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

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IMPORTANCE Atrial fibrillation is the most common arrhythmia and increases the risk of stroke.

OBJECTIVE To review the evidence on screening for nonvalvular atrial fibrillation with electrocardiography (ECG) and stroke prevention treatment in asymptomatic adults 65 years or older to inform the US Preventive Services Task Force.

DATA SOURCES MEDLINE, Cochrane Library, and trial registries through May 2017; references; experts; literature surveillance through June 6, 2018.

STUDY SELECTION English-language randomized clinical trials (RCTs), prospective cohort studies evaluating detection rates of atrial fibrillation or harms of screening, and systematic reviews evaluating stroke prevention treatment. Eligible treatment studies compared warfarin, aspirin, or novel oral anticoagulants (NOACs) with placebo or no treatment. Studies were excluded that focused on persons with a history of cardiovascular disease.

DATA EXTRACTION AND SYNTHESIS Dual review of abstracts, full-text articles, and study quality. When at least 3 similar studies were available, random-effects meta-analyses were conducted.

MAIN OUTCOMES AND MEASURES Detection of previously undiagnosed atrial fibrillation, mortality, stroke, stroke-related morbidity, and harms.

RESULTS Seventeen studies were included (n = 135 300). No studies evaluated screening compared with no screening and focused on health outcomes. Systematic screening with ECG identified more new cases of atrial fibrillation than no screening (absolute increase, from 0.6% [95% CI, 0.1%-0.9%] to 2.8% [95% CI, 0.9%-4.7%] over 12 months; 2 RCTs, n = 15 803), but a systematic approach using ECG did not detect more cases than an approach using pulse palpation (2 RCTs, n = 17 803). For potential harms, no eligible studies compared screening with no screening. Warfarin (mean, 1.5 years) was associated with a reduced risk of ischemic stroke (relative risk [RR], 0.32 [95% CI, 0.20-0.51]) and all-cause mortality (RR, 0.68 [95% CI, 0.50-0.93]) and with increased risk of bleeding (5 trials, n = 2415). Participants in treatment trials were not screen detected, and most had long-standing persistent atrial fibrillation. A network meta-analysis reported that NOACs were associated with a significantly lower risk of a composite outcome of stroke and systemic embolism (adjusted odds ratios compared with placebo or control ranged from 0.32-0.44); the risk of bleeding was increased (adjusted odds ratios, 1.4-2.2), but confidence intervals were wide and differences between groups were not statistically significant.

CONCLUSIONS AND RELEVANCE Although screening with ECG can detect previously unknown cases of atrial fibrillation, it has not been shown to detect more cases than screening focused on pulse palpation. Treatments for atrial fibrillation reduce the risk of stroke and all-cause mortality and increase the risk of bleeding, but trials have not assessed whether treatment of screen-detected asymptomatic older adults results in better health outcomes than treatment after detection by usual care or after symptoms develop.

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Atrial fibrillation is a supraventricular tachyarrhythmia characterized by uncoordinated electrical activity and resulting inefficient atrial contraction.[1] Atrial fibrillation can be categorized as paroxysmal, persistent, permanent, and nonvalvular (eTable 1 in the Supplement). Prevalence increases with age, from less than 0.2% for persons younger than 55 years to about 10% for those 85 years or older, and is higher for men than women (eTable 2 in the Supplement).[2] About 25% of atrial fibrillation is paroxysmal.[3]

Atrial fibrillation increases the risk for stroke and thromboembolism by reducing cardiac blood flow and predisposing to thrombus formation, particularly in the left atrial appendage.[1,4] For persons with atrial fibrillation, the annual incidence of stroke increases by about 1.5% per decade, from 1.3% in persons aged 50 to 59 years to 5.1% in persons aged 80 to 89 years.[5] Strokes attributable to atrial fibrillation are associated with a poor prognosis.[6-9] Approximately 30% of patients with atrial fibrillation who have a stroke die within 1 year of the stroke, and up to 30% of survivors are permanently disabled.[10]

Patients may not notice symptoms of atrial fibrillation before a serious event, such as stroke. Of patients who have a stroke attributable to atrial fibrillation, an estimated 20% or more are diagnosed with atrial fibrillation at the time of the stroke or shortly thereafter.[11-13] Thus, identifying asymptomatic atrial fibrillation and starting anticoagulation therapy may prevent strokes and deaths. To inform a recommendation by the US Preventive Services Task Force (USPSTF), the evidence on detection of previously undiagnosed atrial fibrillation and benefits and harms of screening and stroke prevention treatment for atrial fibrillation in populations and settings relevant to US primary care was reviewed.

Methods

Scope of Review

Detailed methods and additional details of results and analyses are available in the full evidence report at https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/atrial-fibrillation-screening-with-electrocardiography. Additional descriptions of studies evaluating aspirin and other published systematic reviews are available in the full evidence report. **Figure 1** shows the analytic framework and key questions (KQs) that guided the review.

Data Sources and Searches

PubMed/MEDLINE and the Cochrane Library were searched for English-language articles published from inception through May 2017. Search strategies are listed in the eMethods in the Supplement. ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry platform were searched for unpublished literature. To supplement electronic searches, investigators reviewed reference lists of pertinent articles, studies suggested by reviewers, and comments received during public commenting periods. Since May 2017, ongoing surveillance was conducted through 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. The last surveillance was conducted on June 6, 2018 and identified no eligible studies.

Study Selection

Two investigators independently reviewed titles, abstracts, and full-text articles to determine eligibility using prespecified criteria for each key question (eTable 3 in the Supplement). Disagreements were resolved by discussion. The review included English-language studies focused on adults 65 years or older conducted in countries categorized as "very high" on the United Nations Human Development Index. Only studies rated as good or fair quality were included. Studies focused on adults with a history of stroke, transient ischemic attack (TIA), coronary heart disease, or heart failure were excluded.

For KQ1 (direct evidence that screening improves health outcomes), KQ2 (detection of undiagnosed atrial fibrillation), and KQ3 (harms of screening), studies were required to enroll unselected or explicitly asymptomatic adults. Eligible screening tests included systematic screening with electrocardiography (ECG) (eg, 12-lead ECG, intermittent use of handheld ECG) or systematic screening with both pulse palpation and ECG for all participants. Studies whose interventions used other technologies (eg, blood pressure monitoring) or physical examination only were excluded. For KQ1, randomized clinical trials (RCTs) and nonrandomized controlled intervention studies were eligible. For KQ2 and KQ3, prospective cohort studies were also eligible.

For benefits (KQ4) and harms (KQ5) of stroke prevention treatment, eligible studies compared treatment with aspirin or oral anticoagulants (warfarin or the novel oral anticoagulants [NOACs] apixaban, dabigatran, edoxaban, or rivaroxaban) vs placebo or no treatment controls. RCTs and nonrandomized controlled intervention studies were eligible. Systematic reviews of trials were also eligible if they were directly relevant (eg, focused on primary prevention; included the relevant warfarin trials). For KQ5, prospective cohort studies were also eligible.

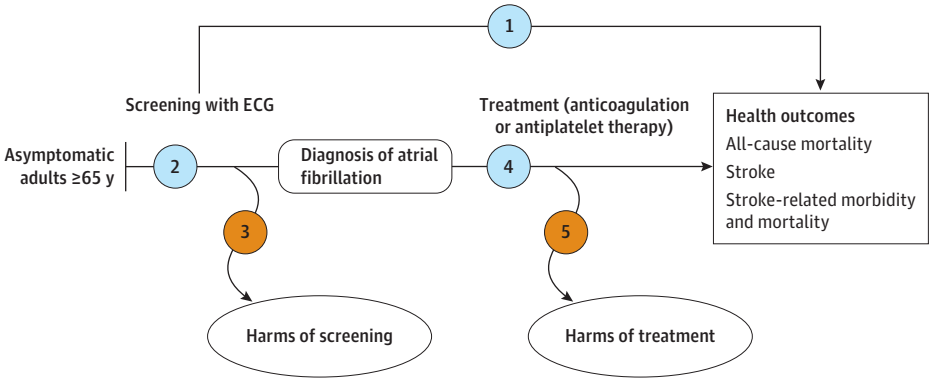
Data Extraction and Quality Assessment

For each included study, 1 investigator extracted pertinent information about the populations, tests or treatments, comparators, outcomes, settings, and designs, and a second investigator reviewed for completeness and accuracy. Two independent investigators assessed the quality of studies as good, fair, or poor, using predefined criteria developed by the USPSTF and adapted for this topic.[14] Disagreements were resolved by discussion. Individual study quality ratings are reported in eTables 4-9 in the Supplement.

