JAMA | US Preventive Services Task Force | EVIDENCE REPORT

Screening for Atrial Fibrillation
Updated Evidence Report and Systematic Review for the US Preventive Services Task Force

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IMPORTANCE Atrial fibrillation (AF), the most common arrhythmia, increases the risk of stroke.

OBJECTIVE To review the evidence on screening for AF in adults without prior stroke to inform the US Preventive Services Task Force.

DATA SOURCES PubMed, Cochrane Library, and trial registries through October 5, 2020; references, experts, and literature surveillance through October 31, 2021.

STUDY SELECTION Randomized clinical trials (RCTs) of screening among asymptomatic persons without known AF or prior stroke; test accuracy studies; RCTs of anticoagulation among persons with AF; systematic reviews; and observational studies reporting harms.

DATA EXTRACTION AND SYNTHESIS Two reviewers assessed titles/abstracts, full-text articles, and study quality and extracted data; when at least 3 similar studies were available, meta-analyses were conducted.

MAIN OUTCOMES AND MEASURES Detection of undiagnosed AF, test accuracy, mortality, stroke, stroke-related morbidity, and harms.

RESULTS Twenty-six studies (N = 113 784) were included. In 1 RCT (n = 28 768) of twice-daily electrocardiography (ECG) screening for 2 weeks, the likelihood of a composite end point (ischemic stroke, hemorrhagic stroke, systemic embolism, all-cause mortality, and hospitalization for bleeding) was lower in the screened group over 6.9 years (hazard ratio, 0.96 [95% CI, 0.92-1.00]; *P* = .045), but that study had numerous limitations. In 4 RCTs (n = 32 491), significantly more AF was detected with intermittent and continuous ECG screening compared with no screening (risk difference range, 1.0%-4.8%). Treatment with warfarin over a mean of 1.5 years in populations with clinical, mostly persistent AF was associated with fewer ischemic strokes (pooled risk ratio [RR], 0.32 [95% CI, 0.20-0.51]; 5 RCTs; n = 2415) and lower all-cause mortality (pooled RR, 0.68 [95% CI, 0.50-0.93]) compared with placebo. Treatment with direct oral anticoagulants was also associated with lower incidence of stroke (adjusted odds ratios range, 0.32-0.44) in indirect comparisons with placebo. The pooled RR for major bleeding for warfarin compared with placebo was 1.8 (95% CI, 0.85-3.7; 5 RCTs; n = 2415), and the adjusted odds ratio for major bleeding for direct oral anticoagulants compared with placebo or no treatment ranged from 1.38 to 2.21, but CIs did not exclude a null effect.

CONCLUSIONS AND RELEVANCE Although screening can detect more cases of unknown AF, evidence regarding effects on health outcomes is limited. Anticoagulation was associated with lower risk of first stroke and mortality but with increased risk of major bleeding, although estimates for this harm are imprecise; no trials assessed benefits and harms of anticoagulation among screen-detected populations.

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Atrial fibrillation (AF) is the most common arrhythmia and may be symptomatic or asymptomatic.[1] Increasing age is a risk for AF,[2] and persons with AF have an increased risk for thromboembolic stroke and related morbidity and mortality.[3] The treatment for people with symptomatic AF involves rate and rhythm control; anticoagulation for stroke prevention may also be warranted when benefits outweigh the harms.[4,5]

The primary rationale for screening for AF is to identify asymptomatic persons before a thromboembolic event occurs. In 2018, the US Preventive Services Task Force (USPSTF) concluded that the evidence was insufficient to assess the balance of benefits and harms of screening for AF with electrocardiography (ECG) in older adults (I statement).[6] This updated review evaluated the current evidence on screening for AF for populations and settings relevant to primary care in the US to inform an updated recommendation by the USPSTF.

Methods

Scope of the Review

The analytic framework and key questions (KQs) that guided the review are shown in **Figure 1**. Detailed methods, evidence tables, and contextual information are available in the full evidence report.[7]

Data Sources and Searches

PubMed and the Cochrane Library were searched for English-language articles published from May 1, 2017, through October 5, 2020. ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform were also searched. To supplement systematic electronic searches (eMethods page 1 in the Supplement), reference lists of pertinent articles and studies suggested by reviewers were searched. Article alerts and targeted searches of journals to identify major studies published in the interim that may affect the conclusions or understanding of the evidence and the related USPSTF recommendation were used as part of ongoing surveillance. The last surveillance was conducted on October 31, 2021.

Study Selection

Two investigators independently reviewed titles, abstracts, and full-text articles using prespecified inclusion criteria for each KQ (eMethods page 16 in the Supplement); disagreements were resolved by discussion or by a third reviewer. English-language studies that met all study selection criteria, were fair or good methodological quality, and were conducted in countries categorized as very highly developed by the 2018 United Nations Human Development Index[8] were eligible. Studies included in the prior 2018 review for the USPSTF were reassessed against the study selection and methodological quality criteria for this update. Studies performed in emergency department, inpatient, and procedural settings were excluded.

For KQ1, KQ2, and KQ4, the focus was on unselected or explicitly asymptomatic adults 50 years or older without known AF or history of prior stroke or transient ischemic attack. For these KQs, randomized clinical trials (RCTs) or nonrandomized controlled intervention studies of screening (compared with no screening or nonsystematic screening) that reported health outcomes (KQ1), detection of AF (KQ2), or harms of screening (KQ4) were included. For screening accuracy (KQ3), case-control studies were excluded because these designs have a high risk of bias, and studies for which persons who were symptomatic or who had known AF comprised the majority of the population were excluded. For KQs 1 through 4, studies assessing index tests feasible for use in or referable from primary care including single-point-in-time tests typically conducted in an office setting (eg, single- or 12-lead ECG, automated heart rhythm assessment built into oscillometric blood pressure monitors or devices using photoplethysmography such as pulse oximeters), intermittent or continuous ambulatory strategies using ECG or other technologies, and 2-stage screening approaches were included. Pulse palpation and other components of a standard physical examination (eg, heart auscultation) were not eligible because the USPSTF considers these usual care. For KQ1 and KQ2, a no-screening or usual care (which could include pulse palpation) comparator was required. For KQ3, studies were required to use 1 of the following reference tests: 12-lead ECG interpreted by a cardiologist, continuous ambulatory ECG interpreted by a cardiologist, or implantable cardiac monitor.

For treatment effectiveness (KQ5) and harms (KQ6), RCTs and nonrandomized controlled intervention studies or systematic reviews of RCTs comparing anticoagulation with placebo or no treatment that reported health outcomes or harms were included. The scopes of these KQs were revised for this update to remove antiplatelet therapy as an eligible treatment because it is no longer standard practice for primary stroke prevention in AF. For harms (KQ6), large prospective cohort studies or systematic reviews of prospective cohort studies were also included.

Data Extraction and Quality Assessment

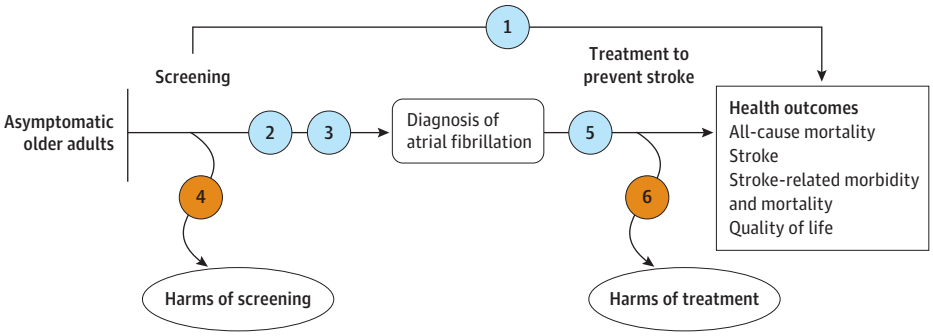
For each included study, 1 reviewer abstracted relevant study characteristics (ie, population, intervention, comparator) and data for eligible outcomes into a structured form. A second reviewer checked all data for completeness and accuracy. Two senior reviewers independently assessed each study's methodological quality using predefined criteria established by the USPSTF (eMethods page 19 in the Supplement) and others.[9,10] Disagreements in study quality ratings were resolved through discussion or by a third senior reviewer. Detailed study quality assessments are provided in eTables 1 through 21 in the Supplement.

Data Synthesis and Analysis

Data were synthesized in tabular and narrative forms. When at least 3 similar studies were available, a quantitative synthesis was performed using random-effects models with the inverse-variance weighted method of DerSimonian and Laird in Stata version 16 (StataCorp) to generate pooled estimates of the relative risk ratio (RR).[11] The I^2 statistic was calculated to assess statistical heterogeneity in effects.[12,13] Significance testing was based on the exclusion of the null value by the 95% CI around the pooled estimate; all testing was 2-sided.

The strength of evidence was assessed as high, moderate, low, or insufficient using methods developed for the USPSTF and the Agency for Healthcare Research and Quality Evidence-based Practice Center program.[14] These methods specify the assessment of methodological quality of studies, consistency of results between studies, precision of findings, risk of reporting bias, and limitations of the body of evidence for each intervention/comparison and major outcome of interest. Two senior reviewers independently developed initial assessments of strength of evidence; disagreements were resolved through discussion or input of a third senior reviewer.

Figure 1. Analytic Framework: Screening for Atrial Fibrillation



Key questions

1. Does screening for AF with selected tests improve health outcomes (ie, reduce all-cause mortality, reduce morbidity or mortality from stroke, or improve quality of life) in asymptomatic older adults?
   a. Does improvement in health outcomes vary for subgroups defined by stroke risk, age, sex, or race and ethnicity?
2. Does systematic screening for AF with selected tests identify older adults with previously undiagnosed AF more effectively than usual care?
3. What is the accuracy of selected screening tests for diagnosing AF in asymptomatic adults?
4. What are the harms of screening for AF with selected tests in older adults?
   a. Do the harms of screening vary for subgroups defined by stroke risk, age, sex, or race and ethnicity?
5. What are the benefits of anticoagulation therapy on health outcomes in asymptomatic, screen-detected older adults with AF?
   a. Do the benefits of anticoagulation vary for subgroups defined by stroke or bleeding risk, age, sex, race and ethnicity, or AF burden (ie, number of episodes, duration of episodes, and proportion of time spent in AF)?
6. What are the harms of anticoagulation therapy in asymptomatic, screen-detected older adults with AF?
   a. Do the harms of anticoagulation therapy vary for subgroups defined by stroke risk or bleeding risk, age, sex, race and ethnicity, or AF burden?

