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Screening for Atrial Fibrillation With Electrocardiography: An Evidence Review for the U.S. Preventive Services Task Force

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The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information (i.e., in the context of available resources and circumstances presented by individual patients).

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Structured Abstract

Purpose: To systematically review the evidence on screening for and stroke prevention treatment of nonvalvular atrial fibrillation (AF) in adults age 65 years or older for populations and settings relevant to primary care in the United States.

Data Sources: PubMed/MEDLINE, the Cochrane Library, and trial registries through May 24, 2017; reference lists of retrieved articles; outside experts; and reviewers, with surveillance of the literature through June 2017.

Study Selection: Two investigators selected English-language studies using a priori criteria. Eligible studies included controlled trials of screening for or treatment of AF, controlled prospective cohort studies evaluating detection rates of previously unknown AF or harms of screening or treatment, and systematic reviews of trials evaluating benefits or harms of treatment. Eligible screening tests included electrocardiogram (ECG) screening (e.g., 12-lead ECG, intermittent handheld ECG) or screening with both pulse palpation and ECG for all participants. Eligible treatment studies compared warfarin, aspirin, or novel oral anticoagulants (NOACs: apixaban, dabigatran, edoxaban, or rivaroxaban) with placebo or no treatment. Studies focused on persons younger than age 65 or those with a history of stroke, transient ischemic attack, known heart disease, or heart failure were excluded.

Data Extraction: One investigator extracted data and a second checked accuracy. Two reviewers independently rated quality for all included studies using predefined criteria.

Data Synthesis: Sixteen unique studies (described in 21 publications) were included. No eligible studies evaluated screening compared with no screening and reported health outcomes. Screening with 12-lead ECG identified more new cases of AF than usual care (absolute increase, 0.6% [0.2% to 0.98%] over 12 months), but a systematic approach using ECG did not detect more cases than an opportunistic approach focused on pulse palpation. Warfarin treatment for an average of 1.5 years was associated with a reduced risk of ischemic stroke (pooled relative risk [RR], 0.32 [0.20 to 0.51]) and all-cause mortality (pooled RR, 0.68 [0.50 to 0.93]), and an increased risk of major bleeding (pooled RR, 1.8 [0.85 to 3.7]) compared with controls (5 trials; 2,415 participants). Trial participants were not screen-detected; mean age was 67 to 74 years; very few had a history of TIA or stroke (3%-8%); most had long-standing persistent AF; and baseline stroke risk scores were not reported. For a population of 1,000 adults age 65 or older with an annual stroke risk of 4 percent, this translates to an absolute reduction of 28 ischemic strokes and 16 deaths per year and an absolute increase of five major bleeding events per year. Aspirin treatment for an average of 1.5 years was associated with a reduced risk of ischemic stroke (pooled RR, 0.76 [0.52 to 1.1]) and all-cause mortality (pooled RR, 0.84 [0.62 to 1.14]) compared with controls, but the differences were not statistically significant (3 trials; 2,663 participants). A network meta-analysis found that all treatments reduced the risk of a composite outcome (any stroke and systemic embolism) and all-cause mortality. For NOACs, it found statistically significant associations with reduction in the composite outcome compared with placebo/control (adjusted odds ratios [ORs] from 0.32 to 0.44), and an increased risk of bleeding compared with placebo/control (adjusted ORs from 1.38 to 2.21), but confidence intervals for the risk of bleeding were wide and differences between groups were not statistically significant.

Limitations: This review is limited in the ability to describe the direct evidence on the effectiveness or harms of screening for AF because we identified no eligible studies addressing the overarching question. For potential harms of screening (e.g., overdiagnosis from misinterpretation of ECGs, subsequent interventions leading to harms), no eligible studies provided information that allowed comparison between screening and no-screening. No eligible stroke prevention treatment studies focused on asymptomatic, screen-detected participants. The included trials that evaluated warfarin benefits and harms had an average of 1.5 years of followup and were stopped early. Estimates for benefits and harms of lifelong anticoagulation and for screen-detected persons were not available.

Conclusions: There is uncertainty about the benefits and harms of screening for AF with ECG. Although screening with ECG can detect previously unknown cases of AF, it has not been shown to detect more cases than opportunistic screening that is focused on pulse palpation. Most older adults with previously unknown AF have a stroke risk above the threshold for anticoagulation. Multiple treatments for AF 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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Chapter 1. Introduction

Scope and Purpose

The U.S. Preventive Services Task Force (USPSTF) will use this report to inform a recommendation on the topic of screening asymptomatic adults for atrial fibrillation (AF) using an electrocardiogram (ECG). The USPSTF has not previously made a recommendation on AF. This report systematically evaluates the current evidence on screening for and treatment of AF for populations and settings relevant to primary care in the United States.

Condition Definition

AF is a supraventricular tachyarrhythmia characterized by uncoordinated electrical activity and resulting inefficient atrial contraction.[1] On an ECG, AF has the following features: (1) R-R intervals (intervals from the onset of one R wave to the onset of the next one, one complete cardiac cycle) are "irregularly irregular" (i.e., they follow no repetitive pattern) and (2) there are no distinct repeating P waves (the waves on an ECG associated with atrial depolarization), although atrial electrical activity (fibrillatory f waves) may be seen in some leads.[2] Clinically helpful labels include paroxysmal, persistent, permanent, and nonvalvular (**Table 1**).

Etiology and Natural History

A number of disease pathways and mechanisms can cause structural or electrophysiological abnormalities that alter the atrial tissue, resulting in AF. Underlying heart disease (e.g., ischemic heart disease, valvular heart disease, cardiomyopathies, heart failure) can lead to inflammation, fibrosis, and hypertrophy in the atrial architecture, leading to increased left atrial pressure with subsequent atrial dilation and changes in wall stress.[3, 4] Multiple electrophysiological mechanisms may contribute to the initiation and perpetuation of AF in an individual with an anatomical vulnerability; the natural history of the condition generally involves a gradual worsening over time.[5, 6] Factors such as suboptimal ventricular rate control, loss of atrial contraction, variability in ventricular filling, and sympathetic activation can lead to the adverse hemodynamic effects of AF, resulting in reduced cardiac output with potential for fatigue, palpitations, dyspnea, hypotension, syncope, or heart failure.[7-9] However, some patients have silent AF, with no obvious symptoms relevant to the disease.[10] Persons may attribute mild symptoms (e.g., fatigue) to other causes.

Before widespread anticoagulant use, AF was associated with a fivefold increase in the risk of stroke, after adjustment for other factors.[11] AF reduces cardiac blood flow; along with changes in blood composition involving platelets, other coagulatory proteins, and inflammatory cytokines, a reduction in cardiac blood flow predisposes patients to thrombus formation (particularly in the left atrial appendage) and confers an increased risk of stroke and systemic thromboembolism.[12] Although earlier studies suggest similar risks of stroke for persons with paroxysmal AF compared with those who have persistent or permanent AF,[13-16] more recent studies show lower risk for those with paroxysmal AF.[17-23] For example, a recent randomized, controlled trial (RCT) comparing edoxaban with warfarin (21,105 participants in 46 countries) found lower mean annual rates of stroke or systemic embolism (the primary efficacy outcome) for those with

paroxysmal AF than those with persistent AF or permanent AF over a median of 2.8 years of followup (1.49% vs. 1.83% vs. 1.95%, $p<0.05$ for both comparisons with paroxysmal AF).[17, 18]

Increasing age is an independent predictor of stroke in persons with AF, associated with an increased risk of about 1.5 percent per decade; the annual stroke incidence increases from 1.3 percent in those ages 50 to 59 years to 5.1 percent in those ages 80 to 89 years.[24] Strokes due to AF are associated with a poor prognosis as measured by both 28-day and 3-month mortality, disability, and discharge to institution rather than home.[25-27] Approximately 30 percent of AF patients die within 1 year of a stroke, and up to 30 percent of survivors are permanently disabled.[28]

Risk Factors

Risk factors for AF include diabetes, previous cardiothoracic surgery, smoking, prior stroke, age, underlying heart disease, hypertension, sleep apnea, obesity, alcohol/drug use, and hyperthyroidism.[29] Models for predicting the risk of future AF have been developed from several large longitudinal study cohorts,[30] including the Atherosclerosis Risk in Communities Study[31] and the Framingham Heart Study, and externally validated in additional population-based cohorts.[30] An externally validated risk prediction model derived from the Atherosclerosis Risk in Communities Study, Cardiovascular Health Study, and Framingham Heart Study cohorts includes age, race, height, weight, systolic and diastolic blood pressure, current smoking, use of antihypertensive medication, diabetes, and history of myocardial infarction and heart failure as predictors of future AF risk.[31, 32]

Prevalence and Burden

AF is the most common arrhythmia. Prevalence increases with age, from less than 0.2 percent for those younger than age 55 years to about 10 percent for those age 85 years or older, and is higher for men than women (**Appendix A Table 1**).[33] In 2013, the estimated prevalence was 8.3 percent for U.S. Medicare beneficiaries.[34] About 25 percent of AF is paroxysmal;[35] however, assessing the prevalence of AF—particularly paroxysmal AF—is challenging because episodes may be brief and undetected.[36]

In 2011, AF was mentioned in the death certificates of 116,247 persons in the United States and was listed as the underlying cause of death in 17,729 cases. The National Center for Health Statistics reported 479,000 hospitalizations in 2010 with AF as the primary diagnosis. According to Medicare and MarketScan databases from 2004–2006, persons with AF are approximately twice as likely to be hospitalized as age- and sex- matched control individuals (37.5 vs. 17.5%). This analysis also revealed that care for AF adds approximately $8,700 per year to the cost of a patient's health care and accounts for $26 billion in U.S. health care expenditures annually.[37]

Rationale for Screening and Screening Strategies

Because patients may not notice any symptoms of AF before a serious first event, such as stroke, identifying asymptomatic persons for treatment may reduce risk for future morbidity and mortality. Of patients who have a stroke because of AF, it is estimated that 20 percent or more are diagnosed with AF at the time of the stroke or shortly thereafter.[38-40] For subclinical AF,

screening with ECG could identify patients with asymptomatic AF who might benefit from treatment to reduce the risk for thromboembolic events, reduce frequency or severity of future symptoms related to AF, and reduce overall mortality.

To characterize the potential yield of screening for AF with ECG or pulse palpation, a 2013 systematic review found an overall incidence of screen-detected, previously unknown AF of 1 percent (95% confidence interval [CI], 0.89% to 1.04%; 14 studies, 67,772 participants) and an incidence of 1.4 percent (95% CI, 1.2% to 1.6%; 8 studies, 18,189 participants) for those age 65 years or older.[41] However, the review did not require studies to have control groups, so it may have overestimated the added yield beyond usual medical care.

Screening for AF could potentially use a variety of approaches, including 12-lead ECG, devices that record fewer than 12 leads (including handheld ECG), pulse oximetry, ambulatory pulse monitors, consumer-directed devices (e.g., smartphone applications), or pulse palpation. A 2015 systematic review evaluated the accuracy of methods for identifying an irregular pulse and found that pulse palpation had the lowest accuracy among various methods, largely because of its lower specificity.[42] Health care professionals, including medical assistants, nurses, and physicians, routinely perform pulse measurement and/or palpation using automated or manual approaches during routine or acute care encounters, which is sometimes referred to as "opportunistic screening" (and this approach could be considered usual medical care). When an irregular pulse is detected during usual medical care, a diagnostic evaluation that includes a standard 12-lead ECG typically is performed and may result in AF case-finding. This approach assumes that the patient is in AF at the time of the 12-lead ECG and may not identify patients with paroxysmal AF. Further, some patients have tremors or other rate or rhythm disturbances that make interpretation of ECG challenging.[43]

Treatment Approaches

Oral anticoagulant medications can prevent thromboembolic events in AF patients by reducing the formation of clots in the left atrium or atrial appendage.[44] Oral anticoagulants to prevent stroke and reduce all-cause mortality in persons with AF include warfarin (a vitamin K antagonist) and the newer target-specific anticoagulants, direct thrombin and Factor Xa inhibitors.[1] Dabigatran etexilate (Pradaxa) is the only currently available oral direct thrombin inhibitor in the United States. Oral Factor Xa inhibitors include apixaban (Eliquis), edoxaban (Savaysa), and rivaroxaban (Xarelto).[1] Reviews of current global treatment practices for stroke prevention in AF, including those in the United States, reported underuse of anticoagulation and antiplatelet therapy in AF patients at every level of stroke risk.[45, 46] Aspirin, an antiplatelet agent, might be considered as a treatment option for persons with AF who have a low risk of stroke (i.e., those who do not warrant anticoagulation).

Randomized trials have shown anticoagulant therapies to be more effective than antiplatelet therapies in reducing stroke; however, their use is associated with an increased risk of bleeding.[47, 48] Individualized assessment of the balance of potential benefits (i.e., risk reduction in stroke or embolism) versus potential harms (i.e., risk increase in major bleeding) is recommended when choosing a therapeutic strategy. Validated risk prediction tools (**Appendix A Tables 2** and **3**) for stroke risk (e.g., the Congestive heart failure, Hypertension, Age ≥75 years [doubled], Diabetes mellitus, prior Stroke or TIA or thromboembolism [doubled], Vascular

disease, Age 65-74 years, Sex category [CHA_2DS_2-VASc] score) and bleeding risk (e.g., HAS-BLED, $HEMORR_2HAGES$[1]) have been developed to aid in this assessment, which is complicated because many risk factors for anticoagulation-related bleeding are also risk factors for stroke in patients with AF.

A U.S. Food and Drug Administration–approved device, the WATCHMAN™, offers a nonpharmacologic alternative to oral anticoagulation.[49] In patients with nonvalvular AF at increased risk for embolism (based on the Congestive heart failure, Hypertension, Age≥75 years, Diabetes mellitus, prior Stroke or TIA or thromboembolism [$CHADS_2$] or CHA_2DS_2-VASc scores) and eligible for treatment with warfarin, this catheter-delivered heart implant is designed to reduce the risk of thromboembolism by closing off the left atrial appendage.

Therapies for rate or rhythm control are also routinely used in clinical practice, primarily to prevent and treat hemodynamic consequences of AF. Rate control therapies include beta blockers and nondihydropyridine calcium channel blockers. When pharmacologic therapy is inadequate to control symptoms, atrioventricular (AV) nodal ablation with ventricular pacing is an option. Rhythm control strategies (i.e., direct current or pharmacologic cardioversion or radiofrequency catheter ablation) may be appropriate for select persons (e.g., persons who have persistent symptoms, are not able to achieve rate control, or are young[1]); however, RCTs have not demonstrated a mortality benefit for rhythm control over rate control strategies.[50, 51] Neither rate nor rhythm control of AF is intended to prevent strokes.

Recommendations and Clinical Practice in the United States

In recent years, several U.S. and international professional organizations have issued recommendations for managing AF and preventing stroke (**Appendix A Table 4**). A few organizations recommended screening for AF in selected patients using pulse palpation followed by ECG as appropriate. The 2014 guidelines from the American Heart Association and the American Stroke Association recommended conducting active screening in older adults.[52, 53] Guidelines from both the European Society of Cardiology and the Royal College of Physicians of Edinburgh (one of the founding groups of the Scottish Intercollegiate Guidelines Network [SIGN]) recommended opportunistic screening for persons age 65 years or older.[54, 55] All of the guidelines recommending screening for AF state that screening should be performed using pulse palpation and the diagnosis confirmed using ECG; no recommendations are given for screening frequency.[53-55] The 2010 guidelines from the American College of Cardiology Foundation and American Heart Association stated that ECG was reasonable for cardiovascular risk assessment (not specific to AF) in asymptomatic adults with hypertension or diabetes.[56]

Professional organizations have consistently recommended the use of risk prediction tools to guide the appropriate use of therapy in patients with AF. Recent guidelines recommend using the CHA_2DS_2-VASc score. In general, guidelines recommend no antithrombotic therapy or antiplatelet therapy for those at lowest risk of stroke (CHA_2DS_2-VASc score=0) and recommend anticoagulant therapy for those at high risk (CHA_2DS_2-VASc score≥2). Recent guidelines are mixed in their recommendations for those with a CHA_2DS_2-VASc score of 1, with some recommending anticoagulant therapy[57-59] and others recommending treatment based on risk and patient preference.[1, 54, 60] Older guideline recommendations based on the $CHADS_2$ score differ somewhat in their recommendations.[61-64]

Chapter 2. Methods

Key Questions and Analytic Framework

The Evidence-based Practice Center (EPC) investigators, USPSTF members, and Agency for Healthcare Research and Quality (AHRQ) Medical Officers developed the scope and key questions (KQs). **Figure 1** shows the analytic framework and KQs that guided the review. Five KQs were developed for this review:

1. Does screening for atrial fibrillation with ECG improve health outcomes (i.e., reduce all-cause mortality or reduce morbidity or mortality from stroke) in asymptomatic older adults? 1.a. Does improvement in health outcomes vary for subgroups defined by stroke risk (e.g., 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? 3.a. Do the harms of screening vary for subgroups defined by stroke risk (e.g., 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? 4.a. Do the benefits of anticoagulation or antiplatelet therapy vary for subgroups defined by stroke risk (e.g., 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? 5.a. Do the harms of anticoagulation or antiplatelet therapy vary for subgroups defined by stroke risk (e.g., based on CHA_2DS_2-VASc score), age, sex, or race/ethnicity?

In addition to our KQs, we looked for evidence related to three contextual questions that focused on the prevalence of previously unrecognized or undiagnosed AF among asymptomatic adults by age, the stroke risk in asymptomatic older adults with previously unrecognized or undiagnosed AF, and the recommendations on and frequency of use of rate or rhythm control treatments for AF in asymptomatic adults ages 65 years and older. These contextual questions were not a part of our systematic review. They are intended to provide additional background information. Literature addressing these questions is summarized in **Appendix A**.

Data Sources and Searches

We searched PubMed/MEDLINE and the Cochrane Library for English-language articles published through May 24, 2017. We used Medical Subject Headings as search terms when available and keywords when appropriate, focusing on terms to describe relevant populations, tests, interventions, outcomes, and study designs. Complete search terms and limits are detailed in **Appendix B-1**. We conducted targeted searches for unpublished literature by searching ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform. To supplement electronic searches, we reviewed the reference lists of pertinent review articles and studies that met our inclusion criteria, and we added all previously unidentified relevant articles. We will review all literature suggested by peer reviewers or public comment respondents and incorporate eligible studies into the final review. We will also conduct literature

surveillance through article alerts and targeted searches of high-visibility journals to identify studies published in the interim that may affect conclusions.

Study Selection

We developed inclusion and exclusion criteria for populations, interventions, comparators, outcomes, settings, and study designs with input from the USPSTF (**Appendix B-2**). We included English-language studies focused on adults ages 65 years or older conducted in countries categorized as "very high" on the Human Development Index. We excluded studies focused on children, adolescents, adults younger than age 65, and adults with a history of stroke or transient ischemic attack (TIA).

For KQs 1 (direct evidence that screening improves health outcomes), 2 (detection of undiagnosed AF), and 3 (harms of screening), we required studies to enroll unselected or explicitly asymptomatic older adults or those selected for increased risk of nonvalvular AF (e.g., those with obesity, smoking, alcohol use, or hypertension). Studies of mixed asymptomatic and symptomatic populations were eligible if the results were reported separately for asymptomatic adults or if less than 10 percent of the sample was symptomatic. We tracked whether any studies were excluded because of the 10 percent threshold so that we could conduct sensitivity analyses by adding studies in which 10 to 50 percent of the population was symptomatic; however, no such studies were identified. Studies consisting of mostly symptomatic adults, those with a known history of AF, and those with mitral valve disease or repair/replacement were not eligible. Eligible screening tests for KQs 1, 2, and 3 included systematic ECG screening (e.g., in-office, single-application 12-lead ECG, continuous ECG, intermittent use of handheld ECG) or systematic screening with both pulse palpation and ECG for all participants in a given study. We excluded studies whose interventions were limited to physical examination (including pulse palpation), blood pressure monitoring, pulse oximetry, and all other technologies (e.g., consumer devices, such as smartphones). Eligible comparisons included screened versus nonscreened groups and systematic screening versus usual care (which may include opportunistic screening; i.e., pulse palpation, automated blood pressure measurement, or cardiac auscultation during the course of a physical examination, or examination for another reason, with subsequent ECG if an irregular heart beat or pulse is noted). For KQ 1, RCTs and controlled clinical trials were eligible. For KQs 2 and 3, prospective cohort studies were also eligible.

For KQs on benefits (KQ 4) and harms (KQ 5) of treatment, we excluded studies of adults with known heart disease, heart failure, and/or previous stroke or TIA. Eligible studies compared medical treatment with aspirin or oral anticoagulants (warfarin, apixaban, dabigatran, edoxaban, or rivaroxaban) versus no treatment (with or without placebo). We excluded all nonpharmacologic treatments and forms of treatment or management of AF for reasons other than prevention of stroke (e.g., rate or rhythm control, cardioversion, ablation). RCTs and controlled clinical trials of older adults with AF were eligible. Systematic reviews of trials were also eligible if they were directly relevant (i.e., met our eligibility criteria, focused on primary prevention studies, included the relevant aspirin or oral anticoagulant trials, and had not been updated). **Appendix D Table 7** details our assessment of the relevance of potentially eligible systematic reviews. For KQ 5, prospective cohort studies were also eligible.

Two investigators independently reviewed titles and abstracts; those marked for potential inclusion by either reviewer were retrieved for evaluation of the full text. Two investigators independently reviewed the full text to determine final inclusion or exclusion. Disagreements were resolved by discussion and consensus.

Quality Assessment and Data Abstraction

For each included study, one investigator extracted pertinent information about the methods, populations, interventions, comparators, outcomes, timing, settings, and study designs. A second team member reviewed all data extractions for completeness and accuracy.

We assessed the quality of studies as good, fair, or poor, using predefined criteria developed by the USPSTF and adapted for this topic (**Appendix B-3**). Two independent investigators assigned quality ratings for each study. Disagreements were resolved by discussion. We included only studies with good or fair quality.

Data Synthesis and Analysis

We qualitatively synthesized findings for each KQ by summarizing the characteristics and results of included studies in tabular and narrative format. To determine whether meta-analyses were appropriate, we assessed the clinical and methodological heterogeneity of the studies following established guidance.[65] We qualitatively assessed the populations, tests, treatments, comparators, outcomes, and study designs, looking for similarities and differences.

For KQs 4 and 5, when at least three 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.[66] We calculated relative risks and 95 percent CIs for all-cause mortality, cardiovascular-related mortality, all ischemic stroke, moderately to severely disabling stroke, TIA, major bleeding, major extracranial bleeding, intracerebral hemorrhage, minor bleeding, and a composite outcome of all ischemic stroke or intracerebral hemorrhage. Results for the composite outcome, which includes a benefit and a harm, are provided in KQ 4. Statistical significance was assumed when 95 percent CIs of pooled results did not cross the null. All testing was two-sided. For all quantitative syntheses, the I^2 statistic was calculated to assess statistical heterogeneity in effects between studies.[67, 68] An I^2 from 0 to 40 percent might not be important; 30 to 60 percent may represent moderate heterogeneity; 50 to 90 percent may represent substantial heterogeneity; and 75 percent or greater represents considerable heterogeneity.[69] We conducted sensitivity analyses by adding one trial rated as poor quality that evaluated aspirin.[70] The results of the sensitivity analyses are provided in appendices of this report; estimates of effect were similar to main analyses, and statistical significance (or lack thereof) did not change. Quantitative analyses were conducted using Comprehensive Meta-Analysis version 3.3 (Biostat, Inc.) and Stata version 14 (StataCorp).

Expert Review and Public Comment

A draft report was reviewed by content experts, representatives of Federal partners, USPSTF members, and AHRQ Medical Officers and was revised based on comments, as appropriate. It will also be posted for public comment.

USPSTF Involvement

This review was funded by AHRQ. AHRQ staff and members of the USPSTF participated in developing the scope of work and reviewed draft reports, but the authors are solely responsible for the content.

Chapter 3. Results

Literature Search

We identified 4,120 unique records and assessed 388 full-text articles for eligibility (**Figure 2**). We excluded 367 studies for various reasons, detailed in **Appendix C** and included 16 unique studies (described in 21 publications) of good or fair quality. Of the included studies, two RCTs (described in 6 publications) addressed detection of previously undiagnosed AF (KQ 2), and one of those two (described in 5 publications) was also included for KQ 3 (harms of ECG screening). Six RCTs (described in 7 publications) and eight systematic reviews addressed the benefits (KQ 4) and/or harms (KQ 5) of anticoagulation or antiplatelet therapy. We identified no eligible studies for KQ1 (direct evidence of screening). Details of quality assessments of included studies and studies excluded because of poor quality are in **Appendix D Tables 1-6.**

Results by Key Question

Key Question 1. Does screening for AF with ECG improve health outcomes (i.e., reduce all-cause mortality or morbidity or mortality from strokes) in asymptomatic older adults?

We found no eligible studies that have addressed this question and reported results. We identified one RCT, the STROKESTOP Study, that is currently ongoing and has not yet reported results for the outcomes and comparisons eligible for our review.[71-73] The primary outcome listed in clinicaltrials.gov is reduced incidence of stroke among 75-year-old subjects, with a planned time frame of 5 years (and interim analysis after 3 years). The estimated study completion date is March 2019.[73] The STROKESTOP study randomized 28,768 persons ages 75 to 76 years in two regions in Sweden to screening program invitations for AF or to no invitations. More than half of those invited (53.8%) participated in the screening. The screening program used an initial ECG and then a handheld one-lead ECG recorder for intermittent recordings over 2 weeks (average of 26 completed recordings per participant). The handheld recorder uses an integrated mobile transmitter to send 30-second ECG strips to a database. Participants were instructed to place their thumbs on the device twice daily and whenever they noticed palpitations. The detection rate for previously unknown AF was 3 percent (95% CI, 2.7 to 3.5; 218/7,173 participants) in the intervention group; incidence data for AF in the control group has not yet been reported. Of the new cases detected in the intervention group, few of them were identified on the initial ECG (37/218=17%). More than 90 percent of the new cases of AF accepted initiation of oral anticoagulant therapy.

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

Characteristics of Included Trials

We included two fair-quality RCTs (described in 6 articles).[74-79] The characteristics of the

included studies are summarized in **Table 2**, and the results are summarized in **Table 3**. Both trials compared systematic screening with opportunistic screening (i.e., opportunistic case finding); one also included a comparison with no screening. The Screening for Atrial Fibrillation in the Elderly (SAFE) study was a multicenter cluster randomized trial (14,802 participants) that randomized 50 primary care practices to screening versus no screening.[74-78] Within the 25 practices randomized to screening, individual participants were randomized to systematic screening or opportunistic screening. Those in the systematic screening arm were invited by mail to attend a nurse-led screening clinic where their radial pulse was palpated, and a 12-lead ECG was performed. For those in the opportunistic arm, paper or computer flags were placed in their notes to encourage pulse recording; those with an irregular pulse were invited to attend a screening clinic and have a 12-lead ECG. For the screening practices, primary care physicians and other members of the health care team attended educational days covering the importance of detecting AF and available treatment options. The other trial randomized 3,001 participants from four primary care practices to systematic screening or opportunistic screening.[79] Those in the systematic screening arm were invited by mail to attend a nurse-led screening clinic where their radial pulse was palpated and a lead II rhythm strip was performed. Those unable to attend the clinic were offered screening at home. For those in the opportunistic arm, a reminder flag was placed in their notes. Nurses or physicians who assessed the pulse during routine care of the patient were asked to indicate on the flag whether the pulse was suspicious of AF and whether they wished to investigate further with an ECG. Nurses conducting screenings received 2 hours of training in the clinical assessment of the pulse rhythm.