Data Synthesis and Analysis

Findings for each question were summarized in tabular and narrative format. To determine whether meta-analyses were appropriate, clinical and methodological heterogeneity were assessed. When at least 3 similar studies were available, quantitative synthesis was conducted with random-effects models using the inverse-variance weighted method (DerSimonian and Laird) to estimate pooled effects.[15] For KQ2, fewer than 3 studies were available for each comparison, and absolute risk differences and odds ratios (ORs) were calculated for detection of unknown atrial fibrillation. For KQ4 and KQ5, relative risks (RRs) and 95% CIs were calculated for all-cause mortality, cardiovascular-related mortality, ischemic stroke, moderately to severely disabling stroke, TIA, major bleeding, major extracranial bleeding, intracerebral hemorrhage, minor bleeding, and a composite outcome of ischemic stroke or intracerebral hemorrhage.

Figure 1. Analytic Framework: Screening for Atrial Fibrillation With Electrocardiography



Key questions

1 Does screening for atrial fibrillation with ECG improve health outcomes (ie, reduce all-cause mortality or reduce morbidity or mortality from stroke) in asymptomatic older adults?
a. Does improvement in health outcomes vary for subgroups defined by stroke risk (eg, based on CHA_2DS_2-VASc score), age, sex, or race/ethnicity?

2 Does systematic screening for atrial fibrillation with ECG identify older adults with previously undiagnosed atrial fibrillation more effectively than usual care?

3 What are the harms of screening for atrial fibrillation with ECG in older adults?
a. Do the harms of screening vary for subgroups defined by stroke risk (eg, based on CHA_2DS_2-VASc score), age, sex, or race/ethnicity?

4 What are the benefits of anticoagulation or antiplatelet therapy on health outcomes in asymptomatic, screen-detected older adults with atrial fibrillation?
a. Do the benefits of anticoagulation or antiplatelet therapy vary for subgroups defined by stroke risk (eg, based on CHA_2DS_2-VASc score), age, sex, or race/ethnicity?

5 What are the harms of anticoagulation or antiplatelet therapy in asymptomatic, screen-detected older adults with atrial fibrillation?
a. Do the harms of anticoagulation or antiplatelet therapy vary for subgroups defined by stroke risk (eg, based on CHA_2DS_2-VASc score), age, sex, or race/ethnicity?

Evidence reviews for the US Preventive Services Task Force (USPSTF) use an analytic framework to visually display the key questions that the review will address to allow the USPSTF to evaluate the effectiveness and safety of a preventive service. The questions are depicted by linkages that relate to interventions and outcomes. Further details are available from the USPSTF procedure manual.[14]

For all quantitative syntheses, the I^2 statistic was calculated to assess statistical heterogeneity.[16,17] Quantitative analyses were conducted using Comprehensive Meta-Analysis version 3.3 (Biostat Inc) and Stata version 14 (StataCorp).

The overall strength of the body of evidence was assessed for each key question as high, moderate, low, or insufficient using methods developed for the USPSTF (and the Evidence-based Practice Center program), based on the overall quality of studies, consistency of results between studies, precision of findings, and risk of reporting bias.[14]

Results

A total of 17 studies (22 articles) with 135 300 participants were included (**Figure 2**). The main results for each key question are summarized below.

Benefits of Screening

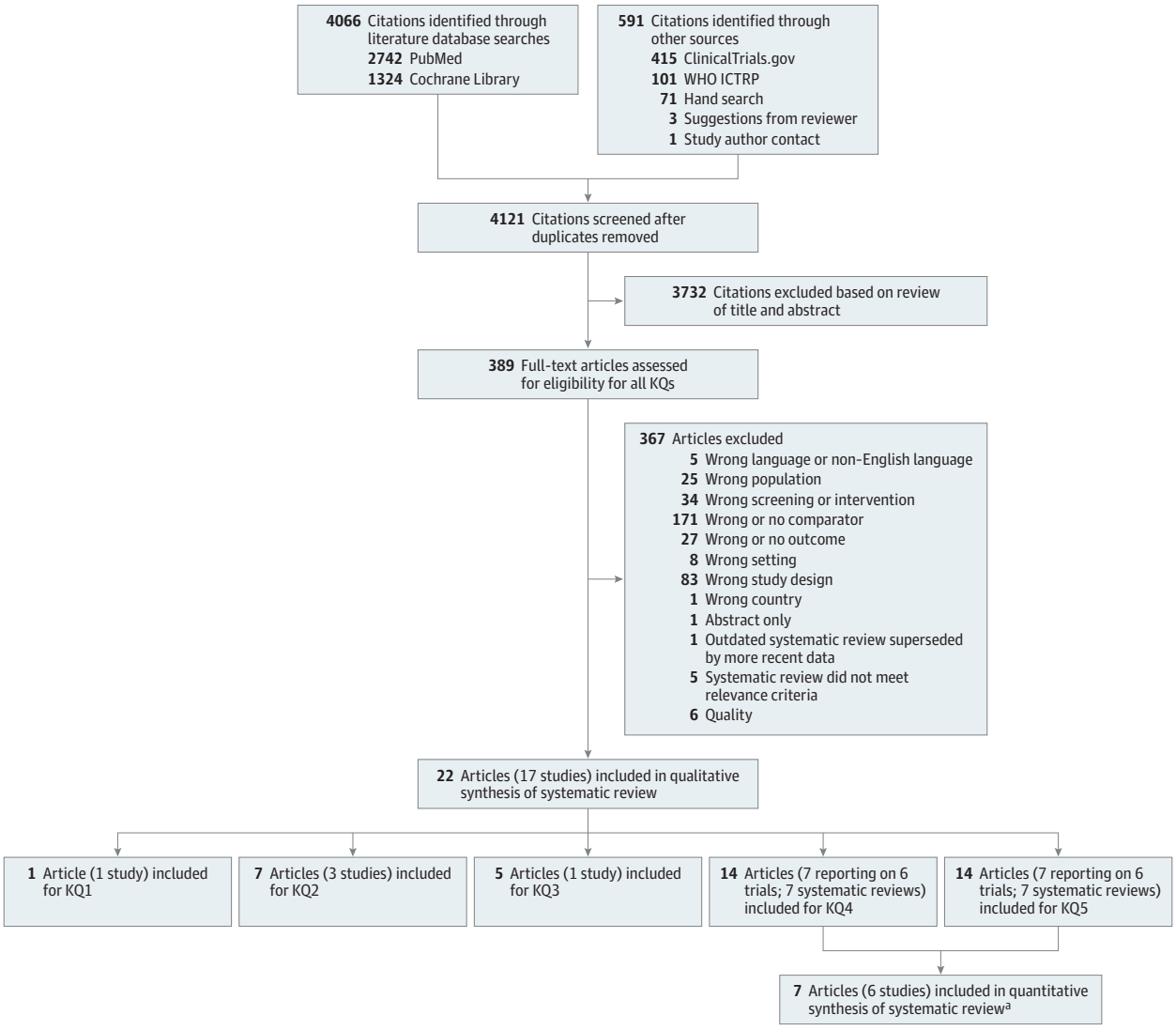
Key Question 1. Does screening for atrial fibrillation with ECG improve health outcomes (ie, reduce all-cause mortality or reduce morbidity or mortality from stroke) in asymptomatic older adults?

Key Question 1a. Does improvement in health outcomes vary for subgroups defined by stroke risk (eg, based on CHA_2DS_2-VASc score), age, sex, or race/ethnicity?

No eligible studies were identified that focused on this question and reported results. One fair-quality RCT of 1001 participants and a primary outcome of time to diagnosis of atrial fibrillation, the Assessment of Remote Heart Rhythm Sampling Using the AliveCor Heart Monitor to Screen for Atrial Fibrillation (REHEARSE-AF) trial (described in KQ2), reported limited information on health outcomes but was not designed or powered to evaluate them.[19] For all-cause mortality, the authors reported 3 deaths in the screening group and 5 in the no screening group (P = .51). For a composite of stroke, TIA, or systemic embolism, there were 6 vs 10 events, respectively (hazard ratio [HR], 0.6 [95% CI, 0.2-1.7]; P = .34).