AF indicates atrial fibrillation.

Results

Twenty-six studies (N = 113 784) from 33 publications were included (**Figure 2**).[4,15-42] Twelve of these studies were new to this update.[33-46] Three RCTs reported on the benefits of screening (KQ1); 8 RCTs reported on the diagnostic yield of screening (KQ2); 9 studies reported on the accuracy of various screening strategies (KQ3); 4 RCTs and 1 cohort study reported on the harms of screening (KQ4); 5 RCTs and 5 systematic reviews reported on the health benefits of treatment with anticoagulation (KQ5); and 5 RCTs, 6 systematic reviews, and 1 cohort study reported on the harms of treatment with anticoagulation (KQ6). A list of full-text articles screened but excluded is provided in the Supplement (page 101).

Benefits of Screening

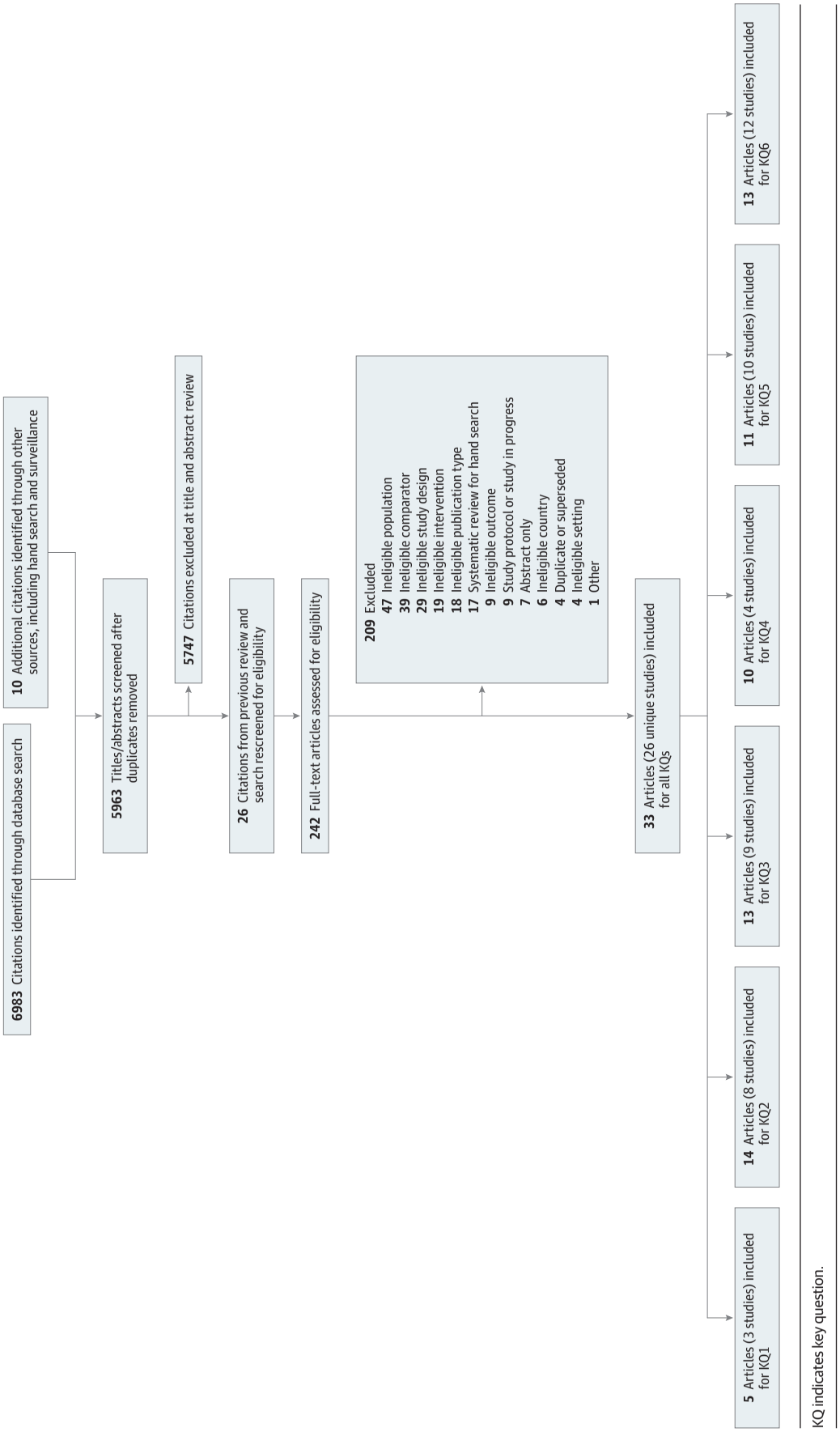
Key Question 1. Does screening for AF with selected tests improve health outcomes (ie, reduce all-cause mortality, reduce morbidity or mortality from stroke, or improve quality of life) in asymptomatic older adults?

Key Question 1a. Does improvement in health outcomes vary for subgroups defined by stroke risk, age, sex, or race and ethnicity?

Three RCTs randomized persons to screening vs no screening; however, only 1 of these studies was designed and powered for evaluating health outcomes.[44,45,47] Although the other 2 RCTs were powered for evaluating differences in the detection of AF (a KQ2 outcome), they reported a limited amount of information related to health outcomes, but events were rare.[32,43] Findings from these 2 RCTs are reported in eTables 22 through 25 in the Supplement.

The fair-quality STROKESTOP study randomized adults aged 75 or 76 years living in 2 regions of Sweden to an invitation to screening (n = 14 387) or to a control group that did not receive an invitation to screening (n = 14 381).[44,45,47] At baseline, 12.1% of the intervention group and 12.8% of the control group had known AF.[44] Of those invited to screening, 51.3% participated in the screening intervention, which was 2 weeks of twice-daily intermittent single-lead ECG monitoring with a handheld device for 30 seconds.[44,45,47] The intervention was not masked, and outcome ascertainment was through national health registry data; outcome assessment was not formally masked, and outcomes were not centrally adjudicated. The primary outcome was originally specified as ischemic stroke but was changed by study investigators in 2017 before any data analysis to a composite end point that included ischemic stroke, hemorrhagic stroke, systemic embolism, bleeding leading to hospitalization, and

Figure 2. Literature Search Flow Diagram: Screening for Atrial Fibrillation



KQ indicates key question.

all-cause mortality. At a median follow-up of 6.9 years, the rate of composite end point events was significantly lower in the invitation-to-screening group (5.45 events/100 person-years) compared with the control group (5.68 events/100 person-years) with an unadjusted hazard ratio (HR) of 0.96 (95% CI, 0.92-1.00; $P = .045$).[44] No significant differences were observed between the invitation-to-screening group and the control group for any of the individual outcomes contributing to the composite end point (eTable 25 in the Supplement).[44] No findings were reported for the subgroup of participants without known AF at baseline.

Detection of AF

Key Question 2. Does systematic screening for AF with selected tests identify older adults with previously undiagnosed AF more effectively than usual care?

Eight fair-quality RCTs in 14 articles (n = 86 590) were included[15-19,29,32,33,36,41,43-45,47]; 5 RCTs were new to this update.[33,36,41,43-45,47] Study, population, and intervention characteristics are reported in **Table 1**, with detailed characteristics reported in eTables 22 through 24 in the Supplement. Six trials[32,33,36,41,43-45,47] compared ECG screening with no screening, 1 trial[29] compared ECG screening with pulse palpation chart reminders, and 1 trial[15-19] compared both. Four trials[15-19,29,36,41] used a 1-time approach to screening (eg, single-lead ECG during an office visit), 2 trials evaluated intermittent screening with a handheld ECG twice daily for 2 weeks[44,45,47] or for 1 year,[32] and 2 trials[33,43] used 2 rounds of a continuous patch ECG patch for 2 weeks; 1 of these trials also included twice-daily blood pressure screening with automated AF detection.[32,43]

Across studies, the detection of previously unknown AF was reported at 4 to 12 months of follow-up. Findings are summarized in **Figure 3** and in eTable 25 in the Supplement. Screening identified numerically more cases of AF compared with no screening in the 3 cluster-randomized trials using 1-time approaches to screening compared with no screening (absolute risk difference range, 0.06-0.60 percentage points; RR range, 1.04-1.58)[15-19,36,41]; however, this difference was statistically significant only in the Screening for Atrial Fibrillation in the Elderly (SAFE) trial (n = 14 802).[15-19] In 2 of these trials, only 10.7%[36] and 44.5%[41] of eligible participants at intervention practices received the screening test. Detection of previously unknown AF was significantly higher in the 4 trials comparing intermittent or continuous ECG screening approaches with no screening, with absolute risk differences ranging from 1.0% to 4.8% and RRs ranging from 1.1 to 11.2.[32,33,43-45,47] Intervention fidelity ranged from 51.3% to 74.0% in the intermittent screening trials and from 65.0% to 79.0% in the continuous screening trials.[15,29,32,33]

Accuracy of Screening Tests

Key Question 3. What is the accuracy of selected screening tests for diagnosing AF in asymptomatic adults?

Nine studies published in 13 articles[15,34,37-43] (n = 4978) reported on the accuracy of primary care–feasible screening tests; population, index test, and reference test characteristics are summarized in **Table 2**, with details reported in eTables 26 through 28 in the Supplement. All are new to this update because this KQ was not included in the previous report.

The sensitivity and specificity of various screening tests varied and are summarized in **Table 3**, with details reported in eTable 29 in the Supplement. The 1 study[43] using a continuous ECG reference standard reported a lower sensitivity (0.35) compared with the studies that used a 1-time 12-lead ECG interpreted by a cardiologist, likely a result of increased detection of paroxysmal AF. In a population of 1000 persons with a prevalence of undiagnosed AF of 1.3%,[7] there would be between 4 and 13 true-positive test results, 0 to 237 false-positive results, 0 to 9 false-negative results, and 750 to 987 true-negative results based on extrapolation of the accuracy data reported by included studies.

Harms of Screening

Key Question 4. What are the harms of screening for AF with selected tests in older adults?

Key Question 4a. Do the harms of screening vary for subgroups defined by stroke risk, age, sex, or race and ethnicity?

Four RCTs (SAFE,[15-19] SCREEN-AF,[43] STROKESTOP,[45,47,48] and mHealth Screening to Prevent Strokes [mSToPS][33]) reported harms of screening; all were described in the KQ1 and KQ2 sections of this article and are included in Table 1. SAFE[15-19] was included in the prior review for the USPSTF; the rest are new to this update. The mSToPS RCT also included a prospective cohort component that reported relevant outcomes.[33] Detailed study characteristics and results are reported in eTables 30 and 31 in the Supplement.

