5
42		X	X			X	yearly	17.866	17.545	10.463	28.007	25.531	98.2	32.6
43	X		X			X	yearly	17.855	17.541	10.901	28.442	25.495	98.2	33.9
44			X			X	yearly	17.779	17.507	13.471	30.978	25.524	98.5	41.8
45		X					yearly	17.679	17.027	20.499	37.526	25.487	96.3	63.4

*False positive rate in no screening condition attributable to use of patch monitor following stroke

Effective strategies (defined as improvement in QALYs of ≥ 200 per 100,000 individuals versus no screening) highlighted in gray

Table S5. Screening effectiveness among individuals aged ≥ 70 years.

#								Life expectancy (yr)	Quality-adjusted life expectancy (yr)	Ischemic stroke (per 1,000 person-yr)	Major bleed (per 1,000 person-yr)	Intracranial Bleed (per 1,000 person-yr)	AF true positive rate (%)	AF false positive rate (%)
Rank	PP	1L	12L	PPG	1L	PM	Freq							
4		X	X	X	X		life	10.231	7.235	15.858	6.633	2.154	85.3	0.7
3		X	X	X	X	X	life	10.231	7.234	15.986	6.441	2.096	82.5	0.5
1	X		X	X	X	X	life	10.231	7.234	15.985	6.459	2.099	82.5	0.7
2	X		X	X	X		life	10.230	7.234	15.858	6.653	2.158	85.3	0.8
5			X	X	X	X	life	10.226	7.231	15.977	6.630	2.129	82.9	2.1
6			X	X	X		life	10.226	7.231	15.860	6.813	2.184	85.5	2.2
7		X	X	X		X	life	10.227	7.230	15.998	6.569	2.132	82.7	1.4
8	X		X	X		X	life	10.228	7.230	15.994	6.588	2.137	82.8	1.6
9			X	X		X	life	10.224	7.227	15.993	6.753	2.164	83.1	2.9
14		X	X				yearly	10.219	7.223	15.887	6.780	2.196	85.6	2.0
10		X	X				q5y	10.218	7.222	16.012	6.493	2.110	83.2	0.8
12	X		X				q5y	10.217	7.222	16.026	6.517	2.117	83.0	1.1
15		X	X	X	X	X	12m	10.213	7.221	16.026	6.444	2.095	82.3	0.5
20	X		X	X	X	X	12m	10.214	7.221	16.026	6.461	2.099	82.4	0.6
18	X		X	X		X	12m	10.213	7.221	16.020	6.483	2.107	82.5	0.7
16		X	X	X	X		12m	10.213	7.221	15.898	6.626	2.149	85.1	0.5
17	X		X	X	X		12m	10.217	7.221	16.180	6.274	2.045	79.4	0.5
13		X	X				once	10.215	7.221	15.855	6.940	2.244	85.9	3.4
22	X		X				yearly	10.217	7.221	16.194	6.276	2.045	79.2	0.7
11	X		X				once	10.213	7.221	15.896	6.643	2.155	85.1	0.6
19		X	X	X		X	12m	10.213	7.220	16.024	6.466	2.102	82.5	0.6
			no screening					10.216	7.219	16.359	6.086	2.009	76.5	0.3*
21			X				once	10.215	7.219	16.160	6.468	2.081	80.0	2.0

25			X	X	X	X	12m	10.210	7.218	16.020	6.630	2.130	82.7	2.0
23			X	X	X		12m	10.210	7.218	15.898	6.805	2.183	85.4	2.0
26			X				q5y	10.213	7.218	15.952	6.932	2.218	84.7	4.4
24			X	X		X	12m	10.210	7.217	16.014	6.654	2.138	82.8	2.1
27		X	X			X	once	10.206	7.213	16.000	6.959	2.246	83.0	3.9
28	X		X			X	once	10.206	7.213	16.002	6.980	2.251	83.1	4.1
30		X	X	X			12m	10.203	7.212	15.866	7.113	2.293	85.8	3.9
29	X		X	X			12m	10.203	7.212	15.864	7.129	2.298	85.8	4.0
31			X			X	once	10.204	7.211	15.995	7.132	2.275	83.4	5.4
32			X	X			12m	10.199	7.209	15.868	7.283	2.322	86.0	5.3
33		X	X			X	q5y	10.201	7.209	15.637	7.867	2.515	91.8	8.5
34	X		X			X	q5y	10.200	7.209	15.634	7.906	2.528	91.8	8.8
36			X			X	q5y	10.196	7.205	15.622	8.229	2.602	92.3	11.8
35		X					once	10.195	7.203	16.105	7.537	2.283	82.0	10.8
37			X				yearly	10.193	7.200	15.703	8.451	2.667	90.0	15.2
38		X					q5y	10.180	7.189	15.816	9.066	2.733	88.2	23.0
40		X	X	X			life	10.173	7.184	15.664	9.819	3.082	88.7	26.7
39	X		X	X			life	10.173	7.184	15.661	9.834	3.088	88.7	26.8
41			X	X			life	10.169	7.181	15.670	9.957	3.102	88.9	27.8
43	X		X			X	yearly	10.162	7.174	15.336	10.528	3.287	97.9	27.8
42		X	X			X	yearly	10.163	7.174	15.320	10.671	3.326	97.9	29.1
44			X			X	yearly	10.142	7.158	15.292	11.548	3.559	98.2	36.3
45		X					yearly	10.093	7.115	15.458	14.007	4.134	95.5	57.5