Another RCT, the STROKESTOP study, is ongoing (anticipated completion, March 2019) and has not yet reported results for the outcomes and comparisons eligible for this review.[20-22] The primary outcome is incidence of stroke over 5 years. The study randomized 28 768 persons aged 75 to 76 years in 2 regions in Sweden to screening program invitations for atrial fibrillation or no invitations. The screening program used an initial 12-lead ECG and then a handheld 1-lead ECG recorder for intermittent recordings

Figure 2. Literature Search Flow Diagram



All eligible full-text articles were reviewed for all key questions (KQs). Reasons for exclusion: Wrong language/non-English: Publication was not in English. Wrong population: Study was not conducted in an eligible population. Wrong screening/intervention: Screening/intervention was not eligible. Wrong or no comparator: Study did not use an eligible comparator. Outcomes: Study did not report eligible outcomes. Setting: Study setting was not eligible. Design: Study did not use an included design. Wrong country: Study was not conducted in a country categorized as "very high" on the Human Development Index. Abstract only: Study details were only reported in an abstract. Outdated systematic review superseded by more recent data: Systematic review had been updated and a more recent version was available. Systematic review did not meet relevance criteria: Systematic review did not meet relevance criteria. Quality: Study was poor quality. KQ indicates key question; WHO ICTRP, World Health Organization International Clinical Trials Registry Platform.

[a] One study rated poor quality was used in sensitivity analyses.[18]

over 2 weeks. The detection rate for previously unknown atrial fibrillation was 3.0% (95% CI, 2.7%-3.5%; n = 218/7173) in the intervention group; incidence data for atrial fibrillation in the control group have not yet been reported. Of the new cases detected in the intervention group, few were identified on the initial 12-lead ECG (37/218 [17%]). More than 90% of patients with newly diagnosed atrial fibrillation accepted initiation of oral anticoagulant therapy.

Detection With ECG

Key Question 2. Does systematic screening for atrial fibrillation with ECG identify older adults with previously undiagnosed atrial fibrillation more effectively than usual care?

The review included 3 fair-quality RCTs described in 7 articles (**Table 1**).[19,23-28] All 3 trials were conducted in the United Kingdom. Two compared systematic screening (with pulse palpation and single-lead or 12-lead ECG) with opportunistic screening[23-28]; 1 of those also included a comparison with no screening.[23-27] One trial compared systematic, twice-weekly screening using a single-lead handheld ECG vs no screening.[19]

The Screening for Atrial Fibrillation in the Elderly (SAFE) study was a multicenter cluster trial (n = 14 802) that randomized 50 practices to screening vs no screening.[23-27] Within the 25 practices randomized to screening, individual participants were randomized to systematic screening or opportunistic screening. For the screening

Table 1. Characteristics of Included RCTs Evaluating Detection of Previously Undiagnosed Atrial Fibrillation (KQ2)[a]

Source	Source of Patients	Age, Mean (SD), y	Women, No. (%)	Screening Group	Screening Approach	Duration of Follow-up, mo
SAFE[b] Fitzmaurice et al,[23] 2014 Fitzmaurice et al,[24] 2007 Mant et al,[25] 2007 Hobbs et al,[26] 2005 Swancutt et al,[27] 2004 (United Kingdom)	50 primary care practices; cluster RCT with randomization at the practice level (n = 14 802)	75.3 (7.2)	8500 (57.4)	Systematic (n = 4933)	Patients invited by letter to attend a nurse-led screening clinic where their radial pulse was palpated and a 12-lead ECG was performed	12
				Opportunistic (n = 4933)	Nurses and physicians encouraged to record pulse during routine visits; patients with irregular pulses invited to attend a nurse-led screening clinic and receive 12-lead ECG[c]	
				No screening (n = 4936)	NA	
Morgan et al,[28] 2002[b] (United Kingdom)	4 general practices (n = 3001)	75.5 (NR)	1765 (58.8)	Systematic (n = 1499)	Patients invited by letter to attend a nurse-led screening clinic where their radial pulse was palpated and a lead II rhythm strip was performed[d]	6
				Opportunistic (n = 1502)	Nurses and physicians encouraged to record pulse during routine visits; if pulse was suspicious for AF, they decided whether to request ECG depending on the history and clinical context[e]	
REHEARSE-AF Halcox et al,[19] 2017 (United Kingdom)	General practices (n = 1001)	72.6 (5.4)	535 (53.4)	Systematic (n = 500)	Twice-weekly, 30-second, single-lead ECG using a handheld device, plus additional recordings if symptomatic	12
				No screening (n = 501)	NA	

Abbreviations: AF, atrial fibrillation; ECG, electrocardiogram; KQ, key question; NA, not applicable; NR, not reported; RCT, randomized clinical trial; REHEARSE-AF, Assessment of Remote Heart Rhythm Sampling Using the AliveCor Heart Monitor to Screen for Atrial Fibrillation; SAFE, Screening for Atrial Fibrillation in the Elderly.

[a] All trials in table were fair quality.

[b] Neither trial reported information about the race or ethnicity of participants; the proportion of participants with a history of transient ischemic attack or stroke; or the baseline prevalence of hypertension, diabetes, heart failure, or heart valve disease.

[c] Paper or computer flags were placed in the notes to encourage pulse recording.

[d] Patients unable to attend the clinic were offered screening at home.

[e] A reminder flag was placed in the notes to encourage pulse recording.

practices, primary care physicians and other members of the health care team attended educational days covering the importance of detecting atrial fibrillation and available treatment options. Another trial randomized 3001 participants from 4 practices.[28] Nurses conducting screenings received 2 hours of training on the assessment of the pulse rhythm. The third trial, REHEARSE-AF, randomized 1001 participants to a twice-weekly screening with a single-lead ECG using a handheld device vs no screening.[19] All trials enrolled patients 65 years or older; the mean age of participants was 72 to 75 years. Only REHEARSE-AF reported baseline stroke risk scores for participants; the mean CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years [doubled], diabetes, stroke/transient ischemic attack/thromboembolism [doubled], vascular disease [prior myocardial infarction, peripheral artery disease, or aortic plaque], age 65-74 years, sex category [female]) score was 3 (SD, 1). The SAFE study reported the $CHADS_2$ (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism [doubled]) scores for the 149 newly identified cases of atrial fibrillation and reported that more cases in the systematic screening group had scores of 2 or more than in the opportunistic group, but the difference was not statistically significant (43.2% vs 29.3%, $P = .08$).[23]

The trials did not find a statistically significant difference between systematic and opportunistic screening for detection of new cases of atrial fibrillation (**Figure 3**). The SAFE study found that more new cases of atrial fibrillation were detected in patients undergoing any screening (systematic or opportunistic) compared with no screening (149 vs 47; risk difference, 0.6% [95% CI, 0.2%-0.9%]; OR, 1.6 [95% CI, 1.1-2.2]). The subgroup analyses reported from the SAFE study found that screening may not increase detection of new cases among women. Men in the systematic (OR, 2.7 [95% CI, 1.5-4.7]) and opportunistic (OR, 2.3 [95% CI, 1.3-4.2]) screening groups had greater odds of having atrial fibrillation diagnosed than men in the no screening group. The odds were not significantly increased for women in either screening group compared with no screening (OR, 1.0 [95% CI, 0.6-1.6] and OR, 1.2 [95% CI, 0.7-1.9], respectively). Patients aged 65 to 74 years and those older than 75 years had similar odds of having atrial fibrillation diagnosed in both the systematic screening (OR, 1.6 [95% CI, 0.9-2.9] and OR, 1.6 [95% CI, 0.98-2.5], respectively) and opportunistic (OR, 1.6 [95% CI, 0.9-2.9] and OR, 1.6 [95% CI, 1.0-2.6], respectively) screening groups, compared with no screening. The REHEARSE-AF study reported that more new cases of atrial fibrillation were detected in those undergoing screening compared with no screening (19 vs 5; HR, 3.9 [95% CI, 1.4-10.4]; risk difference, 2.8% [95% CI, 0.9%-4.7%]; OR, 3.9 [95% CI, 1.5-10.6]).