SAFE reported no difference in anxiety scores between those screened with ECG compared with pulse palpation reminders.[15-19] In STROKESTOP, the rate of hemorrhagic stroke was 0.16 events per 100 person-years in the invitation-to-screening group compared with 0.18 in the control group (HR, 0.88 [95% CI, 0.70-1.11]).[44] The rate of hospitalization for major bleeding was 1.71 events per 100 person-years in the invitation-to-screening group, compared with 1.74 in the control group (HR, 0.98 [95% CI, 0.91-1.06]). In SCREEN-AF, authors reported 0 intracranial hemorrhages.[43] The 2 RCTs evaluating continuous patch ECG screening reported an incidence of skin irritation ranging from 1.2% to 1.5%[33,43] and an incidence of non-AF arrhythmias ranging from 0% to 3.9% depending on the arrhythmia, although the clinical consequences of this detection are not known. In the mSToPS cohort study (n = 5214), the frequency of initiation of anticoagulation, antiarrhythmics, and procedures was higher among the cohort that got screened compared with the matched cohort that did not get screened. In the SCREEN-AF trial, no statistically significant differences were reported for emergency department visits, hospitalizations, or pacemaker implantations, although all of these events were rare in both the screening and control groups.[43] No studies reported on variation in harms by subgroups.

Benefits of Anticoagulation

Key Question 5. What are the benefits of anticoagulation therapy on health outcomes in asymptomatic, screen-detected older adults with AF?

Key Question 5a. Do the benefits of anticoagulation vary for subgroups defined by stroke or bleeding risk, age, sex, race and ethnicity, or AF burden (ie, number of episodes, duration of episodes, and proportion of time spent in AF)?

Although the aim of this KQ was to determine the benefits of treatment in screen-detected older adults with AF, no trials or systematic reviews that focused solely on this population were identified. Five fair-quality RCTs of anticoagulation in persons with clinically detected AF were identified[21-26]; none were new to this update. Most study participants had long-standing, persistent AF; few had

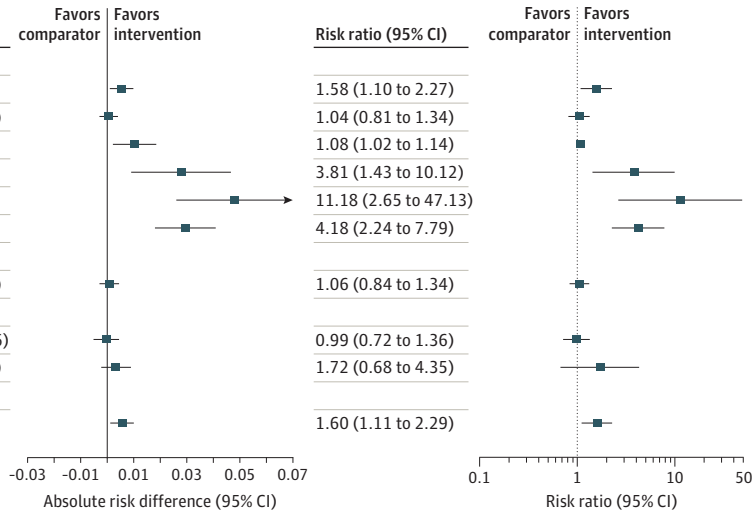
Table 1. Study Characteristics of Randomized Clinical Trials of Screening Reporting Detection of Atrial Fibrillation (Key Question 2)

Study, source	Study design (country)	Recruitment setting	Age, mean (SD), y	Women, No. (%)	Intervention groups (No. participants randomized)	Study duration, mo	Study quality
REHEARSE-AF Halcox et al,[32] 2017	Parallel-group RCT (UK)	General practices (No. unknown)	72.6 (5.4)	535 (53)	No screening, care as usual (501) Twice-weekly 30-s, single-lead ECG with handheld device (AliveCor Heart Monitor), plus additional recordings if symptomatic (500)	12	Fair
SAFE Hobbs et al,[15] 2005 Fitzmaurice et al,[17] 2007 Fitzmaurice et al,[16] 2014 Mant et al,[18] 2007 Swancutt et al,[19] 2004	Cluster-group RCT (UK)	50 Primary care practices	75.3 (7.2)	8500 (57.4)	No screening, care as usual (4936) Reminder for pulse palpation in the chart; clinicians encouraged to record pulse during routine visits; patients with irregular pulses invited to attend a nurse-led screening clinic and have 12-lead ECG (4933) Patients invited to attend a nurse-led screening clinic for pulse palpation and 12-lead ECG (4933)	12	Fair
IDEAL-MD Kaasenbrood et al,[36] 2020	Cluster-group RCT (the Netherlands)	31 General practices	Intervention: 74.3 (7.3) Control: 74.5 (7.3)	Intervention: 4680 (54.5) Control: 4610 (54.1)	No screening, care as usual (8526) Practices instructed to screen persons ≥65 y without AF during visits using a single-lead ECG; implementation left to the discretion of practices (8581)	12	Fair
Morgan and Mant,[29] 2002	Parallel-group RCT (UK)	4 General practices	75.5 (NR)	1756 (58.8)	Reminder for pulse palpation in the chart; clinicians encouraged to record pulse during routine visits (1502) Patients invited to attend a nurse-led screening clinic for pulse palpation and single-lead ECG (1499)	6	Fair
mSToPS Steinhubl et al,[33] 2018	Parallel-group RCT (US)	Siteless trial with health plan members recruited by mail	72.4 (7.3)	1026 (38.6)	Delayed screening initiated 4 mo after enrollment date (1293) Single-use, 14-d, ambulatory ECG skin patch for 2 wk on enrollment and a second patch 3 mo later for another 2 wk (1366)	4	Fair
D2AF Uittenbogaart et al,[41] 2020	Cluster-group RCT (the Netherlands)	96 General practices	Intervention: 75.2 (6.8) Control: 75.0 (6.9)	10 248 (53.4)	No screening, care as usual (9789) Reminder in chart of eligible patients randomly selected at each practice to conduct pulse palpation, oscillometric blood pressure monitor with AF detection feature, and single-lead handheld ECG with optional Holter monitoring if all 3 test results negative (9400)	12	Fair

Abbreviations: AF, atrial fibrillation; D2AF, Detecting and Diagnosing Atrial Fibrillation; ECG, electrocardiograph; IDEAL-MD, Improving Detection of Atrial Fibrillation in Primary Care With the MyDiagnostick; mSToPS, mHealth Screening to Prevent Strokes; NR, not reported; RCT, randomized clinical trial; REHEARSE-AF, Remote Heart Rhythm Sampling Using the AliveCor Heart Monitor to Screen for Atrial Fibrillation; SAFE, Screening for Atrial Fibrillation in the Elderly.

Figure 3. Comparative Detection of Atrial Fibrillation From RCTs of Screening (KQ2)

Source, y	Duration, mo	Type	No. of cases/total (%)		Absolute risk difference (95% CI)	Risk ratio (95% CI)
			Intervention	Comparator		
ECG vs no screening						
SAFE,[15] 2005	12	One-time	74/4933 (1.5)	47/4936 (1.0)	0.0055 (0.0011 to 0.0098)	1.58 (1.10 to 2.27)
IDEAL-MD,[36] 2020	12	One-time	123/8581 (1.4)	117/8526 (1.4)	0.0006 (-0.0029 to 0.0041)	1.04 (0.81 to 1.34)
STROKESTOP,[44] 2021	6	Intermittent (2 wk)	1991/13 779 (14.5)[a]	1850/13 798 (13.4)[a]	0.0104 (0.0022 to 0.0186)	1.08 (1.02 to 1.14)
REHEARSE-AF,[32] 2017	12	Intermittent (12 mo)	19/500 (3.8)	5/501 (1.0)	0.0280 (0.0091 to 0.0469)	3.81 (1.43 to 10.12)
SCREEN-AF,[43] 2021	6	Continuous	23/434 (5.3)	2/422 (0.5)	0.0483 (0.0262 to 0.0703)	11.18 (2.65 to 47.13)
mSToPS,[33] 2018	4	Continuous	53/1366 (3.9)	12/1293 (0.9)	0.0295 (0.0180 to 0.0410)	4.18 (2.24 to 7.79)
Systematic BP and ECG vs no screening						
D2AF,[41] 2020	12	One-time	144/8874 (1.6)	139/9102 (1.5)	0.0010 (-0.0027 to 0.0046)	1.06 (0.84 to 1.34)
ECG screening vs pulse palpation reminders						
SAFE,[15] 2005	12	One-time	74/4933 (1.5)	75/4933 (1.5)	-0.0002 (-0.0050 to 0.0046)	0.99 (0.72 to 1.36)
Morgan and Mant,[29] 2002	6	One-time	12/1499 (0.8)	7/1502 (0.5)	0.0033 (-0.0023 to 0.0090)	1.72 (0.68 to 4.35)
Pulse palpation reminders vs no screening						
SAFE,[15] 2005	12	One-time	75/4933 (1.5)	47/4936 (1.0)	0.0057 (0.0013 to 0.0100)	1.60 (1.11 to 2.29)



To calculate the absolute risk difference in percentage points, multiply value by 100 (eg, 0.0010 multiplied by 100 = 0.1 percentage points). BP indicates blood pressure; D2AF, Detecting and Diagnosing Atrial Fibrillation; ECG, electrocardiography; IDEAL-MD, Improving Detection of Atrial Fibrillation in Primary Care With the MyDiagnostick; KQ, key question; mSToPS, mHealth Screening to Prevent Strokes; RCT, randomized clinical trial; REHEARSE-AF, Remote Heart Rhythm Sampling Using the AliveCor Heart Monitor to Screen for Atrial Fibrillation; SAFE, Screening for Atrial Fibrillation in the Elderly.