Both trials were conducted in the United Kingdom. Followup lasted 12 months for the SAFE study and 6 months for the other trial. Both enrolled patients age 65 years and older; the mean age of participants was about 75 years in both trials. More than half of participants were women in both (57% to 59%). Neither trial reported information about the race or ethnicity of participants. Neither study reported the baseline prevalence of hypertension, diabetes, heart failure, or heart valve disease, or the proportion of participants with a history of TIA or stroke. Neither study reported baseline stroke risk scores (e.g., $CHADS_2$) for participants, but the SAFE study reported the $CHADS_2$ scores for the 149 newly identified cases of AF.[75] More cases in the systematic screening arm had scores of 2 or more than in the opportunistic arm, but the difference was not statistically significant (43.2% [95% CI, 32.6% to 54.6%] vs. 29.3% [20.2% to 40.4%], p=0.077).

Results of Included Trials

Neither study followed patients over time to report health outcomes such as mortality or strokes; both focused on detection of AF. Neither study found a significant difference between systematic and opportunistic screening for detection of new cases of AF (**Figure 3** and **Table 3**). The SAFE study reported about a 60 percent increase in the odds of detecting new cases with either screening approach compared with no screening (**Figure 3** and **Table 3**).

The SAFE study reported that more new cases of AF were detected in those undergoing screening (systematic or opportunistic) than in the no screening group (149 vs. 47; 1.63% vs. 1.04%; odds ratio [OR], 1.58 [95% CI, 1.12 to 2.22]). There was no difference in detection of new cases between opportunistic and systematic screening groups (75 vs. 74; 1.64% vs. 1.62%; OR, 0.99 [95% CI, 0.7 to 1.4]). The trial that used lead II rhythm strips found no statistically significant difference between systematic and opportunistic screening groups, although there

were few new cases and the CI was wide (12 vs. 7; 0.8% vs. 0.5%; OR, 1.7 [95% CI, 0.7 to 4.4]).

The SAFE study reported subgroup analyses by sex and age for systematic or opportunistic screening compared with no screening. The subgroup analyses show that screening may not increase detection of new cases among women. Men in the systematic (44 vs. 16; OR, 2.68 [95% CI, 1.52 to 4.73]) and opportunistic screening groups (38 vs. 16; OR, 2.33 [95%, 1.30 to 4.15]) had greater odds of having AF diagnosed than men in the no screening group. The odds were not significantly increased for women in either screening group compared with no screening (30 vs. 31; OR, 0.98 [95% CI, 0.59 to 1.61] and 37 vs. 31; OR, 1.20 [95% CI, 0.74 to 1.92], respectively). Patients ages 65 to 74 years and those older than 75 had similar odds of having AF diagnosed in both the systematic screening (30 vs. 18; OR 1.62 [95% CI, 0.91 to 2.88] and 44 vs. 29; OR, 1.56 [95% CI, 0.98 to 2.49], respectively) and opportunistic screening arms (31 vs. 18; OR, 1.63 [95% CI, 0.92 to 2.89] and 44 vs. 29; OR, 1.60 [95% CI, 1.00 to 2.56], respectively), compared with no screening.

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

3a. Do the harms of screening vary for subgroups defined by stroke risk (e.g., based on CHA_2DS_2-VASc score), age, sex, or race/ethnicity?

We identified no eligible studies assessing labeling or harms of subsequent procedures or interventions initiated because of screening with ECG (e.g., subsequent ablation with complications). One of the trials included for KQ 2, the SAFE study, assessed anxiety associated with screening. It did not, however, collect anxiety data from patients within the no screening arm of the study, which would have allowed for a comparison between screening and no screening. As a result, we cannot make conclusions about whether screening causes more or less anxiety than usual care.

The SAFE study used the Spielberger Six-Item Anxiety Questionnaire (S6AQ) to evaluate anxiety in the opportunistic and systematic screening arms at three different time points.[74] To allow for baseline score adjustment later in the study, 750 patients (out of more than 9,000 in the screening groups) were sent the S6AQ before randomization into either the opportunistic or screening arm. Patients who underwent ECGs in both screening arms were sent the S6AQ immediately after ECG screening. Seventeen months after baseline, investigators sent the S6AQ to all patients who screened positive and all 750 patients who had received the questionnaire before randomization.[51, 77] Of the 750 questionnaires sent to patients before randomization, 620 (84%) were returned and 493 were completed (66%). Investigators provided S6AQs to all 2,595 patients who underwent ECG screening immediately after ECG screening, and 1,940 were returned (response rate 75%). Of the 777 questionnaires sent to patients 17 months after baseline, 535 were returned (response rate 69%).[77]

Anxiety levels were not significantly different between the opportunistic and systematic screening arms at baseline (Mean Spielberger State Anxiety inventory 35.78 [95% CI, 33.80 to 37.76] vs. 36.44 [95% CI, 34.35 to 38.53], p=0.695). The two arms had similar results on the questionnaires administered immediately after screening (28.77 [95% CI, 28.27 to 29.26] vs. 28.25 [95% CI, 26.78 to 29.73], unadjusted p=0.732). Mean scores for the systematic and opportunistic screening arms were also similar at 17 months (35.92 [95% CI, 34.29 to 37.55] vs.

37.50 [95% CI, 35.82 to 39.18], p=0.844 adjusted for baseline scores). When comparing screen-positive and screen-negative respondents, anxiety scores collected 17 months after initial chart review were significantly different (p=0.028), with screen-positive participants having higher mean anxiety scores (38.12 [95% CI, 35.89 to 40.35]) than screen-negative participants (34.61, 95% CI, 32.41 to 36.81) (unadjusted p=0.028), although relatively few participants were included in that analysis (142 screen-positive and 128 screen-negative participants).[77]

Potential harms of screening include overdiagnosis (e.g., from misinterpretation of ECGs) and overtreatment (e.g., warfarin for someone without AF). An analysis of 2,595 participants in the SAFE study from 49 general practices assessed the accuracy of general practitioners and interpretive software for diagnosing AF.[76] General practitioners missed 20 percent of AF cases on 12-lead ECG and misinterpreted 8 percent of sinus rhythm cases (as AF) compared with reference standard cardiologists (sensitivity 79.8 [95% CI, 70.5 to 87.2]; specificity 91.6 [90.1 to 93.1]; 79 out of 99 AF cases detected; misinterpreted sinus rhythm as AF for 114 out of 1,355). False-positive rates varied from 0 to 44 percent for individual general practitioners (standard deviation, 13%). Combining general practitioners' interpretations with those of interpretive software increased the sensitivity (91.9 [86.6 to 97.3]), but specificity was about the same (91.1 [89.6 to 92.6]). Use of single-lead or limb-lead ECGs resulted in slightly lower specificity.

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

Although we aimed to determine the benefits of treatment for asymptomatic, screen-detected older adults with AF, we found no trials or systematic reviews that focused on asymptomatic, screen-detected participants. We included six RCTs of people who were not screen-detected; most had long-standing persistent nonvalvular AF; few had a history of TIA or stroke (<8%); prevalence of baseline or past symptoms (e.g., palpitations, dyspnea) was generally not reported. Three evaluated warfarin,[80-82] one evaluated aspirin,[83] and two (described in 3 articles) evaluated both warfarin and aspirin.[80, 84, 85] The characteristics of the included RCTs are summarized in **Tables 4** and **5**, and the results are summarized in **Appendix E Tables 1 and 2**. One trial evaluating aspirin was excluded for poor quality but was used in sensitivity analyses.[70] We included seven systematic reviews (**Appendix E Table 3**): three were traditional systematic reviews with meta-analyses,[44, 86, 87] three were meta-analyses of individual patient data,[88-90] and one was a network meta-analysis.[91] The systematic reviews included a total of 38 unique studies (including the 6 RCTs in our review). Many of the unique studies included in other systematic reviews were not eligible for this review because they evaluated secondary prevention (i.e., some of the eligible systematic reviews evaluated treatments for people with a history of TIA or stroke in addition to addressing primary prevention) or because they were head-to-head studies (most of the 21 studies included in the network meta-analysis were head-to-head studies).

Warfarin: Characteristics of Randomized, Controlled Trials

Five trials (described in 6 articles) evaluated warfarin.[80-82, 84, 92, 93] Four of the five trials compared warfarin with a placebo (Atrial Fibrillation, ASpirin, and AntiKoagulation study [AFASAK I],[84] Canadian Atrial Fibrillation Anticoagulation [CAFA],[81] Stroke Prevention in

Atrial Fibrillation [SPAF I],[92, 93] Stroke Prevention in Nonrheumatic Atrial Fibrillation [SPINAF][82]) and one (Boston Area Anticoagulation Trial for Atrial Fibrillation [BAATAF])[80] compared warfarin with no treatment. BAATAF allowed participants in the no treatment group to take aspirin (and 46% of all patient years in the control group were contributed by participants taking aspirin), but use of aspirin or other antithrombotic medications was not permitted in the four placebo-controlled trials. Two trials (AFASAK I and SPAF I) were three-arm studies that included aspirin arms (in addition to warfarin and placebo or no treatment). Two trials were double-blind (CAFA, SPINAF), and three were open label (AFASAK I, BAATAF, SPAF I). Three trials were conducted in the United States (BAATAF, SPAF I, and SPINAF), one in Canada (CAFA), and one in Denmark (AFASAK I). Mean duration of followup ranged from 1.2 to 2.2 years. All five trials began in the 1980s and were completed by 1992. All five trials were stopped early, primarily because of evidence favoring warfarin for stroke reduction.

None of the trials focused on participants who were detected by screening in primary care or the general population. The mean age of participants ranged from 67 to 74 years. Most participants were men, with four out of five trials enrolling fewer than 30 percent women. Just one trial reported any information about the race or ethnicity of participants (16% were nonwhite in SPAF I). Few participants had a history of TIA or stroke (range 3% to 8%). The baseline prevalence of hypertension and diabetes ranged from 32 to 58 percent and 12 to 18 percent, respectively. AFASAK I and SPINAF did not include participants with paroxysmal AF; the other three trials reported that 7 percent to 34 percent had paroxysmal AF. Most participants in the trials had AF for more than a year. Three trials (CAFA, SPAF I, and BAATAF) reported that between 19 percent and 32 percent had AF for less than a year; SPINAF I reported that 12 percent had AF less than 6 months (and a mean duration of AF of 8 years); and AFASAK I did not report information about the duration of AF prior to enrollment. Baseline stroke risk (e.g., $CHADS_2$) was not reported by any of the trials because stroke risk scores used in current practice were not yet developed; some future publications have used the baseline characteristics of subjects to estimate that the mean $CHADS_2$ scores of participants in these trials ranged from 1 to 1.6.[91]

All trials titrated doses of warfarin on the basis of either prothrombin time (PT) or international normalized ratio (INR). The INR target ranges spanned from 1.4 to 4.5. The mean INRs achieved ranged from 2 to 2.6. The reported time in therapeutic range (TTR) spanned from 44 percent (CAFA) to 83 percent (BAATAF), and three trials reported TTR over 70 percent (SPAF I, AFASAK I, and BAATAF).

Warfarin: Results of Meta-Analyses

All-Cause Mortality

Across included trials, the mean annual mortality rate in control groups was 5 percent. Warfarin treatment over an average of 1.5 years was associated with a 32 percent reduction in all-cause mortality compared with controls (pooled RR, 0.68 [95% CI, 0.50 to 0.93]; I^2=0%; 5 trials; 2,415 participants, **Figure 4**).

Cardiovascular-Related Mortality

Across included trials, the mean annual cardiovascular-related mortality rate in control groups was 2.8 percent. Warfarin treatment over an average of 1.5 years was associated with a reduction

in cardiovascular-related mortality, but the difference between warfarin and controls was not statistically significant (pooled RR, 0.66 [95% CI, 0.33 to 1.29]; I^2=53.3%; 5 trials; 2,415 participants, **Figure 4**).

All Ischemic Stroke

Across included trials, the mean annual ischemic stroke rate in control groups was 4 percent. Four of the five trials reported a statistically significant reduction in ischemic strokes. Warfarin treatment over an average of 1.5 years was associated with a 68 percent reduction in ischemic strokes compared with controls (pooled RR, 0.32 [95% CI, 0.20 to 0.51]; I^2=0%; 5 trials; 2,415 participants, **Figure 4**).

Moderately to Severely Disabling Stroke

Across included trials, the mean annual event rate in control groups was 1.5 percent. Warfarin treatment over an average of 1.5 years was associated with a 62 percent reduction in moderately to severely disabling stroke compared with controls (pooled RR, 0.38 [95% CI, 0.19 to 0.78]; I^2=0%; 5 trials; 2,415 participants, **Figure 4**).

Transient Ischemic Attack

Across included trials, the mean annual event rate in control groups was 0.8 percent. Warfarin was associated with a reduction in TIAs, but the difference between warfarin and controls was not statistically significant (pooled RR, 0.66 [95% CI, 0.26 to 1.68]; I^2=0%; 4 trials; 1,890 participants, **Appendix E Figure 1**).

All Ischemic Stroke or Intracranial Hemorrhage

Across included trials, the mean annual event rate in control groups was 4.1 percent. Warfarin treatment over an average of 1.5 years was associated with a 62 percent reduction in all ischemic stroke or intracranial hemorrhage compared with controls (pooled RR, 0.38 [95% CI, 0.25 to 0.59]; I^2=0%; 5 trials; 2,415 participants, **Figure 4**).

Aspirin: Characteristics of Randomized, Controlled Trials

Our review included three RCTs (described in 4 articles) that evaluated aspirin.[83, 84, 92, 93] One trial, which was conducted in Spain and evaluated aspirin 125 mg daily versus 125 mg every other day versus control (Low-dose Aspirin, Stroke, Atrial Fibrillation [LASAF] pilot study), was excluded for poor quality but was used in sensitivity analyses.[70] Two of the three included trials compared aspirin with placebo (AFASAK I[84] and SPAF I[92, 93]), and one (Japanese Atrial fibrillation Stroke Trial [JAST])[83] compared aspirin with a control group taking no antiplatelet or anticoagulant therapy. The doses of aspirin used in the included trials were 75 mg daily (AFASAK I), 325 mg daily (SPAF I), and 150–200 mg daily (JAST). AFASAK I was a three-arm trial that also included a warfarin arm. SPAF I divided participants into two groups based on their eligibility for warfarin (i.e., willingness to take it, bleeding risk, and risk of embolism): those eligible for warfarin were randomized to warfarin, aspirin, or placebo, and those not eligible for warfarin were randomized to aspirin or placebo. Participants from both groups were combined in analyses comparing aspirin with placebo. AFASAK I and SPAF I were double-

blind, and JAST was open label. SPAF I was conducted in the United States, AFASAK was conducted in Denmark, and JAST was conducted in Japan. On average, followup lasted 1.2 to 2.1 years. AFASAK I and SPAF I began in the 1980s and were concluded by 1991, and JAST began in 1998 and was stopped in 2002.

None of the trials focused on asymptomatic participants who were screen-detected. AFASAK I did not include participants with paroxysmal AF, but 33 percent of those in SPAF I and 45 percent of those in JAST had paroxysmal AF. The mean age of participants ranged from 65 to 74 years. Most participants in all trials were men; 29 to 46 percent of participants were women. SPAF I reported that 16 percent were nonwhite, and neither JAST nor AFASAK I reported on the race or ethnicity of their participants. Few participants had a history of TIA or stroke (range 2.5% to 7%). The baseline prevalence of hypertension and diabetes ranged from 32 to 52 percent and 12 to 15 percent, respectively.

Aspirin: Results of Meta-analyses

All-Cause Mortality

Across included studies, the mean annual mortality rate in control groups was 4.2 percent. Aspirin treatment over an average of 1.5 years was associated with a lower risk of death than controls, but the difference between aspirin and controls was not statistically significant (pooled RR, 0.84 [95% CI, 0.62 to 1.14]; I^2=0%; 3 trials; 2,663 participants, **Figure 5**).

Cardiovascular-Related Mortality

Across included trials, the mean annual cardiovascular-related mortality rate in control groups was 2.2 percent. Aspirin treatment over an average of 1.5 years was associated with a reduction in cardiovascular-related mortality, but the difference between aspirin and controls was not statistically significant (pooled RR, 0.86 [95% CI, 0.56 to 1.32]; I^2=0%; 3 trials; 2,663 participants, **Figure 5**).

All Ischemic Stroke

Across included trials, the mean annual ischemic stroke rate in control groups was 3.7 percent. Aspirin treatment over an average of 1.5 years was associated with a reduction in ischemic strokes, but the difference between aspirin and controls was not statistically significant (pooled RR, 0.76 [95% CI, 0.52 to 1.1]; I^2=15.7%; 3 trials; 2,663 participants, **Figure 5**).

Moderately to Severely Disabling Stroke

Two of the three included trials reported on disabling strokes (AFASAK I and SPAF I). Both reported nonstatistically significant reductions in events for those treated with aspirin (RR 0.57 [95% CI, 0.17 to 1.9] in AFASAK I over an average followup of 1.2 years, with 672 participants; RR 0.64 [95% CI, 0.29 to 1.4] in SPAF I over an average followup of 1.3 years, with 1,120 participants, **Appendix F Figure 7**).

All Ischemic Stroke or Intracranial Hemorrhage

Across included trials, the mean annual event rate in control groups was 3.9 percent. Aspirin treatment over an average of 1.5 years was associated with a reduction in events, but the difference between aspirin and controls was not statistically significant (pooled RR, 0.81 [95% CI, 0.54 to 1.21]; I^2=31.7%; 3 trials; 2,663 participants, **Figure 5**).

Results of Previously Published Systematic Reviews and Meta-analyses

Results of previously published systematic reviews[44, 86-91] were generally consistent with our findings and are summarized in **Appendix E Table 3**. Here we highlight the findings from those reviews that provide additional information (beyond what we have described already in this KQ). Overall, the included systematic reviews provide some additional details about subgroups (from individual patient data meta-analyses) and some information about head-to-head comparisons, including comparisons with novel oral anticoagulants (NOACs).

Warfarin Versus Placebo or Control

One systematic review from the Cochrane collaboration evaluated warfarin for primary prevention.[86] It included the same five RCTs in our review but obtained unpublished data excluding the 3 to 8 percent of participants with prior stroke or TIA. The findings were very similar to those of our meta-analyses, although they reported ORs (e.g., for all-cause mortality, they reported OR 0.69 [0.50 to 0.94] vs. our pooled result of RR 0.68 [0.50 to 0.93]) (**Appendix E Table 3**).

Aspirin Versus Placebo or Control

One systematic review from the Cochrane collaboration evaluated aspirin for primary prevention.[87] It included two of the three RCTs (AFASAK I and SPAF I) that were in our main analyses and included LASAF, which we excluded because of poor quality but used in sensitivity analyses. The review authors obtained unpublished data excluding participants with prior stroke or TIA. The findings were very similar to those of our meta-analyses, showing that aspirin treatment was associated with a reduced risk of several outcomes and that the difference between aspirin and controls was not statistically significant (e.g., for all-cause mortality, they reported OR 0.75 [0.54 to 1.04] vs. our pooled result of RR 0.84 [0.62 to 1.14]) (**Appendix E Table 3**). However, they reported one composite outcome that we did not pool data for (all stroke, myocardial infarction, or vascular death) and found a significant reduction in risk with aspirin compared with controls (OR, 0.71 [0.51 to 0.97]).

Subgroups

Three individual patient data meta-analyses used the Atrial Fibrillation Investigators database from clinical trials evaluating warfarin or aspirin.[88-90] That database included all five warfarin trials described in this report (AFASAK I, CAFA, SPAF I, SPINAF, BAATAF) and two of the aspirin trials (AFASAK I and SPAF I). One evaluated subgroups based on sex and history of hypertension for both warfarin and aspirin,[88] one evaluated whether benefits vary by age for both warfarin and aspirin,[90] and one evaluated multiple subgroups for aspirin.[89] The aspirin analyses are all limited by not including the JAST study (which was published after these analyses).

The individual patient data meta-analysis that evaluated subgroups based on sex and history of hypertension[88] used the same five RCTs evaluating warfarin that we included in KQ 4. It reported that the efficacy of warfarin was consistent across subgroups. Warfarin was associated with a reduction in stroke for both men and women, without a statistically significant difference between them (relative risk reduction, 60% [35% to 76%] and 84% [55% to 95%], respectively). For aspirin, the analyses included two of the RCTs (AFASAK I and SPAF I) eligible for our report (JAST was not yet published). Aspirin was associated with a reduction in stroke for both men and women, without a statistically significant difference between them (relative risk reduction, all participants: 36% [4% to 57%]; p=0.03; men: 44% [3% to 68%], p=0.04; women: 23% [40% to 58%], p=0.38, test for interaction not reported). However, the effect of aspirin was found to vary by history of hypertension. For those with a history of hypertension, aspirin was associated with a reduction in stroke (relative risk reduction [RRR], 59% [28% to 77%]; p=0.002), but for those with no history of hypertension, it was not (10% [40% to 100%]; p=0.76; and p=0.02 for difference in effectiveness between those with and without hypertension).

The individual patient data meta-analysis that evaluated subgroups based on age[90] used the same five RCTs evaluating warfarin that we included in KQ 4, but also included a secondary prevention trial (European Atrial Fibrillation Trial [EAFT], 439 participants treated with warfarin or placebo).[94] Warfarin was associated with a reduced risk of ishemic stroke (compared with placebo/control) for all ages, but the authors found a trend toward decreased relative benefit with increasing age. Hazard ratios (HRs) moved closer to 1 for older patients (e.g., HR, 0.22 [95% CI, 0.11 to 0.41] for 50-year-olds; HR, 0.53 [0.35 to 0.81] for 90-year-olds), but the interaction did not reach statistical significance (interaction of age and warfarin, p=0.07). For aspirin, the analyses included two of the RCTs (AFASAK I and SPAF I) eligible for our report and one secondary prevention trial (EAFT, 782 participants treated with aspirin or placebo). The relative benefit of aspirin for preventing ischemic stroke decreased significantly with increasing age. At age 50 years, the HR was 0.40 (95% CI, 0.22 to 0.72); by age 77 years, the HR no longer excluded the null; at age 82 years, the HR exceeded 1 (interaction of age and aspirin, p=0.01). Although the analyses included EAFT, the authors report conducting sensitivity analyses with serial exclusion of individual studies that did not alter estimates. Neither warfarin nor aspirin interacted significantly for cardiovascular events.

The individual patient data meta-analysis that evaluated multiple subgroups for aspirin[89] included two of the RCTs (AFASAK I and SPAF I) eligible for our report and a secondary prevention trial (EAFT). The analyses considered age, sex, history of hypertension, systolic blood pressure 160 or lower versus not, history of CHF, and history of diabetes. The analyses reported finding no convincing evidence of specific subgroups for whom aspirin was more effective for reducing the risk of ischemic stroke. Like the individual patient data meta-analysis described above,[88] the authors reported that those with a history of hypertension had a significant reduction in the risk of ischemic stroke (RR, 0.64; 95% CI, 0.46 to 0.89), but those without a history of hypertension did not (RR, 0.98; 95% CI, 0.79 to 1.39). Unlike the individual patient data meta-analysis above, however, the interaction between a history of hypertension and aspirin use was not significant (p=0.08). The difference between the two meta-analyses is likely because of including versus not including EAFT. A secondary (post hoc) analysis found that among patients without a previous stroke or TIA (thus excluding EAFT and 6% of participants from AFASAK I and SPAF I), those with a history of hypertension or diabetes had a greater reduction in ischemic stroke risk (RRR, 54% [17% to 74%]) than those without a history of hypertension or diabetes (RRR not reported) (interaction p=0.02).

Results of Previously Published Network Meta-Analysis

The one included network meta-analysis used 21 RCTs (96,017 participants) of treatment for nonvalvular AF.[91] It was not limited to primary prevention populations, but most of the data was from studies in which most of the particiants had no history of stroke or TIA. Four of the 21 RCTs reported that more than 35 percent of their participants had a history of stroke or TIA: 100 percent in EAFT (warfarin vs. aspirin vs. placebo), 64 percent in the Japanese Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (rivaroxaban vs. warfarin), 55 percent in the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (rivaroxaban vs. warfarin), and 38 percent in SPAF III (low-intensity fixed-dose warfarin adjusted to INR, 1.2–1.5 combined with aspirin 325 mg once daily vs. adjusted-dose warfarin with target INR, 2.0–3.0). The percentage of participants with a history of stroke or TIA was less than 10% in nine trials (AFASAK I, BAATAF, SPAF I, CAFA, SPAF II, AFASAK II, the Primary Prevention of Arterial Thromboembolism in Nonrheumatic Atrial Fibrillation study, Swedish Atrial Fibrillation Trial, and JAST) and ranged from 13 to 28 percent in the other eight included trials. Limitations of the network meta-analysis include (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.

The primary efficacy outcome was the combination of stroke (of any type) and systemic embolism. All-cause mortality was the secondary efficacy outcome. The authors provided both unadjusted results and results adjusted for population characteristics ($CHADS_2$ scores, TTR, duration of followup). The analysis found that all treatments (aspirin, vitamin K antagonists [VKAs], all four NOACs, and the Watchman device) reduced the risk of the primary and secondary efficacy outcomes in unadjusted analyses (**Appendix E Table 3**). Effect sizes for VKAs and aspirin compared with placebo/control were nearly identical to those from our pairwise meta-analyses for warfarin and aspirin. For the four NOACs (apixaban, dabigatran, edoxaban, and rivaroxaban), the authors reported statistically significant associations with reduction in the primary outcome compared with placebo/control (unadjusted ORs from 0.27 to 0.38; adjusted ORs from 0.32 to 0.44, **Appendix E Table 3**), but no statistically significant differences for the four NOACs in comparison to one another. In adjusted analyses, the NOACs were not statistically different from VKAs for either efficacy outcome. VKAs and the NOACs showed greater reduction in risk of the primary outcome compared with aspirin.

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

All six RCTs described in KQ 4 for benefits of warfarin or aspirin also reported harms.[80-84, 92, 93] As for KQ 4, we found no trials or systematic reviews that focused on asymptomatic, screen-detected participants. **Tables 4** and **5** summarize the characteristics of the included studies and **Appendix E Tables 1 and 2** summarize the results. We also included seven systematic reviews (**Appendix E Table 3**): four were traditional systematic reviews with meta-analyses,[44, 86, 87, 95]

two were individual patient data meta-analyses,[88, 90] and one was a network meta-analysis.[91]

Warfarin: Results of Meta-analyses

Major Bleeding. Across trials, 31 major bleeding events occurred, 20 in warfarin groups and 11 in control groups. Warfarin treatment over an average of 1.5 years was associated with an increased risk of major bleeding compared with controls, but the CI was wide, and the difference between groups was not statistically significant (pooled RR, 1.8 [95% CI, 0.85 to 3.7]; I^2=0%; 5 trials; 2,415 participants, **Figure 4**).

Major Extracranial Bleeding. Across trials, 23 events occurred, 14 in warfarin groups and 9 in control groups. Warfarin treatment over an average of 1.6 years was associated with an increased risk of major extracranial bleeding compared with controls, but the CI was wide, and the difference between groups was not statistically significant (pooled RR, 1.6 [95% CI, 0.67 to 3.6]; I^2=0%; 4 trials; 1,744 participants, **Figure 4**).

Intracranial Hemorrhage. Eight intracranial hemorrhages occurred, six in warfarin groups and two in control groups. Warfarin treatment over an average of 1.5 years was associated with an increased risk of intracranial hemorrhage compared with controls, but the CI was wide, and the difference between groups was not statistically significant (pooled RR, 1.9 [95% CI, 0.56 to 6.7]; I^2=0%; 5 trials; 2,415 participants, **Figure 4**).

Minor Bleeding
A total of 222 minor bleeding events occurred, 136 in warfarin groups and 86 in control groups. Warfarin treatment over an average of 1.6 years was associated with an increase in minor bleeding compared with controls (pooled RR, 1.6 [95% CI, 1.2 to 2.0]; I^2=0%; 4 trials; 1,744 participants, **Appendix F Figure 2**).