*False positive rate in no screening condition attributable to application of patch monitor following stroke events

Effective strategies (defined as improvement in QALYs of ≥ 200 per 100,000 individuals versus no screening) highlighted in gray

Table S6. Screening effectiveness among individuals aged ≥ 75 years.

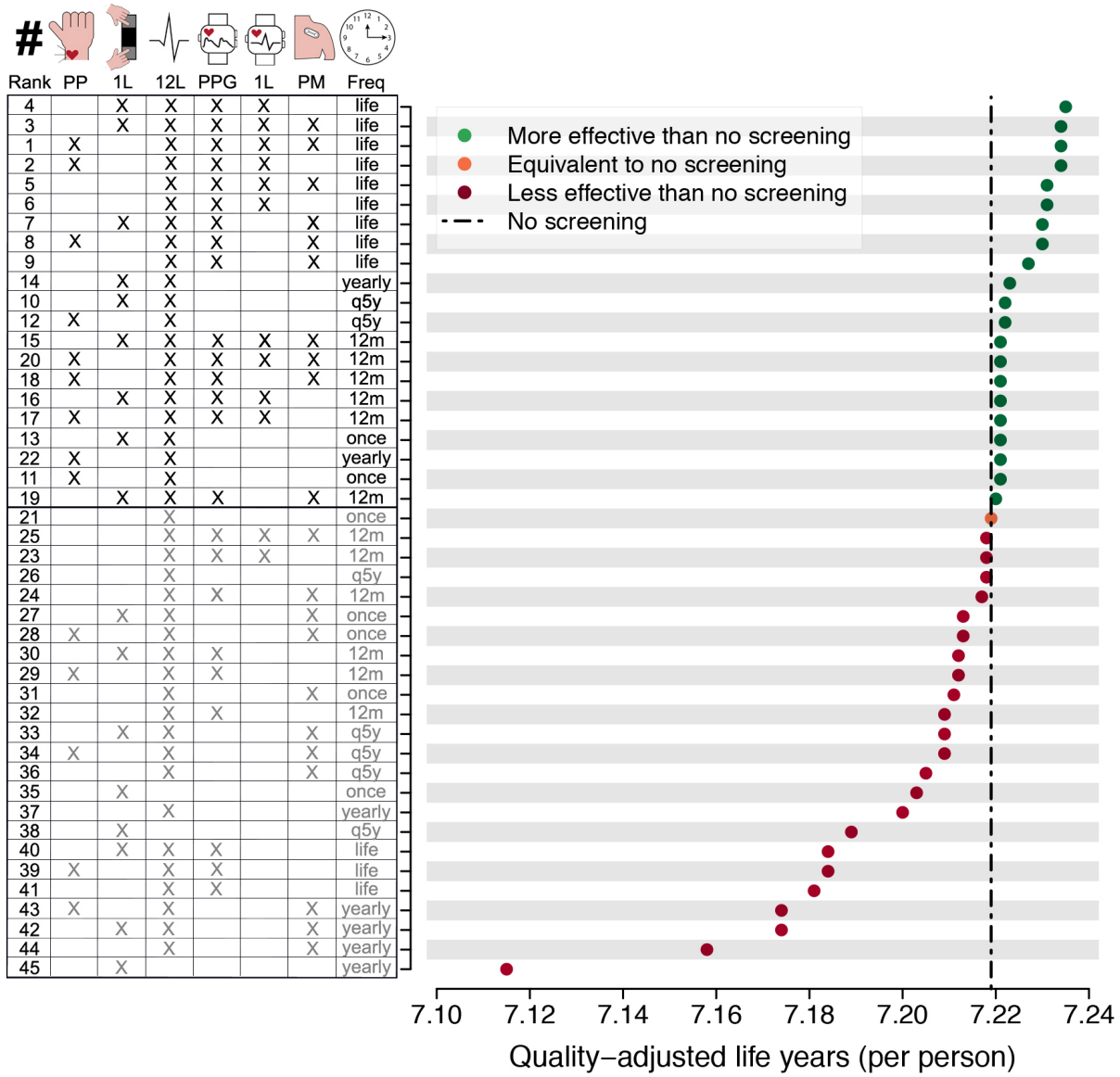
#								Life expectancy (yr)	Quality-adjusted life expectancy (yr)	Ischemic stroke rate (per 1,000 person-yr)	Major bleed rate (per 1,000 person-yr)	Intracranial Bleed (per 1,000 person-yr)	AF true positive rate (%)	AF false positive rate (%)
Rank	PP	1L	12L	PPG	1L	PM	Freq							
3		X	X	X	X	X	life	7.908	5.485	16.526	7.348	2.321	83.1	0.5
1	X		X	X	X	X	life	7.908	5.484	16.517	7.369	2.327	83.1	0.6
4		X	X	X	X		life	7.907	5.484	16.361	7.637	2.410	86.7	0.6
2	X		X	X	X		life	7.907	5.484	16.352	7.655	2.414	86.7	0.7
5			X	X	X	X	life	7.904	5.481	16.514	7.558	2.359	83.5	2.0
7		X	X	X		X	life	7.905	5.481	16.524	7.462	2.355	83.3	1.2
8	X		X	X		X	life	7.905	5.481	16.507	7.487	2.363	83.3	1.3
6			X	X	X		life	7.903	5.481	16.354	7.827	2.441	86.9	2.1
9			X	X		X	life	7.903	5.479	16.506	7.664	2.390	83.7	2.7
10		X	X				q5y	7.899	5.476	16.614	7.296	2.306	82.4	0.6
13		X	X				once	7.900	5.476	16.753	7.081	2.240	79.0	0.5
11	X		X				once	7.899	5.476	16.772	7.076	2.238	78.8	0.6
			no screening					7.900	5.475	16.993	6.790	2.184	75.0	0.3
14		X	X				yearly	7.898	5.475	16.487	7.588	2.393	84.8	1.6
22	X		X				yearly	7.897	5.475	16.459	7.721	2.432	85.1	2.7
12	X		X				q5y	7.899	5.475	16.632	7.309	2.309	82.2	0.9
21			X				once	7.898	5.475	16.721	7.302	2.283	79.7	2.0
17	X		X	X	X		12m	7.894	5.474	16.394	7.648	2.416	86.5	0.6
15		X	X	X	X	X	12m	7.894	5.473	16.565	7.352	2.327	82.9	0.4
20	X		X	X	X	X	12m	7.894	5.473	16.563	7.370	2.331	82.9	0.6
19		X	X	X		X	12m	7.893	5.473	16.552	7.381	2.336	83.1	0.5
18	X		X	X		X	12m	7.894	5.473	16.547	7.399	2.340	83.1	0.7