Table 2. Characteristics of Included Test Accuracy Studies (Key Question 3)

Study, source	Recruitment setting (total No.)	Inclusion criteria	Age, mean (SD), y	Female, No. (%)	Index test(s)	Reference test(s)	Study quality
Himmelreich et al,[37] 2019	10 General practices in the Netherlands (106)	Age ≥18 y with 12-lead ECG ordered for nonacute indications	69.3 (10.7)	62 (58)	Single-lead, handheld ECG (KardiaMobile) with automated AF detection during an office visit[a]	12-Lead ECG independently interpreted by 2 cardiologists	Good
SAFE Hobbs et al,[15] 2005	25 General practices in the UK (1452)	Age ≥65 y	75.3 (7.2)[b]	8500 (57.4)	(1) General practitioner-interpreted 12-lead ECG (2) General practitioner-interpreted limb-lead II ECG (3) General practitioner-interpreted thoracic-lead ECG	12-Lead ECG independently interpreted by 2 cardiologists	Good
Kearley et al,[38] 2014	6 General practices in the UK (999)	Age ≥75 y	79.7 (NR)	507 (50.7)[c]	(1) Modified oscillometric BP monitor (Microlife WatchBP) with automated AF detection during an office visit[d] (2) Single-lead ECG (OMRON model HCG-801) with and without automated AF detection during an office visit[e]	12-Lead ECG interpreted by 2 cardiologists	Fair
Marazzi et al,[40] 2012	Hypertension clinic in Italy (383)	None specified	67 (10.5)	230 (46)	(1) Oscillometric BP monitor (Microlife BP A200 Plus) with automated AF detection during an office visit (2) Oscillometric BP monitor (OMRON M6) with automated AF detection during an office visit	12-Lead ECG interpreted by cardiologist	Good
Philippsen et al,[34] 2017	Diabetes and cardiology outpatient clinics in Denmark (82)	Age ≥65 y and treatment for diabetes and hypertension with stable medications	71 (4)	30 (37)[c]	2-Channel, 72-hour Holter monitor adjudicated by 2 cardiologists AF defined as at least 1 episode lasting ≥30 s	Continuous ECG with an insertable cardiac monitor (median, 588 d), with AF defined as at least 1 episode lasting ≥2 min	Good
Sabar et al,[42] 2019	Outpatient hospital cardiology clinic (632)	Age ≥18 y attending outpatient cardiology for routine 12-lead ECGs or other appointments	66 (range 18-97)	384 (51)	6-lead ECG (RhythmPad, Cadiocity) with automated detection during an office visit	12-Lead ECG independently interpreted by 2 cardiologists	Fair
Uittenbogaart et al,[41] 2020	96 Primary care practices in the Netherlands (742)	Age ≥65 y	75[b]	NR (53.4)[b]	Combined approach that included pulse palpation, oscillometric blood pressure monitor with automated AF detection (WatchBP Home A, Microlife), and single-lead handheld ECG (MyDiagnostick)	12-Lead ECG interpreted by cardiologists (only 10% random sample of participants with negative index test results received reference test)	Fair
Wiesel et al,[39] 2014	2 Outpatient cardiology clinics in the US (148)	Age ≥50 y	74 (NR)	75 (41)[c]	(1) Oscillometric blood pressure monitor (OMRON M6 Comfort) with automated irregular rhythm detection during an office visit (2) Oscillometric blood pressure monitor (Microlife BP A 200) with automated AF detection during an office visit[f]	12-Lead ECG interpreted by a cardiologist	Fair

Abbreviations: AF, atrial fibrillation; BP, blood pressure; ECG, electrocardiograph; KQ, key question; NR, not reported; SAFE, Screening for Atrial Fibrillation in the Elderly.

[a] Rhythms classified by algorithm as AF, normal, unreadable, or no classification. For this analysis, screening was considered positive for any "possible AF" tracings and was considered negative for all other tracings. The AF classification refers to both atrial fibrillation and atrial flutter.

[b] For entire study population; not all study participants from the trial were included in the KQ3 analyses.

[c] Calculated value.

[d] Inconclusive results treated as "positive."

[e] "Analysis impossible" and "inconclusive results" were counted as positive test results.

[f] Test result is considered positive if at least 2 of the 3 readings are positive for AF.

Table 3. Results From Included Test Accuracy Studies (Key Question 3)

Source	Device/method	Sensitivity (95% CI)	Specificity (95% CI)	Results per 1000 tests (1.3% prevalence of AF)	
				False-negative	False-positive
Oscillometric BP monitor with automated AF detection vs 12-lead ECG interpreted by cardiologist					
Kearley et al,[38] 2014	Microlife Watch BP Home A	0.95 (0.88-0.99)	0.90 (0.88-0.92)	1	99
Marazzi et al,[40] 2012	Microlife BP A200	0.92 (NR)	Calculated: 0.95	1	49
			Study reported: 0.97(NR)		
Marazzi et al,[40] 2012	OMRON M6	1.0 (NR)	0.94 (NR)	0	59
Wiesel et al,[39] 2014	Microlife BP A200	1.0 (0.86-1.0)[a]	0.92 (0.86-0.96)	0	79
Wiesel et al,[39] 2014	OMRON M6	0.30 (0.15-0.49)[a]	0.97 (0.93-0.99)	9	30
Single-lead ECG with automated AF detection vs 12-lead ECG interpreted by cardiologist					
Himmelreich et al,[37] 2019	KardiaMobile	0.88 (0.47-1.0)	1.0 (0.96-1.0)	2	0
Kearley et al,[38] 2014	OMRON	0.99 (0.93-1.0)	0.76 (0.73-0.79)	<1	237
6-lead ECG with automated AF detection vs 12-lead ECG interpreted by cardiologist					
Sabar et al,[42] 2019	6-Lead ECG	0.95 (NR)	0.99 (NR)	1	10
General practitioner–interpreted ECG vs 12-lead ECG interpreted by cardiologist					
SAFE,[15] 2005	12-lead ECG	0.80 (0.71-0.87)	0.92 (0.90-0.93)	3	79
	Single limb lead	0.83 (0.75-0.88)	0.88 (0.87-0.90)	2	118
	Single thoracic lead	0.85 (0.79-0.91)	0.86 (0.84-0.88)	2	138
Combined pulse palpation, oscillometric BP, and single-lead ECG both with automated AF detection vs 12-lead ECG interpreted by cardiologist					
D2AF,[41] 2020	MyDiagnostick device and MIcrolife Watch BP Home A	ND[b]	ND[b]	ND[b]	ND[b]
72-h continuous Holter monitoring vs continuous ECG monitoring with insertable cardiac monitor over median 588 d[c]					
Philippsen et al,[34] 2017		Calculated: 0.12	Calculated: 1	NA	NA

Abbreviations: AF, atrial fibrillation; BP, blood pressure; D2AF, Detecting and Diagnosing Atrial Fibrillation; ECG, electrocardiograph; KQ, key question; NA, not available; ND, not determinable; NR, not reported; SAFE, Screening for Atrial Fibrillation in the Elderly.

[a] The author of this study disclosed holding a patent for the AF detection algorithm present in the Microlife BP device; the sensitivity of the OMRON oscillometric device was markedly lower in this study when compared with the estimate for Microlife and when compared with the OMRON device reported in the study by Marazzi et al.[40]

[b] The study only performed a 12-lead referent test on a random sample of participants who tested negative on the index screening test; thus, data to determine sensitivity and specificity were not available. However, based on data reported, the positive predictive value is 6% and the negative predictive value is 100%, suggesting a test with very high sensitivity but poor specificity.

[c] Holter monitoring occurred approximately 1 month after placement of implantable cardiac monitor. When limited to the same 72-hour monitoring window, sensitivity was 1.0.

a history of transient ischemic attack or stroke (<8%). All trials evaluated titrated doses of warfarin. Study characteristics are detailed in eTables 32 and 33 in the Supplement.

In pooled analysis of the 5 RCTs (n = 2145), warfarin treatment over a mean of 1.5 years was significantly associated with reductions in all-cause mortality (pooled RR, 0.68 [95% CI, 0.50-0.93]; I^2 = 0%), ischemic stroke (pooled RR, 0.32 [95% CI, 0.20-0.51]; I^2 = 0%), and moderately to severely disabling stroke (pooled RR, 0.38 [95% CI, 0.19-0.78]; I^2 = 0%), compared with controls (**Figure 4**). For a population with a baseline annual stroke risk of 4%, such as patients with CHA_2DS_2-VASc scores of 3 or 4, warfarin would be associated with a number needed to treat of 24 (95% CI, 17-36) to prevent 1 ischemic stroke over 1.5 years. Individual study results are detailed in eTable 34 in the Supplement.

Results of 5 previously included systematic reviews (including 2 individual patient data meta-analyses) evaluating warfarin compared with placebo or control were consistent with the findings from the pooled analysis of included studies and are summarized in eTables 13 and 36 in the Supplement.[4,20,28,30,31] Authors of a network meta-analysis of 21 RCTs (n = 96 017) reported statistically significant associations for reductions in stroke or systemic embolism and all-cause mortality for 4 direct oral anticoagulants compared with placebo (adjusted odds ratios ranged from 0.32 to 0.44; eTable 36 in the Supplement).[30]

With respect to subgroup findings, an individual patient data meta-analysis[31] reported lower stroke risk with warfarin in male patients (relative risk reduction, 60% [95% CI, 35%-76%]) and in female patients (relative risk reduction, 84% [95% CI, 55%-95%]), but the difference between male and female patients was not statistically significant.[31] In another individual patient data meta-analysis,[20] warfarin was associated with reduced risk for ischemic stroke for all ages, with no statistically significant interaction with increasing age.[20]

Harms of Anticoagulation

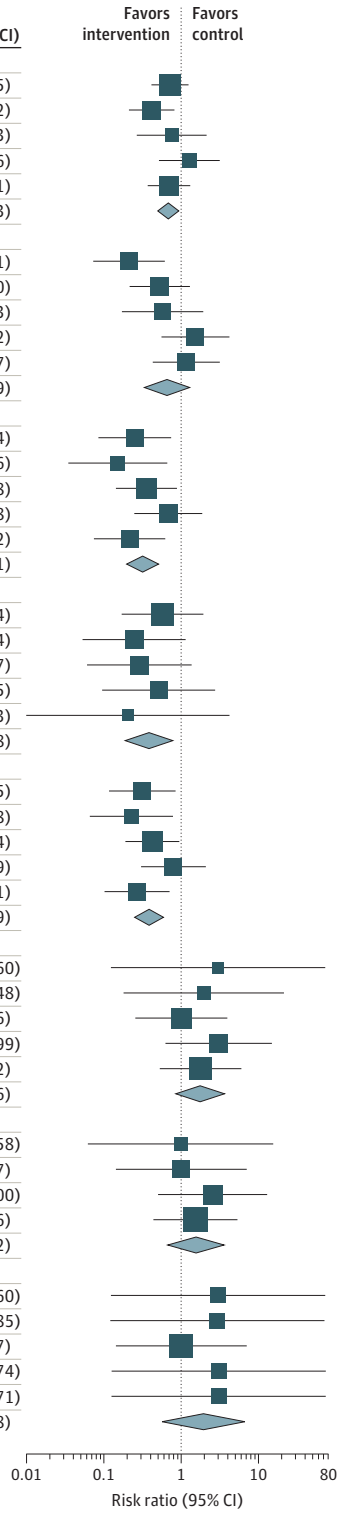
Key Question 6. What are the harms of anticoagulation therapy in asymptomatic, screen-detected older adults with AF?