Aspirin: Results of Meta-Analyses

Major Bleeding. In the included trials, 34 major bleeding events occurred, 18 in aspirin groups and 16 in control groups. Aspirin treatment over an average of 1.5 years was associated with an increased risk of major bleeding compared with controls, but the CI was wide, and the difference between groups was not statistically significant (pooled RR, 1.5 [95% CI, 0.44 to 5.0]; I^2=45%; 3 trials; 2,663 participants, **Figure 5**).

Major Extracranial Bleeding. In the included trials, 24 major extracranial bleeding events occurred, 12 in aspirin groups and 12 in control groups. Aspirin treatment over an average of 1.5 years was associated with a trend toward an increased risk of major extracranial bleeding compared with controls, but the CI was wide, and the difference between groups was not statistically significant (pooled RR, 1.4 [95% CI, 0.32 to 5.8]; I^2=31.5%; 3 trials; 2,663 participants, **Figure 5**).

Intracranial Hemorrhage. Ten intracranial hemorrhages occurred, six in aspirin groups and four in control groups (**Appendix F Figure 9**). AFASAK I reported no events in either group. SPAF I reported two events in both groups (RR, 1.0 [95% CI, 0.15 to 7.3]), and JAST reported four events in the aspirin group and two events in the control group (RR, 2.1 [95% CI, 0.38 to 11.4]).

Previously Published Systematic Reviews and Meta-Analyses

Results of previously published systematic reviews[44, 86-88, 90, 91, 95] were generally consistent with our findings and are summarized in **Appendix E Table 3**. Here we highlight the findings from those reviews that provide additional information (beyond what we have described already in this KQ). Overall, the included systematic reviews provide some additional details about subgroups (from individual patient data meta-analyses) and some information about head-to-head comparisons, including comparisons with NOACs.

Warfarin Versus Placebo or Control

One systematic review from the Cochrane collaboration evaluated warfarin for primary prevention.[86] It included the same five RCTs in our review but obtained unpublished data excluding the 3 to 8 percent of participants with prior stroke or TIA. The findings were very similar to those of our meta-analyses, although they reported ORs (e.g., for intracranial hemorrhage, they reported OR 2.38 [0.54 to 10.5] vs. our pooled result of RR 1.94 [0.56 to 6.68]) (**Appendix E Table 3**).

Aspirin Versus Placebo or Control

One systematic review from the Cochrane collaboration evaluated aspirin for primary prevention.[87] It included two of the three RCTs (AFASAK I and SPAF I) that were in our main analyses and included LASAF, which we excluded because of poor quality but used in sensitivity analyses. The review authors obtained unpublished data excluding participants with prior stroke or TIA. The findings were very similar to those of our meta-analyses, showing that aspirin treatment was associated with an increased risk of bleeding compared with controls, but the CIs were wide and the difference between groups was not statistically significant (e.g., for major extracranial bleeding, they reported OR 1.14 [0.44 to 2.98] vs. our pooled result of RR, 1.4 [0.32 to 5.8]) (**Appendix E Table 3**).

Subgroups

Two of the individual patient data meta-analyses described in KQ 4 provided information about whether the risk of harms varies for subgroups.[88, 90] Both used the Atrial Fibrillation Investigators database of clinical trials evaluating warfarin or aspirin. That database included all five warfarin trials described in this report (AFASAK I, CAFA, SPAF I, SPINAF, BAATAF) and two of the aspirin trials (AFASAK I and SPAF I). The aspirin analyses are all limited by not including the JAST study (which was published later).

One meta-analysis of individual patient data concluded that the small number of patients with intracranial bleeding does not allow for reliable conclusions about whether the risk varies for subgroups.[88] They also reported that the six warfarin-treated patients who had intracranial bleeding had higher blood pressure than warfarin-treated patients who did not have intracranial bleeding (169/93 vs. 141/83mm Hg, p=0.001 for systolic and p=0.016 for diastolic). The mean age for patients with intracranial bleeding events was higher than for those without bleeding, but the difference between groups was not statistically significantly different (73 vs. 69 years, p not significant and not reported).

The other individual patient data meta-analysis evaluated subgroups based on age for risk of serious hemorrhage (intracranial hemorrhages or major bleeding).[90] The analyses used the same five RCTs evaluating warfarin that we included, but also included a secondary prevention trial (EAFT). They found that neither warfarin nor aspirin interacted significantly with patient age for serious hemorrhage (data not reported; shown in figures only).

Results of Previously Published Network Meta-Analysis

The one included network meta-analysis used 21 RCTs (96,017 participants) of treatment for nonvalvular AF and is described in KQ 4.[91] The primary safety outcome was major bleeding (the combination of major extracranial bleeding and intracranial hemorrhage). The authors provided both unadjusted results and results adjusted for population characteristics ($CHADS_2$ scores, TTR, duration of followup). Effect sizes for VKAs and aspirin compared with placebo/control were nearly identical to those from our pairwise meta-analyses for warfarin and aspirin. Aspirin was associated with an increased risk of major bleeding compared with placebo/control, but the CI was wide, and the difference between groups was not statistically significant (adjusted OR, 1.65 [0.77 to 3.51]). Similarly, for the four NOACs (apixaban, dabigatran, edoxaban, and rivaroxaban), the authors reported associations with an increased risk of bleeding, but the CIs were wide, and differences between groups were not statistically significant (adjusted ORs from 1.38 to 2.21; **Appendix E Table 3**), and there were no statistically significant differences between any of the four NOACs. Compared with VKAs, three of the NOACs (apixaban, dabigatran, and edoxaban) were associated with a lower risk of bleeding (range of ORs [95% CIs] from 0.64 [0.46, 0.90] to 0.85 [0.65, 1.11]), but the difference was only statistically significant for edoxaban (OR, 0.64 [0.46, 0.90]) (**Appendix E Table 3**). For rivaroxaban compared with VKAs, the odds of major bleeding was 1.03 (95% CI, 0.68 to 1.57).

Chapter 4. Discussion

Summary of Evidence

Table 6 provides a summary of findings in this evidence review. This table is organized by KQ and provides a summary of the main findings along with a description of consistency, precision, quality, limitations, strength of evidence, and applicability.

Evidence for Benefit and Harms of Screening

We did not identify any eligible studies evaluating screening for AF with ECG compared with no screening that reported health outcomes (i.e., no eligible studies were identified for the overarching question, KQ 1). We identified one ongoing RCT, the STROKESTOP study, that aims to do so and is estimated to be completed by March 2019.[71, 73] It randomized 28,768 older adults to screening program invitations for AF or to no invitations. The screening program involves an initial 12-lead ECG and then a handheld 1-lead ECG for intermittent recordings over 2 weeks. The primary outcome is incidence of stroke.

For harms of screening, no eligible studies provided information that allowed comparison between screening and no screening. The SAFE study provided limited evidence showing that anxiety may be increased among people who undergo ECG and screen positive compared with those who undergo ECG and screen negative; relatively few participants were included in the analysis (270 of the 14,802 participants in the trial). Although the difference was statistically significant, it is unclear whether the difference between groups was clinically meaningful (mean S6AQ score at 17 months: 38.1 [35.9 to 40.4] vs. 34.6 [32.4 to 36.8], p=0.028). Though it may be expected that anxiety would be slightly higher after a positive screen (than after a negative screen) because it is associated with a new diagnosis of AF.

Potential harms of screening with ECG include overdiagnosis (e.g., from misinterpretation of ECGs) and overtreatment (e.g., with anticoagulation for someone without AF, with rate or rhythm control agents when not indicated) for asymptomatic persons who either do not have AF or who would never have had symptoms of or problems from AF. Some evidence suggests that many primary care providers cannot accurately detect AF on ECG.[76] For example, an analysis of 2,595 participants from 49 general practices in central England participating in the SAFE study assessed the accuracy of general practitioners and interpretive software for diagnosing AF.[76] General practitioners missed 20 percent of AF cases on 12-lead ECG and misinterpreted 8 percent of sinus rhythm cases (as AF) compared with reference standard cardiologists (sensitivity 79.8 [95% CI, 70.5 to 87.2]; specificity 91.6 [90.1 to 93.1]; 79 out of 99 AF cases detected; misinterpreted sinus rhythm as AF for 114 out of 1,355). False-positive rates varied from 0 to 44 percent for individual general practitioners (standard deviation, 13%). Combining general practitioners' interpretations with those of interpretive software increased the sensitivity (91.9 [86.6 to 97.3]), but specificity was about the same (91.1 [89.6 to 92.6]). Use of single-lead or limb-lead ECGs resulted in slightly lower specificity. The analysis did not evaluate the accuracy of primary care providers for other ECG findings (e.g., findings that may suggest ischemia and could lead to subsequent testing). Another study using a database from a U.S. hospital that evaluated 2,298 ECGs (from 1,085 patients) with a computerized interpretation of AF found that 442 (19%) ECGs from 382 (35%) patients had been misinterpreted.[43] For 92 patients, physicians

did not correct the computerized misinterpretation and initiated inappropriate and potentially harmful treatments, and pursued unnecessary additional testing. Potential harms could also result from additional testing (e.g., unnecessary stress tests or angiographies that were done because of ECG findings suggestive of ischemia, which turned out to be false positives and resulted in complications).

Detection of Previously Undiagnosed AF

Our review found that one-time screening with 12-lead ECG identifies more new cases of AF than usual care (absolute increase in new cases, 0.6% [0.2% to 0.98%] over 12 months). Extrapolating to the U.S. population of adults age 65 or older (estimated as 46 million in 2016[96]) suggests that 276,000 additional new cases would be identified if ECG screening programs were implemented in the United States. Studies without control groups (summarized in **Appendix A, Contextual Question 1**) estimated twice as many new cases (pooled proportion 1.2% [0.9% to 1.6%], 19 studies, 100,247 participants); although those data provide an estimate of the total burden of undiagnosed AF, they do not account for differences in detection of undiagnosed AF between screening programs and usual care (i.e., the new cases detected that would be attributable to screening). Also, those studies and the STROKESTOP study suggest that the number of new AF cases detected is greater with intermittent or continuous ECG recordings over the course of 2 weeks than with one-time ECG.

Most asymptomatic older adults with previously unrecognized or undiagnosed AF have a stroke risk (based on $CHADS_2$ scores or CHA_2DS_2-VASc scores) above the threshold for initiating anticoagulation (**Appendix A Table 2; Appendix A, Contextual Question 2**). Seven studies that described CHA_2DS_2-VASc scores reported a range of mean scores from 3.1 to 3.8, scores that would typically be associated with initiation of anticoagulation (in the absence of contraindications). In STROKESTOP, over 90 percent of new cases of AF were offered and accepted initiation of oral anticoagulant therapy.[71] The SAFE study reported that 78 percent of new cases identified with systematic screening had $CHADS_2$ scores of 1 or more and that 43 percent had scores of 2 or more.[75] Of note, if screening programs were implemented, they could be limited to people age 65 or older who have CHA_2DS_2-VASc scores of 2 or higher (to avoid screening people for whom anticoagulation would not be indicated).

Benefits and Harms of Anticoagulation and Antiplatelet Treatment for Nonvalvular AF

Our review found consistent evidence that anticoagulation reduces the risk of stroke and all-cause mortality and increases the risk of bleeding for people with nonvalvular AF who do not have a history of stroke or TIA (i.e., for primary prevention). Warfarin treatment (mean 1.5 years) was associated with a 68 percent reduction in ischemic stroke (pooled RR, 0.32 [0.20 to 0.51]) and 32 percent reduction in all-cause mortality (pooled RR, 0.68 [0.50 to 0.93]) compared with controls. For a population with baseline annual stroke risk of 4 percent (e.g., such as those with $CHADS_2$ scores of 2), warfarin was associated with a corresponding NNT of 24 (95% CI, 17 to 36) to prevent one ischemic stroke over an average of 1.5 years of followup. For a population of 1,000 adults age 65 or older with an annual stroke risk of 4 percent, the results translate to an absolute reduction of approximately 28 ischemic strokes per year, an absolute reduction of 16 deaths per year, and an absolute increase of five major bleeding events per year.

Aspirin was associated with reduction in mortality and ischemic stroke, but differences between aspirin and controls were not statistically significant. Of note, aspirin for the treatment of AF is either not recommended or is only recommended if the stroke risk is low (CHA_2DS_2-VASc score=1) (**Appendix A Table 2**). A previously published network meta-analysis[91] included in our review found that NOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) were not statistically different from VKAs for a composite outcome (any stroke and systemic embolism) or for all-cause mortality. VKAs and the NOACs showed greater reduction in risk of the composite outcome compared with aspirin.

Although we aimed to determine the benefits of treatment for asymptomatic, screen-detected older adults with nonvalvular AF, we found no trials or systematic reviews that focused on this population, and it is uncertain whether benefits of medications vary for symptomatic people and those who have never had symptoms (asymptomatic screen-detected people).

Limitations

This review is limited in the ability to describe the direct evidence on the effectiveness or harms of screening for AF because we identified no eligible studies addressing the overarching question (KQ 1). Therefore, we attempted to review literature that might establish an indirect chain of evidence from multiple questions that link screening to health outcomes (KQs 2 through 5). **Table 6** provides a summary of key limitations of the evidence for each KQ.

We did not systematically review the evidence regarding the diagnostic accuracy of screening tests for AF 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 (e.g., primary care, preoperative clinics, cardiology practices) that were related to diagnostic accuracy for AF.[97] Based on data from seven studies, a 12-lead ECG interpreted by a nurse, general practitioner, or the ECG machine's automated algorithm had a sensitivity of 92.7 percent (95% CI, 85.9% to 96.8%) and a specificity of 97.4% (95% CI, 95.0% to 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 percent to 100 percent and specificity ranged from 76 percent to 100 percent.

We did not systematically review all the evidence on rate control or rhythm control for AF; however, we summarized the recommendations on rate and rhythm control and the main evidence cited by those recommendations in **Appendix A** (**Contextual Question 3a**). Briefly, rhythm control is not recommended for asymptomatic adults with AF. 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 AF based on the results from one trial (Rate Control Efficacy in Permanent Atrial Fibrillation: a Comparison between Lenient versus Strict Rate Control II [RACE II]) that concluded noninferiority of a lenient (<110 bpm) versus a strict (<80 bpm resting HR) rate control strategy in patients with permanent AF (for up to 12 months prior to enrollment).[51] RACE II compared strict (<80 bpm resting HR) versus lenient (<110 bpm) rate control strategies in patients with permanent AF (for up to 12 months prior to enrollment). Forty-three percent of the study population was asymptomatic at baseline (defined as no palpitations,

dyspnea, or fatigue), although it is not clear how many were never symptomatic (i.e., how many did not have symptoms around the time of their AF diagnosis or prior to it).

We did not include head-to-head trials of treatments for AF because our intention was to provide evidence on benefits of treatments compared with placebo/no treatment for the USPSTF rather than to assess the comparative effectiveness of treatments. Nevertheless, we did include and summarize a previously published network meta-analysis that provides comparative effectiveness estimates.

For KQs 4 and 5, all five included trials that evaluated warfarin began in the 1980s and were completed by 1992. Baseline population rates of stroke may have decreased since then with the increased use of statins and antihypertensive medications. Therefore, the absolute benefits of anticoagulation compared with placebo/control might be less in current clinical practice than in the RCTs, although the relative benefits would not be expected to have changed. Also, the current clinical approach to anticoagulation has evolved since the trials were conducted. Target INR ranges in current practice are typically 2 to 3 for patients with nonvalvular AF. The INR target ranges in the included trials were 2.8 to 4.2 (AFASAK I), 1.5 to 2.7 (BAATAF), 2 to 3 (CAFA), 2 to 4.5 (SPAF I), and 1.4 to 2.8 (SPINAF). In three of the trials (BAATAF, SPAF I, and SPINAF), PT was used to adjust warfarin doses, and the corresponding INR target ranges and mean INRs achieved were estimated. There is some uncertainty about the INR target ranges of these three trials because they used PT targets and conversion of PT to INR cannot be done precisely because of uncertain sensitivity of thromboplastin agents. In addition, trials enrolled somewhat selected participants and followed protocols (e.g., for warfarin dosing); routine clinical practice may not be as rigorous, and whether the results apply to routine clinical practice might be questioned. However, observational studies of anticoagulation suggest that the results are applicable to routine clinical practice.[98] Finally, the trials included in KQs 4 and 5 that evaluated warfarin had a mean duration of followup from 1.2 to 2.2 years (on average, 1.5 years of followup) and were stopped early. It is possible that estimates for reduction in strokes and all-cause mortality are not accurate for lifelong anticoagulation.

The aspirin evidence may be somewhat limited by heterogeneity of doses used. Just one (SPAF I) of the trials evaluating aspirin used a full-dose aspirin (325 mg daily), and it found benefit for stroke reduction, unlike the pooled data.

Future Research Needs

To better understand the potential benefits and harms of screening for AF with ECG, randomized trials of asymptomatic persons that directly compare screening with usual care and assess health outcomes are needed (i.e., trials that address KQ 1, the overarching question, and KQ 3 on harms). The ongoing STROKESTOP study may help to fill this evidence gap. Other relevant ongoing RCTs listed in clinicaltrials.gov that have not yet reported results include SCREEN-AF (NCT02392754) and IDEAL-MD (NCT02270151). SCREEN-AF plans to randomize 822 Canadians age 75 or older with hypertension to screening with Zio XT Patch (2-week continuous ECG monitoring) plus home blood pressure monitoring or to no screening. The primary outcome is new diagnosis of AF or atrial flutter within 6 months. Secondary outcomes include stroke, TIA, and major bleeding. IDEAL-MD is a cluster randomized trial in the Netherlands aiming to enroll 16,000 participants (from 42 general practices randomized to screening vs. usual care) age 65 or older. In the screening arm, a single lead handheld ECG recorder (for up to one minute)

will be used at every visit to the practice for 1 year. The primary outcome is new diagnosis of AF over 1 year. Secondary outcomes include major cardiovascular events and all-cause mortality over 1 year. Finally, the Detecting and Diagnosing Atrial Fibrillation (D_2AF) trial (listed in The Netherlands Trial Register, NTR4914) is a multicenter cluster randomized trial that will compare different approaches to case finding among adults 65 and older.[99] The case finding protocol includes pulse palpation, sphygmomanometer with automated AF detection, and handheld single-lead ECG. Participants with a positive test and a random sample of those with negative tests will undergo 12-lead ECG. Participants without AF on 12-lead ECG will undergo additional continuous Holter monitoring and use the handheld single-lead ECG at home for 2 weeks. The primary outcome is the difference in detection rate of new AF over 1 year (compared with usual care).

Conclusion

There is uncertainty about the benefits and harms of screening for AF with ECG, and screening can potentially lead to harms that have not been well studied. Although screening can detect previously unknown cases of AF, it has not been shown to detect more cases than opportunistic screening that is focused on pulse palpation. Most older adults with previously unknown AF have a stroke risk above the threshold for anticoagulation. Multiple treatments for AF 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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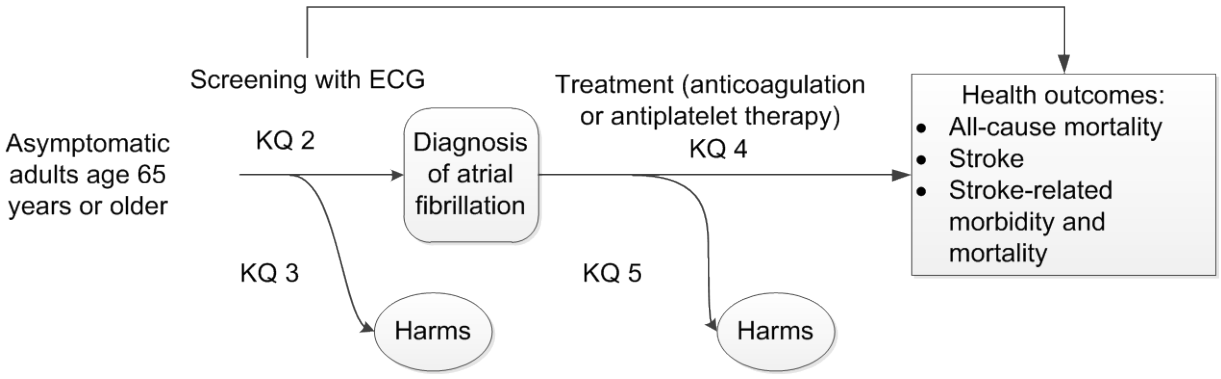
Figure 1. Analytic Framework



Abbreviations: CHA_2DS_2-VASc=Congestive heart failure, Hypertension, Age≥75 years (doubled), Diabetes mellitus, prior Stroke or TIA or thromboembolism (doubled), Vascular disease, Age 65-74 years, Sex category; ECG=electrocardiography; KQ=key question.

Key Questions to Be Systematically Reviewed

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

    1.a. Does improvement in health outcomes vary for subgroups defined by stroke risk (e.g., 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?

    3.a. Do the harms of screening vary for subgroups defined by stroke risk (e.g., based on CHA_2DS_2-VASc score), age, sex, or race/ethnicity?

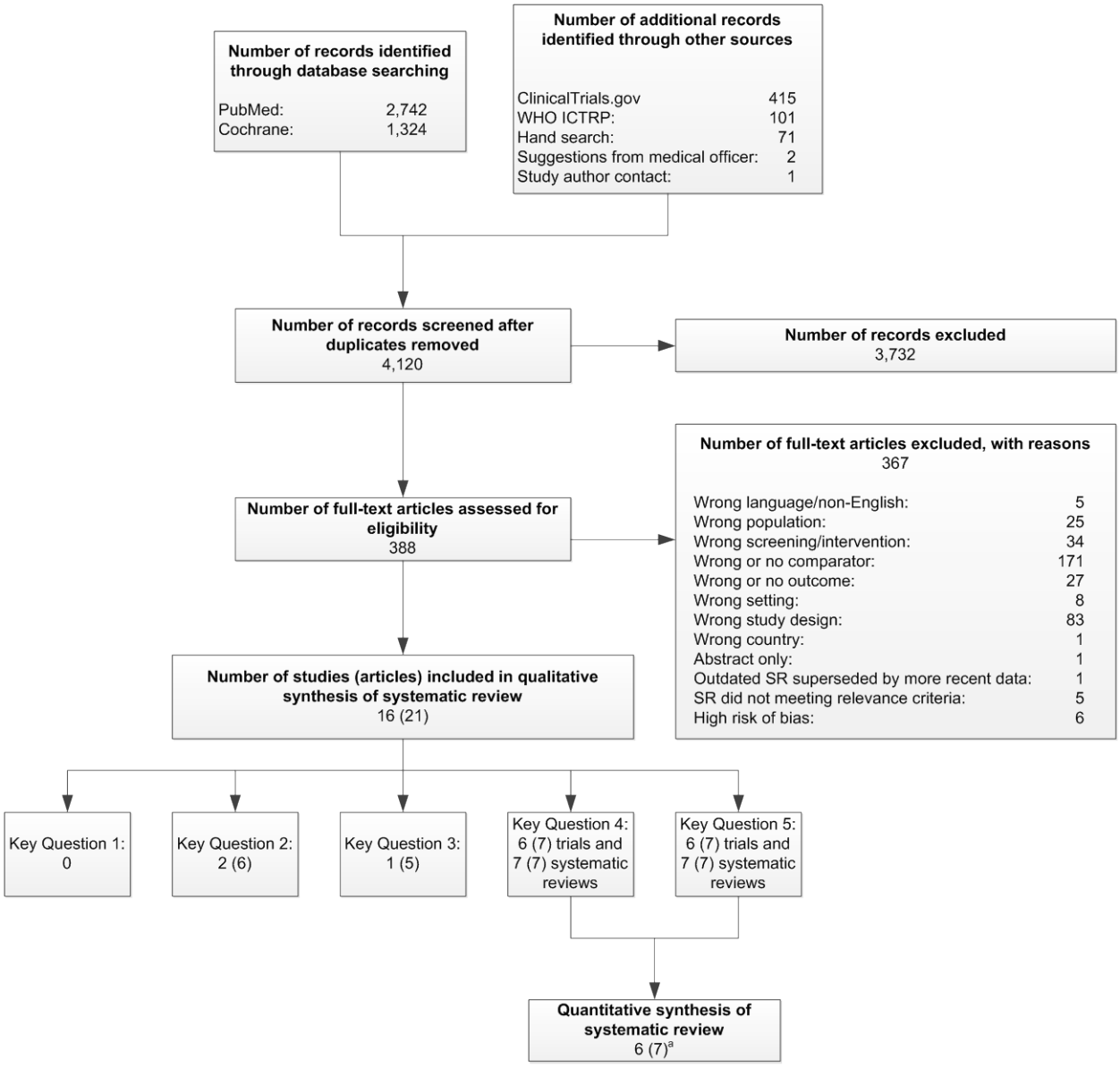
4. What are the benefits of anticoagulation or antiplatelet therapy on health outcomes in asymptomatic, screen-detected older adults with atrial fibrillation?

    4.a. Do the benefits of anticoagulation or antiplatelet therapy vary for subgroups defined by stroke risk (e.g., 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?

    5.a. Do the harms of anticoagulation or antiplatelet therapy vary for subgroups defined by stroke risk (e.g., based on CHA_2DS_2-VASc score), age, sex, or race/ethnicity?

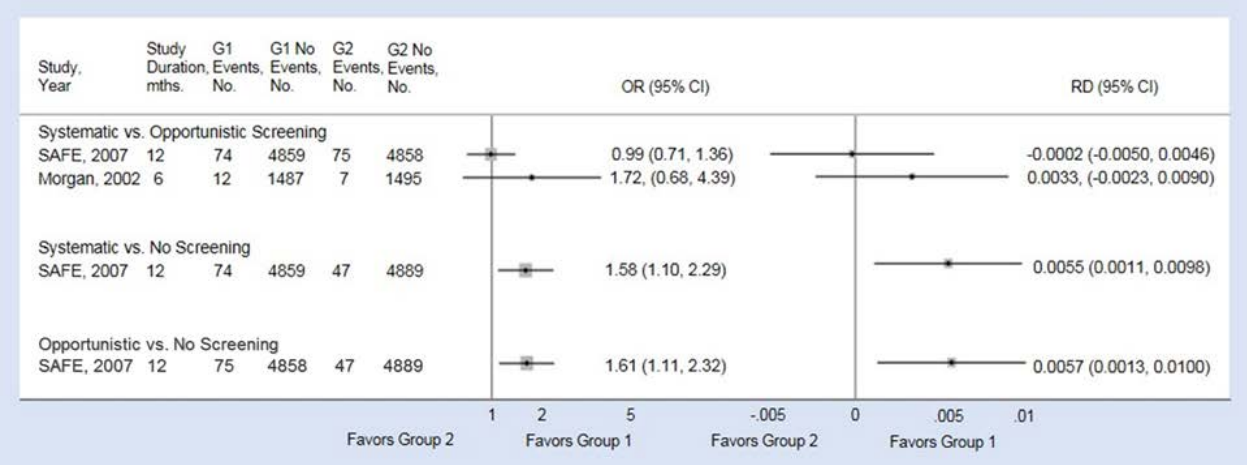
Figure 2. Summary of Evidence Search and Selection



[a] We also used one study rated poor quality in sensitivity analyses.[70]

Abbreviations: SR=systematic review; WHO ICTRP=World Health Organization International Clinical Trials Registry Platform.