Harms of Screening

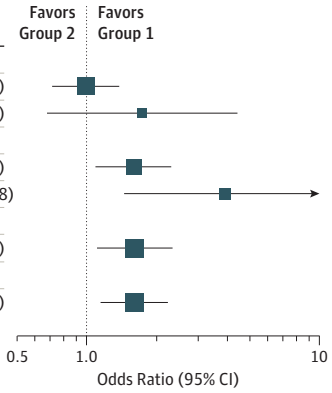
Key Question 3. What are the harms of screening for atrial fibrillation with ECG in older adults?

Key Question 3a. Do the harms of screening vary for subgroups defined by stroke risk, age, sex, or race/ethnicity?

No eligible studies assessing labeling or harms of subsequent interventions initiated because of screening with ECG (eg, subsequent ablation with complications) were identified. One of the trials included for KQ2, the SAFE study, assessed anxiety associated with screening and provided limited evidence showing that anxiety scores were not significantly different for systematic and opportunistic

Figure 3. Absolute Difference in New Cases of Atrial Fibrillation Detected and Odds of Detecting New Cases, by Comparison

Source	Duration of follow-up, mo	No. of New AF Cases/ Total No. of Individuals (%) Group 1	Group 2	Risk Difference, % (95% CI)	Odds Ratio (95% CI)
Systematic vs opportunistic screening					
SAFE,[23-27] 2007	12	74/4933 (1.5)	75/4933 (1.5)	-0.02 (-0.50 to 0.46)	0.99 (0.71-1.36)
Morgan,[28] 2002	6	12/1499 (0.8)	7/1502 (0.5)	0.33 (-0.23 to 0.90)	1.72 (0.68-4.39)
Systematic vs no screening					
SAFE,[23-27] 2007	12	74/4933 (1.5)	47/4936 (1.0)	0.55 (0.11 to 0.98)	1.58 (1.10-2.29)
REHEARSE-AF,[19] 2017	12	19/500 (3.8)	5/501 (1.0)	2.80 (0.91 to 4.69)	3.92 (1.45-10.58)
Opportunistic vs no screening					
SAFE,[23-27] 2007	12	75/4933 (1.5)	47/4936 (1.0)	0.57 (0.13 to 1.00)	1.61 (1.11-2.32)
Any screening vs no screening					
SAFE,[23-27] 2007	12	149/9866 (1.5)	47/4936 (1.0)	0.56 (0.20 to 0.92)	1.60 (1.15-2.22)



Analyses for this figure used the full study denominators. If using smaller denominators that exclude persons determined to have a prior history of atrial fibrillation, the results were almost identical. Size of data markers indicates the relative number of events in the study compared with other studies making the same comparison. REHEARSE-AF indicates Assessment of Remote Heart Rhythm Sampling Using the AliveCor Heart Monitor to Screen for Atrial Fibrillation; SAFE, Screening for Atrial Fibrillation in the Elderly.

screening groups after screening or after 17 months.[23,24] It did not, however, collect anxiety data from patients in the no screening group, which would have allowed for a comparison between screening and no screening.

Potential harms of screening include misinterpretation of ECGs and subsequent unnecessary treatment (eg, warfarin for someone without atrial fibrillation). An analysis of 2595 participants in the SAFE study from 49 general practices assessed the accuracy of general practitioners and interpretive software for diagnosing atrial fibrillation.[25] General practitioners missed 20 of 99 atrial fibrillation cases (20%) on 12-lead ECG and misinterpreted 114 of 1355 cases (8%) of normal sinus rhythm as atrial fibrillation, compared with reference standard cardiologists (sensitivity, 79.8% [95% CI, 70.5%-87.2%]; specificity, 91.6% [95% CI, 90.1%-93.1%]). False-positive rates varied from 0% to 44% for individual general practitioners (SD, 13%). Combining general practitioners' interpretations with those of interpretive software increased the sensitivity (91.9% [95% CI, 86.6%-97.3%]), but specificity was about the same (91.1% [95% CI, 89.6%-92.6%]). Use of single-lead or limb-lead ECGs resulted in slightly lower specificity.

Benefits of Stroke Prevention Treatment

Key Question 4. What are the benefits of anticoagulation or antiplatelet therapy on health outcomes in asymptomatic, screen-detected older adults with atrial fibrillation?

Key Question 4a. Do the benefits of anticoagulation or antiplatelet therapy vary for subgroups defined by stroke risk, age, sex, or race/ethnicity?

No trials or systematic reviews that focused on asymptomatic, screen-detected participants were found. Six RCTs of persons who were not screen detected (**Table 2**) were included; most had long-standing persistent nonvalvular atrial fibrillation; prevalence of baseline or past symptoms (eg, palpitations, dyspnea) was generally not reported. Three RCTs evaluated warfarin,[30,33,34] 1 evaluated aspirin,[35] and 2 (described in 3 articles) evaluated both warfarin and aspirin.[29,31,32] Seven systematic reviews (eTable 10 in the Supplement) were included: 3 were traditional systematic reviews with meta-analyses,[36-38] 3 were meta-analyses of individual patient data,[39-41] and 1 was a network meta-analysis.[42]

Five trials (6 articles) evaluated warfarin.[29-34] Four of the 5 trials compared warfarin with placebo (Atrial Fibrillation, Aspirin, and Antikoagulation study [AFASAK I],[29] Canadian Atrial Fibrillation Anticoagulation [CAFA],[33] Stroke Prevention in Atrial Fibrillation [SPAF I],[31,32] Stroke Prevention in Nonrheumatic Atrial Fibrillation [SPINAF][34]), and 1 (Boston Area Anticoagulation Trial for Atrial Fibrillation [BAATAF])[30] compared warfarin with no treatment. The BAATAF trial allowed participants in the no treatment group to take aspirin, but use of aspirin or other antithrombotic medications was not permitted in the 4 placebo-controlled trials. Two trials (AFASAK I and SPAF I) were 3-group studies that included aspirin groups (in addition to warfarin and placebo or no treatment). Two trials were double-blinded (CAFA, SPINAF), and 3 were open label (AFASAK I, BAATAF, SPAF I). All trials began in the 1980s, were completed by 1992, and were stopped early because of evidence favoring warfarin.

The mean age of participants in trials evaluating warfarin ranged from 67 to 74 years. Four trials enrolled fewer than 30% women and just 1 reported race or ethnicity (16% of participants were nonwhite in SPAF I). The baseline prevalence of hypertension and diabetes ranged from 32% to 58% and 12% to 18%, respectively. AFASAK I and SPINAF did not include participants with paroxysmal atrial fibrillation; the other 3 trials reported that 7% to 34% had paroxysmal atrial fibrillation. Most participants in the trials had atrial fibrillation for more than 1 year, although AFASAK I did not report information about the duration of atrial fibrillation before enrollment. Baseline stroke risk was not reported by the trials because stroke risk scores used in current practice were not yet developed. All trials titrated doses of warfarin using either prothrombin time or international normalized ratio (INR).

Warfarin treatment over an average of 1.5 years was associated with reductions in all-cause mortality (RR, 0.68 [95% CI, 0.50-0.93]), ischemic stroke (RR, 0.32 [95% CI, 0.20-0.51]), and

Table 2. Characteristics of Included RCTs Evaluating Benefits and Harms of Warfarin or Aspirin Compared With Placebo or Control, and Baseline Participant Characteristics (KQ4 and KQ5)