Key Question 6a. Do the harms of anticoagulation therapy vary for subgroups defined by stroke risk or bleeding risk, age, sex, race and ethnicity, or AF burden?

Although the aim was to determine the harms of anticoagulation treatment for screen-detected older adults with AF, no trials or systematic reviews that focused solely on this population were identified. The same 5 RCTs included for KQ5 also reported on harms of anticoagulation.[21-26] One new observational study (n = 28 628) was identified for this update; the Global Anticoagulant Registry in the Field-Atrial Fibrillation (GARFIELD-AF) study is a fair-quality, ongoing prospective registry of persons with newly diagnosed AF from more than 1000 primary and specialty care clinics in 32 countries.[35]

Figure 4. Benefits and Harms of Warfarin for Stroke Prevention Compared With Placebo or Control

Source	Mean follow-up, y	Target INR range	Intervention Events, No.	Intervention No events, No.	Control Events, No.	Control No events, No.	Risk ratio (95% CI)
All-cause mortality[a]							
AFASAK I,[26] 1989	1.2	2.8 to 4.2	20	315	28	308	0.72 (0.41-1.25)
BATAAF,[24] 1990	2.2	1.5 to 2.7	11	201	26	182	0.42 (0.21-0.82)
SPAF I,[22] 1991	1.3	2.0 to 4.5	6	204	8	203	0.75 (0.27-2.13)
CAFA,[23] 1991	1.3	2.0 to 3.0	10	177	8	183	1.28 (0.52-3.16)
SPINAF,[21] 1992	1.7	1.4 to 2.8	15	245	22	243	0.69 (0.37-1.31)
Subtotal: I^2 = 0.0%; P = .41							0.68 (0.50-0.93)
Cardiovascular-related mortality							
AFASAK I,[26] 1989	1.2	2.8 to 4.2	4	331	19	317	0.21 (0.07-0.61)
BATAAF,[24] 1990	2.2	1.5 to 2.7	7	205	13	195	0.53 (0.22-1.30)
SPAF I,[22] 1991	1.3	2.0 to 4.5	4	206	7	204	0.57 (0.17-1.93)
CAFA,[23] 1991	1.3	2.0 to 3.0	9	178	6	185	1.53 (0.56-4.22)
SPINAF,[21] 1992	1.7	1.4 to 2.8	8	252	7	258	1.16 (0.43-3.17)
Subtotal: I^2 = 53.7%; P = .07							0.66 (0.33-1.29)
All ischemic stroke							
AFASAK I,[26] 1989	1.2	2.8 to 4.2	4	331	16	320	0.25 (0.08-0.74)
BATAAF,[24] 1990	2.2	1.5 to 2.7	2	210	13	195	0.15 (0.03-0.66)
SPAF I,[22] 1991	1.3	2.0 to 4.5	6	204	17	194	0.35 (0.14-0.88)
CAFA,[23] 1991	1.3	2.0 to 3.0	6	181	9	182	0.68 (0.25-1.88)
SPINAF,[21] 1992	1.7	1.4 to 2.8	4	256	19	246	0.21 (0.07-0.62)
Subtotal: I^2 = 0.0%; P = .41							0.32 (0.20-0.51)
Moderately to severely disabling stroke							
AFASAK I,[26] 1989	1.2	2.8 to 4.2	4	331	7	329	0.57 (0.17-1.94)
BATAAF,[24] 1990	2.2	1.5 to 2.7	2	210	8	200	0.25 (0.05-1.14)
SPAF I,[22] 1991	1.3	2.0 to 4.5	2	208	7	204	0.29 (0.06-1.37)
CAFA,[23] 1991	1.3	2.0 to 3.0	2	185	4	187	0.51 (0.09-2.75)
SPINAF,[21] 1992	1.7	1.4 to 2.8	0	260	2	263	0.20 (0.01-4.23)
Subtotal: I^2 = 0.0%; P = .88							0.38 (0.19-0.78)
All ischemic stroke or intracranial hemorrhage							
AFASAK I,[26] 1989	1.2	2.8 to 4.2	5	330	16	320	0.31 (0.12-0.85)
BATAAF,[24] 1990	2.2	1.5 to 2.7	3	209	13	195	0.23 (0.07-0.78)
SPAF I,[22] 1991	1.3	2.0 to 4.5	8	202	19	192	0.42 (0.19-0.94)
CAFA,[23] 1991	1.3	2.0 to 3.0	7	180	9	182	0.79 (0.30-2.09)
SPINAF,[21] 1992	1.7	1.4 to 2.8	5	255	19	246	0.27 (0.10-0.71)
Subtotal: I^2 = 0.0%; P = .45							0.38 (0.25-0.59)
Major bleeding[b]							
AFASAK I,[26] 1989	1.2	2.8 to 4.2	1	334	0	336	3.01 (0.12-73.60)
BATAAF,[24] 1990	2.2	1.5 to 2.7	2	210	1	207	1.96 (0.18-21.48)
SPAF I,[22] 1991	1.3	2.0 to 4.5	4	206	4	207	1.00 (0.25-3.96)
CAFA,[23] 1991	1.3	2.0 to 3.0	6	181	2	189	3.06 (0.63-14.99)
SPINAF,[21] 1992	1.7	1.4 to 2.8	7	253	4	261	1.78 (0.53-6.02)
Subtotal: I^2 = 0.0%; P = .87							1.76 (0.85-3.66)
Major extracranial bleeding							
BATAAF,[24] 1990	2.2	1.5 to 2.7	1	211	1	207	0.98 (0.06-15.58)
SPAF I,[22] 1991	1.3	2.0 to 4.5	2	208	2	209	1.00 (0.14-7.07)
CAFA,[23] 1991	1.3	2.0 to 3.0	5	182	2	189	2.55 (0.50-13.00)
SPINAF,[21] 1992	1.7	1.4 to 2.8	6	254	4	261	1.53 (0.44-5.36)
Subtotal: I^2 = 0.0%; P = .88							1.56 (0.67-3.62)
Intracranial hemorrhage[c]							
AFASAK I,[26] 1989	1.2	2.8 to 4.2	1	334	0	336	3.01 (0.12-73.60)
BATAAF,[24] 1990	2.2	1.5 to 2.7	1	211	0	208	2.94 (0.12-71.85)
SPAF I,[22] 1991	1.3	2.0 to 4.5	2	208	2	209	1.00 (0.14-7.07)
CAFA,[23] 1991	1.3	2.0 to 3.0	1	186	0	191	3.06 (0.13-74.74)
SPINAF,[21] 1992	1.7	1.4 to 2.8	1	259	0	265	3.06 (0.13-74.71)
Subtotal: I^2 = 0.0%; P = .95							1.94 (0.56-6.68)



[a] SPINAF includes only those without history of stroke. AFASAK includes data from a published meta-analysis obtained from the original study authors. [b] AFASAK did not specify severity of most bleeding events; it reported 1 fatal intracerebral hemorrhage in the warfarin group and only reported bleeding events leading to withdrawal from study (warfarin, 21; placebo, 0). BAATAF defines major bleeding as intracranial bleeding, fatal bleeding, or bleeding that led to transfusion (≥4 units within 48 h); SPAF I, as bleeding that involved the central nervous system, management requiring hospitalization with transfusion and/or surgery, or permanent residual impairment; CAFA, as life-threatening bleeding; SPINAF, as bleeding that required transfusion, emergency procedure, or removal of a hematoma or that led to ICU admission. [c] SPAF I included 1 fatal intracerebral hemorrhage and 1 subdural hematoma with full recovery (warfarin) and 2 subdural hematomas with full recovery (placebo).

In a pooled analysis of the 5 RCTs (2415 participants), major bleeding events occurred in 20 participants from the warfarin groups and 11 participants from the placebo/control groups over 1.5 years (pooled RR, 1.8 [95% CI, 0.85-3.70]; I^2 = 0%). Additional bleeding outcomes are reported in Figure 4 and in eTable 35 in the Supplement. Results of 6 previously included systematic reviews were consistent with the findings from the analysis of the primary studies and are summarized in eTable 36 in the Supplement.[4,20,27,28,30,31] Authors of the previously described network meta-analysis of 21 RCTs (n = 96 017) reported adjusted odds ratios for major bleeding ranging from 1.38 to 2.21 in indirect comparisons of 4 direct oral anticoagulants compared with placebo; the CIs around these estimates were wide, and findings were not statistically significant (eTable 36 in the Supplement).[30]

In the GARFIELD-AF observational study, the adjusted HR for first occurrence of major bleeding was 1.73 (95% CI, 1.33-2.25) for participants receiving any anticoagulation treatment (warfarin, direct oral anticoagulant, antiplatelets, or combination), compared with participants receiving no treatment (eTable 35 in the Supplement).[35]

With respect to subgroups, an individual patient data meta-analysis[31] reported a higher mean age for patients with intracranial hemorrhage (73 years) compared with those without bleeding (69 years), but bleeding events were rare, and this difference was not statistically significant.[31] The other individual patient data meta-analyis[20] reported that no statistical interaction between age and risk of serious hemorrhage associated with warfarin was found.[20]

Discussion

This updated evidence review examined screening for AF in older adults without a history of stroke; the evidence is summarized in **Table 4**.

STROKESTOP is the only included trial of screening that was designed and powered to evaluate health outcomes.[44,45,47] Authors reported a small but statistically significant difference favoring the screening group in the intention-to-treat analysis using a composite end point that included both benefit and harm outcomes, despite uptake of screening by only 51% of those randomized to the invitation to screening. However, this study had numerous limitations; the outcomes evaluated were diagnosed through routine clinical care, without formal masking, and were not based on standard diagnostic criteria with central, blinded adjudication. Whether benefit and harm end points should be combined into a "net benefit" composite is an area of debate and violates assumptions recommended for composite end points.[49-51] This study enrolled persons with known AF, many of whom were already taking oral anticoagulants, limiting applicability to screening among persons without known AF. The other 2 studies reporting health outcomes from screening compared with no screening were not powered for such outcomes; events were rare or absent in these studies. The potential for reporting bias is also present because 1 of the studies reporting KQ2 outcomes designated major cardiovascular events and all-cause mortality as secondary outcomes, but these have not been reported.[36] Several ongoing studies comparing screening with no screening may provide additional evidence for this KQ in the future (eTable 37 in the Supplement).