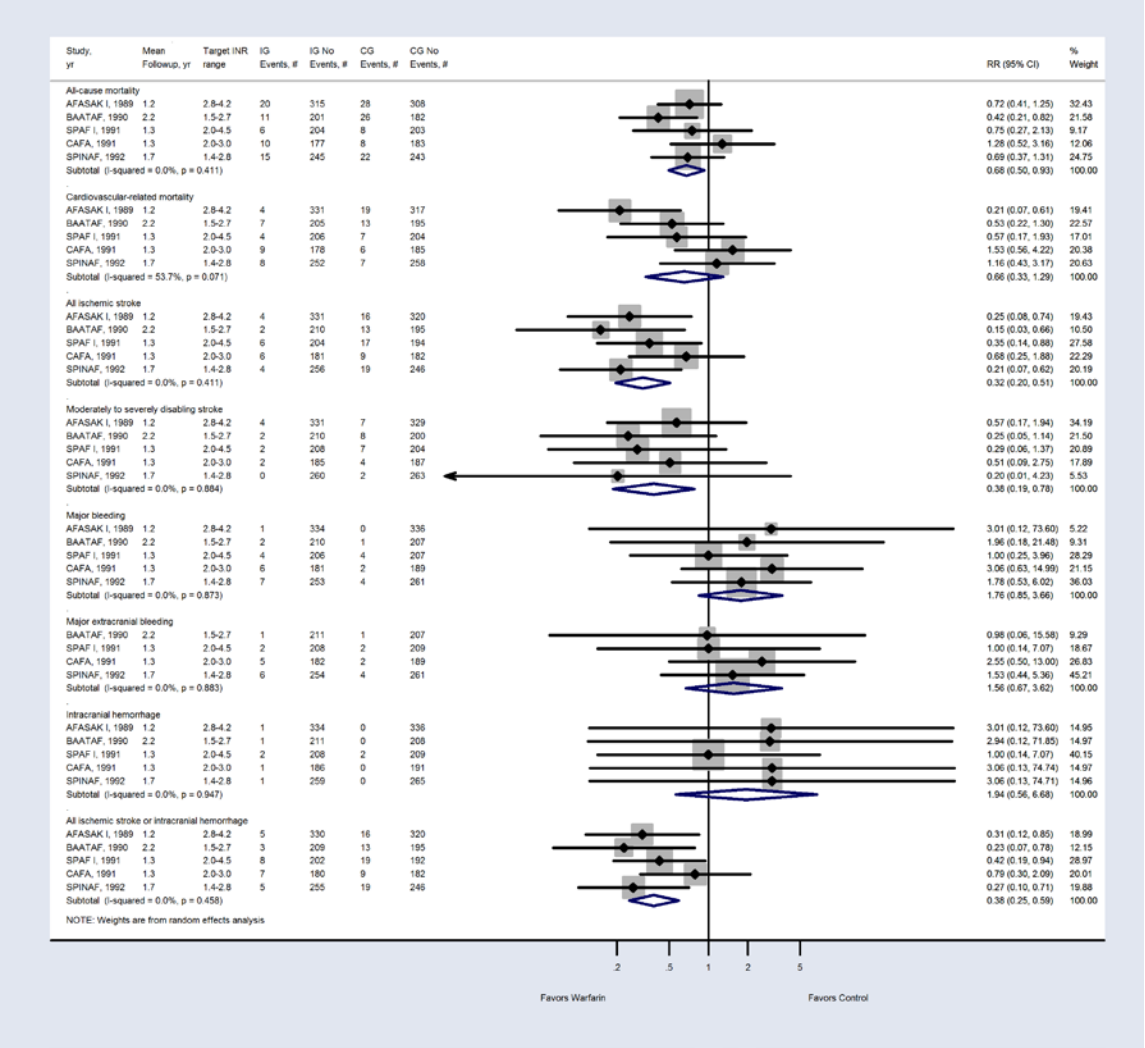
Figure 3. Odds of Detecting New Cases of Atrial Fibrillation and Absolute Difference in New Cases Detected, by Comparison



Analyses for this figure used the full study denominators. If using smaller denominators that exclude persons determined to have a prior history of AF, the results were almost identical. Specifically, for the ORs (95% CIs) from top to bottom they were: 0.99 (0.71, 1.36); 1.78 (0.70, 4.52); 1.57 (1.09, 2.26); 1.59 (1.10, 2.29). For the RDs (95% CIs), they were: -0.0002 (-0.0054, 0.0049), 0.0036 (-0.0022, 0.0094); 0.0058 (0.0011, 0.0105); 0.0060 (0.0013, 0.0107).

Abbreviations: CI=confidence interval; G=group; ICU=intensive care unit; IG=intervention group; INR=international normalized ratio; No.=number; OR=odds ratio; RD=risk difference; SAFE=Screening for Atrial Fibrillation in the Elderly.

Figure 4. Relative Risk of All-Cause Mortality, Cardiovascular-Related Mortality, All Ischemic Stroke, Moderately to Severely Disabling Stroke, Major Bleeding, Major Extracranial Bleeding, Intracranial Hemorrhage, and All Ischemic Stroke or Intracranial Hemorrhage for Warfarin Compared With Controls



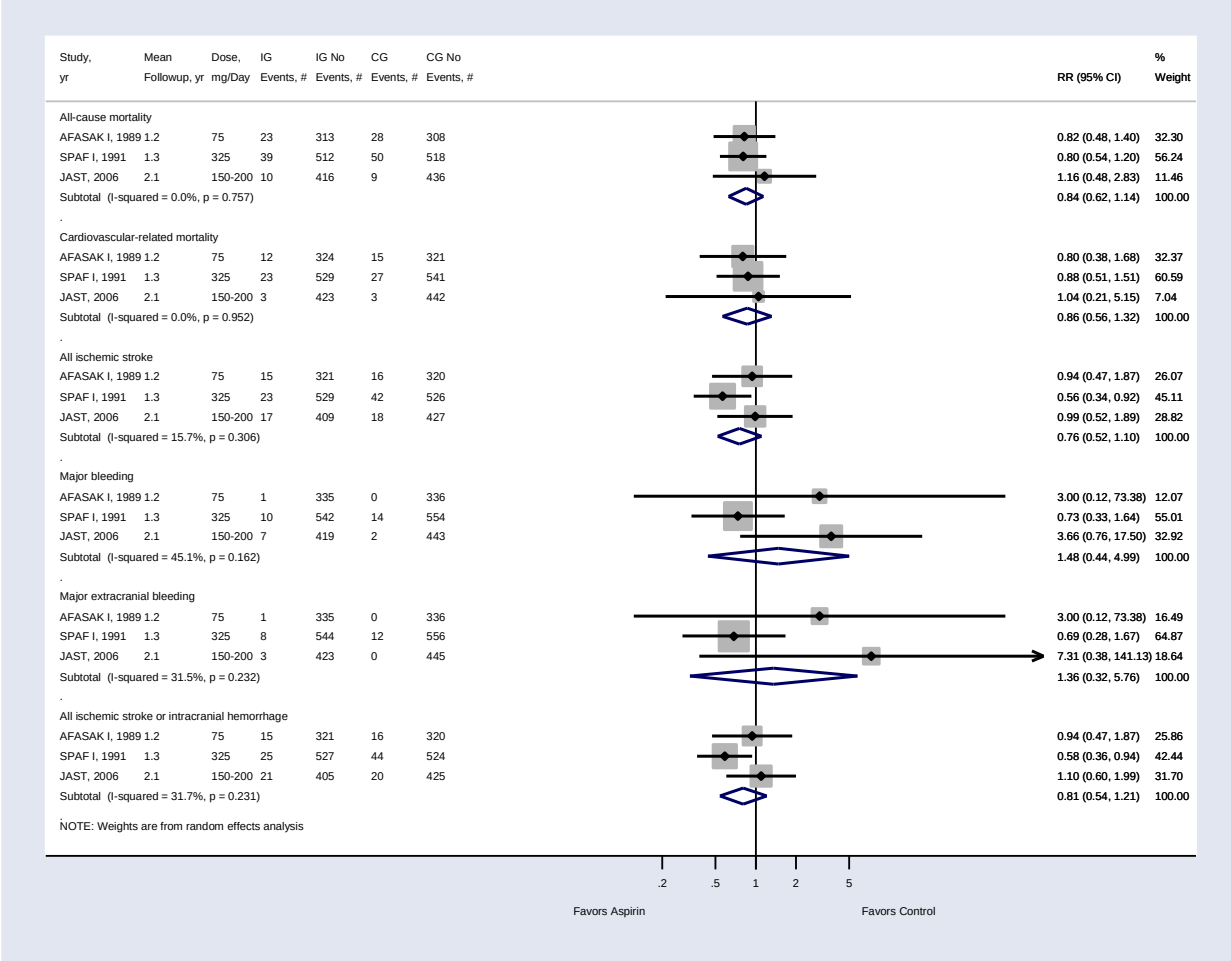
All-cause mortality: SPINAF includes only those without a history of stroke. AFASAK includes data from a previously published meta-analysis that they obtained data from the original study authors.

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 and 0 for placebo. BAATAF defines major bleeding as intracranial bleeding, fatal bleeding, or bleeding that led to a blood transfusion (four or more units of blood within 48 hours). SPAF I defines major bleeding as bleeding that involved the central nervous system, management requiring hospitalization with transfusion and/or surgery, 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 ICU admission.

Intracranial Hemorrhage: SPAF I events included one fatal intracerebral hemorrhage and one subdural hematoma with full recovery in the warfarin group, and two subdural hematomas with full recovery in the placebo group.

Abbreviations: AFASAK=Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation study; BAATAF=Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA=Canadian Atrial Fibrillation Anticoagulation study; CG=control group; CI=confidence interval; ICU=intensive care unit; IG=intervention group; INR=international normalized ratio; No.=number; RR=risk ratio; SPAF=Stroke Prevention in Atrial Fibrillation Study; SPINAF=Stroke Prevention in Atrial Fibrillation study; yr=year.

Figure 5. Relative Risk of All-Cause Mortality, Cardiovascular-Related Mortality, All Ischemic Stroke, Major Bleeding, Major Extracranial Bleeding, and All Ischemic Stroke or Intracranial Hemorrhage for Aspirin Compared With Controls



All-cause mortality: AFASAK includes data from a previously published meta-analysis that they obtained from the original study authors.

Major bleeding: AFASAK did not specify the severity of most bleeding events; it only reported that there were two aspirin bleeding episodes that required a blood transfusion and zero bleeding episodes in the placebo group. SPAF I defined major bleeding as bleeding that involved the central nervous system, management requiring hospitalization with transfusion and/or surgery, or permanent residual impairment. JAST defined major bleeding as fatal bleeding, bleeding that required hospital admission for treatment, bleeding that required a blood transfusion, or a decrease of hemoglobin concentration by more than 4g/dL.

Abbreviations: AFASAK=Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation study; CG=control group; CI=confidence interval; g/dL=grams per deciliter; JAST=Japan Atrial Fibrillation Stroke Trial; IG=intervention group; INR=international normalized ratio; No.=number; RR=risk ratio; SPAF=Stroke Prevention in Atrial Fibrillation Study; yr=year.

Table 1. Classification of Atrial Fibrillation

Type of AF	Definition
Paroxysmal	AF that terminates spontaneously or with intervention within 7 days of onset; episodes may recur with variable frequency.
Persistent	Continuous AF for more than 7 days.
Long-standing persistent	Continuous AF for more than 12 months.
Permanent	AF when the patient and clinician make a joint decision to stop further attempts to restore and/or maintain sinus rhythm; does not reflect a pathophysiological attribute of AF.
Nonvalvular	AF in the absence of rheumatic mitral valve disease, mitral valve repair, or valve replacement.

Source: Adapted from 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines.[1]

Abbreviations: AF=atrial fibrillation.

Table 2. Characteristics of Included Randomized, Controlled Trials for KQs 2 and 3

First Author, Year Trial Name	G1 (N) G2 (N) G3 (N)	Screening Approaches	Source of Patients	Country	Duration of Study, Months	Mean Age	% F	Quality
Fitzmaurice, 2014[75]; Fitzmaurice, 2007[74]; Mant, 2007[76]; Hobbs, 2005[77]; Swancutt, 2004[78] SAFE	Opportunistic screening (4,933) Systematic screening (4,933) No screening (4,936)	Opportunistic screening: Nurses and physicians encouraged to record pulse during routine visits; patients with irregular pulses invited to attend a nurse-led screening clinic and have 12-lead ECG Systematic screening: Patients invited by letter to attend a nurse-led screening clinic where their radial pulse was palpated, and a 12-lead ECG was performed	50 primary care practices	United Kingdom	12	75.3	57.4	Fair
Morgan, 2002 [79]	Opportunistic screening (1,502) Systematic screening (1,499)	Opportunistic screening: Nurses and physicians were encouraged to record pulse during routine visits; if pulse was suspicious for atrial fibrillation, they decided whether to request ECG depending on the history and clinical context Systematic screening: 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	4 general practices	United Kingdom	6	75.5	58.8	Fair

Abbreviations: ECG=electrocardiogram; F=Female; G=group; N=sample size; SAFE=Screening for Atrial Fibrillation in the Elderly.

Table 3. Results of Included Randomized, Controlled Trials for KQs 2 and 3

First Author, Year Trial Name	G1 (N) G2 (N) G3 (N)	Atrial Fibrillation G1 N (%) G2 N (%) G3 N (%) Between-Group Difference or OR (95% CI)	Anxiety G1 N (%) G2 N (%) Mean State Anxiety (95% CI), p-Value (Unadjusted Except Where Indicated), Response Rate (Questionnaires Completed/Sent)
Fitzmaurice, 2014[75]; Fitzmaurice, 2007[74]; Mant, 2007[76]; Hobbs, 2005[77]; Swancutt, 2004[78] SAFE	Opportunistic screening (4,933) Systematic screening (4,933) No screening (4,936)	New cases identified (percentage of those randomized; percentage if excluding those with a history of atrial fibrillation and those with missing notes from the denominator): 75 (1.5; 1.64) 74 (1.5; 1.62) 47 (0.95; 1.04) *Screening (either approach) vs. no screening* Between-group difference: 0.59% (0.20% to 0.98%); the difference was similar and statistically significant for both opportunistic vs. no screening and systematic vs. no screening (p≤0.02 for both) OR: 1.58 (1.12 to 2.22), p=0.01 without accounting for baseline prevalence OR: 1.61 (1.14 to 2.29), p=0.0085 accounting for baseline prevalence *Opportunistic screening vs. systematic screening* Between-group difference: 0.02% (-0.5% to 0.5%) OR: 0.99 (0.72 to 1.37), p=0.95	*Systematic vs. opportunistic* Baseline: 35.78 (33.80 to 37.76) vs. 36.44 (34.35 to 38.53), p=0.695, 66% (493/750) Postscreening: 28.77 (28.27 to 29.26) vs. 28.25 (26.78 to 29.73), p=0.732, 75% (1940/2595) After 17 months: 35.92 (34.29 to 37.55) vs. 37.50 (35.82 to 39.18), p=0.089, p=0.844 (adjusted), 69% (535/777) *Screen positive (n=142) vs. screen negative (n=128)* (after 17 months): 38.12 (35.89 to 40.35) vs. 34.61 (32.41 to 36.81), p=0.028
Morgan, 2002 [79]	Opportunistic screening (1,502) Systematic screening (1,499)	*New cases identified* 7 (0.5) 12 (0.8) OR: 1.7 (0.68 to 4.4), p=0.25 *All cases identified (most of these had a prior diagnosis of atrial fibrillation)* 19 (1.3) 67 (4.5) Between-group difference: 3.2% (2.0% to 4.4%), p<0.001	NR

Abbreviations: CI=confidence interval; G=group; n=number (of patients); N=sample size; NR=not reported; OR=odds ratio; SAFE=Screening for Atrial Fibrillation in the Elderly.

Table 4. Characteristics of Included Randomized, Controlled Trials for KQs 4 and 5: Part 1

First Author, Year Trial Name	G1 (N) G2 (N) G3 (N)	Source of Patients	Country	Mean Followup, yr	Mean Age	% F	% Non-white
Petersen, 1989[84] AFASAK	Warfarin, adjusted dose (335) Aspirin 75 mg daily (336) Placebo (336)	Those with chronic AF from 2 outpatient ECG laboratories	Denmark	1.2	74	46	NR
The Boston Area Trial for Atrial Fibrillation Investigators, 1990[80] BAATAF	Warfarin, adjusted dose (212) Control[a] (208)	32 centers and 3 private medical offices	United States	2.2	68	28	NR
Stroke Prevention in Atrial Fibrillation Investigators, 1990 & 1991[92, 93] SPAF I	*Group 1 (anti-coagulation candidates)* Warfarin, adjusted dose (210) Aspirin 325 mg/day (206) Placebo (211) *Group 2 (non-anticoagulation candidates)* Aspirin 325 mg/day (346) Placebo (357)	15 centers	United States	1.3	67	29	16
Connolly, 1991[81] CAFA	Warfarin, dose adjusted per subject (187) Placebo (191)	11 centers (hospitals, outpatient laboratories, and direct physician referrals)	Canada	1.3	68	25	NR
Ezekowitz et al, 1992[82] SPINAF	Warfarin, adjusted dose (4-mg/day and adjusted to meet PT ratios) (260) Control (265)[b]	16 Department of Veterans Affairs medical centers	United States	1.7	67	0	NR
Sato et al, 2006[83] JAST	Aspirin 150-200 mg/day (426) Control (445)	13 centers and 76 affiliated hospitals	Japan	2.1	65	30	NR

Table 5. Characteristics of Included Randomized, Controlled Trials for KQs 4 and 5: Part 2

First Author, Year Trial Name	% TIA % Stroke	% HF % Heart Valve dz % CAD % HTN % DM	Target INR (PT)	TTR%
Petersen, 1989[84] AFASAK	2 4	52 NR 8 prior MI 32 12	2.8 to 4.2 (NR)	73
The Boston Area Trial for Atrial Fibrillation Investigators, 1990[80] BAATAF	NR 3	26 23 MR>1+ 52 51 15	1.5 to 2.7 (1.2 to 1.5)	83
Stroke Prevention in Atrial Fibrillation Investigators, 1990 & 1991[92, 93] SPAF I	7 Stroke or TIA	19 6 MVP 8 with prior MI 52 16	G1: 2 to 4.5 (1.3 to 1.8)	71 within target PT
Connolly, 1991[81] CAFA	4 Stroke or TIA	*22* NR 13 prior MI *39* *12*	2 to 3 (NR)	44
Ezekowitz et al, 1992[82] SPINAF	NR 8	30 15 MR>1+ 19 prior MI 58 18	1.4 to 2.8 (1.2 to 1.5)	56
Sato et al, 2006[83] JAST	2.5	9 NR 3 38 14	NA	NA

[a] Control group was allowed to take aspirin.

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

Abbreviations: AF=atrial fibrillation; AFASAK=Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation study; BAATAF=Boston Area Anticoagulation Trial for Atrial Fibrillation; CAD=coronary artery disease; CAFA=Canadian Atrial Fibrillation Anticoagulation study; DM=diabetes mellitus; dz=disease; ECG=electrocardiogram; F=female; G=group; HF=heart failure; HTN=hypertension; INR=international normalized ratio; JAST=Japan Atrial Fibrillation Stroke Trial; mg=milligrams; MI=myocardial infarction; MR=mitral regurgitation; N=sample size; MR=mitral regurgitation; MVP=mitral valve prolapse; NA=not applicable; NR=not reported; OR=odds ratio; PT=prothrombin time; SPAF=Stroke Prevention in Atrial Fibrillation Study; SPINAF=Stroke Prevention in Atrial Fibrillation study; TIA=transient ischemic attack; TTR=time in therapeutic range; yr=year.

Table 6. Summary of Evidence for Screening With ECG for Atrial Fibrillation

Key Question and Topic	No. of Studies & Study Design	No. of Participants	Summary of Main Findings (Including Consistency and Precision)	Quality	Limitations (Including Reporting Bias)	Strength of Evidence	Applicability
1: Benefits of screening	0	0	NA	NA	NA	Insufficient	NA
2: Identifying new cases of atrial fibrillation	2 RCTs	17,803	No significant difference between systematic and opportunistic screening; ORs were 0.99 (0.72 to 1.37) and 1.7 (0.68 to 4.4), respectively; consistent, imprecise. Screening identifies more new cases than no screening (absolute increase in new cases, 0.6% [0.2% to 0.98%]; OR, 1.6 [1.1 to 2.3] accounting for baseline prevalence); consistent[a]; imprecise.	Fair	Allocation concealment was inadequate or not reported; limited reporting of baseline characteristics to allow assessment for baseline differences (studies reported only age and sex); potential ascertainment bias for previous atrial fibrillation diagnoses in 1 study (done by 1 person and masking to allocation was NR);[79] reporting bias not detected.	Low	Adults age 65 or older without a known history of atrial fibrillation Questionable applicability to women One time, 12-lead ECG
3: Harms of screening	1 RCT	False positives: 2,595 Anxiety: 1,940[b] (of the 14,802 participants in the SAFE study)	General practitioners misinterpreted 8% of sinus rhythm cases as AF compared with reference standard cardiologists (sensitivity 79.8 [95% CI, 70.5 to 87.2]; specificity 91.6 [90.1 to 93.1]) Mean anxiety (S6AQ) scores were not significantly different for systematic and opportunistic screening arms postscreening (28.8 [95% CI, 28.3 to 29.3] vs. 28.3 [26.8 to 29.7], p=0.73) or after 17 months (35.9 [34.3 to 37.6] vs. 37.5 [35.8 to 39.2], p=0.84 adjusted for baseline scores). Mean scores were higher for screen-positive vs. screen-negative respondents at 17 months (38.1 [35.9 to 40.4] vs. (34.6 [32.4 to 36.8], p=0.03); consistency unknown (single study); precise.	Fair	Relatively few participants were included in the analysis of screen-positive vs. screen-negative respondents (270 participants). *Screening vs no screening:* no anxiety data collected from no-screening group to allow comparison between screening and no-screening arms. Reporting bias not detected.	Low for false positives; low for anxiety for systematic vs. opportunistic and screen-positive vs. negative Insufficient for other harms and screening vs. no screening for all harms	Adults age 65 or older who were screened with an ECG

Table 6. Summary of Evidence for Screening With ECG for Atrial Fibrillation

Key Question and Topic	No. of Studies & Study Design	No. of Participants	Summary of Main Findings (Including Consistency and Precision)	Quality	Limitations (Including Reporting Bias)	Strength of Evidence	Applicability
4: Benefits of treatment	6 RCTs and 7 SRs	4,531 in the RCTs and 108,942 in the SRs	Warfarin treatment (mean 1.5 years) was associated with reduced all-cause mortality (pooled RR, 0.68 [0.50 to 0.93]) and ischemic stroke (pooled RR, 0.32 [0.20 to 0.51]) compared with controls (5 trials; 2,415 participants). Findings were consistent and precise. Aspirin was associated with reduced all-cause mortality and ischemic stroke compared with controls, but differences were not statistically significant.[c] Network meta-analysis (previously published[91]) found that all treatments (aspirin, VKAs, and all four NOACs)[d] reduced the risk of a primary outcome (composite of any stroke and systemic embolism) and all-cause mortality. For NOACs, it found statistically significant associations with reduction in the primary outcome compared with placebo/control (unadjusted ORs from 0.27 to 0.38; adjusted ORs from 0.32 to 0.44).[e]	Fair	All warfarin trials were stopped early; 3 of the 5 warfarin trials were open label; 4 of the 5 warfarin trials had inadequate or unclear methods of allocation concealment. Reporting bias not detected. Limitations of the network meta-analysis include (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	Adults with nonvalvular atrial fibrillation and no history of stroke or TIA; uncertain whether the results are applicable to asymptomatic screen-detected people with AF. Most participants had AF for more than a year and few had paroxysmal AF. Warfarin trials were mean 1.5 years; estimates for lifelong benefits are not available.
5: Harms of treatment	6 RCTs and 7 SRs	4,531 in the RCTs and 116,496 in the SRs	Warfarin treatment for an average of 1.5 to 1.6 years was associated with increased risk of major bleeding (pooled RR, 1.8 [0.85 to 3.7]) and intracranial hemorrhage (pooled RR, 1.9 [0.56 to 6.7]) compared with controls, but confidence intervals were wide and differences between groups were not statistically significant	Fair	All warfarin trials were stopped early; 3 of the 5 warfarin trials were open label; 4 of the 5 warfarin trials had inadequate or unclear methods of allocation concealment; reporting bias not detected. Limitations of the network meta-analysis include (1) the lack of sensitivity analyses removing the	Moderate[g]	Adults with nonvalvular AF and no history of stroke or TIA

Table 6. Summary of Evidence for Screening With ECG for Atrial Fibrillation

Key Question and Topic	No. of Studies & Study Design	No. of Participants	Summary of Main Findings (Including Consistency and Precision)	Quality	Limitations (Including Reporting Bias)	Strength of Evidence	Applicability
			(5 trials; 2,415 participants). Findings were consistent and imprecise. Aspirin was associated with increased risk of bleeding compared with controls; confidence intervals were wide, and differences were not statistically significant.[f] Network meta-analysis (previously published[91]) found that the four NOACs were associated with increased risk of bleeding compared with placebo/controls (adjusted ORs from 1.38 to 2.21); confidence intervals were wide and differences between groups were not statistically significant).[h]		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.		

[a] Consistent when considering the studies described in Appendix A for Contextual Question 1 and considering that the results were consistent for systematic screening versus no screening when compared with those for opportunistic screening versus no screening.
[b] The number of participants may be slightly greater than 1,940 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 were also in the post-ECG screening sample. The study reported that 493 participants completed the baseline S6AQ, 1,940 completed the postscreening S6AQ, and 535 returned the end-of-study S6AQ.
[c] Aspirin treatment for an average of 1.5 years was associated with a reduction in all-cause mortality (pooled RR, 0.84 [0.62 to 1.14]) and ischemic stroke (pooled RR, 0.76 [95% CI, 0.52 to 1.1]) compared with controls, but the differences were not statistically significant; 3 trials; 2,663 participants. Findings were consistent and imprecise.
[d] The four NOACs are apixaban, dabigatran, edoxaban, and rivaroxaban.
[e] The network meta-analysis also found no statistically significant differences for the four NOACs in comparison to one another. In adjusted analyses, the NOACs were not statistically different from VKAs for the primary outcome or for all-cause mortality. VKAs and the NOACs showed greater reduction in risk of the primary outcome compared with aspirin.
[f] Aspirin treatment for an average of 1.5 years was associated with an increased risk of major bleeding compared with controls, but the confidence interval was wide and the difference between groups was not statistically significant (pooled RR, 1.5 [95% CI, 0.44 to 5.0]; 3 trials; 2,663 participants).
[g] Although findings were imprecise and quality was fair, we graded the strength of evidence as Moderate considering evidence on dose response (with higher INRs increasing bleeding risk) and evidence on treatment of other conditions showing consistent evidence of bleeding risk.
[h]The network meta-analysis also found no statistically significant differences for the four NOACs in comparison to one another. Compared with VKAs, three of the NOACs (apixaban, dabigatran, and edoxaban) were associated with a lower risk of bleeding (range of ORs [95% CIs] from 0.64 [0.46 to 0.90] to 0.85 [0.65 to 1.11]), but the difference was only statistically significant for edoxaban (0.64 [0.46 to 0.90]). For rivaroxaban compared with VKAs, the odds of major bleeding was 1.03 (95% CI, 0.68, 1.57).

Abbreviations: $CHADS_2$=Congestive heart failure, Hypertension, Age≥75 years, Diabetes mellitus, prior Stroke or TIA or thromboembolism; CI=confidence intervals; ECG=electrocardiogram; INR=international normalized ratio; NA=not applicable; No.=number; NOAC=novel oral anticoagulant; NR=not reported; OR=odds ratio; RCT=randomized control trial; RR=relative risk; S6AQ=Spielberger 6-item Anxiety Questionnaire; SR=systematic review; TIA=transient ischemic attack; VKA=vitamin K antagonist.