16		X	X	X	X		12m	7.893	5.473	16.397	7.631	2.413	86.5	0.4
26			X				q5y	7.896	5.473	16.544	7.709	2.406	83.9	3.6
25			X	X	X	X	12m	7.892	5.471	16.549	7.558	2.363	83.3	1.9
24			X	X		X	12m	7.891	5.471	16.536	7.586	2.371	83.5	2.0
23			X	X	X		12m	7.890	5.471	16.387	7.826	2.444	86.7	2.0
27		X	X			X	once	7.892	5.470	16.515	7.918	2.492	83.6	3.9
28	X		X			X	once	7.893	5.470	16.516	7.938	2.497	83.6	4.0
31			X			X	once	7.891	5.469	16.498	8.112	2.527	84.0	5.3
30		X	X	X			12m	7.887	5.468	16.335	8.157	2.569	87.2	3.8
29	X		X	X			12m	7.887	5.468	16.335	8.172	2.572	87.2	3.9
33		X	X			X	q5y	7.888	5.467	16.206	8.711	2.733	91.2	7.1
34	X		X			X	q5y	7.888	5.467	16.200	8.749	2.744	91.2	7.3
32			X	X			12m	7.885	5.466	16.329	8.344	2.600	87.4	5.2
36			X			X	q5y	7.886	5.465	16.174	9.047	2.809	91.7	9.8
35		X					once	7.887	5.465	16.602	8.465	2.507	81.8	10.7
37			X				yearly	7.885	5.463	16.274	9.080	2.819	88.9	12.1
40		X	X	X			life	7.880	5.458	16.135	10.389	3.231	89.2	21.4
39	X		X	X			life	7.879	5.458	16.119	10.414	3.237	89.2	21.5
38		X					q5y	7.879	5.458	16.342	9.692	2.877	87.1	19.5
41			X	X			life	7.877	5.456	16.134	10.543	3.251	89.4	22.6
43	X		X			X	yearly	7.872	5.450	15.806	11.275	3.492	97.6	23.5
42		X	X			X	yearly	7.868	5.448	15.830	11.151	3.458	97.5	22.5
44			X			X	yearly	7.859	5.442	15.754	12.080	3.703	97.8	29.9
45		X					yearly	7.836	5.418	15.862	14.349	4.244	94.2	49.9