Source[a]	Mean Age (Range or SD)	No. (%)					Treatment Group	Mean Follow-up, y	Target INR	Target PT, s	TTR, %
		Women	Nonwhite Race/Ethnicity	Stroke	Heart Failure	CAD					
AFASAK Petersen et al,[29] 1989 (Denmark)	74 (38-91)[b]	467 (46)	NR	43 (4)	521 (52)	77 (8) prior MI	Warfarin, adjusted dose (n = 335) Aspirin, 75 mg/d (n = 336) Placebo (n = 336)	1.2	2.8-4.2	NR	73
BAATAF Singer et al,[30]1990 (United States)	68 (8.9)	116 (28)	NR	14 (3)	109 (26)	218 (52)	Warfarin, adjusted dose (n = 212) Control (n = 208)[c]	2.2	1.5-2.7	1.2-1.5	83
SPAF I Stroke Prevention in Atrial Fibrillation Investigators,[31] 1990 Stroke Prevention in Atrial Fibrillation Investigators,[32] 1991 (United States)	67 (NR)	387 (29)	213 (16)	93 (7) stroke or TIA	253 (19)	106 (8) prior MI	Group 1[d]: Warfarin, adjusted dose (n = 210) Aspirin, 325 mg/d (n = 206) Placebo (n = 211) Group 2[d]: Aspirin, 325 mg/d (n = 346) Placebo (n = 357)	1.3	2-4.5[e]	1.3-1.8[e]	71 within target PT range
CAFA Connolly et al,[33] 1991 (Canada)	68 (9.5)	96 (25)	NR	14 (4) stroke or TIA	83 (22)	51 (13) prior MI	Warfarin, adjusted dose (n = 187) Placebo (n = 191)	1.3	2-3	NR	44
SPINAF Ezekowitz et al,[34] 1992 (United States)	67 (7)	0	NR	46 (8)	160 (30)	100 (19) prior MI	Warfarin, adjusted dose (n = 260) Placebo (n = 265)[f]	1.7	1.4-2.8	1.2-1.5	56
JAST Sato et al,[35] 2006 (Japan)	65 (NR)	258 (30)	NR	22 (2.5)	80 (9)	0	Aspirin, 150-200 mg/d (n = 426) Control (n = 445)	2.1	NA	NA	NA

Abbreviations: AFASAK, Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation; BAATAF, Boston Area Anticoagulation Trial for Atrial Fibrillation; CAD, coronary artery disease; CAFA, Canadian Atrial Fibrillation Anticoagulation; INR, international normalized ratio; JAST, Japan Atrial Fibrillation Stroke Trial; KQ, key question; MI, myocardial infarction; NA, not applicable; NR, not reported; PT, prothrombin time; RCT, randomized clinical trial; SPAF I, Stroke Prevention in Atrial Fibrillation I; SPINAF, Stroke Prevention in Nonrheumatic Atrial Fibrillation; TIA, transient ischemic attack; TTR, time in therapeutic range.

[a] Some studies reported baseline characteristics as percentages only; for such studies, numbers were calculated.

[b] Study reported median (rather than mean) age.

[c] Control group was allowed to take aspirin, and 46% of all patient-years in the control group were contributed by participants taking aspirin.

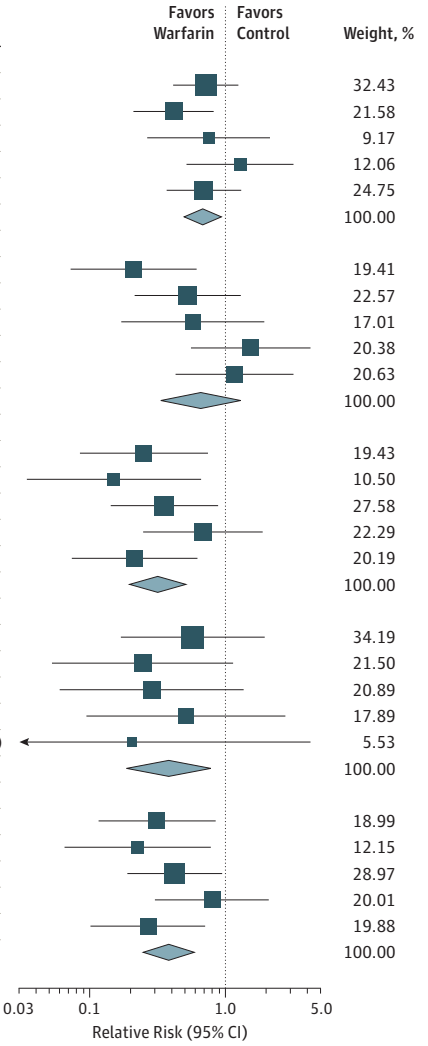
[d] Group 1 comprised anticoagulation candidates; group 2, nonanticoagulation candidates.

[e] For group 1 only.

[f] Study reported findings separately for patients with and without previous cerebral infarctions. Patients with previous cerebral infarction: warfarin (21) vs control (25).

Figure 4. Relative Risk of All-Cause Mortality and Selected Health Outcomes for Warfarin Compared With Controls (KQ4)

Source	Mean Follow-up, y	Target INR Range	No. of Individuals With Event/ Total No. of Individuals		Relative Risk (95% CI)	Weight, %
			Intervention	Control		
All-cause mortality						
AFASAK I,[29] 1989	1.2	2.8 to 4.2	20/335 (6.0)	28/336 (8.3)	0.72 (0.41-1.25)	32.43
BAATAF,[30] 1990	2.2	1.5 to 2.7	11/212 (5.2)	26/208 (12.5)	0.42 (0.21-0.82)	21.58
SPAF I,[31,32] 1991	1.3	2.0 to 4.5	6/210 (2.9)	8/211 (3.8)	0.75 (0.27-2.13)	9.17
CAFA,[33] 1991	1.3	2.0 to 3.0	10/187 (5.3)	8/191 (4.2)	1.28 (0.52-3.16)	12.06
SPINAF,[34] 1992	1.7	1.4 to 2.8	15/260 (5.8)	22/265 (8.3)	0.69 (0.37-1.31)	24.75
Subtotal (I^2 = 0.0%, P = .41)					0.68 (0.50-0.93)	100.00
Cardiovascular-related mortality						
AFASAK I,[29] 1989	1.2	2.8 to 4.2	4/335 (1.2)	19/336 (5.7)	0.21 (0.07-0.61)	19.41
BAATAF,[30] 1990	2.2	1.5 to 2.7	7/212 (3.3)	13/208 (6.3)	0.53 (0.22-1.30)	22.57
SPAF I,[31,32] 1991	1.3	2.0 to 4.5	4/210 (1.9)	7/211 (3.3)	0.57 (0.17-1.93)	17.01
CAFA,[33] 1991	1.3	2.0 to 3.0	9/187 (4.8)	6/191 (3.1)	1.53 (0.56-4.22)	20.38
SPINAF,[34] 1992	1.7	1.4 to 2.8	8/260 (3.1)	7/265 (2.6)	1.16 (0.43-3.17)	20.63
Subtotal (I^2 = 53.7%, P = .07)					0.66 (0.33-1.29)	100.00
All ischemic stroke						
AFASAK I,[29] 1989	1.2	2.8 to 4.2	4/335 (1.2)	16/336 (4.8)	0.25 (0.08-0.74)	19.43
BAATAF,[30] 1990	2.2	1.5 to 2.7	2/212 (0.9)	13/208 (6.3)	0.15 (0.03-0.66)	10.50
SPAF I,[31,32] 1991	1.3	2.0 to 4.5	6/210 (2.9)	17/211 (8.1)	0.35 (0.14-0.88)	27.58
CAFA,[33] 1991	1.3	2.0 to 3.0	6/187 (3.2)	9/191 (4.7)	0.68 (0.25-1.88)	22.29
SPINAF,[34] 1992	1.7	1.4 to 2.8	4/260 (1.5)	19/265 (7.2)	0.21 (0.07-0.62)	20.19
Subtotal (I^2 = 0.0%, P = .41)					0.32 (0.20-0.51)	100.00
Moderately to severely disabling stroke						
AFASAK I,[29] 1989	1.2	2.8 to 4.2	4/335 (1.2)	7/336 (2.1)	0.57 (0.17-1.94)	34.19
BAATAF,[30] 1990	2.2	1.5 to 2.7	2/212 (0.9)	8/208 (3.8)	0.25 (0.05-1.14)	21.50
SPAF I,[31,32] 1991	1.3	2.0 to 4.5	2/210 (1.0)	7/211 (3.3)	0.29 (0.06-1.37)	20.89
CAFA,[33] 1991	1.3	2.0 to 3.0	2/187 (1.1)	4/191 (2.1)	0.51 (0.09-2.75)	17.89
SPINAF,[34] 1992	1.7	1.4 to 2.8	0/260 (0.0)	2/265 (0.8)	0.20 (0.01- 4.23)	5.53
Subtotal (I^2 = 0.0%, P = .88)					0.38 (0.19-0.78)	100.00
All ischemic stroke or intracranial hemorrhage						
AFASAK I,[29] 1989	1.2	2.8 to 4.2	5/335 (1.5)	16/336 (4.8)	0.31 (0.12-0.85)	18.99
BAATAF,[30] 1990	2.2	1.5 to 2.7	3/212 (1.4)	13/208 (6.3)	0.23 (0.07-0.78)	12.15
SPAF I,[31,32] 1991	1.3	2.0 to 4.5	8/210 (3.8)	19/211 (9.0)	0.42 (0.19-0.94)	28.97
CAFA,[33] 1991	1.3	2.0 to 3.0	7/187 (3.7)	9/191 (4.7)	0.79 (0.30-2.09)	20.01
SPINAF,[34] 1992	1.7	1.4 to 2.8	5/260 (1.9)	19/265 (7.2)	0.27 (0.10-0.71)	19.88
Subtotal (I^2 = 0.0%, P = .46)					0.38 (0.25-0.59)	100.00