Appendix A Table 1. Prevalence of Atrial Fibrillation by Age and Sex in the ATRIA Study[1]

Prevalence

On the basis of 1990s data from 1.89 million adult members of a health maintenance organization in California, the AnTicoagulation and Risk factors In Atrial fibrillation (ATRIA) study reported a prevalence of diagnosed AF among the general population of 0.95 percent, increasing with age (**Appendix A Table 1**).[1] The ATRIA study also identified differences in AF prevalence based on race. Although African American and white patients between 50 and 59 years of age patients had similar rates of AF, higher rates were reported among white patients in older age groups: 1.8 percent versus 1.3 percent in patients ages 60 to 69 years, 5.2 percent versus 4.4 percent in patients ages 70 to 79 years, and 9.9 percent versus 7.7 percent among those age 80 years or older.[1]

Age Band (years)	Prevalence in Women (%)	Prevalence in Men (%)
<55	0.1	0.2
55–59	0.4	0.9
60–64	1.0	1.7
65–69	1.7	3.0
70–74	3.4	5.0
75–79	5.0	7.3
80–84	7.2	10.3
≥85	9.1	11.1

Abbreviation: ATRIA=AnTicoagulation and Risk factors In Atrial fibrillation.

Appendix A Table 2. Validated Risk Prediction Tools for Stroke Risk

	Stroke Risk Tool				
	$CHADS_2$[2]	CHA_2DS_2-VASc[3]	R_2CHADS_2[4]	QStroke[5]	ATRIA[a,6]
Risk Factor Category	**Scoring/Points**				
Congestive heart failure	1 (recent)	1 (or LV dysfunction)	1 (recent)	Y/N	1
Hypertension	1 (history of)	1	1 (history of)	Continuous (SBP)	1
Age (years)	1 (75+)	1 (65–74) 2 (75+)	1 (75+)	Range, 25–84	6/9 (85+) 5/7 (75–84) 3/7 (65–74) 0/8 (<65)
Diabetes mellitus	1	1	1	Y/N (T1DM, T2DM)	1
Stroke/TIA/TE	2	2	2		
Renal dysfunction			2 (creatinine clearance <60 mL/min)		1 (proteinuria) 1 (eGFR<45 mL/min/1.73 m^2 or ESRD)
Sex		1 (female)		Separate models for M/F	1 (female)
Vascular disease		1 (prior MI, PAD, or aortic plaque)			
Valvular heart disease				Y/N	
Family history CHD				Y/N	
TC:HDLC ratio				Continuous	
Atrial fibrillation				Y/N	
Rheumatoid arthritis				Y/N	
BMI				Continuous	
Smoking status				5 categories	
Ethnicity				9 categories	
Deprivation				Continuous (TDI score)	

[a] Scored for age categories with/without prior stroke.

Abbreviations: ATRIA=AnTicoagulation and Risk factors In Atrial fibrillation; BMI=body mass index; $CHADS_2$= Congestive heart failure, Hypertension, Age≥75 years, Diabetes mellitus, Prior stroke or TIA or thromboembolism; CHA_2DS_2-VASc=Congestive heart failure (or left ventricular systolic dysfunction), Hypertension, Age≥75 years, Diabetes mellitus, Prior stroke or TIA or thromboembolism, Vascular disease, Age 65–74 years, Sex category; CHD=coronary heart disease; eGFR=estimated glomerular filtration rate; ESRD=end stage renal disease; HDLC=high density lipoprotein cholesterol; LV=left ventricular; m^2=square meters; M/F=male/female; MI=myocardial infarction; min=minute; mL=milliliters; PAD=peripheral artery disease; R_2CHADS_2=Renal Dysfunction, Congestive Heart Failure, Hypertension, Age, Diabetes, Stroke/Transient Ischemic Attack; SBP=systolic blood pressure; T1DM=type 1 diabetes mellitus; T2DM=type 2 diabetes mellitus; TC=total cholesterol; TDI=Townsend deprivation index; TE=thromboembolism; TIA=transient ischemic attack; Y/N=yes/no.

Appendix A Table 3. Validated Risk Prediction Tools for Bleeding Risk

	Bleeding Risk Tool			
	HAS-BLED[a,7]	**HEMORR$_2$HAGES[8]**		**ATRIA[9]**
Risk Factor Category	**Scoring/Points**			
Hypertension	1	1 (uncontrolled)		1
Age (years)	1 (65+ or frail)	1 (75+)		2 (75+)
Stroke	1	1		
Hepatic and/or renal dysfunction	1 or 2	1		3 (severe renal disease)
Ethanol abuse	1	1		
Anemia		1		3
Bleeding-associated factors	1 (bleeding tendency or predisposition)	1 (reduced platelet count/function)	2 (rebleeding risk)	1 (prior hemorrhage)
Malignancy		1		
Genetic factors (CYP2C9 SNP)		1		
Excessive fall risk		1		
Labile INRs (if on warfarin)	1			
Drugs (e.g., anti-platelet or NSAIDs)	1			

[a] A 2013 review by the AHRQ Effective Health Care Program found that, based on limited evidence, the HAS-BLED tool best discriminates the bleeding risk in patients with AF;[10] recent guidelines from the United Kingdom, Europe, and Canada also recommend its use for the stratification of bleeding risk in AF patients before treatment decisions.[11-13]

Abbreviations: ATRIA=AnTicoagulation and Risk factors In Atrial fibrillation; CYP2C9 SNP=Gene variant (single nucleotide polymorphism) affecting drug metabolism; HAS-BLED=Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile international normalized ratios, Elderly, Drugs or alcohol; HEMORR$_2$HAGES=Hepatic or renal disease, ethanol abuse, Malignancy, Older age, Reduced platelet count or function, Rebleeding risk, Hypertension, Anemia, Genetic factors, Excessive fall risk, Stroke; INR=International Normalized Ratio, assay used to determine clotting tendency; NSAID=non-steroidal anti-inflammatory drug.

Appendix A Table 4. Recent Recommendations (2010–2015) on Primary Prevention of Stroke (including screening and/or treatment) in Patients with Atrial Fibrillation

Society or Professional Organization, Year Scope	Screening	Anticoagulation[a]	Antiplatelet[a]
UK NSC, 2014[14] Screening for AF	Age ≥65 years, screening not recommended	Not addressed	Not addressed
NICE, 2014[13] Management of AF	Not directly addressed, pulse palpation for symptoms and ECG when AF is suspected because of irregular pulse (symptomatic or not)	VKA or NOAC[b]	Not recommended
AHA/ACC/HRS, 2014[15] Management of AF	Not addressed	VKA or NOAC[b]	Low stroke risk only[c]
AHA/ASA 2014[16] Prevention of stroke	Age ≥65 years, pulse w/ECG as appropriate	VKA or NOAC[b]	Low stroke risk only[c]
AAN, 2014[17] Prevention of stroke in NVAF	Not addressed	VKA or NOAC[d]	Low stroke risk only[c]
CADTH, 2013[18] Antithrombotic agents in AF	Not addressed	VKA or NOAC[e]	Not addressed
SIGN, 2013[19] Antithrombotic indications	Not addressed	VKA or NOAC[f, g]	Limited to persons refusing VKA/NOAC
ACCP, 2012[20] Antithrombotic therapy for AF	Not addressed	NOAC > VKA[f]	Low stroke risk[c] or patients refusing VKA/NOAC
AHA/ASA, 2012[21] Antithrombotic agents in NVAF	Not addressed	VKA or NOAC	Low stroke risk only
CCS, 2014[22] stroke prevention in AF	Not addressed	NOAC > VKA[f]	Low stroke risk only
ESC, 2012[23] Management of AF	Age ≥65 years, pulse w/ECG as appropriate	VKA or NOAC[b]	Limited to persons refusing VKA/NOAC
RCPE, 2012[24] Management of AF	Age ≥65 years, pulse w/ECG as appropriate	VKA or NOAC[g]	Not recommended
ACCF/AHA 2010[25] CV risk in asymptomatic adults	Consider resting ECG in adults with HTN or DM (not specific to AF)	Not addressed	Not addressed
CSN, 2010[26] Prevention of stroke	Not addressed	VKA or NOAC[f]	Low stroke risk only[h]

[a] All treatment recommendations are for patients found to be appropriate candidates for treatment based on risk stratification
[b] Recommended for patients with CHA_2DS_2-VASc score ≥2, variable recommendations for score=1
[c] Consider for patients with CHA_2DS_2-VASc score=1
[d] Recommended for elderly patients (older than 75 years of age) with no history of recent unprovoked bleeding, variable for patients with dementia or occasional falls
[e] NOAC for patients with a $CHADS_2$ score ≥1 who are unable to achieve adequate anticoagulation with warfarin
[f] Recommended for patients ≥ age 65 or with $CHADS_2$ score ≥1
[g] Recommended for patients with CHA_2DS_2-VASc score ≥1
[h] Recommended for patients with $CHADS_2$ score ≥1

Abbreviations: AAN=American Academy of Neurology; ACC=American College of Cardiology; ACCF=American College of Cardiology Foundation; ACCP=American College of Chest Physicians; AF=atrial fibrillation; AHA=American Heart Association; ASA=American Stroke Association; CADTH=Canadian Agency for Drugs and Technologies in Health; CCS=Canadian Cardiovascular Society; CSN=Canadian Stroke Network; CV=cardiovascular; DM=diabetes mellitus; ECG=electrocardiogram; ESC=European Society of Cardiology; HRS=Heart Rhythm Society; HTN=hypertension; NICE=National Institute for Health and Care Excellence; NOAC=novel oral anticoagulants; NSC=National Screening Committee; NVAF=non-valvular atrial fibrillation; RCPE=Royal College of Physicians of Edinburgh; SIGN=Scottish Intercollegiate Guidelines Network; UK=United Kingdom; VKA=vitamin K antagonists.

CQ 1. What is the prevalence of previously unrecognized or undiagnosed atrial fibrillation among asymptomatic adults, by age (groups), in primary care and community settings?

We identified 19 studies that reported on the prevalence of previously undiagnosed atrial fibrillation (AF) among adults. **Appendix A Table 5** [CQ1] summarizes the study populations, detection method used, and findings from these studies. Ten studies were conducted among population-based samples or participants recruited from community settings, and nine studies were conducted among participants recruited from primary care clinical settings. A variety of approaches to detecting AF were used in these studies. Six studies used one-time single-lead ECG via handheld devices for intervals between 10 and 30 seconds.[27-32] Nine studies used a single, resting 12-lead ECG.[33-41] The remaining studies used intermittent[42, 43] or continuous[44] single-lead ECG over a period of 2 weeks or a combination approach of a single-lead ECG with a followup confirmatory 12-lead ECG.[45] Studies that included both younger and older adults did not provide results stratified by age. The pooled prevalence of previously undiagnosed AF among clinic-based populations is 1.1 percent (95% CI, 0.8% to 1.6%; I^2=83%; 9 studies; 21,919 participants, **Appendix A Figure 1**), and the pooled prevalence among community-based populations is 1.3 percent (95% CI, 0.8% to 2.0%; I^2=98%; 10 studies; 78,328 participants; **Appendix A Figure 1**). These data provide an estimate of the total burden of undiagnosed AF but do not offer evidence about differences in detection of undiagnosed AF between routine screening and usual care. This is addressed in KQ 2 of this review.

Appendix A Table 5 [CQ1]. Summary of Studies Published Since 2000 Reporting the Prevalence of Previously Undiagnosed Atrial Fibrillation

ID; Author, Year; Trial Name (if applicable)	Study Design	Sample Size	Country	Study Population	Method of Detection	Previously Undiagnosed Atrial Fibrillation Prevalence (95% CI)
Population or Community-Based Samples						
Chan et al., 2016[27]	Uncontrolled trial	8,797	Hong Kong	Population-based sample of adults age 18 years or older. Mean age 64.7 (SD 13.4) 71.5% men 38.2% HTN 14.8% DM 0.7 % heart failure 2.2 coronary heart disease 2.7 cardiothoracic surgery	One-time single-lead ECG for 30-second interval using handheld device with smartphone application (AliveCor device). Detection based on presence of full 30-second interval of AF.	1.1% (NR)
Svennberg et al., 2015, STROKESTOP[42]	Uncontrolled trial	7,173	Sweden	Population-based sample of 75- and 76-year-old adults. % men NR No clinical characteristics reported for the overall study population.	12-lead ECG at index visit followed by intermittent single-lead ECG with handheld device twice daily and whenever palpitations occurred over 2 weeks. Detection based on AF or atrial flutter at index visit, during intermittent monitoring or in subsequent followup Holter monitoring or 12-lead ECGs.	3.0% (95% CI, 2.7% to 3.5%) (218 cases total, 37 diagnosed at the index visit; 140 diagnosed with intermittent ECG, and 41 required Holter monitor or other repeat 12-lead ECG; 8 cases were atrial flutter)
Lowres et al., 2014, SEARCH-AF[31]	Uncontrolled trial	1,000	Australia	Community-based sample of adults age 65 years or older recruited from community pharmacies. Mean age 76 (SD 7) 44% men	Pulse palpation and one-time single lead via handheld device connected to smartphone. Criteria for detection NR.	1.0% (95% CI, 0.5% to 1.8%) (Of the 10 cases of new AF, 2 had paroxysmal AF that reverted to sinus rhythm by the time of confirmation with 12-lead ECG)
Engdahl et al., 2013[43]	Uncontrolled trial	767	Sweden	Population based sample of 75- and 76-year-old adults. 43% men 4% heart failure 53% hypertension 11% diabetes 10% stroke/TIA	Stepwise screening approach, initial 12-lead ECG, if normal and $CHADS_2$ equal to 2 or more (i.e., 1 risk factor besides age) then intermittent single-lead ECG via handheld device twice daily for 2 weeks (55% of study population qualified for this second step). Detection based on 30-second interval of AF or two separate intervals at least 10 seconds.	5.2% (3.8 to 7.7) (40 cases total, 10 cases identified on initial 12-lead ECG, 30 cases identified on intermittent monitoring)

Appendix A Table 5 [CQ1]. Summary of Studies Published Since 2000 Reporting the Prevalence of Previously Undiagnosed Atrial Fibrillation

ID; Author, Year; Trial Name (if applicable)	Study Design	Sample Size	Country	Study Population	Method of Detection	Previously Undiagnosed Atrial Fibrillation Prevalence (95% CI)
Frewen et al., 2013, TILDA[38]	Cohort study	4,890	Ireland	Population-based sample of community-dwelling adults age 50 years or older from a longitudinal study on ageing. Mean age NR 54% men	12-lead ECG (lasting 10 minutes). Detection of AF by two independent clinicians according to European Society of Cardiology guidelines, with adjudication by a cardiologist.	0.9% (NR)
Claes et al., 2012[32]	Uncontrolled trial	10,758	Belgium	Community-based sample of adults 40 years or older recruited through media advertisements. Mean age 59 (SD, 11) 38% men	One-time single-lead ECG via a handheld device. Detection based on RR intervals, absence of p waves, and variable atrial cycle length.	1.5% (NR)
Schnabel et al., 2012[34]	Cohort study	5,000	Germany	Population-based sample of adults between ages 35 and 74 years. Mean age 52 (SD 11) 49.9% men 45.4% hypertension 6.0% diabetes 17.7% heart failure 1.5% stroke	12-lead ECG; detection based on confirmed AF by two independent cardiologists.	0.5% (NR)
Meschia et al., 2010[35]	Cohort study	29,861	USA	Racially and ethnically diverse population-based sample of adults age 45 years or older. Median age 74 (IQR 69 to 79) 45% men 11% stroke 59% hypertension 221% diabetes	12-lead ECG or 7-lead ECG obtained during in-home visit and interpreted centrally. Detection based on presence of AF on ECG.	0.6% (NR)
Doliwa et al., 2009[28]	Diagnostic accuracy study	606	Sweden	Community-based sample of adults age 18 years or older. 49% were age 60 or older 64% men	One-time single-lead ECG via handheld device for 10-second interval. Detection criteria NR.	1.0% (NR)
Furberg et al., 1994[39]	Cohort study	5,151	USA	Population recruited from Medicare eligibility lists of adults age 65 or older from four U.S. communities. Mean age 73 (NR) 43% men 94.7% white	One time, 12-lead ECG, interpreted centrally.	1.5% (NR)

Appendix A Table 5 [CQ1]. Summary of Studies Published Since 2000 Reporting the Prevalence of Previously Undiagnosed Atrial Fibrillation

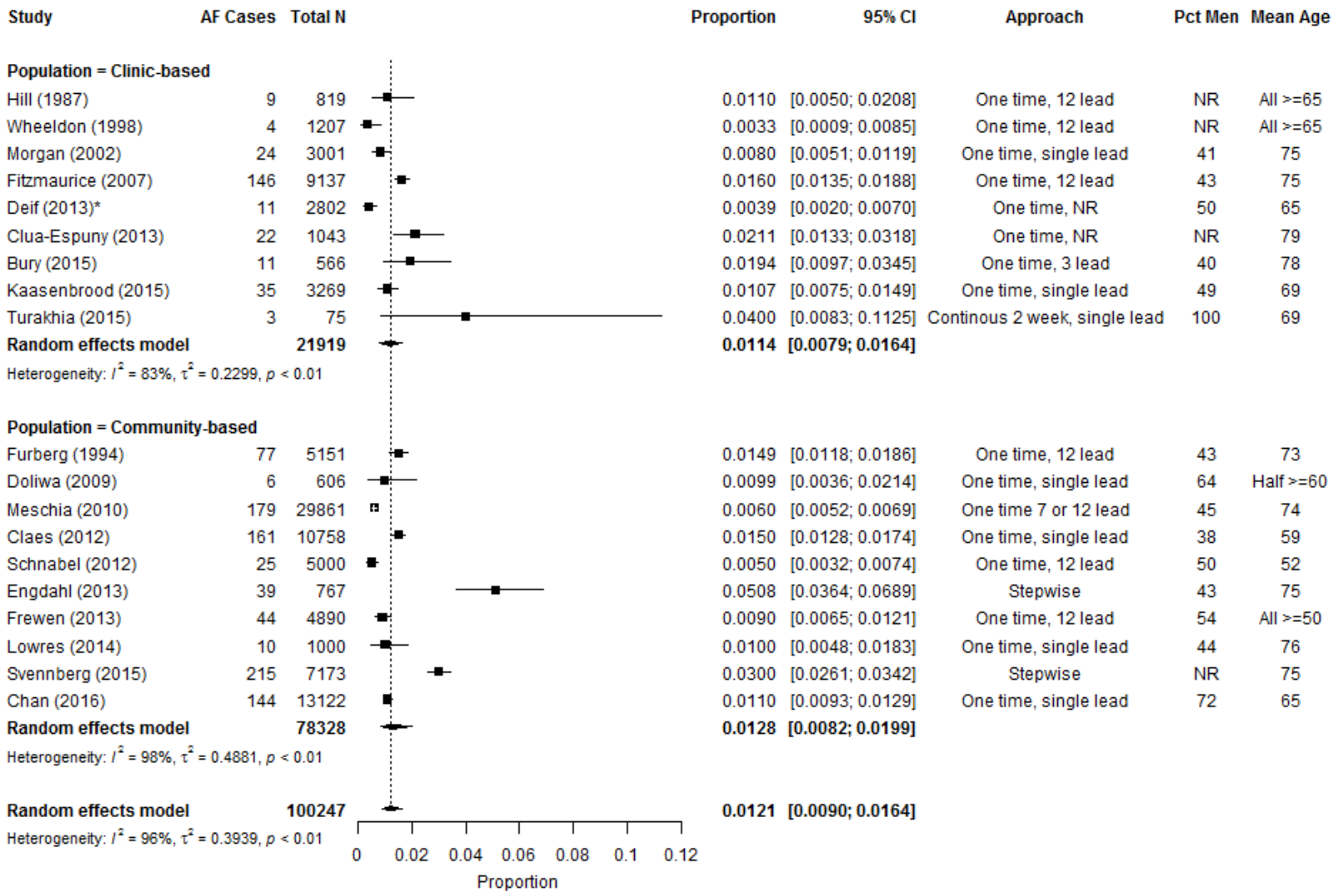
ID; Author, Year; Trial Name (if applicable)	Study Design	Sample Size	Country	Study Population	Method of Detection	Previously Undiagnosed Atrial Fibrillation Prevalence (95% CI)
Clinic-Based Samples						
Bury et al., 2015[45]	Uncontrolled trial	566	Ireland	Convenience sample of patients age 70 or older from 25 general practices. Mean age 78 (SD NR) 40% men 48.2% hypertension 10.6% diabetes 22.5% coronary heart disease 2.6% stroke 3.1% other heart surgery or cardiac procedures	One-time 3-lead ECG using the ECG component of an automated external defibrillator followed by confirmatory 12-lead ECG. Criteria for detection NR but included both AF and atrial flutter.	2.1% (NR) (2 of 12 cases were atrial flutter)
Kaasenbrood, 2016[29]	Uncontrolled trial	3,269	The Nether-lands	Patients age 60 or older recruited from 10 general practices at the time of yearly flu vaccination. Mean age 69.4 (SD 8.9) 49.0% men	One-time single lead ECG via handheld device for 60 seconds. Detection based on positive signal confirmed by cardiologist(s).	1.1% (NR)
Turakhia et al., 2015, STUDY-AF[44]	Uncontrolled trial	75	USA	Single Veteran's Health Administration clinic-based sample of adults age 55 years or older with 2 or more AF risk factors including CHD, heart failure, hypertension, diabetes, and sleep apnea. Mean age 69 (SD 8.0) 100% men 95% with hypertension 17% with heart failure 77% with coronary artery disease 56% with diabetes	Continuous single-lead ECG via a wearable patch-based device for 2 weeks. AF based on presence of 30 seconds or more interval of AF.	5.3% (NR)
Clua-Espuny et al., 2013[36]	Cross-sectional study	1,043	Spain	Patients recruited from primary care clinics. Mean age 78.9 (SD 7.3) % men NR	ECG in clinic setting, further details NR. Detection based on cardiologist confirmation of AF.	2.2% (NR)

Appendix A Table 5 [CQ1]. Summary of Studies Published Since 2000 Reporting the Prevalence of Previously Undiagnosed Atrial Fibrillation

ID; Author, Year; Trial Name (if applicable)	Study Design	Sample Size	Country	Study Population	Method of Detection	Previously Undiagnosed Atrial Fibrillation Prevalence (95% CI)
Deif et al., 2012[33]	Uncontrolled trial	2,802	Australia	Ambulatory adults age 40 or older undergoing preoperative evaluation for minor procedures or elective surgery. Mean age 65 (SD 13) 50% men	"Routine" ECG; detection criteria NR.	0.4% (NR) all participants 0.7% (NR) in participants age 65 years or older
Fitzmaurice et al., 2007; SAFE study[37]	Cluster RCT	9,137	UK	Patients age 65 or older from 50 general practices. Mean age 75.3 (SD 7.2) 42.8% men	Practices were allocated to screening or control, and screening practices were subsequently allocated to systematic (invitation to attend screening clinic with 12-lead ECG) or opportunistic screening (pulse check at usual care visits with referral to screening clinic if abnormal). Detection based on AF on 12-lead ECG.	1.6% (in practices allocated to screening) 1.0% (in practices allocated to control)
Morgan et al., 2002[30]	Parallel group RCT with two active comparators	3,001	UK	Patients ages 65 to 100 from four general practices. Mean age 75 (SD NR) 41% men	Systematic pulse and single-lead (II) ECG vs. opportunistic screening (reminder placed on patient chart to perform pulse screening). Detection based on AF on confirmatory ECG (in systematically screened arm).	Yield of new AF cases in systematically screened arm: 0.8% (NR) (systematically screened) 0.5% (NR) (opportunistically screened)
Wheeldon et al., 1998[41]	Uncontrolled trial	1,207	UK	Patients age 65 or older from four general practices. Mean age NR % Men NR	Single 12-lead ECG in clinic setting. Detection based on interpretation by cardiologist.	0.4% (NR)
Hill et al., 1987[40]	Uncontrolled trial	819	UK	Symptomless patients age 65 or older from a single general practice. Mean age	Single 12-lead ECG in clinic setting. Detection based on interpretation by two physicians.	1.2% (NR)

Abbreviations: AF=atrial fibrillation; CHD=coronary heart disease; CI=confidence interval; DM=diabetes mellitus; ECG=electrocardiogram; HTN=hypertension; ID=identification number; IQR=interquartile range; NR=not reported; RCT=randomized, controlled trial; RR= relative risk; SAFE=Screening for AF in the elderly; SD=standard deviation; STUDY-AF=Screening Study for Undiagnosed Atrial Fibrillation; TIA=transient ischemic attack; TILDA= The Irish Longitudinal Study on Ageing ; UK=United Kingdom; USA=United States of America.

Appendix A Figure 1. Meta-Analysis of Studies Assessing Proportion of Participants With Undiagnosed Atrial Fibrillation



CQ 2. What is the stroke risk in asymptomatic older adults with previously unrecognized or undiagnosed atrial fibrillation?

Incidence of Stroke for Incidentally Detected AF

Limited evidence was found regarding the incidence of stroke in asymptomatic older adults with unrecognized or undiagnosed AF conducted among the general population. Martinez et al. identified 5,555 persons with incidentally detected AF (and reportedly asymptomatic based on review of Read Medical Codes and ICD codes) through hospital and general practice databases.[46] These were not screen detected as far as the article reports but rather seem to have been detected in the course of usual care. Just over half were treated with oral anticoagulant therapy with or without antiplatelet therapy. The cohort included people with a history of CAD without MI (10.6%), MI (4.2%), and stroke or TIA (9.2%). Mean CHA_2DS_2-VASc score was 2.5 (SD, 1.5, and 73% had a score of 2 or greater) and mean $CHADS_2$ score was 1.3 (1.1). Limitations of the study include that patients were not screen detected and that using Read Medical Codes and ICD codes has limitations regarding the ability to identify asymptomatic people and to accurately identify previously undiagnosed AF. The study reported stroke incidence rates per 1,000 person-years over a maximum of 3 years by age group for those with incidentally detected AF as follows:

- Ages 18 to 49 years: 0 (95% CI, 0 to 6.5)
- Ages 50 to 64 years: 9.1 (95% CI, 5.9 to 13.4)
- Ages 65 to 74 years: 16.5 (95% CI, 13.1 to 20.6)
- Ages 75 to 84 years: 29.6 (95% CI, 25.1 to 34.7)

The study also provided data for a matched comparison group of people without AF (but not comparing asymptomatic vs. symptomatic people). Stoke incidence rates per 1,000 were 19.4 (17.1 to 21.9) for those with incidentally detected AF (all ages) and 8.4 (7.7 to 9.1) for the matched controls without AF.

Predicted Stroke Risk

Fitzmaurice et al. compared $CHADS_2$ scores among persons with newly diagnosed AF (149 cases) identified through either opportunistic screening or systematic screening in the SAFE study (described in KQ 2).[47] The proportion with scores greater than or equal to 1 was similar (82.7% [95% CI, 72.6 to 89.6] opportunistic screening group; 78.4% [95% CI, 67.7 to 86.2] systematically screened group; p=0.51). The proportion with scores of 2 or more was slightly lower in the opportunistic arm, but the difference was not statistically significant (29.3% [95% CI, 20.2 to 40.4] opportunistic arm vs. 43.2% [95% CI, 32.6 to 54.6] in the systematic screening arm; p=0.077). Eight of the 19 studies described in CQ 1 provided data on the mean predicted risk of stroke among persons with previously unrecognized or undiagnosed AF;[27, 29, 31, 33, 43-45] findings are summarized in **Appendix A Table 6 (CQ 2)**. The range of mean $CHADS_2$ scores was 1.8 to 2.2 (3 studies), and the range of mean CHA_2DS_2-VASc scores was 3.1 to 3.8 (7 studies), ranges that would typically be associated with initiation of anticoagulation (in the absence of contraindications).