*False positive rate in no screening condition attributable to application of patch monitor following stroke events

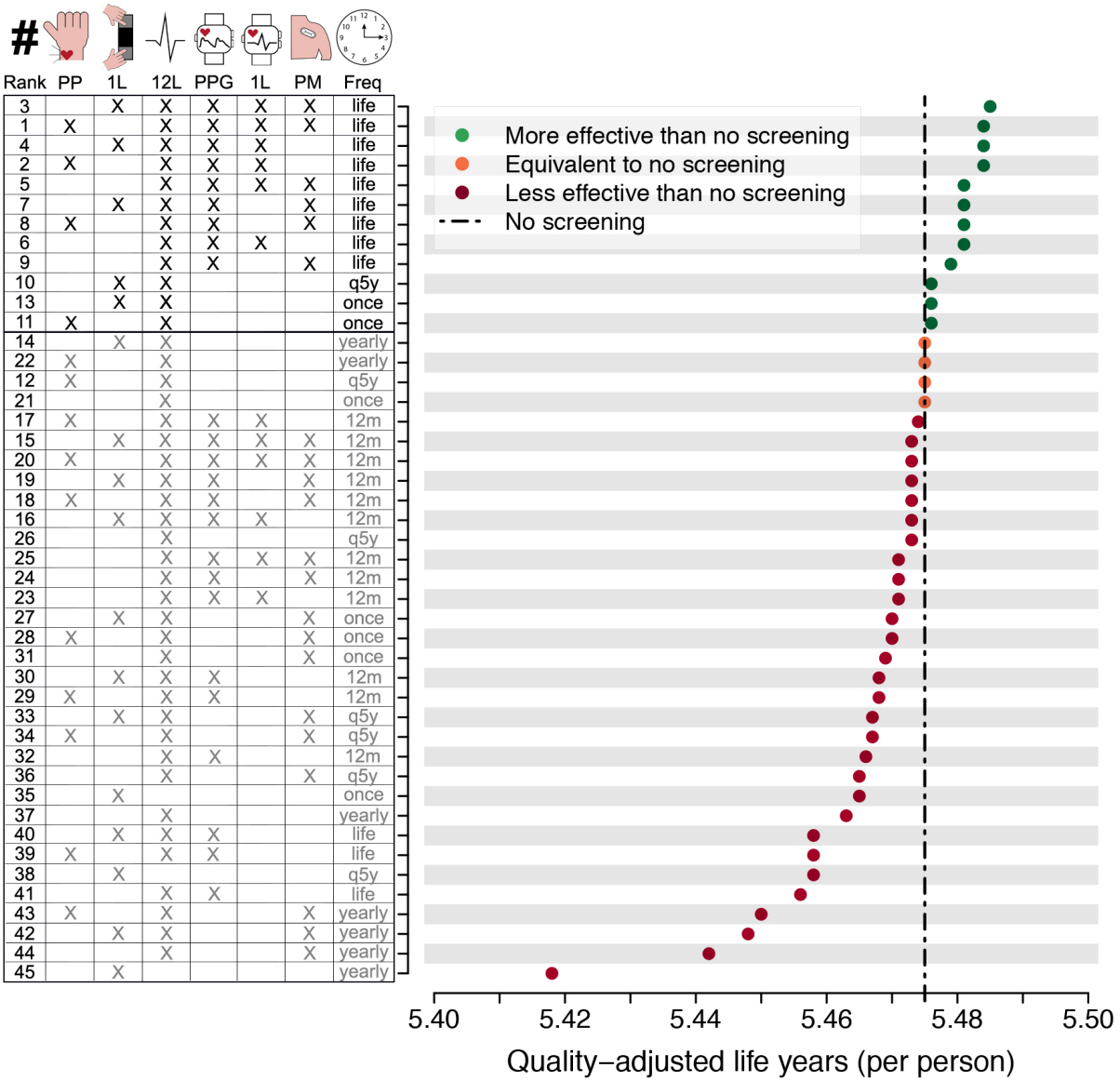
Effective strategies (defined as improvement in QALYs of ≥ 200 per 100,000 individuals versus no screening) highlighted in gray

Figure S1. Screening effectiveness among individuals aged ≥ 70 years.