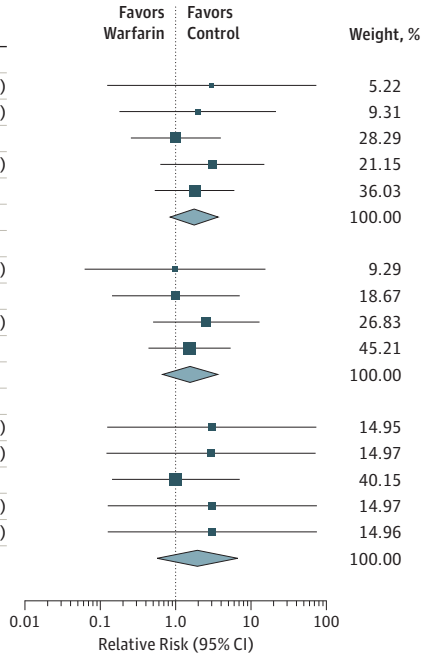
Weights are from random-effects meta-analysis; size of data markers indicates the weight of the study in the analysis. All-cause mortality: SPINAF includes only those without a history of stroke. For AFASAK, the figure includes data from a previously published meta-analysis that obtained data from the original study authors. AFASAK indicates Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation study; BAATAF, Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA, Canadian Atrial Fibrillation Anticoagulation; INR, international normalized ratio; SPAF I, Stroke Prevention in Atrial Fibrillation I; SPINAF, Stroke Prevention in Nonrheumatic Atrial Fibrillation.

moderately to severely disabling stroke (RR, 0.38 [95% CI, 0.19-0.78]; 5 trials, 2415 participants), compared with controls (**Figure 4**). For a population with baseline annual stroke risk of 4%, such as patients with $CHADS_2$ scores of 2, the results indicate that warfarin was associated with a number needed to treat of 24 (95% CI, 17-36) to prevent 1 ischemic stroke over 1.5 years. For a population of 1000 adults 65 years or older with an annual stroke risk of 4%, this translates to an absolute reduction of 28 ischemic strokes per year and an absolute reduction of 16 deaths per year.

Results of previously published systematic reviews were consistent with the findings of this review and provide some additional details about subgroups and about NOACs. An individual patient data meta-analysis reported that warfarin was associated with a reduction in stroke for both men and women, without a statistically significant difference between them (relative risk reduction, 60% [95% CI, 35%-76%] for men and 84% [95% CI, 55%-95%] for women).[39] Another individual patient data meta-analysis found that warfarin was associated with a reduced risk of ischemic stroke for all ages; for the assessment of relative benefit with increasing age, the interaction did not reach statistical significance (eg, HR, 0.22 [95% CI, 0.11-0.41] for 50-year-olds; HR, 0.53 [95% CI, 0.35-0.81] for 90-year-olds; P = .07 for age × warfarin interaction).[41] A previously published network meta-analysis that used 21 RCTs (96 017 participants) of treatment for nonvalvular atrial fibrillation found that vitamin K antagonists and all 4 NOACs were associated with lower risk of a primary composite outcome of stroke (any type) and systemic embolism (eTable 10 in the Supplement).[42] For the NOACs, the authors reported an association with a significant

Figure 5. Relative Risk of Major Bleeding, Major Extracranial Bleeding, and Intracranial Hemorrhage for Warfarin Compared With Controls (KQ5)

Source	Mean Follow-up, y	Target INR Range	No. of Individuals With Event/ Total No. of Individuals		Relative Risk (95% CI)	Weight, %
			Intervention	Control		
Major bleeding						
AFASAK I,[29] 1989	1.2	2.8 to 4.2	1/335 (0.3)	0/336 (0.0)	3.01 (0.12-73.60)	5.22
BAATAF,[30] 1990	2.2	1.5 to 2.7	2/212 (0.9)	1/208 (0.5)	1.96 (0.18-21.48)	9.31
SPAF I,[31,32] 1991	1.3	2.0 to 4.5	4/210 (1.9)	4/211 (1.9)	1.00 (0.25-3.96)	28.29
CAFA,[33] 1991	1.3	2.0 to 3.0	6/187 (3.2)	2/191 (1.0)	3.06 (0.63-14.99)	21.15
SPINAF,[34] 1992	1.7	1.4 to 2.8	7/260 (2.7)	4/265 (1.5)	1.78 (0.53-6.02)	36.03
Subtotal (I^2 = 0.0%, P = .87)					1.76 (0.85-3.66)	100.00
Major extracranial bleeding						
BAATAF,[30] 1990	2.2	1.5 to 2.7	1/212 (0.5)	1/208 (0.5)	0.98 (0.06-15.58)	9.29
SPAF I,[31,32] 1991	1.3	2.0 to 4.5	2/210 (1.0)	2/211 (0.9)	1.00 (0.14-7.07)	18.67
CAFA,[33] 1991	1.3	2.0 to 3.0	5/187 (2.7)	2/191 (1.0)	2.55 (0.50-13.00)	26.83
SPINAF,[34] 1992	1.7	1.4 to 2.8	6/260 (2.3)	4/265 (1.5)	1.53 (0.44-5.36)	45.21
Subtotal (I^2 = 0.0%, P = .88)					1.56 (0.67-3.62)	100.00
Intracranial hemorrhage						
AFASAK I,[29] 1989	1.2	2.8 to 4.2	1/335 (0.3)	0/336 (0.0)	3.01 (0.12-73.60)	14.95
BAATAF,[30] 1990	2.2	1.5 to 2.7	1/212 (0.5)	0/208 (0.0)	2.94 (0.12-71.85)	14.97
SPAF I,[31,32] 1991	1.3	2.0 to 4.5	2/210 (1.0)	2/211 (0.9)	1.00 (0.14-7.07)	40.15
CAFA,[33] 1991	1.3	2.0 to 3.0	1/187 (0.5)	0/191 (0.0)	3.06 (0.13-74.74)	14.97
SPINAF,[34] 1992	1.7	1.4 to 2.8	1/260 (0.4)	0/265 (0.0)	3.06 (0.13-74.71)	14.96
Subtotal (I^2 = 0.0%, P = .95)					1.94 (0.56-6.68)	100.00



Weights are from random-effects meta-analysis; size of data markers indicates the weight of the study in the analysis. Major bleeding: AFASAK did not specify bleeding 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 (21 for warfarin, 0 for placebo). BAATAF defines major bleeding as intracranial bleeding, fatal bleeding, or bleeding that led to a blood transfusion (≥4 units of blood within 48 hours). SPAF I defines major bleeding as bleeding that involved the central nervous system; management requiring hospitalization with transfusion, surgery, or both; or permanent residual impairment. CAFA defines major bleeding as life-threatening bleeding. SPINAF defines major bleeding as bleeding that required a blood transfusion, an emergency procedure, or removal of a hematoma or bleeding that led to intensive care unit admission. Intracranial hemorrhage: SPAF I events included 1 fatal intracerebral hemorrhage and 1 subdural hematoma with full recovery in the warfarin group and 2 subdural hematomas with full recovery in the placebo group. AFASAK indicates Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation; BAATAF, Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA, Canadian Atrial Fibrillation Anticoagulation; INR, international normalized ratio; RR, risk ratio; SPAF I, Stroke Prevention in Atrial Fibrillation I; SPINAF, Stroke Prevention in Nonrheumatic Atrial Fibrillation study.

reduction in the primary outcome compared with placebo or control (unadjusted ORs from 0.27-0.38; adjusted ORs from 0.32-0.44) but no statistically significant differences for the NOACs in comparison with one another. In adjusted analyses (for $CHADS_2$ scores, time in therapeutic range, duration of follow-up), the NOACs were not statistically different from vitamin K antagonists (eTable 10 in the Supplement).