Appendix A Table 6 (CQ2). Mean Predicted Stroke Risk Among Persons With Previously Unrecognized Atrial Fibrillation

Author, Year	n Previously Undiagnosed AF/ N Total Study Sample	Risk Instrument/ Mean (SD) Predicted Stroke Risk
Chan et al. (2016)[27]	101/8,797	CHA_2DS_2-VASc 3.1 (1.3)
Bury et al. (2015)[45]	12/566	CHA_2DS_2-VASc (median) 4
Kaasenbrood et al. (2015)[29]	37/3,269	CHA_2DS_2-VASc 3.4 (1.9)
Turakhia et al. (2015) [44]	4/75	CHA_2DS_2-VASc ≥2 in all 4 participants
Engdahl et al. (2013)[43]	10/767	$CHADS_2$ 1.8 (NR)
Dief et al. (2012)[33]	10/1,459	Among persons age 65 or older $CHADS_2$ 2.2 (1.5) CHA_2DS_2-VASc 3.8 (SD 2.0)
Svennberg et al. (2015)[42]	218/7,173	CHA_2DS_2-VASc 3.5 (1.2)
Lowres et al. (2013)[31]	15/1,000	$CHADS_2$ 1.9 (1.1) CHA_2DS_2-VASc 3.7 (1.1)

Abbreviations: AF=atrial fibrillation; CHA_2DS_2-VASc=Congestive heart failure, Hypertension, Age ≥75 years [doubled], Diabetes mellitus, prior Stroke or TIA or thromboembolism [doubled], Vascular disease, Age 65-74 years, Sex category; CQ=contextual question; n=number of patients; N=number of patients in sample; NR=not reported; SD=standard deviation.

Relative Risk of Stroke in Asymptomatic AF Versus Symptomatic AF

Four cohort studies provide information related to the relative risk of stroke among persons with asymptomatic AF compared with persons with symptomatic AF. Study details and limitations are summarized in **Appendix A Table 7**. These studies were conducted among different patient populations using different approaches to ascertain AF, and some reported a higher absolute incidence of stroke among persons with asymptomatic AF compared with persons with symptomatic AF. Adjusted analyses in two of the four studies showed no statistically significant difference between those with asymptomatic and symptomatic AF. Although some of the studies adjusted for known differences in baseline characteristics, the potential for residual confounding in these studies is high because asymptomatic and symptomatic persons differed on baseline characteristics across all studies for which this information was available. Some studies did not consider important risk factors for stroke in their adjusted analyses (e.g., CHA_2DS_2-VASc score or its components, smoking). Further, although some information about rates of anticoagulation treatment among persons with asymptomatic AF was provided, differences in treatment to prevent stroke between groups cannot be ruled out. The risk of selection bias in most of these studies is high, because many identified patients were from cardiology or AF registries, and may not be representative of patients seen in primary care. Over 60 percent of participants in two of the studies had heart disease at baseline, and one study did not report baseline descriptive information (published as abstract only). Risk of ascertainment bias for determining symptom status (i.e., whether people were asymptomatic) is also a concern because the studies typically reported limited information about methods for ascertainment, and they relied on retrospective chart reviews or claims to determine whether patients were asymptomatic. Only one clearly distinguished fully asymptomatic (no current or past symptoms of AF) patients (Boriani et al., 2015) from patients who are currently asymptomatic, indicating a more appropriately detailed ascertainment of symptom status;[48] it reported no difference in outcomes for symptomatic and asymptomatic patients in adjusted analyses.

Appendix A Table 7. Stroke Incidence for People With Asymptomatic, Previously Unrecognized AF vs. People With Symptomatic AF Reported by Observational Studies

Author, Year Country	Study Population and Setting	Stroke Incidence	Study Limitations
Potpara, 2013[49] Serbia	146 asymptomatic patients with initial AF diagnosis between 1997 and 2007 diagnosed with 12-lead ECG during period medical exam based on registry of patients with AF. (Total cohort=1,100 individuals with AF) 47.9% were placed on aspirin and 40.4% were placed on oral anticoagulants after diagnosis	14 (9.6%) vs. 44 (5.6%) with ischemic stroke during mean followup of 9.9 years Adjusted HR 1.8 (95% CI, 1.0 to 3.4, p=0.051) compared with individuals in cohort with symptomatic AF (adjustment for age, sex, and treatment at baseline)	-High potential for confounding (e.g., no adjustment for smoking status and other relevant imbalances between symptomatic and asymptomatic individuals at baseline) -Limited information regarding ascertainment of AF symptoms -60% had prior heart disease, so not applicable to general population
Tsang, 2011[50] US	1,152 asymptomatic adults (mean age 74 years) with ECG-confirmed diagnosis of first AF between 1980 and 2000 in Olmsted County, Minnesota, based on medical record review (Total cohort=4,618)	Number (%) of events NR for either group. Compared with persons with symptomatic AF, persons with asymptomatic AF were three times more likely to have sustained an ischemic stroke prior to their diagnosis after adjustment for age, sex, and other stroke risk factors ($p<0.0001$)	-Data published in abstract format only, limiting assessment of risk of bias -No information to assess whether groups were similar at baseline or what specific stroke risk factors were included in analysis (it reported adjusting for age, sex, and "multiple other stroke risk factors"). -Methods of ascertaining symptom status NR (other than stating that medical records were used)
Siontis, 2016[51] US	161 asymptomatic adults (mean age 69.2) from among 1,000 randomly selected patients from a total cohort of 3,344 adults with incident AF between 2000 and 2010 in Olmsted County, Minnesota	Total of 59 strokes (among the 1,000). Persons with asymptomatic AF had higher incidence of stroke over median followup of 5.6 years compared with persons with typical AF (adjusted HR 2.6, 95% CI 1.10 to 6.11, adjusted for CHA_2DS_2-VASc score, age, BMI, smoking status, COPD, eGFR, dementia, malignancy, warfarin use and time in therapeutic range)	-Potential for residual confounding due to unmeasured differences in baseline characteristics among persons with typical, atypical, and asymptomatic AF as these groups were clearly different on numerous measured baseline characteristics -Symptom status ascertained retrospectively by medical records review (by trained abstractors looking for information about palpitations, atypical symptoms, etc.)
Boriani, 2015[48] Europe	1,237 persons with asymptomatic AF (mean age 72; 520/1,237 with "fully asymptomatic" AF, indicating absence of current and previous symptoms) in a AF registry from those presenting to cardiology practices from 9 countries. Most asymptomatic patients had valvular heart	Mean followup about 1 year 112/1064 (10.5%) vs. 80/1409 (5.7%) events for a composite incidence of stroke/TIA/peripheral embolism or death higher in asymptomatic AF compared to symptomatic AF at 1 year ($p < 0.0001$) in unadjusted analyses. Multivariate analyses found no significant association with symptom status for mortality or for the composite of stroke/TIA/peripheral embolism or death[a]	-High potential for residual confounding; asymptomatic patients were more likely to be older, male, and had a higher proportion of related comorbidities, including history of thromboembolic complications and stroke -Analyses did not focus on the 520 "fully asymptomatic" persons for the comparisons reported -Limited applicability to the key questions of this review

Appendix A Table 7. Stroke Incidence for People With Asymptomatic, Previously Unrecognized AF vs. People With Symptomatic AF Reported by Observational Studies

Author, Year Country	Study Population and Setting	Stroke Incidence	Study Limitations
	disease (64.5%), chronic heart failure (44.3%), or CAD (40.1%). (Total cohort=3,119 in the EORP-AF)		because most participants had known heart disease

[a] Outcomes compared the 1,237 currently asymptomatic people (but not the fully asymptomatic) with symptomatic people.

Abbreviations: AF=atrial fibrillation; BMI=body mass index; CAD=coronary artery disease; CI=confidence interval; COPD=chronic obstructive pulmonary disease; CVD=cardiovascular disease; ECG= electrocardiogram; eGFR=estimated glomerular filtration rate; EORP=EurObservational Research Programme – Atrial Fibrillation; HR=hazard ratio; NR=not reported; TIA=transient ischemic attack; US=United States.

3a. What are the recommendations on use of rate or rhythm control for the treatment of atrial fibrillation in asymptomatic adults age 65 years or older?

We found no recommendations that specifically address the use of rhythm control for asymptomatic adults (it is recommended for selected patients with symptoms); some guidelines recommend rate control to achieve a resting heart rate under 110 beats per minute (bpm) for asymptomatic patients because prolonged rapid ventricular rates increase the risk of cardiomyopathy.[52, 53] There has been an ongoing debate on the use of rate versus rhythm control strategies for patients with AF. However, rate control is now generally preferred for multiple reasons: several clinical trials have not found either rate or rhythm control to be clearly superior for benefits, rate control medications are familiar to a larger number of providers, and evidence shows an increased risk of adverse events with antiarrhythmic agents.[54-56]

According to the AHA/ACC/HRS guidelines, for rate control, beta-blockers are the most commonly used agents, followed by nondihydropyridine calcium channel blockers (e.g., diltiazem), digoxin, and amiodarone.[57] Rhythm control strategies aiming to restore and maintain sinus rhythm include electrical cardioversion, pharmacological cardioversion using antiarrhythmic agents, and surgical or catheter ablation, used either singly or in combination. A meta-analysis of eight RCTs[58] (7,499 AF patients, mean age 68 years) by Caldeira et al. concluded there were no differences in a variety of outcomes between rate and rhythm control strategies: all-cause mortality (RR, 0.95; 95% CI, 0.68 to 1.05; 8 studies), cardiovascular mortality (RR, 0.99; 95% CI, 0.97 to 1.13, 7 trials), arrhythmic and sudden death (RR, 1.12; 95% CI, 0.91 to 1.38; 5 trials), ischemic stroke (RR, 0.89; 95% CI, 0.52 to 1.53; 4 trials), systemic embolism (RR, 0.89; 95% CI, 0.69 to 1.14; 6 trials), and major bleeding (RR, 1.10; 95% CI, 0.89 to 1.36; 5 trials). Sensitivity analysis including studies with more than 50 percent of participants having heart failure demonstrated fewer systemic embolic events with rate control strategies (RR, 0.43; 95% CI, 0.21 to 0.89; 3 trials). For patients with mean age ≥65 years (5 trials), there were no differences between treatment strategies for all of the previously mentioned outcomes, with the exception of arrhythmic and sudden deaths, which were not reported. For these analyses, two studies–AFFIRM (n=4060) and AF-CHF (n=1376)–provided most of the data (weight, 95.3%). AFFIRM,[59] the largest of the RCTs to compare rate versus rhythm control, enrolled 4,060 patients age 65 years or older with AF and risk factors for stroke or death. After 5 years of observation following randomization to either rate or rhythm control strategies, the study found no difference in mortality between the groups (HR, 1.15; 95% CI, 0.99 to 1.34). Visual inspection of the Kaplan-Meier curves, however, suggests an apparent separation of the two groups that appears to widen over time (trending toward favoring a possible benefit for rate control). In a re-analysis of AFFIRM using propensity-matched scoring for participants ages 70 to 80 years, mortality was greater in the rhythm control arm (HR, 1.30; 95% CI, 1.06 to 1.59).[60]

Guidelines for treatment of AF recommend initial rate control strategies for most symptomatic patients with a stepwise approach to rhythm control strategies in those patients who have persistent symptoms or are unable to be treated using rate control alone.[57, 61, 62] The AHA/ACC/HRS recommendations are based largely on the results of two RCTs, which demonstrate the lack of superiority of one strategy over the other,[55, 63] as well as an increase in hospitalizations for rhythm control strategies.[54] The NICE guidelines include a systematic review and meta-analysis of eight RCTs, which drew similar conclusions to the meta-analysis by

Caldeira et al. The NICE guidelines acknowledge moderate-quality evidence supporting the mortality and bleeding outcomes but low- or very low-quality evidence for other outcomes comparing rate versus rhythm control.

While no guideline made a specific recommendation for asymptomatic adults age 65 years or older, the mean age of participants across trials was 61 to 72 years. The AHA/ACC/HRS guideline includes a single recommendation for a lenient rate-control strategy (resting heart rate <110 bpm) when patients remain asymptomatic and left ventricular systolic function is preserved, which is based on a single study (RACE II).[63] RACE II compared strict (<80 bpm resting HR) versus lenient (<110 bpm) rate control strategies in patients with permanent AF (for up to 12 months prior to enrollment). Forty-three percent of the study population was asymptomatic at baseline (defined as no palpitations, dyspnea, or fatigue), although it is not clear how many were never symptomatic (i.e., how many did not have symptoms around the time of their diagnosis or prior to it). RACE II concluded noninferiority between the two strategies for prevention of major cardiac events.[64]

The AHA/ACC guidelines recommend rhythm-control strategies for AF patients with persistent symptoms and with select factors such as inadequate rate control, younger age, tachycardia-mediated cardiomyopathy, first AF episode, AF precipitated by an acute illness, and patient preference.[57] Because AF can progress from paroxysmal to persistent, resulting in electrical and structural remodeling that becomes irreversible over time, the guidelines note that when considering a rhythm control strategy, early intervention may be most beneficial to prevent AF progression.

According to a Cochrane review by Mead et al., electrical cardioversion did not result in any greater reduction in mortality than rate control strategies (OR, 0.83; 95% CI, 0.48 to 1.43; 3 trials, 927 patients) and may increase the risk of stroke (OR, 1.9; 95% CI, 0.99 to 3.64; 3 trials).[65] However, physical function, physical role function, and vitality were better in the cardioversion group. The mean age of participants across the three trials was 60 to 68 years. Other studies report that some patients spontaneously revert to AF within weeks or months, and up to 25 percent will revert within 1 year, which may explain the possible increase in risk of stroke because many patients who are cardioverted often cease taking anticoagulation or antiplatelet agents used to prevent stroke.[66, 67] The AHA/ACC guidelines recommend direct current cardioversion as an option when pursuing a rhythm-control strategy for symptomatic patients and those refractory to pharmacological therapies; they do not make a specific recommendation for asymptomatic patients.[57]

Although the ESC acknowledges the efficacy of pharmacologic cardioversion using antiarrhythmic agents, they also note the elevated adverse event and mortality rates associated with using these agents.[61] Accordingly, they recommend antiarrhythmic drug therapy only in patients with resistant symptoms due to recurrent AF. The AHA/ACC guidelines note that antiarrhythmic drug efficacy is modest, and AF recurrences are common. Lafuente-Lafuente et. al. concluded in a meta-analysis of 59 studies (21,305 patients) that several classes of antiarrhythmic agents were moderately effective at maintaining sinus rhythm after conversion of AF (OR, 0.19 to 0.77; number-needed-to-treat (NNT), 3 to 16), but most agents increased adverse events and mortality (OR, 2.23 to 2.39; number needed to harm 109 to 169).[68]

Concerning catheter ablation, the ESC notes that large trials of ablation therapy are pending and that the risks associated with the procedure need to be carefully weighed against potential for

symptomatic benefit.[61] Although the guideline authors note that catheter ablation is more effective than antiarrhythmic drug therapy, its use as first-line therapy should currently be limited to those with paroxysmal AF preferring interventional treatment and who have a low-risk profile for procedure-associated complications. The AHA recommends AV nodal ablation only sparingly noting that the procedure leads to pacemaker dependency, and is therefore usually reserved for elderly patients.[57] Guidelines from both organizations recommend catheter ablation as a second line treatment in patients who are candidates for first line treatment with antiarrhythmic agents who experience failure or intolerance with these agents.[69] Two recent Cochrane reviews address the question of catheter ablation for AF. However, neither review addressed the use of ablation techniques in screen-detected, asymptomatic patients. Chen et al. assessed the benefits and harms of catheter ablation versus medical therapy for patients with either paroxysmal or persistent AF (32 RCTs, 3,560 patients).[70] They concluded that compared with medical therapy, ablation had a better effect for inhibiting AF recurrence (RR, 0.27; 95% CI, 0.18 to 0.41; 7 trials, 767 patients), and they found no differences between treatments for mortality (RR, 0.50; 95% CI, 0.04 to 5.65), fatal and nonfatal embolic complications (RR, 1.01; 95% CI, 0.18 to 5.68), or thrombo-embolic-specific mortality (RR, 3.04; 95% CI, 0.13 to 73.43). Significant heterogeneity was noted for the comparison of ablation versus medical therapies, and overall, RCTs were small in size and poor quality. Nyong et al. assessed the use of both surgical and catheter ablation in patients with nonparoxysmal AF (3 RCTs, 261 patients with mean age of 60 years).[71] They concluded that radio-frequency catheter ablation was superior to antiarrhythmic agents for achieving freedom from atrial arrhythmias (RR, 1.84; 95% CI, 1.17 to 2.88), reducing further cardioversion (RR, 0.62; 95% CI, 0.47 to 0.82) and reducing cardiac-related hospitalization (RR, 0.27; 95% CI, 0.10 to 0.72). Trials were rated as low or unclear risk of bias, and strength of evidence for these findings was low (hospitalizations) to moderate. Additionally, they identified three ongoing studies comparing catheter ablation to either rate control, electrical cardioversion, or both rate and rhythm control drug treatments. They identified no comparative studies of surgical ablation.

3b. How often are such treatments used in the United States in asymptomatic adults age 65 years or older?

We did not find any data that specifically address how often these treatments are used in asymptomatic adults. The existing data do not describe symptom status of the treated patients. One retrospective administrative claims analysis (using claims from January 1, 2008 through September 30, 2010) of 48,814 patients with a diagnosis of AF reported that 38,502 (79%) received treatment.[72] Of those treated, the majority received rate control medications (67% received beta blockers) and rhythm control medications were used in the initial regimens for 12 percent (and 24% received rhythm control medications at any time). Direct current cardioversion was used in the initial treatment for 8.5 percent (and 18% at any time). Catheter ablation was used in 5 percent of patients and was typically not a first line treatment.

The National Disease and Therapeutic Index is a survey of about 3,000 office-based physicians that collects diagnosis and treatment information on all patient visits over a randomly selected 2-day period in each calendar year. National estimates for treatments by diagnoses are calculated using survey *drug mentions* as a surrogate for actual drug treatments. Between October 1999 and September 2003, mention of digoxin treatment for patients with AF declined from 29 percent to 17 percent, while mentions of beta blockers rose from about 8 percent to 11 percent and

mentions of calcium channel blockers remained stable around 8 percent.[73] When stratified by age, mention of digoxin was more common among patients age 60 years or older (24% vs. 17%), while the use of beta blockers was slightly more common among patients younger than 60 years (13% vs. 10%). Among patients age 60 years or older, 11 percent of visits mentioned use of an anti-arrhythmic agent. Amiodarone was the most commonly cited agent among this age group (5.6%), followed by sotalol, class 1c, and 1a agents. No information was reported from this survey about symptomatic versus asymptomatic treatment. Based on the National Hospital Discharge Survey (NHDS), rates of catheter ablation to treat AF have risen by 15 percent per year between 1990 (0.06% of patients with AF) and 2005 (0.79%). Across all age groups, the rate of increase was similar, including patients older than 80 years (0.00% in 1990 vs. 0.26% in 2005). Overall, 0.42 percent of hospitalized patients (1,144/269,471) identified in NHDS underwent catheter ablation, corresponding to a national estimate of 133,000 ablations in 32 million hospitalizations over the 15-year period.[74]

Appendix B1. Original Search Strategies

PubMed, 7/12/16

Search	Query	Items Found
#1	Search ("Atrial Fibrillation"[Mesh] OR atrial fibril*[tiab] OR atrium fibrillation*[tiab] OR a-fib[tiab] OR atrial flutter*[tiab])	60865
#2	Search ("Electrocardiography"[Mesh] OR electrocardiography[tiab] OR EKG[tiab] OR ECG[tiab])	209997
#3	Search (#1 and #2)	13398
#4	Search ("Mass Screening"[Mesh] OR screen*[tiab])	591510
#5	Search (#3 and #4)	314
#6	Search (((randomized[title/abstract] OR randomised[title/abstract]) AND controlled[title/abstract] AND trial[title/abstract]) OR (controlled[title/abstract] AND trial[title/abstract]) OR "Controlled Clinical Trial"[publication type] OR "Randomized Controlled Trial"[Publication Type] OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH])	642006
#7	Search (#5 and #6)	22
#8	Search ("Cohort Studies"[Mesh] OR "Epidemiologic Studies"[Mesh] OR "Follow-up Studies"[Mesh] OR "prospective cohort" OR "prospective studies"[MeSH] OR (prospective*[All Fields] AND cohort[All Fields] AND (study[All Fields] OR studies[All Fields])))	1902550
#9	Search (#5 and #8)	128
#10	Search (#7 or #9)	140
#11	Search (#7 or #9) Filters: Humans	138
#12	Search (#7 or #9) Filters: Humans; English	132
#13	Search (#7 or #9) Filters: Humans; English; Adult: 19+ years	126
#14	Search ("Anticoagulants"[Mesh] OR anticoagulant*[tiab] OR "Warfarin"[Mesh] OR warfarin OR noac* OR ("Dabigatran"[Mesh] or Dabigatran OR Pradaxa) OR apixaban OR Eliquis OR "Rivaroxaban"[Mesh] OR Rivaroxaban[tiab] OR Xarelto[tiab])	103597
#15	Search (#1 and #14)	10286
#16	Search ("Factor Xa Inhibitors"[Mesh] OR "factor xa"[tiab])	7468
#17	Search (#1 and #16)	839
#18	Search ("Antithrombins"[Mesh] OR antithrombin*[tiab] OR thrombin inhibit*[tiab])	22731
#19	Search (#1 and #18)	1348
#20	Search ("Aspirin"[Mesh] OR aspirin[tiab] OR anti-platelet*[tiab] OR antiplatelet*[tiab] OR Plavix[tiab] OR ASA[tiab] OR "acetylsalicylic acid"[tiab] OR "Aspirin, Dipyridamole Drug Combination"[Mesh] OR Aggrenox[tiab] OR "Dipyridamole"[Mesh] OR Dipyridamole[tiab] OR "clopidogrel"[Supplementary Concept] OR clopidogrel[tiab])	104013
#21	Search (#1 and #20)	2998
#22	Search (#15 or #17 or #19 or #21)	11039
#23	Search (#22 and #6)	798
#24	Search (#22 and #8)	2431
#25	Search (("review"[Publication Type] AND "systematic"[tiab]) OR "systematic review"[All Fields] OR ("review literature as topic"[MeSH] AND "systematic"[tiab]) OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[All Fields])	180177
#26	Search (#22 and #25)	438
#27	Search (#22 and #25) Filters: Publication date from 2011/01/01 to 2016/12/31	294
#28	Search (#23 or #24 or #27)	3191
#29	Search (#23 or #24 or #27) Filters: Humans	3060
#30	Search (#23 or #24 or #27) Filters: Humans; English	2785
#31	Search (#23 or #24 or #27) Filters: Humans; English; Adult: 19+ years	2378
#32	Search (#30 not #13)	2358

Appendix B1. Original Search Strategies

PubMed, 5/22/17

Search	Query	Items Found
#1	Search ("Atrial Fibrillation"[Mesh] OR atrial fibril*[tiab] OR atrium fibrillation*[tiab] OR a-fib[tiab] OR atrial flutter*[tiab])	65870
#2	Search (("Electrocardiography"[Mesh] OR electrocardiography[tiab] OR EKG[tiab] OR ECG[tiab]))	215045
#3	Search (#1 and #2)	14014
#4	Search (("Mass Screening"[Mesh] OR screen*[tiab]))	629166
#5	Search (#3 and #4)	352
#6	Search (((randomized[title/abstract] OR randomised[title/abstract]) AND controlled[title/abstract] AND trial[title/abstract]) OR (controlled[title/abstract] AND trial[title/abstract]) OR "Controlled Clinical Trial"[publication type] OR "Randomized Controlled Trial"[Publication Type] OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH])	671738
#7	Search (#5 and #6)	27
#8	Search ("Cohort Studies"[Mesh] OR "Epidemiologic Studies"[Mesh] OR "Follow-up Studies"[Mesh] OR "prospective cohort" OR "prospective studies"[MeSH] OR (prospective*[All Fields] AND cohort[All Fields] AND (study[All Fields] OR studies[All Fields])))	2020073
#9	Search (#5 and #8)	138
#10	Search (#7 or #9)	155
#11	Search (#7 or #9) Filters: Humans	150
#12	Search (#7 or #9) Filters: Humans; English	144
#13	Search (#7 or #9) Filters: Humans; English; Adult: 19+ years	137
#14	Search (#7 or #9) Filters: Publication date from 2016/01/01 to 2017/12/31; Humans; English; Adult: 19+ years	8
#15	Search ("Anticoagulants"[Mesh] OR anticoagulant*[tiab] OR "Warfarin"[Mesh] OR warfarin OR noac* OR ("Dabigatran"[Mesh] or Dabigatran OR Pradaxa) OR apixaban OR Eliquis OR "Rivaroxaban"[Mesh] OR Rivaroxaban[tiab] OR Xarelto[tiab])	108637
#16	Search (#1 and #15)	11590
#17	Search (("Factor Xa Inhibitors"[Mesh] OR "factor xa"[tiab]))	7957
#18	Search (#1 and #17)	1003
#19	Search (("Antithrombins"[Mesh] OR antithrombin*[tiab] OR thrombin inhibit*[tiab]))	23617
#20	Search (#1 and #19)	1571
#21	Search (("Aspirin"[Mesh] OR aspirin[tiab] OR anti-platelet*[tiab] OR antiplatelet*[tiab] OR Plavix[tiab] OR ASA[tiab] OR "acetylsalicylic acid"[tiab] OR "Aspirin, Dipyridamole Drug Combination"[Mesh] OR Aggrenox[tiab] OR "Dipyridamole"[Mesh] OR Dipyridamole[tiab] OR "clopidogrel"[Supplementary Concept] OR clopidogrel[tiab]))	108308
#22	Search (#1 and #21)	3234
#23	Search (#16 or #18 or #20 or #22)	12388
#24	Search (#23 and #6)	864
#25	Search (#23 and #8)	2756
#26	Search ((("review"[Publication Type] AND "systematic"[tiab]) OR "systematic review"[All Fields] OR ("review literature as topic"[MeSH] AND "systematic"[tiab]) OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[All Fields]))	204884
#27	Search (#23 and #26)	527
#28	Search (#24 or #25 or #27)	3749
#29	Search (#24 or #25 or #27) Filters: Humans	3579
#30	Search (#24 or #25 or #27) Filters: Humans; English	3260
#31	Search (#24 or #25 or #27) Filters: Humans; English; Adult: 19+ years	2731
#32	Search (#24 or #25 or #27) Filters: Publication date from 2016/01/01 to 2017/12/31; Humans; English; Adult: 19+ years	260
#33	Search (#32 NOT #14)	259

Appendix B1. Original Search Strategies

Cochrane Library, 7/12/16

ID	Search	Hits
#1	[mh "Atrial Fibrillation"] or ("atrial fibril*" or "atrium fibrillation*" or a-fib or afib or "atrial flutter*")	7088
#2	[mh Electrocardiography] or electrocardiography or EKG or ECG	13719
#3	#1 and #2	1171
#4	[mh "Mass Screening"] or screen*	37027
#5	#3 and #4	115
#6	(((randomized or randomised) and controlled and trial) or (controlled and trial) or "Controlled Clinical Trial" or "Randomized Controlled Trial" or [mh "Single-Blind Method"] or [mh "Double-Blind Method"] or [mh "Random Allocation"])	675537
#7	#5 and #6 Publication Year from 2011 to 2016	72
#8	[mh "Cohort Studies"] or [mh "Epidemiologic Studies"] or [mh "Follow-up Studies"] or "prospective cohort" or [mh "prospective studies"] or (prospective* and cohort and (study or studies))	139074
#9	#5 and #8	35
#10	[mh Anticoagulants] or anticoagulant* or [mh Warfarin] or warfarin or noac* or [mh Dabigatran] or Dabigatran or Pradaxa or apixaban or Eliquis or [mh Rivaroxaban] or Rivaroxaban or Xarelto	9813
#11	#1 and #10	1591
#12	[mh "Factor Xa Inhibitors"] or "factor xa"	782
#13	#1 and #12	160
#14	[mh Antithrombins] or antithrombin* or "thrombin inhibit*"	2295
#15	#1 and #14	215
#16	[mh Aspirin] or aspirin or "anti-platelet*" or antiplatelet* or Plavix or ASA or "acetylsalicylic acid" or [mh "Aspirin, Dipyridamole Drug Combination"] or Aggrenox or [mh Dipyridamole] or Dipyridamole or clopidogrel	23614
#17	#1 and #16	754
#18	#11 or #13 or #15 or #17	1809
#19	#18 Publication Year from 2011 to 2016, in Cochrane Reviews (Reviews and Protocols) and Other Reviews	192
#20	#18 and (#6 or #8)	1374
#21	#20 not #19	1227
#22	#21 Publication Year from 2011 to 2016	701