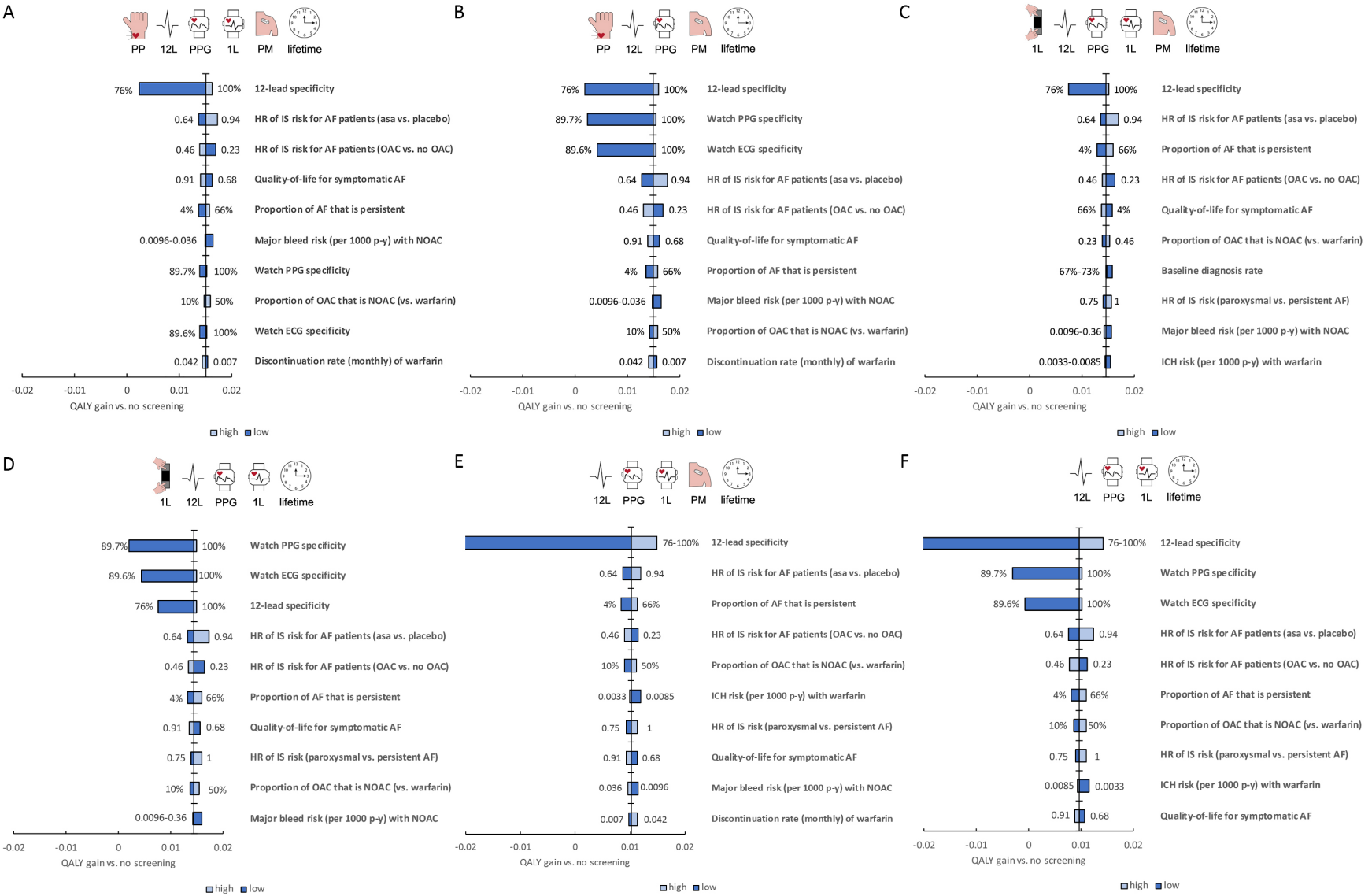
Depicted is the overall effectiveness results for individuals aged ≥ 70 years. The strategies corresponding to each point are depicted by the table to the left of the graph, corresponding to the icons above the table. The vertical dashed line represents the expected quality-adjusted life-years (QALYs) lived without AF screening. Effective screening strategies (i.e., providing an increase in QALYs of ≥200 per 100,000 individuals as compared to no screening) are depicted in green, ineffective screening strategies (i.e., providing a decrease in QALYs of ≥200 per 100,000 individuals as compared to no screening), are depicted in red, while all others are considered equivalent to no screening and depicted in yellow. Strategies are numbered and sorted in rank order of decreasing effectiveness (i.e., decreasing QALYs), starting with the most effective strategies at the top. 1L = 1-lead ECG, 12L = 12-lead ECG, 12m = 12 months, Freq = frequency, PM = patch monitor, PP = pulse palpation, PPG = photoplethysmography, q5y = every 5 years

Figure S2. Screening effectiveness among individuals aged ≥ 75 years.