Harms of Stroke Prevention Treatment

Key Question 5. What are the harms of anticoagulation or antiplatelet therapy in asymptomatic, screen-detected older adults with atrial fibrillation?

Key Question 5a. Do the harms of anticoagulation or antiplatelet therapy vary for subgroups defined by stroke risk, age, sex, or race/ethnicity?

All 6 RCTs described in KQ4 for benefits of warfarin or aspirin also reported harms (Table 2).[29-35] Seven systematic reviews (eTable 10 in the Supplement) were also included: 4 were traditional systematic reviews with meta-analyses,[36-38,43] 2 were individual patient data meta-analyses,[39,41] and 1 was a network meta-analysis.[42]

Warfarin treatment was associated with increased risk of major bleeding (RR, 1.8 [95% CI, 0.9-3.7]; 5 trials, 2415 participants), major extracranial bleeding (RR, 1.6 [95% CI, 0.7-3.6]; 4 trials, 1744 participants), and intracranial hemorrhage (RR, 1.9 [95% CI, 0.6-6.7]; 5 trials, 2415 participants) compared with controls, but confidence intervals were wide and differences between groups were not statistically significant (**Figure 5**). Across trials evaluating warfarin, 31 major bleeding events occurred, 20 in warfarin groups and 11 in control groups. Minor bleeding was much more common, with 136 events in warfarin groups and 86 in control groups over a mean of 1.6 years (pooled RR, 1.6 [95% CI, 1.2-2.0]; 4 trials, 1744 participants) (eFigure 1 in the Supplement).

Results of previously published systematic reviews were consistent with the findings of this review. The previously published network meta-analysis (96 017 participants) reported that the 4 NOACs were associated with an increased risk of major bleeding, but the confidence intervals were wide and differences between groups were not statistically significant (adjusted ORs from 1.4 to 2.2) (eTable 10 in the Supplement), and there were no statistically significant differences between any of the 4 NOACs.[42] Compared with vitamin K antagonists, 3 of the NOACs (apixaban, dabigatran, and edoxaban) were associated with a lower risk of bleeding (range of ORs from 0.64 [95% CI, 0.46-0.90] to 0.85 [95% CI, 0.65-1.1]), but the difference was only statistically significant for edoxaban (OR, 0.64 [95% CI, 0.46-0.90]).

Discussion

Table 3 provides the summary of findings. No eligible studies evaluated screening for atrial fibrillation with ECG compared with no screening and focused on health outcomes. One ongoing RCT, STROKESTOP, is designed to assess health outcomes for this comparison.[20,22] For harms of screening, no eligible studies provided information that allowed comparison between screening and no screening.

This review found that both 1-time systematic screening with 12-lead ECG and twice-weekly screening with a single-lead ECG identify more new cases of atrial fibrillation than no screening (absolute increase over 12 months, 0.6% [95% CI, 0.1%-0.9%] and 2.8% [95% CI, 0.9%-4.7%], respectively), but screening with ECG did not detect more cases than opportunistic screening with pulse palpation. REHEARSE-AF, STROKESTOP, and some uncontrolled studies[20,45,46] suggest that the number of new atrial fibrillation cases detected is greater with intermittent ECG recordings or continuous ECG recordings over 2 weeks than with a 1-time ECG.

Most asymptomatic older adults with previously unrecognized or undiagnosed atrial fibrillation have a stroke risk above the threshold for initiating anticoagulation (eContextual Question 2 in the Supplement). In STROKESTOP, more than 90% of patients with newly diagnosed atrial fibrillation were offered and accepted initiation of oral anticoagulant therapy.[20] The SAFE study reported that 78% of new cases identified with systematic screening had $CHADS_2$ scores of 1 or more and that 43% had scores of 2 or more.[23] If screening programs were implemented, they could be limited to persons 65 years or older who have CHA_2DS_2-VASc scores of 2 or higher to avoid screening persons for whom anticoagulation would not be indicated.

Potential harms of screening with ECG include misinterpretation of ECGs and subsequent treatments for persons without atrial fibrillation. Evidence suggests that some primary care physicians cannot accurately detect atrial fibrillation on an ECG.[25] For example, an analysis of 2595 participants from 49 general practices in central England participating in the SAFE study assessed the accuracy of general practitioners and interpretive software for diagnosing atrial fibrillation.[25] General practitioners misinterpreted (with or without the help of interpretive software) 8% of sinus rhythm cases as atrial fibrillation. The analysis did not evaluate the accuracy of primary care physicians for other ECG findings (eg, those suggesting ischemia) that might also lead to subsequent testing and interventions (eg, angiography) that could result in complications. Another study using a database from a US hospital that evaluated 2298 ECGs (from 1085 patients) with a computerized interpretation of atrial fibrillation 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 (8.5%).[47]

This review found consistent evidence that anticoagulation reduces the risk of stroke and all-cause mortality and increases the risk of bleeding for persons with nonvalvular atrial fibrillation who do not have a history of stroke or TIA. For a population of 1000 adults 65 years or older with an annual stroke risk of 4%, the results translate to an absolute reduction of 28 ischemic strokes per year, an absolute reduction of 16 deaths per year, and an absolute increase of 5 major bleeding events per year. A previously published network meta-analysis[42] included in this review found that NOACs were not statistically different from vitamin K antagonists for a composite outcome (any stroke and systemic embolism) or for all-cause mortality.

All 5 included trials that evaluated warfarin began in the 1980s and were completed by 1992, and stroke incidence may have decreased since then with the increased use of statins and antihypertensive medications. Thus, the absolute benefits of anticoagulation might be less in the current era, although the relative benefits are likely similar. The current clinical approach to anticoagulation has evolved since the trials were conducted. There is some uncertainty about the INR target ranges of 3 trials (BAATAF, SPAF I, and SPINAF) because these trials used prothrombin time targets, and conversion of prothrombin time to INR cannot be precisely achieved because of uncertain sensitivity of thromboplastin agents. In addition, trials followed protocols (eg, for warfarin dosing); routine clinical practice may not be as rigorous. However, observational studies of anticoagulation suggest that results are similar in routine clinical practice.[48] In addition, the trials that evaluated warfarin had a mean duration of follow-up from 1.2 to 2.2 years (mean, 1.5 years) and were stopped early; thus, estimates for stroke and mortality reduction may not be applicable to lifelong anticoagulation. Although the review aimed to determine the benefits of treatment for asymptomatic, screen-detected older adults with nonvalvular atrial fibrillation, no trials or systematic reviews that focused on this population were found, and it is uncertain whether benefits of anticoagulation vary between symptomatic persons and asymptomatic, screen-detected persons (eContextual Question 2 in the Supplement).

Limitations

This review has several limitations. First, it did not include the evidence regarding the diagnostic accuracy of screening tests for atrial fibrillation or the accuracy of a 12-lead ECG conducted and interpreted within primary care settings. A 2017 health technology assessment synthesized studies conducted in a variety of settings (eg, primary care, preoperative clinics, cardiology practices) that were related to diagnostic accuracy of ECG for atrial fibrillation.[49] Based on data from 7 studies, a 12-lead ECG interpreted by a nurse, general practitioner, or the ECG machine's automated algorithm had a sensitivity of 92.7% (95% CI, 85.9%-96.8%) and specificity of 97.4% (95% CI, 95.0%-98.9%) when compared with a reference standard of cardiologist interpretation. The authors derived these estimates from a hierarchical summary receiver operating characteristics curve. Across individual studies, sensitivity ranged from 68% to 100% and specificity ranged from 76% to 100%.