Screening with intermittent or continuous ECG can identify more cases of AF compared with no screening. When 1-time ECG screening was compared with pulse palpation reminders, no significant difference in cases identified was observed. The variation in sensitivity and specificity of various 1-time screening strategies based on ECG or oscillometric blood pressure monitor with automated AF detection may be the result of differences in the underlying populations tested, differences in thresholds used for defining positive index or reference tests, or the fidelity with which screening was conducted. The clinical importance of this variation is uncertain. Given the relatively low prevalence of undiagnosed AF, 1-time spot screening will generate more false-positive results relative to true-positives and relative to false-negatives. Estimates of these results across various AF prevalences are provided in eTable 38 in the Supplement.

For harms of screening, 1 RCT reported that anxiety was not significantly different between participants who received ECG screening and participants whose clinicians received pulse palpation reminders, but a direct comparison of screened with not screened participants was not reported. Data from SCREEN-AF and STROKESTOP suggested no increased risk of serious bleeding events, including hemorrhagic stroke, but such events were rare, and estimates were imprecise, precluding a definitive conclusion about bleeding harms from screening. Although this review identified evidence to estimate the potential number of screening tests with inaccurate results (ie, false-positive and false-negative results), evidence is limited with respect to the consequences of those inaccurate screening results. Potential harms could result from unnecessary stress tests and angiographies initiated to follow up on ECG abnormalities later determined to be false-positives or unnecessary treatment resulting from overdiagnosis. A study using a database from a US hospital that evaluated 2298 ECGs (from 1085 patients) with a computerized interpretation of AF found that ECGs from 382 patients (35%) had been misinterpreted; physicians did not correct the computerized misinterpretation and initiated inappropriate and potentially harmful treatments, and they pursued unnecessary additional testing for 92 patients (9%).[52] However, potential benefits could result from appropriate care provided for medically actionable findings other than AF (eg, high-degree atrioventricular block, ventricular tachycardia).

Among trials enrolling persons with clinical AF without a prior history of stroke, consistent evidence suggests that the risk for stroke and all-cause mortality is reduced with anticoagulation compared with placebo or control. The same body of evidence suggests a possible increased risk for major bleeding, but estimates are imprecise. It is uncertain whether the benefits and harms of treatment are applicable to screen-detected populations, particularly persons with brief episodes of AF.

Limitations

This review has several limitations. First, it was restricted to fair- or good-quality studies conducted in very highly developed countries and published in English. Second, it did not consider screening approaches that are not feasible in or referrable from primary care. Third, non-AF findings resulting from screening were considered harms (eg, because treatment and procedures have inherent disutility, inconvenience, and costs and may be harmful in the setting of false-positive screening results and overdiagnosis). However, treatment offered for medically actionable non-AF findings may provide benefit for some persons. Fourth, the comparative effectiveness of anticoagulation treatments was not evaluated.

Table 4. Summary of Evidence for Screening for Atrial Fibrillation

No. of studies/study designs (No. of participants)	Summary of findings	Consistency and precision	Limitations	Strength of evidence	Applicability
KQ1: Benefits of screening					
1 RCT (27 975)[44,45,47] Designed to address KQ1	Intermittent screening ECG twice daily for 2 wk compared with no screening (1 RCT)[44,45,47] Composite benefit/harm end point[a]: Events/100 person-years, 5.45 (95% CI, 5.29-5.61) vs 5.68 (95% CI, 5.52-5.85); HR, 0.96 (95% CI, 0.92-1.00); *P* = .045 Secondary outcomes: Ischemic stroke: HR, 0.92 (95% CI, 0.83-1.01) All-cause mortality: HR, 0.96 (95% CI, 0.92-1.01) Systemic embolism: HR, 1.10 (95% CI, 0.76-1.59) Ischemic stroke or systemic embolism: HR, 0.92 (95% CI, 0.84-1.02) as randomized; 0.76 (0.67-0.85), as treated[b]	Consistent; imprecise[c]	Fair-quality studies; in largest trial, ≈12% had known AF at baseline and only 51.3% of persons randomized to screening participated, with no formal outcome assessment masking or central adjudication; primary outcome changed to a composite end point that included both benefit and harm outcomes; the other 2 trials were designed for KQ2 and not powered for health outcomes, were not masked, and had some measurement bias; reporting bias detected (1 of the KQ2 studies was also designed to report KQ1 outcomes per trial registry entry but no results published)	Insufficient for addressing question of direct benefits of screening in persons without known AF	Adults with mean age in 70s and 80s, with stroke risks in range recommended for anticoagulation if no contraindication; unclear applicability to screening in persons in primary care practice settings, given population recruitment in only trial powered for health outcomes with clear differences between participants and nonparticipants that make predicting the bias from poor fidelity challenging
2 RCTs (1857)[32,43] Not designed to address KQ1 but reported some health outcomes	Intermittent screening ECG twice weekly for 12 mo compared with no screening (1 RCT)[32] Composite of stroke, TIA, or systemic embolism: 6 (screened) vs 10 (not screened) events; HR, 0.61 (95% CI, 0.22-1.69) Continuous ECG for 2 weeks, twice (total 4 weeks) compared with no screening (1 RCT)[43]: 1 death (no screening), 2 ischemic strokes (screening), 1 TIA (screening), 0 systemic embolism				
KQ2: Identifying new cases of AF					
7 RCTs (74 386)[15-19,32,33,36,41,43-45,47]	Various ECG screening compared with no screening: 1-time (3 RCTs): ARDs, 0.06%-0.60% Intermittent (2 RCTs): ARDs, 1.0%-2.8% Continuous (2 RCTs): ARDs, 3.0%-4.8%	Consistent; imprecise[d,e]	Fair quality, study inclusion/exclusion criteria focused on persons without known AF but most did not routinely assess for potential symptoms at study entry; fidelity low to modest in intervention groups	Moderate for increased detection, with higher detection seen with intermittent and continuous approaches	Applicable to older adults without known AF for various screening modalities (1-time ECG, intermittent ECG, continuous patch ECG, pulse palpation combined with 1-time ECG and oscillometric BP with AF detection).[f]
2 RCTs (12 867)[15-19,29]	ECG screening vs pulse palpation reminders: ARD, −0.02% in 1 trial and 0.3% in other trial (not statistically significant in either)	Consistent; imprecise	Fair quality; fidelity of pulse assessment was 29% in 1 trial and 69% in the other trial; fidelity of ECG screening was 73% in 1 trial and 53% in the other trial	Low for no difference in detection	Applicable to 1-time ECG screening only, reminders in either paper charts or electronic records
1 RCT (9869)[15-19]	Pulse palpation reminders vs no screening: ARD, 0.6% (95% CI, 0.1%-1.0%)	Single study, consistency unknown; precise	Fair quality; fidelity of pulse palpation in response to reminders was 69%	Low for increased detection	Older adults, reminders in either paper charts or electronic records
KQ3: Accuracy of screening tests[g]					
7 studies (4544)[15,34,37-42]	Various screening strategies compared with 12-lead ECG interpreted by cardiologist Sensitivity range: 0.80-1.0h Specificity range: 0.76-1.0	Consistent; precise[h]	Four studies were fair quality because of concerns about applicability and selection bias related to method of enrollment in 2 studies, and lack of masking of index and reference test results in other study and reference standard in 1 study; most studies used 1-time reference standards, which may underestimate the prevalence of paroxysmal AF	Moderate to low depending on screening approach[i]	Applicable to adults and for the following screening modalities: 6-lead ECG, general practitioner–interpreted ECG (12-lead or <12-lead), oscillometric BP monitor with automatic AF detection, single-lead ECG with automatic AF detection
1 study (399)[43]	Oscillometric BP monitor with AF detection feature compared with continuous ECG (4 wk) Sensitivity, 0.35; specificity, 0.81				

(continued)

Table 4. Summary of Evidence for Screening for Atrial Fibrillation (continued)

No. of studies/study designs (No. of participants)	Summary of findings	Consistency and precision	Limitations	Strength of evidence	Applicability
KQ4: Harms of screening					
4 RCTs (43 633)[15-19,33,43-45,47j] 1 cohort (5214)[k]	Anxiety (1 RCT): Mean scores not significantly different for invitation to ECG screening compared with pulse palpation reminders	Consistent; imprecise	Fair quality; anxiety scores not reported for comparison of invitation to ECG screening vs no screening	Insufficient for anxiety	Applicable to older adults for the following screening modalities: general practitioner-interpreted ECG (anxiety), continuous ECG monitoring patch (non-AF arrhythmias, initiation of oral anticoagulants and procedures, and skin irritation), intermittent ECG (initiation of oral anticoagulants and procedures, bleeding outcomes)
	Bleeding outcomes (2 RCTs): 0 intracranial hemorrhages or major bleeding events after 6 mo in the smaller of the RCTs HR, 0.88 (95% CI, 0.70-1.11) for hemorrhagic stroke and HR, 0.98 (95% CI, 0.91-1.06) for hospitalization for major bleeding in a larger RCT after a median follow-up of 6.9 y	Consistency unknown; imprecise	Fair quality; no centralized outcome adjudication, studies underpowered for rare events	Insufficient for bleeding outcomes	
	Non-AF arrhythmias (1 RCT and 1 cohort): detected in 2.6% of participants who received screening in cohort study and between 0 and 3.9% in the RCT depending on the type of arrhythmia; arrhythmias were considered clinically actionable in both studies.	Consistent; precise	Fair quality; no masking	Moderate for increased detection, clinical consequences unknown[l]	
	Initiation of anticoagulation, antiarrhythmics, and procedures (2 RCTs and 1 cohort): generally higher among participants who received screening compared with controls who did not get screened but only statistically significant for higher oral anticoagulant use in 2 of the 3 studies[m]	Consistent; imprecise	Fair quality, no masking	Low for increased initiation, clinical consequences unknown[l]	
	Skin irritation from patch (2 RCTs): 1.2% (95% CI, 0.5%-2.7%) to 1.5% (95% CI, 1.1%-2.0%) of participants	Consistent; precise	Fair quality; not masked, methods of ascertainment of skin irritation not reported	Moderate for increased skin irritation	
KQ5: Benefits of anticoagulation treatment					
5 RCTs (2415)[21-26] 5 Systematic reviews[4,20,28,30,31]	Warfarin (mean, 1.5 y) vs placebo/control: Reduced all-cause mortality: pooled RR, 0.68 (95% CI, 0.50-0.93) Reduced ischemic stroke: pooled RR, 0.32 (95% CI, 0.20-0.51) Previously published systematic reviews: Similar findings reported for warfarin compared with placebo In a network meta-analysis, 4 direct oral anticoagulants were also more effective than placebo/control (adjusted ORs, 0.32-0.44).[n]	Consistent; precise	All warfarin trials were fair quality and stopped early; 3 of the 5 trials were open-label; 4 of the 5 trials had inadequate or unclear methods of allocation concealment Reporting bias not detected Limitations of the network meta-analysis included (1) the lack of sensitivity analyses removing the studies with greater focus on secondary prevention, (2) limited ability to adjust for population characteristics (because some included studies were older and did not report $CHADS_2$ scores, and they were estimated from baseline characteristics), and (3) heterogeneity of doses in intervention and control groups	Moderate for benefit	Adults with AF and no history of stroke or TIA; uncertain whether the results are applicable to asymptomatic screen-detected persons with AF Most participants had AF for more than 1 year, and few had paroxysmal AF Estimates for lifelong treatment are not available