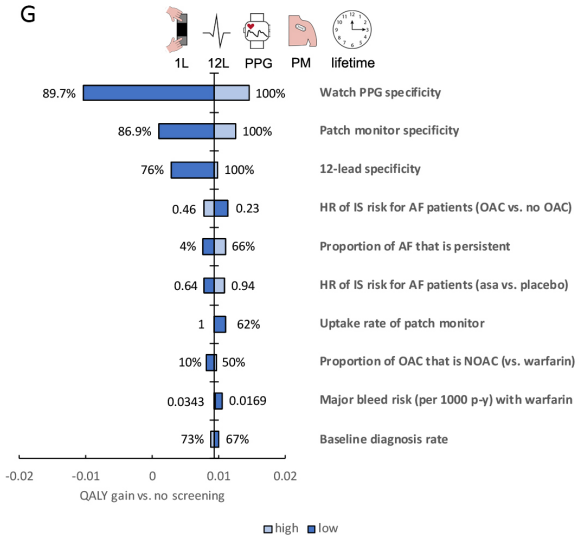


Depicted is the overall effectiveness results for individuals aged ≥ 75 years. The strategies corresponding to each point are depicted by the table to the left of the graph, corresponding to the icons above the table. The vertical dashed line represents the expected quality-adjusted life-years (QALYs) lived without AF screening. Effective screening strategies (i.e., providing an increase in QALYs of ≥200 per 100,000 individuals as compared to no screening) are depicted in green, ineffective screening strategies (i.e., providing a decrease in QALYs of ≥200 per 100,000 individuals as compared to no screening), are depicted in red, while all others are considered equivalent to no screening and depicted in yellow. Strategies are numbered and sorted in rank order of decreasing effectiveness (i.e., decreasing QALYs), starting with the most effective strategies at the top. 1L = 1-lead ECG, 12L = 12-lead ECG, 12m = 12 months, Freq = frequency, PM = patch monitor, PP = pulse palpation, PPG = photoplethysmography, q5y = every 5 years

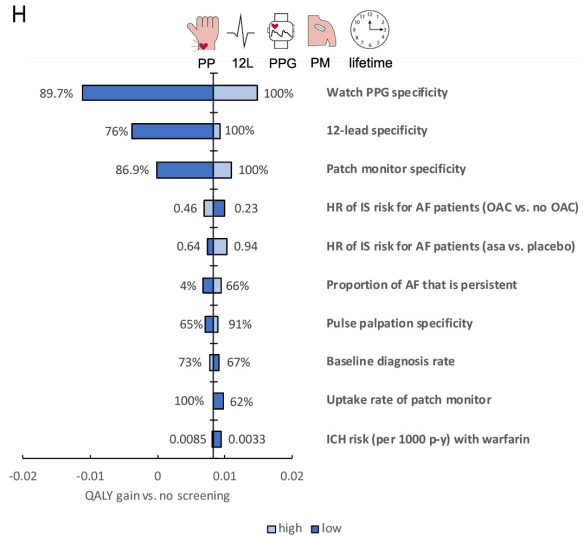
Figure S3. One-way sensitivity analysis.