Cochrane Library, 5/23/17

ID	Search	Hits
#1	[mh "Atrial Fibrillation"] or ("atrial fibril*" or "atrium fibrillation*" or a-fib or afib or "atrial flutter*")	8442
#2	[mh Electrocardiography] or electrocardiography or EKG or ECG	14832
#3	#1 and #2	1354
#4	[mh "Mass Screening"] or screen*	42666
#5	#3 and #4	149
#6	(((randomized or randomised) and controlled and trial) or (controlled and trial) or "Controlled Clinical Trial" or "Randomized Controlled Trial" or [mh "Single-Blind Method"] or [mh "Double-Blind Method"] or [mh "Random Allocation"])	767332
#7	#5 and #6 Publication Year from 2016 to 2017	**48**
#8	[mh "Cohort Studies"] or [mh "Epidemiologic Studies"] or [mh "Follow-up Studies"] or "prospective cohort" or [mh "prospective studies"] or (prospective* and cohort and (study or studies))	149954
#9	#5 and #8	**42**
#10	[mh Anticoagulants] or anticoagulant* or [mh Warfarin] or warfarin or noac* or [mh Dabigatran] or Dabigatran or Pradaxa or apixaban or Eliquis or [mh Rivaroxaban] or Rivaroxaban or Xarelto	11249
#11	#1 and #10	2038
#12	[mh "Factor Xa Inhibitors"] or "factor xa"	954
#13	#1 and #12	229
#14	[mh Antithrombins] or antithrombin* or "thrombin inhibit*"	2505
#15	#1 and #14	260
#16	[mh Aspirin] or aspirin or "anti-platelet*" or antiplatelet* or Plavix or ASA or "acetylsalicylic acid" or [mh "Aspirin, Dipyridamole Drug Combination"] or Aggrenox or [mh Dipyridamole] or Dipyridamole or clopidogrel	25992
#17	#1 and #16	938
#18	#11 or #13 or #15 or #17	2297
#19	#18 Publication Year from 2016 to 2017, in Cochrane Reviews (Reviews and Protocols)	**59**
#20	#18 and (#6 or #8)	1834
#21	#20 not #19	1775
#22	#21 Publication Year from 2016 to 2017	418

Gray Literature Searches, July 15-22, 2016
ClinicalTrials.gov Searches
Advanced Search
Limit to
Adults
Last Updated 01/01/2011 – 12/31/2016
Screening
CONDITION box: atrial fibril* OR atrium fibrillation* OR a-fib OR atrial flutter*
INTERVENTION box: electrocardiography OR EKG OR ECG
Translates to in CT.gov:
atrial fibril* OR atrium fibrillation* OR a-fib OR atrial flutter* | electrocardiography OR EKG OR ECG | Adult | Studies updated from 01/01/2011 to 12/31/2016
81 studies, all imported
Treatment
CONDITION box: atrial fibril* OR atrium fibrillation* OR a-fib OR atrial flutter*
INTERVENTION box: anticoagulant* OR "Warfarin" OR warfarin OR noac* OR Dabigatran OR Pradaxa OR apixaban OR Eliquis OR Rivaroxaban OR Xarelto OR "factor xa" OR antithrombin* OR thrombin inhibit* OR aspirin OR anti-platelet* OR antiplatelet* OR Plavix OR ASA OR "acetylsalicylic acid" OR Aggrenox OR Dipyridamole OR clopidogrel
232 studies, 230 imported

REDONE WITH SENIORS:
Screening:
atrial fibril* OR atrial fibrillation OR atrium fibrillation* OR a-fib OR atrial flutter* | electrocardiography OR EKG OR ECG | Adult, Senior | Studies updated from 01/01/2011 to 12/31/2016
85 results, all imported
Treatment:
atrial fibril* OR atrial fibrillation OR atrium fibrillation* OR a-fib OR atrial flutter* | anticoagulant* OR "Warfarin" OR warfarin OR noac* OR Dabigatran OR Pradaxa OR apixaban OR Eliquis OR Rivaroxaban OR Xarelto OR "factor xa" OR antithrombin* OR thrombin inhibit* OR aspirin OR anti-platelet* OR antiplatelet* OR Plavix OR ASA OR "acetylsalicylic acid" OR Aggrenox OR Dipyridamole OR clopidogrel | Adult, Senior | Studies updated from 01/01/2011 to 12/31/2016
239 results, 237 imported. 2 were duplicates with the screening search.

WHO ICRTRP Advanced searches, July 15-22, 2016
Screening:
Recruitment status: ALL
Date of registration is between 01/01/2011 – 31/12/2016
Condition box: atrial fibril* OR atrium fibrillation* OR a-fib OR atrial flutter*
Intervention box: electrocardiography OR EKG OR ECG
0 results.
Tried searching the intervention terms in Title box: electrocardiography OR EKG OR ECG
Condition box: atrial fibril* OR atrium fibrillation* OR a-fib OR atrial flutter*
1 result, imported
Treatment:
In Title box:
anticoagulant* OR "Warfarin" OR warfarin OR noac* OR Dabigatran OR Pradaxa OR apixaban OR Eliquis OR Rivaroxaban OR Xarelto OR "factor xa" OR antithrombin* OR thrombin inhibit* OR aspirin OR anti-platelet* OR antiplatelet* OR Plavix OR ASA OR "acetylsalicylic acid" OR Aggrenox OR Dipyridamole OR clopidogrel
In Condition box:
atrial fibril* OR atrium fibrillation* OR a-fib OR atrial flutter*
19 results, 9 imported

Gray Literature Searches, May 24, 2017
ClinicalTrials.gov Searches
Advanced Search
Limit to
Adults
Last Updated 01/01/2016 – 12/31/2017
Screening
CONDITION box: atrial fibril* OR atrium fibrillation* OR a-fib OR atrial flutter*
INTERVENTION box: electrocardiography OR EKG OR ECG
Translates to in ClinicalTrials.gov

atrial fibril* OR atrium fibrillation* OR a-fib OR atrial flutter* | electrocardiography OR EKG OR ECG | Adult, Senior | Studies updated from 01/01/2016 to 12/31/2017
22 studies, all imported
Treatment:
CONDITION box: atrial fibril* OR atrium fibrillation* OR a-fib OR atrial flutter*
INTERVENTION box: anticoagulant* OR "Warfarin" OR warfarin OR noac* OR Dabigatran OR Pradaxa OR apixaban OR Eliquis OR Rivaroxaban OR Xarelto OR "factor xa" OR antithrombin* OR thrombin inhibit* OR aspirin OR anti-platelet* OR antiplatelet* OR Plavix OR ASA OR "acetylsalicylic acid" OR Aggrenox OR Dipyridamole OR clopidogrel
Translates to in ClinicalTrials.gov
atrial fibril* OR atrial fibrillation OR atrium fibrillation* OR a-fib OR atrial flutter* | anticoagulant* OR "Warfarin" OR warfarin OR noac* OR Dabigatran OR Pradaxa OR apixaban OR Eliquis OR Rivaroxaban OR Xarelto OR "factor xa" OR antithrombin* OR thrombin inhibit* OR aspirin OR anti-platelet* OR antiplatelet* OR Plavix OR ASA OR "acetylsalicylic acid" OR Aggrenox OR Dipyridamole OR clopidogrel | Adult, Senior | Studies updated from 01/01/2016 to 12/31/2017
71 results, 70 imported

WHO ICRTRP Advanced searches, May 24, 2017
Advanced search, Recruitment status: ALL
Date of registration is between 01/01/2016 – 12/31/2017
Screening:
Condition box: atrial fibril* OR atrium fibrillation* OR a-fib OR atrial flutter*
Intervention box: electrocardiography OR EKG OR ECG
21 results, all imported
Also performed the search with the intervention terms in Title box: electrocardiography OR EKG OR ECG
Condition box: atrial fibril* OR atrium fibrillation* OR a-fib OR atrial flutter*
6 results, 1 imported
Treatment:
In Title box:
anticoagulant* OR "Warfarin" OR warfarin OR noac* OR Dabigatran OR Pradaxa OR apixaban OR Eliquis OR Rivaroxaban OR Xarelto OR "factor xa" OR antithrombin* OR thrombin inhibit* OR aspirin OR anti-platelet* OR antiplatelet* OR Plavix OR ASA OR "acetylsalicylic acid" OR Aggrenox OR Dipyridamole OR clopidogrel
In Condition box:
atrial fibril* OR atrium fibrillation* OR a-fib OR atrial flutter*
74 results, all imported

Appendix B2. Eligibility Criteria

	Include	Exclude
Condition definition	Atrial fibrillation (paroxysmal or persistent)	Other cardiac arrhythmias, nonarrhythmia-related CVD (e.g., coronary heart disease, hypertension)
Populations	KQs 1–3: Unselected or explicitly asymptomatic older adults (age 65 years or older); older adults selected for increased risk of nonvalvular atrial fibrillation (e.g., those with obesity, smoking, alcohol use, hypertension); studies of mixed populations of asymptomatic and symptomatic persons are eligible if results are reported separately for asymptomatic persons or less than 10% of the sample is symptomatic. KQs 4, 5: Older adults with atrial fibrillation. To approximate screen-detected persons with atrial fibrillation, we will aim to stratify analyses based on whether participants are asymptomatic/screen-detected vs. symptomatic (if possible); however, knowing that most studies enroll mixed populations or do not clearly enroll screen-detected or asymptomatic populations, we will not exclude studies based on whether participants were screen detected. To approximate "screening" vs. "disease management" populations, we will limit our analyses to studies of individuals not selected because of known heart disease, heart failure, and/or previous stroke or transient ischemic attack	KQs 1–3: Symptomatic adults; adults with known (history of) atrial fibrillation; children, adolescents, and adults age 65 years or older; adults at high(est) risk for atrial fibrillation (including but not limited to those with mitral valve disease or repair/replacement); and adults with history of stroke or transient ischemic attack KQs 4, 5: Adults needing antiplatelet or anticoagulation medications for conditions other than atrial fibrillation; adults with atrial fibrillation and known heart disease, heart failure, and/or previous stroke or transient ischemic attack
Screening test or intervention	KQs 1–3: Systematic ECG screening using any approach (e.g., in-office single-application 12-lead ECG, continuous ECG, intermittent use of handheld ECG); systematic screening with both pulse palpation and ECG for all participants KQs 4, 5: Medical treatment with antiplatelet agents (aspirin) or anticoagulants (apixaban, dabigatran, edoxaban, rivaroxaban, warfarin). Results will be stratified by type of medication.	KQs 1–3: Physical examination (including pulse palpation); blood pressure monitoring; pulse oximetry; all other technologies (e.g., consumer devices, such as smartphones); studies that only use ECG for participants with irregular pulse (as opposed to all participants) KQs 4, 5: Nonpharmacologic treatment to prevent stroke (e.g., implantable devices), treatment or management of atrial fibrillation for reasons other than prevention of stroke (e.g., rate or rhythm control, cardioversion, ablation), combinations of treatment (e.g., aspirin plus warfarin)
Comparisons	KQs 1–3: Screened vs. nonscreened groups, systematic screening vs. usual care (which may include opportunistic screening; that is, pulse palpation, automated blood pressure measurement, or cardiac auscultation during the course of a physical examination, or examination for another reason, with subsequent ECG if an irregular heart beat or pulse is noted) KQs 4, 5: No treatment	All KQs: No comparison, nonconcordant historical control KQs 4, 5: Active treatment (i.e., antiplatelet or anticoagulation medications)
Outcomes	KQ 1: All-cause mortality, stroke, and stroke-related morbidity or mortality KQ 2: Comparative/relative yield (i.e., number of persons diagnosed with atrial fibrillation in one group vs. another [unscreened/differently screened] group) KQ 3: Anxiety, labeling, harms of subsequent procedures or interventions initiated as a result of screening (e.g., subsequent ablation with complications) KQ 4: All-cause mortality, cardioembolic stroke, and cardioembolic stroke-related morbidity or mortality KQ 5: Any harms requiring unexpected or unwanted	KQs 3, 5: Nonserious events (e.g., bleeding not requiring or resulting in medical attention)

Appendix B2. Eligibility Criteria

	Include	Exclude
	medical attention (e.g., hemorrhagic stroke, major bleeding, allergic reaction)	
Study designs	All KQs: Randomized, controlled trials and controlled clinical trials KQs 2, 3: Large prospective cohort studies are also eligible KQ 4: Systematic reviews[a] of trials are also eligible KQ 5: Systematic reviews[a] of trials, systematic reviews[a] of observational studies, and large prospective cohort studies are also eligible	All other designs, narrative reviews, case reports, case series, editorials, letters, cross-sectional studies, case-control studies, and retrospective cohort studies
Setting	KQs 1–3: Studies performed in primary care settings KQs 4, 5: Studies performed in primary care or specialty settings	KQs 1–3: Studies performed in specialty settings, studies of patients undergoing preoperative evaluation, and inpatient settings KQs 4, 5: Studies conducted primarily in inpatient settings
Country	Studies conducted in countries categorized as "Very High" on the 2014 Human Development Index (as defined by the United Nations Development Program)	Studies conducted in countries that are not categorized as "Very High" on the 2014 Human Development Index
Language	English	Non-English
Study quality	Good or fair	Poor (according to design-specific USPSTF criteria)

[a] We assessed the relevance of systematic reviews (as described in the Methods) to address KQs 4 and 5 to determine their eligibility.

Abbreviations: CVD=cardiovascular disease; ECG=electrocardiogram; KQ=key question; USPSTF=U.S. Preventive Services Task Force.

Randomized, Controlled Trials and Cohort Studies

Criteria

- Initial assembly of comparable groups
- Randomized, controlled trials (RCTs)—adequate randomization, including concealment and whether potential confounders were distributed equally among groups; cohort studies—consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, crossovers, adherence, and contamination)
- Important differential loss to followup or overall high loss to followup
- Measurements that are equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- Important outcomes considered
- Analysis: Adjustment for potential confounders for cohort studies or intention-to-treat analysis for RCTs; for cluster RCTs, correction for correlation coefficient

Definition of Ratings Based on Above Criteria

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (followup ≥80%); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; important outcomes are considered; and appropriate attention is given to confounders in analysis. In addition, intention-to-treat analysis is used for RCTs.

Fair: Studies will be graded "fair" if any or all of the following problems occur, without the important limitations noted in the "poor" category below: Generally comparable groups are assembled initially, but some question remains on whether some (although not major) differences occurred in followup; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention-to-treat analysis is lacking for RCTs.

Poor: Studies will be graded "poor" if any of the following major limitations exist: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. Intention-to-treat analysis is lacking for RCTs.

Sources: U.S. Preventive Services Task Force. U.S. Preventive Services Task Force, Procedure Manual, Appendix VI. Rockville, MD: U.S. Preventive Services Task Force; 2015[75]; Harris et al., 2001.[76]

Systematic Reviews

Criteria

- Comprehensiveness of sources considered/search strategy used
- Standard appraisal of included studies
- Validity of conclusions
- Recency and relevance (especially important for systematic reviews)

Definition of Ratings Based on Above Criteria

Good: Recent, relevant review with comprehensive sources and search strategies; explicit and relevant selection criteria; standard appraisal of included studies; and valid conclusions

Fair: Recent, relevant review that is not clearly biased but lacks comprehensive sources and search strategies

Poor: Outdated, irrelevant, or biased review without systematic search for studies, explicit selection criteria, or standard appraisal of studies

Sources: U.S. Preventive Services Task Force. U.S. Preventive Services Task Force, Procedure Manual, Appendix VI. Rockville, MD: U.S. Preventive Services Task Force; 2015[75]; Harris et al., 2001.[76]

Appendix C. Excluded Studies

X1: Non-English
X2: Ineligible population
X3: Ineligible screening or treatment
X4: Ineligible or no comparator
X5: No relevant outcome reported
X6: Ineligible setting
X7: Ineligible study design
X8: Ineligible country
X9: Meets all criteria but abstract only
X10: Outdated publication superseded by more recent data
X11: Systematic Review that did not meet relevance criteria
X12: Poor quality rating

1. Cost-Effectiveness of antiarrhythmic drugs for prevention of thromboembolism in patients with paroxysmal atrial fibrillation. Jpn Circ J. 2001 Sep;65(9):765-8. PMID: 11548872. Exclusion Code: X3.
2. Summaries for patients. What is the appropriate level of blood-thinning medication for elderly people with atrial fibrillation? Ann Intern Med. 2004 Nov 16;141(10):I38. PMID: 15545670. Exclusion Code: X7.
3. Summaries for patients. Net benefit of warfarin in atrial fibrillation. Ann Intern Med. 2009 Sep 1;151(5):I36. PMID: 19721014. Exclusion Code: X7.
4. Irbesartan did not reduce cardio events in atrial fibrillation patients. Australian Journal of Pharmacy. 2011;92(1095):83. PMID: CN-00893899. Exclusion Code: X7.
5. Aspirin and renal insufficiency progression in patients with atrial fibrillation and chronic kidney disease. International Journal of Cardiology. 223 (pp 619-624), 2016. Date of Publication: 15 Nov 2016. 2016doi: 10.1016/j.ijcard.2016.08.224. PMID: CN-01194146. Exclusion Code: X4.
6. Risk of bleeding and thrombosis in patients 70 years or older using Vitamin K antagonists. JAMA Internal Medicine. 176 (8) (pp 1176-1183), 2016. Date of Publication: August 2016. 2016doi: 10.1001/jamainternmed.2016.3057. PMID: CN-01195175. Exclusion Code: X2.
7. Adam SS, McDuffie JR, Ortel TL, et al. Comparative effectiveness of warfarin and new oral anticoagulants for the management of atrial fibrillation and venous thromboembolism: a systematic review (Structured abstract). Ann Intern Med. 2012;157(11):796-807. PMID: DARE-12012045713. Exclusion Code: X4.
8. Agarwal S, Hachamovitch R, Menon V. Current trial-associated outcomes with warfarin in prevention of stroke in patients with nonvalvular atrial fibrillation: a meta-analysis (Structured abstract). Arch Intern Med. 2012;172(8):623-31. PMID: DARE-12012014674. Exclusion Code: X4.
9. Aguilar Maria I, Hart R, Pearce Lesly A. Oral anticoagulants versus antiplatelet therapy for preventing stroke in patients with non-valvular atrial fibrillation and no history of stroke or transient ischemic attacks. Cochrane Database of Systematic Reviews. 2007(3)doi: 10.1002/14651858.CD006186.pub2. PMID: CD006186. Exclusion Code: X4.
10. Akao M, Chun YH, Esato M, et al. Inappropriate use of oral anticoagulants for patients with atrial fibrillation. Circ J. 2014;78(9):2166-72. PMID: 24976391. Exclusion Code: X4.
11. Albertsen IE, Rasmussen LH, Overvad TF, et al. Risk of stroke or systemic embolism in atrial fibrillation patients treated with warfarin: a systematic review and meta-analysis. Stroke. 2013 May;44(5):1329-36. doi: 10.1161/strokeaha.113.000883. PMID: 23482597. Exclusion Code: X4.
12. Alexander J, Andersson U, Lopes R, et al. Apixaban 5 mg twice daily and clinical outcomes in patients with atrial fibrillation and advanced age, low body weight, or high creatinine: a secondary analysis of a randomized clinical trial. JAMA cardiology. 2017;1(6):673-81. PMID: CN-01308892. Exclusion Code: X4.

13. Amin A, Boulanger L, Gatt E, et al. Exposure to warfarin and the risks of stroke and bleeding events among patients with non-valvular atrial fibrillation: Real-world vs. Clinical trial. Circ Cardiovasc Qual Outcomes. 2012;5(3 suppl. 1) PMID: CN-01023993. Exclusion Code: X7.
14. Amin A, Stokes M, Wu N, et al. Application of randomized clinical trial data to actual practice: apixaban therapy for reduction of stroke risk in non-valvular atrial fibrillation patients. Curr Med Res Opin. 2013 Oct;29(10):1253-61. doi: 10.1185/03007995.2013.818967. PMID: 23796193. Exclusion Code: X4.
15. Angoulvant D, Villejoubert O, Bejan-Angoulvant T, et al. Effect of Active Smoking on Comparative Efficacy of Antithrombotic Therapy in Patients With Atrial Fibrillation: The Loire Valley Atrial Fibrillation Project. Chest. 2015 Aug;148(2):491-8. doi: 10.1378/chest.14-3006. PMID: 25812113. Exclusion Code: X4.
16. Apenteng PN, Murray ET, Holder R, et al. An international longitudinal registry of patients with atrial fibrillation at risk of stroke (GARFIELD): the UK protocol. BMC Cardiovasc Disord. 2013;13:31. doi: 10.1186/1471-2261-13-31. PMID: 23617744. Exclusion Code: X5.
17. Ashburner JM, Go AS, Reynolds K, et al. Comparison of frequency and outcome of major gastrointestinal hemorrhage in patients with atrial fibrillation on versus not receiving warfarin therapy (from the ATRIA and ATRIA-CVRN cohorts). Am J Cardiol. 2015 Jan 1;115(1):40-6. doi: 10.1016/j.amjcard.2014.10.006. PMID: 25456871. Exclusion Code: X4.
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Appendix C. Excluded Studies

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Appendix C. Excluded Studies

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Appendix C. Excluded Studies

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Appendix C. Excluded Studies

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Appendix D Table 1. Quality Assessment of Randomized, Controlled Trials (All KQs): Part 1

First Author, Year Trial Name	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	What was the reported intervention fidelity?	What was the reported adherence to the intervention?	Did the study have cross-overs or contamination raising concern for bias?	What was the overall attrition?	What was the differential attrition?	Did the study have differential attrition or overall high attrition raising concern for bias?
Benito, 2015[77] EARLY pilot study	Unclear	Unclear	Yes, for those analyzed, but NR for those randomized; and not many characteris-tics reported (e.g., medications and smoking NR)	NR	NR	Unclear	77% of the 4,000 randomized were not included in analyses; the authors report an overall loss to followup of 5.8% (using a smaller denominator around 900 that does not consider all of the post-randomization exclusions)	9.7% vs. 1.9%	Yes, very high overall attrition
Connolly, 1991[78] CAFA study	Unclear, method of sequence generation NR	NR	Yes	NA	NR	No (<3%)	Lost to followup NR (implied 0 or very low); 25% discontinued medication	NR; 4%	No
Ezekowitz, 1992[79]	Unclear	Unclear	Yes	NA	NR	NR	4% lost to followup; 16% dropped out	2%; 3%	No
Fitzmaurice, 2014[47]; Fitzmaurice, 2007[37]; Mant, 2007[80]; Hobbs, 2005[81]; Swancutt, 2004[82] SAFE	Yes	No	Yes for age and sex; unclear otherwise	53% of patients invited for systematic screening underwent ECG	NA	NR, but not suspected	0.6% missing data	0.1%	No
Morgan, 2002[30]	Yes	Unclear	Yes for age and sex; unclear otherwise	73% of those invited for screening had pulse assessed	NA	NR	NR	NR	Unclear

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First Author, Year Trial Name	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	What was the reported intervention fidelity?	What was the reported adherence to the intervention?	Did the study have cross-overs or contamination raising concern for bias?	What was the overall attrition?	What was the differential attrition?	Did the study have differential attrition or overall high attrition raising concern for bias?
Petersen, 1989[83] AFASAK	Yes	Unclear	Yes	NA	NR	No	Unable to determine amount of missing data (lost to followup NR), Number of withdrawals is reported (222/1,007=22%) but it indicates that these subjects were still followed up for outcomes.	Unable to determine for missing data (lost to followup); For withdrawals, 126 (38%) warfarin vs. 44 (12%) aspirin vs. 52 (16%) placebo and most of the difference was due to refusal to continue the medication.	Unclear
Posada, 1999[84] LASAF Pilot Study	Unclear, method of sequence generation NR	NR	Yes for things in Table 1, but unclear for many risk factors for the outcomes that were NR (e.g., hypertension, smoking, medications)	NA	NR, although they report that 7% of those treated with aspirin withdrew because of GI discomfort or mild bleeding	NR	0% missing data; 18% dropped out (including due to adverse effects and events/outcomes)	0%; 8%	No

Appendix D Table 1. Quality Assessment of Randomized, Controlled Trials (All KQs): Part 1

First Author, Year Trial Name	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	What was the reported intervention fidelity?	What was the reported adherence to the intervention?	Did the study have cross-overs or contamination raising concern for bias?	What was the overall attrition?	What was the differential attrition?	Did the study have differential attrition or overall high attrition raising concern for bias?
Sato, 2006[85] JAST	Unclear, method of sequence generation NR	Yes	Yes	NA	NR	NR	0.3% missing data; 21.2% noncompleters (including due to side effects, cardiac and other diseases, and personal reasons)	0.7%; 2.5%	No
Stroke Prevention in Atrial Fibrillation Study Group, 1990[86] Stroke Prevention in Atrial Fibrillation Study Group, 1991[87] SPAF	Yes	Unclear	Yes	NA	88% of participants averaged over 80% adherence by pill count	NR	0% lost to followup; 1.5% of scheduled followup visits not completed	0%; NR; 11.2% discontinued warfarin vs. 5% for aspirin, vs. 6.6% for placebo	No
The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators, 1990[88] BAATAF	Yes	Yes	Yes	NA	NR, although high time in therapeutic range over 80% suggests high adherence	Yes, aspirin allowed in control group (but not in warfarin group) and was being taken during 46% of all patient-years in control group	0% lost to followup; 10% of warfarin group discontinued the medication (NA for control; no placebo control)	0%; NA	No

Abbreviations: AFASAK=Atrial Fibrillation, Aspirin and Anticoagulation study; BAATAF= Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA=Canadian Atrial Fibrillation Anticoagulation; EARLY=Early diagnosis of Atrial fibrillation: a Randomized triaL in primarY care; ECG=electrocardiogram; GI=gastrointestinal; JAST=Japan Atrial Fibrillation Stroke Trial; KQ=key question; LASAF= low-dose aspirin, stroke atrial fibrillation trial; NA=not applicable; NR=not reported; SAFE= Screening for AF in the elderly study; SPAF= Stroke Prevention in Atrial Fibrillation.