(continued)

Table 4. Summary of Evidence for Screening for Atrial Fibrillation (continued)

No. of studies/study designs (No. of participants)	Summary of findings	Consistency and precision	Limitations	Strength of evidence	Applicability
KQ6: Harms of anticoagulation treatment					
5 RCTs (2415)[21-26] 6 Systematic reviews[4,20,27,28,30,31] 1 prospective cohort study (26 628)[35]	Warfarin (mean, 1.5 y) vs placebo/control: Major bleeding: pooled RR, 1.8 (95% CI, 0.85-3.7) Intracranial hemorrhage: pooled RR, 1.9 (95% CI, 0.56-6.7) Previously published systematic reviews, similar findings reported for warfarin compared with placebo In a network meta-analysis, the adjusted ORs for major bleeding comparing 4 direct oral anticoagulants with placebo/controls ranged from 1.38 to 2.21; CIs were wide and included the null[n,o] Anticoagulation compared with no antiocagulation over 2 y in cohort study: first bleeding event adjusted HR, 1.73 (95% CI, 1.33-2.25)	Consistent, imprecise[p]	All warfarin trials were fair quality and stopped early; 3 of the 5 trials were open label; 4 of the 5 trials had inadequate or unclear methods of allocation concealment; reporting bias not detected Limitations of the network meta-analysis included (1) the lack of sensitivity analyses removing the studies with greater focus on secondary prevention, (2) limited ability to adjust for population characteristics (because some included studies were older and did not report $CHADS_2$ scores, and they were estimated from baseline characteristics), and (3) heterogeneity of doses in intervention and control groups	Moderate for harm[q]	Adults with AF and no history of stroke or TIA

Abbreviations: AF, atrial fibrillation; ARD, absolute risk difference; BP, blood pressure; $CHADS_2$, Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Prior stroke or TIA or thromboembolism; ECG, electrocardiogram; HR, hazard ratio; KQ, key question; NA, not applicable; OR, odds ratio; RCT, randomized clinical trial; RR, risk ratio; TIA, transient ischemic attack.

[a] Includes both benefit and harm outcomes: ischemic stroke, hemorrhagic stroke, systemic arterial embolism, all-cause death, and bleeding leading to hospitalization.

[b] When nonparticipants in the invitation to screening group were excluded (ie, the as-treated analysis), a larger net benefit is observed; however, nonparticipants. compared with participants, had worse socioeconomic status and lower education, higher alcohol use, and higher prevalence of comorbidities that increase both stroke risk and risk for major bleeding. Thus, the as-treated analysis, while mitigating for poor intervention fidelity, could overestimate the benefit because participants were, on average, slightly younger and healthier.

[c] For detecting a small benefit; based on optimal information size criteria would require a trial with 36 896 participants to detect a relative risk reduction of 20% (RR, 0.80) given incidence in comparator group (2%) using 2-tailed α = .05, power = 0.8. Even more participants would be required to detect a smaller risk reduction.

[d] Study was rated consistent because of consistency in detection based on duration and intensity of screening strategy.

[e] Study was rated imprecise because the number of events (ie, cases detected) was low across all studies, and the estimates for some individual studies were imprecise. Further, based on optimal information size criteria for average detection rate in no-screening group (1.2%), a single trial would require a sample size of 74 668 to detect a 20% relative increase in AF detection, 2-tailed α = .05, power = 0.8, and even more participants to detect a smaller increase in detection.

[f] Subgroup findings from 1 of the studies (SAFE trial)[15] suggested that screening may not increase detection among female participants; no subgroup findings were reported by the other 4 studies, all of which included female participants; thus, this finding is uncertain.

[g] The study by Phillippsen et al was not included when considering strength of evidence; that study compared a 72-hour Holter monitor with an insertable cardiac monitor that was left in place for a median of 588 days; the Holter monitor was placed approximately 1 month after the insertable monitor was placed, and it is uncertain whether AF events occurring after Holter monitoring period were prevalent cases or new onset.

[h] Consistent for oscillometric BP with automated AF detection algorithm, with exception of 1 study[39] for which sensitivity was reported as 0.30 for 1 brand of oscillometric monitor and for which a study author disclosed conflict of interest. The evidence for single-lead ECG was less consistent, resulting in a low strength of evidence for that strategy.

[i] Moderate for oscillometric BP with automated AF detection and general practitioner ECG interpretation and 6-lead ECG; low for single-lead ECG with automated AF detection. Sensitivity influenced by reference standard used; continuous ECG reference standards are more likely to detect paroxysmal AF, resulting in lower sensitivity for 1-time or intermittent index tests.

[j] Number of participants included a subset of 1940 of the 14 802 participants in the SAFE study, although study reporting relating to anxiety outcomes was unclear.

[k] Includes 1738 participants who were also part of the mSToPS RCT (immediate and delayed monitoring groups combined).[33]

[l] The detection of clinically actionable non-AF arrhythmias could be considered a benefit if it results in treatment or intervention that prevents an untoward outcome. However, it could be a harm if additional treatment or procedures (and related side effects or adverse events) were provided for an arrhythmia that might never have caused symptoms or issues. Similarly, the initiation of treatments or subsequent procedures could be considered a benefit or harm depending on the health consequences of such actions.

[m] Findings were only statistically significantly higher in the cohort study, except for use of oral anticoagulants, which was also significantly higher in the RCT (RR, 4.4 [95% CI, 1.5-12.8]).

[n] The 4 direct oral coagulants were apixaban, dabigatran, edoxaban, and rivaroxaban.

[o] The network meta-analysis also found no statistically significant differences for the 4 direct oral coagulants in comparison with one another. Compared with vitamin K antagonists, 3 of the direct oral coagulants (apixaban, dabigatran, and edoxaban) were associated with a lower risk of bleeding (range of ORs, 0.64 [95% CI, 0.46-0.90] to 0.85 [95% CI, 0.65-1.11]), but the difference was only statistically significant for edoxaban (OR, 0.64 [95% CI, 0.46-0.90]). For rivaroxaban compared with vitamin K antagonists, the odds of major bleeding was 1.03 (95% CI, 0.68-1.57).

[p] Given the event rate in control group (≈1%), a properly powered trial to detect a 60% increase in major bleeding (RR, 1.6) would require 11 838 participants (2-tailed α = .05, power = 0.8).

[q] Although findings were imprecise and quality was fair, the strength of evidence was graded as moderate considering evidence on dose response (with higher international normalized ratios increasing bleeding risk) and evidence on treatment of conditions other than AF that shows consistent evidence of bleeding risk.

Conclusions

Although screening can detect more cases of previously unknown AF, evidence regarding effects on health outcomes is limited. Anticoagulation was associated with lower risk of first stroke and mortality but with increased risk of major bleeding, although estimates for this harm are imprecise; no trials assessed benefits and harms of anticoagulation among screen-detected populations.

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Concept and design: Kahwati, Asher, Keen, Jonas.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Kahwati, Asher, Keen, Ali, Jonas.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Kahwati, Keen.
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REFERENCES

1. Virani SS, Alonso A, Benjamin EJ, et al; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2020 update: a report from the American Heart Association. *Circulation*. 2020;141(9):e139-e596. doi:10.1161/CIR.0000000000000757

2. Schnabel RB, Yin X, Gona P, et al. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. *Lancet*. 2015;386(9989):154-162. doi:10.1016/S0140-6736(14)61774-8

3. Staerk L, Sherer JA, Ko D, Benjamin EJ, Helm RH. Atrial fibrillation: epidemiology, pathophysiology, and clinical outcomes. *Circ Res*. 2017;120(9):1501-1517. doi:10.1161/CIRCRESAHA.117.309732

4. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med*. 2007;146(12):857-867. doi:10.7326/0003-4819-146-12-200706190-00007

5. January CT, Wann LS, Alpert JS, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2014;64(21):e1-e76. doi:10.1016/j.jacc.2014.03.022

6. Curry SJ, Krist AH, Owens DK, et al; US Preventive Services Task Force. Screening for atrial fibrillation with electrocardiography: US Preventive Services Task Force recommendation statement. *JAMA*. 2018;320(5):478-484. doi:10.1001/jama.2018.10321

7. Kahwati L, Asher GN, Kadro Z, et al. *Screening for Atrial Fibrillation: An Evidence Review for the U.S. Preventive Services Task Force. Evidence Synthesis No. 208*. Agency for Healthcare Research and Quality; 2021. AHRQ publication 21-05277.