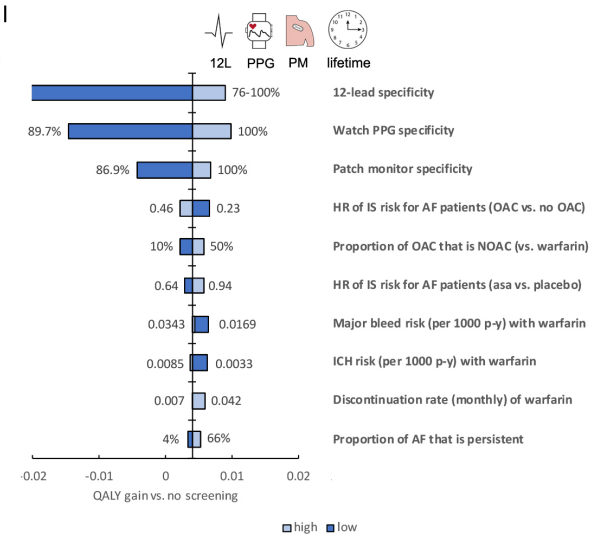
G


1L
12L
PPG
PM
lifetime
89.7%
100%
Watch PPG specificity
86.9%
100%
Patch monitor specificity
76%
100%
12-lead specificity
0.46
0.23
HR of IS risk for AF patients (OAC vs. no OAC)
4%
66%
Proportion of AF that is persistent
0.64
0.94
HR of IS risk for AF patients (asa vs. placebo)
1
62%
Uptake rate of patch monitor
10%
50%
Proportion of OAC that is NOAC (vs. warfarin)
0.0343
0.0169
Major bleed risk (per 1000 p-y) with warfarin
73%
67%
Baseline diagnosis rate
-0.02
-0.01
0
0.01
0.02
QALY gain vs. no screening
high
low

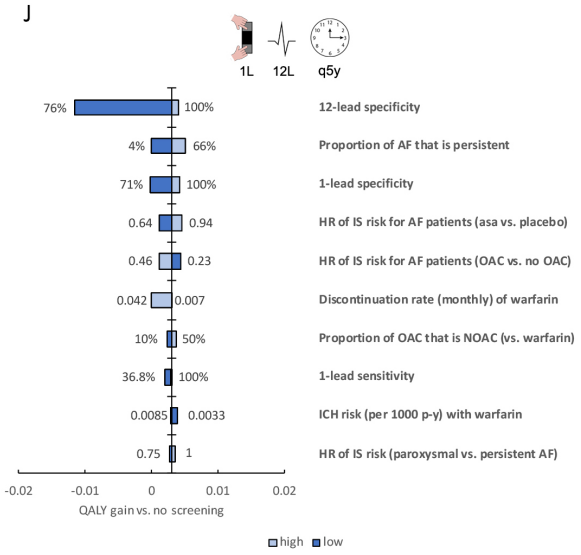
H


PP
12L
PPG
PM
lifetime
89.7%
100%
Watch PPG specificity
76%
100%
12-lead specificity
86.9%
100%
Patch monitor specificity
0.46
0.23
HR of IS risk for AF patients (OAC vs. no OAC)
0.64
0.94
HR of IS risk for AF patients (asa vs. placebo)
4%
66%
Proportion of AF that is persistent
65%
91%
Pulse palpation specificity
73%
67%
Baseline diagnosis rate
100%
62%
Uptake rate of patch monitor
0.0085
0.0033
ICH risk (per 1000 p-y) with warfarin
-0.02
-0.01
0
0.01
0.02
QALY gain vs. no screening
high
low