Second, this review did not include the evidence on rate control or rhythm control for atrial fibrillation. Briefly, rhythm control is not recommended for asymptomatic adults with atrial fibrillation. Some guidelines, including those of the American Heart Association/American College of Cardiology/Heart Rhythm Society, recommend rate control to achieve a resting heart rate under 110 beats per minute for asymptomatic patients with atrial fibrillation.[1]

Third, this review did not include head-to-head trials of treatments for atrial fibrillation because the intention was to provide evidence on benefits of treatments compared with placebo or no treatment rather than to assess the comparative effectiveness of

Table 3. Summary of Evidence for Screening With ECG for Atrial Fibrillation[a]

No. of Studies (No. of Participants)	Summary of Main Findings	Consistency and Precision	Limitations (Including Reporting Bias)	Strength of Evidence	Applicability
KQ1: Benefits of Screening					
1 RCT (n = 1001)	Study not designed or powered to evaluate health outcomes (designed for KQ2) Composite of stroke, TIA, or systemic embolism: 6 vs 10 events; HR, 0.6 (95% CI, 0.2-1.7)	Consistency unknown Imprecise	Moderate risk of measurement bias; lack of masking; reporting bias not detected	Insufficient	NA
KQ2: Identifying New Cases of AF					
3 RCTs (n = 18 804)	Systematic screening with 12-lead ECG identifies more new cases than no screening (absolute increase over 12 mo, 0.6% [95% CI, 0.1%-0.9%]),[b] as does twice-weekly screening with single-lead ECG (absolute increase over 12 mo, 2.8% [95% CI, 0.9%-4.7%]) No significant difference between systematic screening with ECG and opportunistic screening approaches focused on pulse palpation; risk differences were −0.02% (95% CI, −0.5% to 0.5%) and 0.3% (95% CI, −0.2% to 0.9%), respectively	Consistent[c] Imprecise	Allocation concealment was inadequate or not reported; limited reporting to allow assessment for baseline differences in 2 studies (reported only age and sex)[23-28]; potential ascertainment bias for previous AF diagnoses in 1 study (done by 1 person and masking to allocation was NR)[28]; moderate risk of ascertainment bias with lack of masking and uncertain workup to confirm AF in 1 study[19]; reporting bias not detected	Low	Adults 65 y or older without history of AF; questionable applicability to women
KQ3: Harms of Screening					
1 RCT (n = 2595 [false positives] and n = 1940 [anxiety])[d]	General practitioners misinterpreted 8% of sinus rhythm as AF (sensitivity, 79.8 [95% CI, 70.5-87.2]; specificity, 91.6 [95% CI, 90.1-93.1]) Mean anxiety scores were not significantly different for systematic and opportunistic screening	Consistency unknown (single study for each outcome) Precise	No anxiety data collected from no-screening group to allow comparison between screening and no-screening groups; reporting bias not detected	Low for false positives and anxiety; insufficient for other harms	Adults ≥65 y screened with an ECG
KQ4: Benefits of Treatment					
13 (6 RCTs, 7 systematic reviews) (n = 4531 [RCTs] and n = 108 942 [systematic reviews])	Warfarin treatment (mean, 1.5 y) was associated with reduced all-cause mortality (RR, 0.68 [95% CI, 0.50-0.93]) and ischemic stroke (RR, 0.32 [95% CI, 0.20-0.51]) compared with controls (5 trials, 2415 participants) Network meta-analysis (previously published[42]) found that all treatments (including all 4 NOACs) reduced the risk of a primary outcome (composite of any stroke and systemic embolism) and all-cause mortality: for NOACs, adjusted ORs ranged from 0.32-0.44 for the primary outcome compared with placebo or control[e,f]	Consistent Precise	All warfarin trials stopped early; 3/5 warfarin trials were open label; 4/5 warfarin trials had inadequate or unclear methods of allocation concealment Limitations of the network meta-analysis include (1) lack of sensitivity analyses removing studies with greater focus on secondary prevention, (2) limited ability to adjust for population characteristics (some older studies did not report $CHADS_2$ scores, so scores were estimated), and (3) heterogeneity of doses. Reporting bias not detected	Moderate	Adults with nonvalvular AF and no history of stroke or TIA; uncertain applicability to asymptomatic screen-detected people Most participants had AF for more than 1 y, and few had paroxysmal AF Warfarin trials were mean 1.5 y; lifelong estimates not available

(continued)

Table 3. Summary of Evidence for Screening With ECG for Atrial Fibrillation[a] (continued)

No. of Studies (No. of Participants)	Summary of Main Findings	Consistency and Precision	Limitations (Including Reporting Bias)	Strength of Evidence	Applicability
KQ5: Harms of Treatment					
13 (6 RCTs, 7 systematic reviews) (n = 4531 [RCTs] and n = 116 496 [systematic reviews])	Warfarin treatment (mean, 1.5-1.6 y) was associated with increased risk of major bleeding (RR, 1.8 [95% CI, 0.9-3.7]) and intracranial hemorrhage (pooled RR, 1.9 [95% CI, 0.6-6.7]) compared with controls, but confidence intervals were wide and differences between groups were not statistically significant (5 trials; 2415 participants) Network meta-analysis (previously published[42]) found that the 4 NOACs were associated with increased risk of bleeding compared with placebo or controls (adjusted ORs, 1.4-2.2); confidence intervals were wide, and differences between groups were not statistically significant[g]	Consistent Imprecise	Warfarin trials and network meta-analysis have the same limitations as listed for KQ4; reporting bias not detected	Moderate[h]	Adults with nonvalvular AF and no history of stroke or TIA

Abbreviations: AF, atrial fibrillation; $CHADS_2$, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke or transient ischemic attack or thromboembolism (doubled); ECG, electrocardiogram; HR, hazard ratio; KQ, key question; NA, not applicable; NOAC, novel oral anticoagulant; NR, not reported; OR, odds ratio; RCT, randomized clinical trial; RR, relative risk; TIA, transient ischemic attack.

[a] All studies in table were fair quality.

[b] Extrapolating to the US population of adults 65 years or older (estimated as 46 million in 2016[44]) suggests that 276 000 additional new cases would be identified if similar screening programs were implemented.

[c] Consistent when considering the studies described in Contextual Question 1 and considering that the results were consistent for systematic screening vs no screening when compared with those for opportunistic screening vs no screening.

[d] This was a subset of the 14 802 participants in the SAFE (Screening for Atrial Fibrillation in the Elderly) study. The number of participants may be slightly greater than 1940 because the study did not report the total number of unique individuals who completed the Spielberger 6-Item Anxiety Questionnaire (S6AQ), and it is unclear whether everyone in the baseline and end-of-study samples was also in the post-ECG screening sample. The study reported that 493 participants completed the baseline S6AQ, 1940 completed the postscreening S6AQ, and 535 returned the end-of-study S6AQ. The REHEARSE-AF (Assessment of Remote Heart Rhythm Sampling Using the AliveCor Heart Monitor to Screen for Atrial Fibrillation) study also reported some information about anxiety, but it was not included because those outcomes were rated poor quality because of high risk of measurement bias (for not using a valid and reliable measure and lack of masking).

[e] Apixaban, dabigatran, edoxaban, and rivaroxaban.

[f] The network meta-analysis also found no statistically significant differences for the 4 NOACs in comparison with one another. In adjusted analyses, the NOACs were not statistically different from vitamin K antagonists for the primary outcome or for all-cause mortality.

[g] The network meta-analysis also found no statistically significant differences for the 4 NOACs in comparison with one another. Compared with vitamin K antagonists, 3 of the NOACs (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 (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).

[h] Although findings were imprecise and quality was fair, strength of evidence was graded as moderate considering evidence on dose response (with higher INRs increasing bleeding risk), increased risk of minor bleeding, and treatment of other conditions showing consistent evidence of bleeding risk.

treatments. Nevertheless, the review summarized a previously published network meta-analysis that provides comparative effectiveness estimates.

To better understand the potential benefits and harms of systematic screening for atrial fibrillation with ECG, randomized trials of asymptomatic persons that directly compare systematic screening with usual care and assess health outcomes are needed. The ongoing STROKESTOP study may help fill this evidence gap. Other relevant ongoing RCTs are focused on detecting atrial fibrillation (KQ2) as the primary outcome; these include SCREEN-AF,[18] IDEAL-MD,[50] mSToPS,[51] and D_2AF.[52]

Conclusions

Although screening with ECG can detect previously unknown cases of atrial fibrillation, it has not been shown to detect more cases than screening focused on pulse palpation. Treatments for atrial fibrillation reduce the risk of stroke and all-cause mortality and increase the risk of bleeding, but trials have not assessed whether treatment of screen-detected asymptomatic older adults results in better health outcomes than treatment after detection by usual care or after symptoms develop.

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Concept and design: Jonas, Kahwati, Asher.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Jonas, Yun, Middleton, Coker-Schwimmer, Asher.
Critical revision of the manuscript for important intellectual content: Jonas, Kahwati, Yun, Coker-Schwimmer, Asher.
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