8. Statistical update 2018: human development indices and indicators. United Nations Development Programme. Published 2018. Accessed November 22, 2021. http://hdr.undp.org/en/content/human-development-indices-indicators-2018-statistical-update

9. Procedure Manual Appendix VI: Criteria for assessing internal validity of individual studies. US Preventive Services Task Force. Published May 2021. Accessed November 22, 2021. https://www.uspreventiveservicestaskforce.org/uspstf/about-uspstf/methods-and-processes/procedure-manual/procedure-manual-appendix-vi-criteria-assessing-internal-validity-individual-studies

10. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898. doi:10.1136/bmj.l4898

11. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177-188. doi:10.1016/0197-2456(86)90046-2

12. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21(11):1539-1558. doi:10.1002/sim.1186

13. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-560. doi:10.1136/bmj.327.7414.557

14. Procedure Manual Appendix XII: Summary of evidence table for evidence reviews. US Preventive Services Task Force. Published May 2021. Accessed November 22, 2021. https://www.uspreventiveservicestaskforce.org/uspstf/about-uspstf/methods-and-processes/procedure-manual/procedure-manual-appendix-xii-summary-evidence-table-evidence-reviews

15. Hobbs FD, Fitzmaurice DA, Mant J, et al. A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over: the SAFE study. *Health Technol Assess*. 2005;9(40):74. doi:10.3310/hta9400

16. Fitzmaurice DA, McCahon D, Baker J, et al. Is screening for AF worthwhile? stroke risk in a screened population from the SAFE study. *Fam Pract*. 2014;31(3):298-302. doi:10.1093/fampra/cmu011

17. Fitzmaurice DA, Hobbs FD, Jowett S, et al. Screening versus routine practice in detection of atrial fibrillation in patients aged 65 or over: cluster randomised controlled trial. *BMJ*. 2007;335(7616):383. doi:10.1136/bmj.39280.660567.55

18. Mant J, Fitzmaurice DA, Hobbs FD, et al. Accuracy of diagnosing atrial fibrillation on electrocardiogram by primary care practitioners and interpretative diagnostic software: analysis of data from screening for atrial fibrillation in the elderly (SAFE) trial. *BMJ*. 2007;335(7616):380. doi:10.1136/bmj.39227.551713.AE

19. Swancutt D, Hobbs R, Fitzmaurice D, et al. A randomised controlled trial and cost effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in the over 65s: (SAFE) [ISRCTN19633732]. *BMC Cardiovasc Disord*. 2004;4:12. doi:10.1186/1471-2261-4-12

20. van Walraven C, Hart RG, Connolly S, et al. Effect of age on stroke prevention therapy in patients with atrial fibrillation: the atrial fibrillation investigators. *Stroke*. 2009;40(4):1410-1416. doi:10.1161/STROKEAHA.108.526988

21. Ezekowitz MD, Bridgers SL, James KE, et al; Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators. Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. *N Engl J Med*. 1992;327(20):1406-1412. doi:10.1056/NEJM199211123272002

22. Stroke Prevention in Atrial Fibrillation Study: final results. *Circulation*. 1991;84(2):527-539. doi:10.1161/01.CIR.84.2.527

23. Connolly SJ, Laupacis A, Gent M, Roberts RS, Cairns JA, Joyner C. Canadian Atrial Fibrillation Anticoagulation (CAFA) study. *J Am Coll Cardiol*. 1991;18(2):349-355. doi:10.1016/0735-1097(91)90585-W

24. Singer DE, Hughes RA, Gress DR, et al; Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. *N Engl J Med*. 1990;323(22):1505-1511. doi:10.1056/NEJM199011293232201

25. Stroke Prevention in Atrial Fibrillation Study Group Investigators. Preliminary report of the Stroke Prevention in Atrial Fibrillation Study. *N Engl J Med*. 1990;322(12):863-868. doi:10.1056/NEJM199003223221232

26. Petersen P, Boysen G, Godtfredsen J, Andersen ED, Andersen B. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation: the Copenhagen AFASAK study. *Lancet*. 1989;1(8631):175-179. doi:10.1016/S0140-6736(89)91200-2

27. Coleman CI, Sobieraj DM, Winkler S, et al. Effect of pharmacological therapies for stroke prevention on major gastrointestinal bleeding in patients with atrial fibrillation. *Int J Clin Pract*. 2012;66(1):53-63. doi:10.1111/j.1742-1241.2011.02809.x

28. Aguilar MI, Hart R. Oral anticoagulants for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. *Cochrane Database Syst Rev*. 2005;(3):CD001927. doi:10.1002/14651858.CD001927.pub2

29. Morgan S, Mant D. Randomised trial of two approaches to screening for atrial fibrillation in UK general practice. *Br J Gen Pract*. 2002;52(478):373-374, 377-380.

30. Tereshchenko LG, Henrikson CA, Cigarroa J, Steinberg JS. Comparative effectiveness of interventions for stroke prevention in atrial fibrillation: a network meta-analysis. *J Am Heart Assoc*. 2016;5(5):e003206. doi:10.1161/JAHA.116.003206

31. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation: analysis of pooled data from five randomized controlled trials. *Arch Intern Med*. 1994;154(13):1449-1457. doi:10.1001/archinte.1994.00420130036007

32. Halcox JPJ, Wareham K, Cardew A, et al. Assessment of remote heart rhythm sampling using the AliveCor heart monitor to screen for atrial fibrillation: the REHEARSE-AF study. *Circulation*. 2017;136(19):1784-1794. doi:10.1161/CIRCULATIONAHA.117.030583

33. Steinhubl SR, Waalen J, Edwards AM, et al. Effect of a home-based wearable continuous ECG monitoring patch on detection of undiagnosed atrial fibrillation: the mSToPS randomized clinical trial. *JAMA*. 2018;320(2):146-155. doi:10.1001/jama.2018.8102

34. Philippsen TJ, Christensen LS, Hansen MG, Dahl JS, Brandes A. Detection of subclinical atrial fibrillation in high-risk patients using an insertable cardiac monitor. *JACC Clin Electrophysiol*. 2017;3(13):1557-1564. doi:10.1016/j.jacep.2017.06.020

35. Bassand JP, Accetta G, Al Mahmeed W, et al; GARFIELD-AF Investigators. Risk factors for death, stroke, and bleeding in 28,628 patients from the GARFIELD-AF registry: rationale for comprehensive management of atrial fibrillation. *PLoS One*. 2018;13(1):e0191592. doi:10.1371/journal.pone.0191592

36. Kaasenbrood F, Hollander M, de Bruijn SH, et al. Opportunistic screening versus usual care for diagnosing atrial fibrillation in general practice: a cluster randomised controlled trial. *Br J Gen Pract*. 2020;70(695):e427-e433. doi:10.3399/bjgp20X708161

37. Himmelreich JCL, Karregat EPM, Lucassen WAM, et al. Diagnostic accuracy of a smartphone-operated, single-lead electrocardiography device for detection of rhythm and conduction abnormalities in primary care. *Ann Fam Med*. 2019;17(5):403-411. doi:10.1370/afm.2438

38. Kearley K, Selwood M, Van den Bruel A, et al. Triage tests for identifying atrial fibrillation in primary care: a diagnostic accuracy study comparing single-lead ECG and modified BP monitors. *BMJ Open*. 2014;4(5):e004565. doi:10.1136/bmjopen-2013-004565

39. Wiesel J, Arbesfeld B, Schechter D. Comparison of the Microlife blood pressure monitor with the Omron blood pressure monitor for detecting atrial fibrillation. *Am J Cardiol*. 2014;114(7):1046-1048. doi:10.1016/j.amjcard.2014.07.016

40. Marazzi G, Iellamo F, Volterrani M, et al. Comparison of Microlife BP A200 Plus and Omron M6 blood pressure monitors to detect atrial fibrillation in hypertensive patients. *Adv Ther*. 2012;29(1):64-70. doi:10.1007/s12325-011-0087-0

41. Uittenbogaart SB, Verbiest-van Gurp N, Lucassen WAM, et al. Opportunistic screening versus usual care for detection of atrial fibrillation in primary care: cluster randomised controlled trial. *BMJ*. 2020;370:m3208. doi:10.1136/bmj.m3208

42. Sabar MI, Ara F, Henderson A, et al. A study to assess a novel automated electrocardiogram technology in screening for atrial fibrillation. *Pacing Clin Electrophysiol*. 2019;42(10):1383-1389. doi:10.1111/pace.13800

43. Gladstone DJ, Wachter R, Schmalstieg-Bahr K, et al; SCREEN-AF Investigators and Coordinators. Screening for atrial fibrillation in the older population: a randomized clinical trial. *JAMA Cardiol*. 2021;6(5):558-567. doi:10.1001/jamacardio.2021.0038

44. Svennberg E, Friberg L, Frykman V, Al-Khalili F, Engdahl J, Rosenqvist M. Clinical outcomes in systematic screening for atrial fibrillation (STROKESTOP): a multicentre, parallel group, unmasked, randomised controlled trial. *Lancet*. 2021;398(10310):1498-1506. doi:10.1016/S0140-6736(21)01637-8

45. Svennberg E, Engdahl J, Al-Khalili F, Friberg L, Frykman V, Rosenqvist M. Mass screening for untreated atrial fibrillation: the STROKESTOP study. *Circulation*. 2015;131(25):2176-2184. doi:10.1161/CIRCULATIONAHA.114.014343

46. Donal E, Lund LH, Oger E, et al; KaRen Investigators. New echocardiographic predictors of clinical outcome in patients presenting with heart failure and a preserved left ventricular ejection fraction: a subanalysis of the Ka (Karolinska) Ren (Rennes) study. *Eur J Heart Fail*. 2015;17(7):680-688. doi:10.1002/ejhf.291

47. Friberg L, Engdahl J, Frykman V, Svennberg E, Levin LA, Rosenqvist M. Population screening of 75- and 76-year-old men and women for silent atrial fibrillation (STROKESTOP). *Europace*. 2013;15(1):135-140. doi:10.1093/europace/eus217

48. Lahtela H, Rubboli A, Schlitt A, et al; AFCAS (Management of patients with Atrial Fibrillation undergoing Coronary Artery Stenting) Study Group. Heparin bridging vs. uninterrupted oral anticoagulation in patients with atrial fibrillation undergoing coronary artery stenting: results from the AFCAS registry. *Circ J*. 2012;76(6):1363-1368. doi:10.1253/circj.CJ-11-1206

49. Armstrong PW, Westerhout CM. Composite end points in clinical research: a time for reappraisal. *Circulation*. 2017;135(23):2299-2307. doi:10.1161/CIRCULATIONAHA.117.026229

50. Choi SW, Cheung CW. The case of the misleading composite—one outcome is better than two. *Anaesthesia*. 2016;71(9):1101-1103. doi:10.1111/anae.13590

51. Gómez G, Gómez-Mateu M, Dafni U. Informed choice of composite end points in cardiovascular trials. *Circ Cardiovasc Qual Outcomes*. 2014;7(1):170-178. doi:10.1161/CIRCOUTCOMES.113.000149

52. Bogun F, Anh D, Kalahasty G, et al. Misdiagnosis of atrial fibrillation and its clinical consequences. *Am J Med*. 2004;117(9):636-642. doi:10.1016/j.amjmed.2004.06.024