I

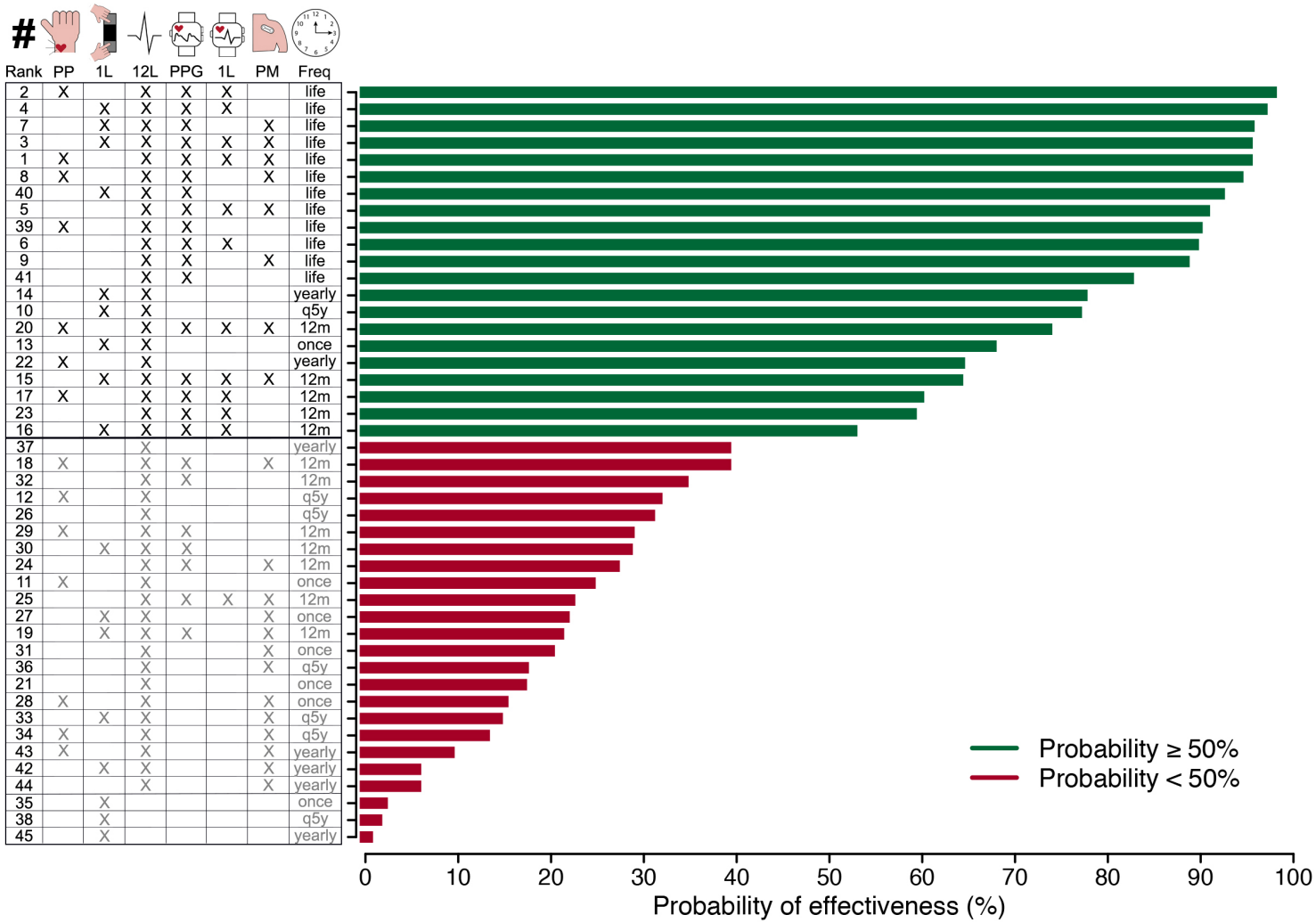

12L
PPG
PM
lifetime
76-100%
12-lead specificity
89.7%
100%
Watch PPG specificity
86.9%
100%
Patch monitor specificity
0.46
0.23
HR of IS risk for AF patients (OAC vs. no OAC)
10%
50%
Proportion of OAC that is NOAC (vs. warfarin)
0.64
0.94
HR of IS risk for AF patients (asa vs. placebo)
0.0343
0.0169
Major bleed risk (per 1000 p-y) with warfarin
0.0085
0.0033
ICH risk (per 1000 p-y) with warfarin
0.007
0.042
Discontinuation rate (monthly) of warfarin
4%
66%
Proportion of AF that is persistent
-0.02
-0.01
0
0.01
0.02
QALY gain vs. no screening
high
low

J


1L
12L
q5y
76%
100%
12-lead specificity
4%
66%
Proportion of AF that is persistent
71%
100%
1-lead specificity
0.64
0.94
HR of IS risk for AF patients (asa vs. placebo)
0.46
0.23
HR of IS risk for AF patients (OAC vs. no OAC)
0.042
0.007
Discontinuation rate (monthly) of warfarin
10%
50%
Proportion of OAC that is NOAC (vs. warfarin)
36.8%
100%
1-lead sensitivity
0.0085
0.0033
ICH risk (per 1000 p-y) with warfarin
0.75
1
HR of IS risk (paroxysmal vs. persistent AF)
-0.02
-0.01
0
0.01
0.02
QALY gain vs. no screening
high
low

Depicted are the results of one-way sensitivity analyses performed on the 10 AF screening strategies identified as effective in the base case analysis. The strategy under consideration is depicted by the icons above each plot. Each plot depicts the quality-adjusted life years (QALY) gained versus no screening when the value of each of the listed parameters is taken to be its base case value (central vertical line), its lower bound (dark blue shade), and its upper bound (light blue shade). The values corresponding to the lower and upper bounds are listed next to their respective bars. 12m = 12 months, 1L = 1-lead ECG, 12L = 12-lead ECG, AF = atrial fibrillation, PP = pulse palpation, PPG = photoplethysmography, q5y = every 5 years

Figure S4. Probabilistic sensitivity analysis.



Depicted are the results of probabilistic sensitivity analyses. The x-axis plots the proportion of simulations (n=500) in which each strategy was more effective than no screening. 12m = 12 months, 1L = 1-lead ECG, 12L = 12-lead ECG, PP = pulse palpation, PPG = photoplethysmography, q5y = every 5 years.