Appendix D Table 2. Quality Assessment of Randomized, Controlled Trials (All KQs): Part 2

First Author, Year Trial Name	Were outcome measurements equal, valid, and reliable?	Were patients masked?	Were providers masked?	Were outcome assessors masked?	Was the duration of followup adequate to assess the outcome?	What was the method used to handle missing data?	Did the study use acceptable statistical methods?	Quality Rating	Comments
Benito, 2015[77] EARLY pilot study	No, outcomes measures were not equal between groups; IG had visits every 6 months that included an ECG, whereas CG only had outcomes based on clinical history from EHR and as needed phone calls	No, not feasible	Yes	Unclear	Yes	NR	Yes	Poor	High risk of selection bias, measurement bias, and confounding. Very high overall attrition (>70% of those randomized were not included in analyses), methods of outcome assessment differed between IG and CG, unclear methods of randomization and allocation concealment, and no information about handling of missing data, or masking of outcome assessors. We note that it is self-described as a pilot study (indicating that the purpose may be mainly for planning a future study).
Connolly, 1991[78] CAFA study	Yes	Yes	Yes, except for person seeing PT/INR and making dose adjustments	Yes	Yes (mean followup 15.2months)	NR	Yes	Fair	Stopped early because of other positive studies with similar design and objectives; planned 630 participants and 2.5 years followup (378 analyzed)
Ezekowitz, 1992[79]	Yes	Yes	No, for those adjusting doses; yes for cardiologist and neurologist	Yes	Yes (mean followup 1.7 to 1.8 years)	Censored	Yes	Fair	Warfarin vs. placebo; Stopped early with DSMB involvement and prespecified interim analyses showing benefit of warfarin and other similar studies being stopped early

Appendix D Table 2. Quality Assessment of Randomized, Controlled Trials (All KQs): Part 2

First Author, Year Trial Name	Were outcome measurements equal, valid, and reliable?	Were patients masked?	Were providers masked?	Were outcome assessors masked?	Was the duration of followup adequate to assess the outcome?	What was the method used to handle missing data?	Did the study use acceptable statistical methods?	Quality Rating	Comments
Fitzmaurice, 2014[47]; Fitzmaurice, 2007[37]; Mant, 2007[80]; Hobbs, 2005[81]; Swancutt, 2004[82] SAFE	Yes	No	No	Yes	Yes	Excluded; complete records only	Yes	Fair	Practices randomized to screening intervention or not (and randomization again within intervention group for opportunistic vs. systematic); no concealment of allocation; baseline comparison only provided for age and sex (no information on other variables or on practice characteristics, although randomization was stratified by practice size); good approach to determining when atrial fibrillation was previously diagnosed
Morgan, 2002[30]	Unclear, single observer reviewed medical records	No	No	NR	Unclear (6 months and few new cases of atrial fibrillation)	NR	Yes	Fair	The main outcomes describe total numbers of atrial fibrillation cases detected (inclusive of both previously known atrial fibrillation and newly diagnosed atrial fibrillation), so their main outcomes are not relevant for our questions; they also report incident cases, but they give somewhat limited details on methods of medical record review process for determining whether patients had previously diagnoses atrial fibrillation, and it was done by a single person (and masking NR); given that there were only 12 vs. 7 new cases (few events) and the study only covered 6 months of screening, the study provides limited information, although it shows pretty good

Appendix D Table 2. Quality Assessment of Randomized, Controlled Trials (All KQs): Part 2

First Author, Year Trial Name	Were outcome measurements equal, valid, and reliable?	Were patients masked?	Were providers masked?	Were outcome assessors masked?	Was the duration of followup adequate to assess the outcome?	What was the method used to handle missing data?	Did the study use acceptable statistical methods?	Quality Rating	Comments
									uptake/fidelity; Allocation concealment NR; baseline comparison only provided for age and sex
Petersen, 1989[83] AFASAK	Yes	No for warfarin Yes for ASA and placebo	No for warfarin Yes for ASA and placebo	Yes	Yes	NR	Yes	Fair	Thromboembolic endpoints were clinically confirmed, and also classified by a neurologist using a priori criteria. Information on missing data NR, unable to determine attrition; open-label for warfarin
Posada, 1999[84] LASAF Pilot Study	Unclear	No	No	NR	Unclear (all followed a minimum 12 months)	NR	Yes	Poor	Open-label; stopped early because of results from other trials on aspirin being published; methods of randomization sequence generation and allocation concealment NR; methods of outcome ascertainment unclear and masking of outcome assessors NR; high risk of measurement bias
Sato, 2006[85] JAST	Yes	No	No	Yes	Unclear, mean followup of 2-3 years planned (stopped early)	NR	Yes	Fair	Open-label; trial stopped early because of interim analysis showing possibly higher risk of bleeding and aspirin unlikely to be superior to no treatment for benefits
Stroke Prevention in Atrial Fibrillation Study Group, 1990[86] Stroke Prevention in Atrial Fibrillation	Yes	No	No	Yes	Yes (mean followup 1.3 years)	NA	Yes	Fair	Placebo arm was stopped early (multi-arm trial, and the warfarin and aspirin arms continued); open-label warfarin (although aspirin and placebo were given in a double-blind fashion); allocation concealment

Appendix D Table 2. Quality Assessment of Randomized, Controlled Trials (All KQs): Part 2

First Author, Year Trial Name	Were outcome measurements equal, valid, and reliable?	Were patients masked?	Were providers masked?	Were outcome assessors masked?	Was the duration of followup adequate to assess the outcome?	What was the method used to handle missing data?	Did the study use acceptable statistical methods?	Quality Rating	Comments
Study Group, 1991[87] SPAF									unclear
The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators, 1990[88] BAATAF	Yes	No	No	Yes	Yes (mean followup 2.2 years)	NA, reported no missing data	Yes	Fair	Stopped early because of evidence favoring warfarin over control (had already enrolled target number of participants, but had not reached the mean 4.1 years planned); contamination with aspirin in control group (might lead to underestimation of both benefits and harms of warfarin); no placebo; open-label

Abbreviations: AFASAK=Copenhagen Atrial Fibrillation, Aspirin and Anticoagulation study; ASA=aspirin; BAATAF= Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA=Canadian Atrial Fibrillation Anticoagulation; CG=control group; DSMB=Data and Safety Monitoring Board; EARLY=Early diagnosis of Atrial fibrillation: a Randomized triaL in primarY care; ECG=electrocardiogram; EHR=electronic health record; IG=intervention group; JAST=Japan Atrial Fibrillation Stroke Trial; LASAF=Low-dose Aspirin, Stroke Atrial Fibrillation trial; NR=not reported; PT/INF=prothrombin time/International Normalized Ratio; SAFE=Screening for AF in the Elderly study; SPAF= Stroke Prevention in Atrial Fibrillation.

Appendix D Table 3. Quality Assessment of Randomized, Controlled Trials: Additional Questions for Studies Reporting Harms (KQs 3 and 5 only)

First Author, Year Trial Name	Were harms pre-specified and defined?	Were ascertainment techniques for harms adequately described?	Were ascertainment techniques for harms equal, valid, and reliable?	Was duration of followup adequate for harms assessment?	Quality Rating	Comments
Benito, 2015[77] EARLY pilot study	No	No	No	Yes	Poor	High risk of selection bias, measurement bias, and confounding
Connolly, 1991[78] Canadian Atrial Fibrillation Anticoagulation (CAFA) study	Yes	Yes	Yes	Yes (mean followup 15.2 months)	Fair	Self-report of bleeding events
Ezekowitz, 1992[79]	Yes	Yes	Yes	Yes (mean followup 1.7 to 1.8 years)	Fair	
Fitzmaurice, 2014[47]; Fitzmaurice, 2007[37]; Mant, 2007[80]; Hobbs, 2005[81]; Swancutt, 2004[82] SAFE	Yes	Yes	NA (only measured for intervention group)	Yes	Fair	Limited information about harms, but protocol/methods paper prespecified measurement of anxiety (intervention group only) and evaluation of primary care provider accuracy of interpretation of ECGs (direct implications for mislabeling and potential harms); the anxiety information was only collected for those getting ECGs and was not collected for the control group (so unable to make any conclusions for anxiety that directly address our question)
Petersen, 1989[83] AFASAK	Yes	Yes	Yes	Yes	Fair	
Posada, 1999[84] LASAF Pilot Study	Unclear whether prespecified; hemorrhagic stroke was defined, bleeding events were not	No	Unclear	Unclear (all followed a minimum of 12 months)	Poor	See comments for KQ 4 quality evaluation of this study
Sato, 2006[85] JAST	Yes	Yes	Yes	Unclear	Fair	Open-label; stopped early

Appendix D Table 3. Quality Assessment of Randomized, Controlled Trials: Additional Questions for Studies Reporting Harms (KQs 3 and 5 only)

First Author, Year Trial Name	Were harms pre-specified and defined?	Were ascertainment techniques for harms adequately described?	Were ascertainment techniques for harms equal, valid, and reliable?	Was duration of followup adequate for harms assessment?	Quality Rating	Comments
Stroke Prevention in Atrial Fibrillation Study Group, 1990[86] Stroke Prevention in Atrial Fibrillation Study Group, 1991[87] SPAF	Yes	Yes	Yes	Yes (mean followup 1.3 years)	Fair	
The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators, 1990[88] BAATAF	Yes	Yes	Yes	Yes (mean followup 2.2 years)	Fair	

Abbreviations: AFASAK=Copenhagen Atrial Fibrillation, Aspirin and Anticoagulation study; BAATAF=Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA=Canadian Atrial Fibrillation Anticoagulation study; EARLY=Early diagnosis of Atrial fibrillation: a Randomized triaL in primarY care; ECG=electrocardiography; JAST=Japan Atrial Fibrillation Stroke Trial; KQ=key question; NA=not applicable; NR=not reported; SAFE= Screening for AF in the elderly study; SPAF=Stroke Prevention in Atrial Fibrillation Study; SPINAF=Stroke Prevention in Atrial Fibrillation study.

Appendix D Table 4. Quality Assessment of Cohort Studies (KQs 2, 3, 5 only): Part 1

First Author, Year, Study Name	Were eligibility criteria clearly described?	Were groups similar at baseline?	What was the reported intervention fidelity?	What was the reported adherence to the intervention?	Did the study have cross-overs or contamination raising concern for bias?	What was the overall attrition?	What was the differential attrition?	Did the study have differential attrition or overall high attrition raising concern for bias?
Caro, 1999[89]	Yes	No	NA	NR	Yes	NR	NR	Unclear
Forslund, 2014[90]	Yes	No	NA	NR	Yes	NR	NR	Unclear
Humphries, 2001[91]	Yes	NR for warfarin vs. no warfarin (only reported for men vs. women, and they were not similar)	NA	NR	Unclear	1% loss to followup; 14% did not complete 3-year visit evaluation	NR	Unclear
Kodani, 2016[92] J-RHYTHM Registry 2	Yes	No	NR. Analysis based on final status of medication use (at time of an event or end of followup).	NR. Analysis based on final status of medication use.	Yes	Loss to followup: 0.7%	NR	NR for differential; no for overall

Abbreviations: KQ=key question; NA=not applicable; NR=not reported; vs=versus.

Appendix D Table 5. Quality Assessment of Cohort Studies (KQs 2, 3, 5 only): Part 2

First Author, Year	Was assessment of the drug exposure (dose and duration) valid and reliable?	Were outcome measure-ments equal, valid, and reliable?	Were outcome assessors masked?	Was the duration of followup adequate to assess the outcome?	What was the method used to handle missing data?	Did the study use acceptable statistical methods?	Did the analysis adjust for potential confounders?	Quality Rating	Comments
Caro, 1999[89]	Unclear for duration (self-report, but vague description of ascertainment methods); no assessment of dose	Yes equal, but uncertain validity and reliability (relied on patient recall, although they sought confirmation from charts)	No	Yes	Censored	Complete data only; and not ITT (reassigned to "blended" group if treatment changed)	No (Cox model but did not report adjusting for anything for the bleeding assessment)	Poor	High risk of confounding and selection bias; no adjustment for potential confounders; high risk of contamination; many baseline characteristics differ significantly between groups; not ITT analysis; sample size under 250 may be inadequate; attrition NR
Forslund, 2014[90]	No	Unclear	No	Yes	NR	No	No	Poor	High risk of selection bias and confounding; no adjustment for potential confounders; not ITT; concern for cross-over and contamination; aspirin ascertainment based on prescriptions only; determined whether participants had atrial fibrillation based on 2005 to 2009 data, but treatment group assignment based on a 6-month window within the 2009 data or the 6 months prior to any event that occurred; 25% not assigned to warfarin group got warfarin prior to 2009

Appendix D Table 5. Quality Assessment of Cohort Studies (KQs 2, 3, 5 only): Part 2

First Author, Year	Was assessment of the drug exposure (dose and duration) valid and reliable?	Were outcome measure-ments equal, valid, and reliable?	Were outcome assessors masked?	Was the duration of followup adequate to assess the outcome?	What was the method used to handle missing data?	Did the study use acceptable statistical methods?	Did the analysis adjust for potential confounders?	Quality Rating	Comments
Humphries, 2001[91]	Yes, for warfarin vs. no warfarin; dose information NR and no assessment of INRs except for people with bleeding events	Yes equal, but uncertain validity and reliability (relied on patient recall, and no mention of verification)	No	Yes	None	Complete data only; no handling of missing data	No, only adjusted for age	Poor	High risk of confounding and selection bias; prospective cohort study focused on comparing sex differences for presentation, treatment, and outcomes; only potentially eligible for our KQ 5 for the information on major bleeds; analysis only adjusted for age, unclear how many in each group were on aspirin, did not report baseline characteristics for warfarin vs. no warfarin groups; and participants had very few major bleeding events (15 total events); differential attrition NR for our comparison of interest
Kodani, 2016[92] J-RHYTHM Registry 2	No (analysis based on final status of use)	Yes	Unclear	Yes	None, excluded from analyses (15% excluded because of unknown OAC status; NR how much missing/ex-cluded for other reasons)	Yes	Adjusted for some potential confounders (CHA_2DS_2 components and antiplatelet use)	Poor	High risk of selection bias and confounding; not an inception cohort, high likelihood of residual confounding and confounding by indication, exposure groups analyzed based on final exposure at end of observation period, not based on exposure at baseline or changes over time; inadequate handling of missing data; unclear masking.

Abbreviations: CHA_2DS_2-VASc=Congestive heart failure, Hypertension, Age ≥75 years [doubled], Diabetes mellitus, prior Stroke or TIA or thromboembolism [doubled], Vascular disease, Age 65-74 years, Sex category; INR=international normalized ratio; ITT=intent to treat; KQ=key question; NA=not applicable; NR=not reported; OAC=oral anticoagulant; TIA=transient ischemic attack.

Appendix D Table 6. Quality Assessment of Systematic Reviews, Network Meta-analyses, and IPD Meta-analyses (KQs 4, 5)

First Author, Year	Was the review based on a focused question of interest?	Was a comprehensive literature search (including grey literature) clearly described?	Were there explicit a priori inclusion/ exclusion criteria for the selection of studies?	Did at least 2 people indepen-dently review studies?	Were the characteristics of the included studies provided?	Was the internal validity (quality) of included studies adequately assessed?	Was hetero-geneity assessed and addressed?	Was the approach used to synthesize the information adequate and appropriate?	Were the authors' conclusions supported by the evidence?	Was publication bias assessed?	Quality Rating
Aguilar Maria, 2005[93]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Good
Aguilar Maria, 2005[94]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Good
Coleman, 2012[95]	Yes	Yes for published literature; no mention of grey literature	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes (some statistical tests reported, although not described in methods)	Fair
Atrial Fibrillation Investi-gators, 1994[96]	Yes	No, but they identified all relevant known studies	Yes	NR	No	No	Yes (it is an IPD meta-analysis allowing greater assessment of heterogeneity (e.g., analyses of women separated)	Yes	Yes	NR	Fair
Teresh-chenko, 2016[97]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
The Atrial Fibrillation Invest-igators, 1997[98]	Yes	No, but they identified all relevant known studies	Yes	NR	Partially	No	Yes (it is an IPD meta-analysis allowing greater assessment of heterogeneity	Yes	Yes	NR	Fair

Appendix D Table 6. Quality Assessment of Systematic Reviews, Network Meta-analyses, and IPD Meta-analyses (KQs 4, 5)

First Author, Year	Was the review based on a focused question of interest?	Was a comprehensive literature search (including grey literature) clearly described?	Were there explicit a priori inclusion/ exclusion criteria for the selection of studies?	Did at least 2 people indepen-dently review studies?	Were the characteristics of the included studies provided?	Was the internal validity (quality) of included studies adequately assessed?	Was hetero-geneity assessed and addressed?	Was the approach used to synthesize the information adequate and appropriate?	Were the authors' conclusions supported by the evidence?	Was publication bias assessed?	Quality Rating
							(e.g., analyses of women separated)				
van Walraven, 2009[99]	Yes	No, but they identified all relevant known studies (IPD analysis of data from a central database of clinical trials on patients with AF)	Yes	NR	Partially	No	Yes	Yes	Yes	NR	Fair
Hart, 2007[100]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good

Abbreviations: AF=atrial fibrillation; IPD=individual patient data; KQ=key question; NR=not reported.

Appendix D Table 7. Relevance of Systematic Reviews and Meta-analyses for the Benefits and Harms of Anticoagulation or Antiplatelet Therapy (KQs 4, 5)

First Author, Year	Review type (IPD, aggregate data SR, NMA)?	Did the review meet our initial eligibility criteria?	Did the review focus only on studies of primary prevention (with no or few participants with history of stroke or TIA)?	Did the review include all relevant trials on aspirin?	Did the review include all relevant trials on warfarin?	If the review is an NMA, did it include the relevant trials for newer OACs?	Has the review been updated?	Was the review relevant and included in our current review?	Comments
Aguilar, 2009[93]	SR with MA	Yes	Yes	NA	Yes	NA	No	Yes	Cochrane review. Focuses on patients without history of stroke or TIA and got unpublished results from the Atrial Fibrillation Investigators that removed the 3% to 8% of participants with prior TIA or stroke from the studies.
Aguilar, 2011[101]	SR with MA	Yes	Yes	No, did not include JAST (JAST was not yet published)	NA	NA	No	Yes	Cochrane review. Focuses on patients without history of stroke or TIA and got unpublished results from the Atrial Fibrillation Investigators that removed the 6% of participants with prior TIA or stroke from the studies.
Assiri, 2013[102]	NMA	Yes	No	Yes	No, did not include CAFA or BAATAF	No, did not include ENGAGE or JROCKET	No	No	Review excludes 2 warfarin trials and 2 trials of NOACs. Also combined studies of primary and secondary prevention.
Atrial Fibrillation Investi-gators, 1994[96]	IPD	Yes	Yes	No, it did not include JAST or LASAF	Yes	NA	No	Yes	Used the Atrial Fibrillation Investigators database; used only the 5 warfarin trials (2 of those also included ASA)
Atrial Fibrillation Investi-gators, 1997[98]	IPD	Yes	No, but it provides separate analyses in some places for the studies that were primary prevention	No, it did not include JAST or LASAF	NA	NA	No	Yes	Used the 3 ASA trials in Atrial Fibrillation Investigators database; 1 of those is secondary prevention (EAFT), but those data are not in all analyses in Tables 2 and 3 (and Table 4 provides data for patients with no clinical risk factors, one of which was prior stroke or TIA)
Cameron, 2014 [103]	NMA	Yes	Yes	No, it did not include LASAF or SPAF-1	No, it did not include SPINAF, BAATAF, or SPAF-1	No, did not include AVERROES or JROCKET	No	No	Review excluded 2 of the aspirin trials, 3 of the warfarin trials, and 2 of NOCAS

Appendix D Table 7. Relevance of Systematic Reviews and Meta-analyses for the Benefits and Harms of Anticoagulation or Antiplatelet Therapy (KQs 4, 5)

First Author, Year	Review type (IPD, aggregate data SR, NMA)?	Did the review meet our initial eligibility criteria?	Did the review focus only on studies of primary prevention (with no or few participants with history of stroke or TIA)?	Did the review include all relevant trials on aspirin?	Did the review include all relevant trials on warfarin?	If the review is an NMA, did it include the relevant trials for newer OACs?	Has the review been updated?	Was the review relevant and included in our current review?	Comments
Coleman, 2012[95]	SR with MA	Yes	No, combines primary prevention and secondary prevention studies; studies in the review were not selected because of history of stroke/TIA	No, it did not include SPAF-1 or LASAF (but those did not report MGIB)	No, it did not include SPAF-1 or CAFA (but those did not report MGIB)	NA	No	Yes	Combined studies of primary and secondary prevention (participants had a TIA or stroke) and does not provide any analyses separating them;[a] possibly limiting applicability
Ezekowitz, 1999[104]	IPD	Yes	No, included 1 secondary prevention trial (EAFT), 1 with over a third having previous stroke or TIA (SPAF3), and 1 with around 20% secondary prevention (NASPEAF)	No, it did not include JAST or LASAF	Yes	NA	No	No	Relevant data were presented in a previous publication. This just reiterates those findings.
Hart, 2007[105]	SR with MA	Yes	No, but separated (primary vs. secondary prevention) results for absolute risk reduction of stroke	No, it did not include JAST	Yes	NA	Yes	No	Excluded, superseded by an updated publication
Hart, 2007[100]	SR with MA	Yes	No, but separated (primary vs. secondary prevention) results for absolute risk reduction of stroke	Yes	Yes	NA	No (it is an update of a 1999 review)[105]	Yes	Although the meta-analyses reporting relative reductions include both primary and secondary prevention studies, they stratify those for the absolute reduction data (in Tables 2 and 3)
Lapner, 2013[106]	SR with MA	No	Yes	No, it did not include JAST, LASAF, SPAF-1,	No, it did not include SPINAF, CAFA,	NA	No	No	Excluded for wrong comparator

Appendix D Table 7. Relevance of Systematic Reviews and Meta-analyses for the Benefits and Harms of Anticoagulation or Antiplatelet Therapy (KQs 4, 5)

First Author, Year	Review type (IPD, aggregate data SR, NMA)?	Did the review meet our initial eligibility criteria?	Did the review focus only on studies of primary prevention (with no or few participants with history of stroke or TIA)?	Did the review include all relevant trials on aspirin?	Did the review include all relevant trials on warfarin?	If the review is an NMA, did it include the relevant trials for newer OACs?	Has the review been updated?	Was the review relevant and included in our current review?	Comments
				AFASAK-1	BAATAF, SPAF-1, AFASAK-1				
Roskell, 2010 [107]	NMA	Yes	Yes	No, it did not include JAST or LASAF	No, it did not include SPINAF	No, published prior to ARISTOTLE, ENGAGE, ROCKET, and JROCKET	No	No	Excluded 2 of the aspirin trials, 1, of the warfarin trials, and 3 of the NOAC trials
Sahay, 2016[108]	NMA	Yes	Yes	No, it did not include JAST or LASAF	No, it did not include SPINAF, CAFA, or BAATAF	No, it did not include AVERROES	No	No	Excluded 2 of the aspirin trials, 3 of the warfarin trials, and 1 NOAC trial
Sardar, 2014[109]	SR and MA	No	Yes	No, it did not include JAST, LASAF, SPAF-1, or AFASAK-1	No, it did not include SPINAF, CAFA, BAATAF, SPAF-1, or AFASAK-1	NA	No	No	Wrong population; only placebo-controlled trials treated VTE
Tawfik, 2016 [110]	NMA	Yes	Yes	Yes	No, it did not include SPINAF or BAATAF	No, it did not include JROCKET	No	No	Review excluded 2 of the warfarin trials
Teresh-chenko, 2016[97]	NMA	Yes	No, but most of the evidence is from trials focused mostly on primary prevention (4 of the 21 included trials had over 35% secondary prevention)[b]	Yes (although ultimately excluded LASAF for poor quality)	Yes	Yes, all the newer relevant trials included (although this excluded phase II trials of NOACs)	No	Yes	Includes some contribution of data from people with a history of TIA or stroke. NOAC phase II studies were excluded.

Appendix D Table 7. Relevance of Systematic Reviews and Meta-analyses for the Benefits and Harms of Anticoagulation or Antiplatelet Therapy (KQs 4, 5)

First Author, Year	Review type (IPD, aggregate data SR, NMA)?	Did the review meet our initial eligibility criteria?	Did the review focus only on studies of primary prevention (with no or few participants with history of stroke or TIA)?	Did the review include all relevant trials on aspirin?	Did the review include all relevant trials on warfarin?	If the review is an NMA, did it include the relevant trials for newer OACs?	Has the review been updated?	Was the review relevant and included in our current review?	Comments
van Walraven, 2009[99] Atrial Fibrillation Investi-gators	IPD	Yes	No, included 1 secondary prevention trial (EAFT), 1 trial with over a third having previous stroke or TIA (SPAF3), and one with around 20% secondary prevention (NASPEAF) but sensitivity analyses provided serial exclusion of individual studies (and those did not alter estimates)	No, it did not include JAST or LASAF	Yes	NA	No	Yes	Used the Atrial Fibrillation Investigators database; included head-to-head studies and placebo-controlled

[a]One quarter studies in VKA meta-analysis, and one third in the aspirin meta-analysis were secondary prevention studies.
[b] The percentage of participants with a history of TIA or stroke was 100% in EAFT (VKA vs. aspirin vs. placebo), 64% in JROCKET (rivaroxaban vs. VKA), 55% in ROCKET AF (rivaroxaban vs. VKA), and 38% in SPAF III. It was <10% in 9 trials (AFASAK I, BAATAF, SPAF I, CAFA, SPAF II, AFASAK II, PATAF, SAFT, and JAST) and ranged from 13% to 28% in the other 8 included trials.

Abbreviations: AFASAK=Copenhagen Atrial Fibrillation, Aspirin and Anticoagulation study; ARISTOTLE=Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; ASA=aspirin; AVERROS=Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment; BAATAF=Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA=Canadian Atrial Fibrillation Anticoagulation study; EAFT=European Atrial Fibrillation Trial Study Group; ENGAGE AF-TIMI=Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation - Thrombolysis in Myocardial Infarction 48; IPD=individual patient data; JAST=Japan Atrial Fibrillation Stroke Trial; JROCKET=Japanese Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; KQ=key question; LASAF=low-dose aspirin, stroke atrial fibrillation trial; MA=meta-analysis; MGIB=major gastrointestinal bleeding; NA=not applicable; NASPEAF=National Study for Prevention of Embolism in Atrial Fibrillation; NMA=network meta-analysis; NOAC=novel oral anticoagulant; OAC=oral anticoagulant; ROCKET AF=Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; SPAF=Stroke Prevention in Atrial Fibrillation Study; SPINAF=Stroke Prevention in Atrial Fibrillation study; SR=systematic review; TIA=transient ischemic attack; VKA=vitamin K antagonist; VTE=venous thrombosis.

Appendix E Table 1. Results of Included Randomized, Controlled Trials for KQs 4 and 5

First Author, Year Trial Name	G1 (N) G2 (N) G3 (N)	All-Cause Mortality G1 N (%) G2 N (%) ES (95% CI)	Stroke-Related or CV-Related Mortality G1 N (%) G2 N (%) ES (95% CI)	Any Stroke G1 N (%) G2 N (%) ES (95% CI)	Cardioembolic or Ischemic Stroke G1 N (%) G2 N (%) ES (95% CI)	Stroke-Related Morbidity G1 N (%) G2 N (%) ES (95% CI)	Other G1 N (%) G2 N (%) ES (95% CI)
Petersen, 1989 [83] AFASAK	Warfarin, adjusted dose (335) Aspirin 75 mg daily (336) Placebo (336)	71 total deaths Total mortality by group NR	*Stroke-related mortality* 1 (0.3) 3 (0.9) 4 (1.2) NR *Vascular deaths* 3 (0.9) 12 (3.6) 15 (4.5) p<0.02	NR	*Cumulative incidence of thromboembolic related complications* 5 (1.5) 15 (6.0) 16 (6.3) p<0.05 *Annual incidence of thromboembolic complications* 2.0%/year (0.6 to4.8%) 5.5%/year (2.9 to 9.4%) 5.5%/year (2.9 to 9.4%)	*Minor stroke* 0 (0) 1 (0.3) 2 (0.6) NR *Nondisabling stroke* 0 (0) 7 (2.1) 3 (0.9) NR *Disabling stroke* 4 (1.2) 4 (1.2) 7 (2.1) NR	*TIA* 0 (0) 2 (0.6) 3 (0.9) NR *Visceral emboli* 0 (0) 2 (0.6) 2 (0.6) NR *Emboli in both extremities* 0 (0) 1 (0.3) 0 (0) NR
The Boston Area Trial for Atrial Fibrillation Investiga-tors, 1990[88] BAATAF	Warfarin, adjusted dose (212) Control (208)	*Total death* 11 (5.2) 26 (12.5) Rate ratio: 0.38 (0.17 to 0.82) p=0.005 *Noncardiac death (includes stroke-related mortality)* 4 (1.9) 14 (6.7) p=0.008	*Stroke-related mortality* 0 (0) 1 (0.5) NR *CV-related mortality* 7 (3.3) 12 (5.8) p=0.17	NR	*Ischemic/cardioembolic stroke* 2 (0.9) 13 (6.3) Incidence ratio: 0.14 (0.04 to 0.49) Risk reduction: 86% (96 to 51)	*Mild* 0 (0) 4 (1.9) NR *Moderate* 1 (0.5) 3 (1.4) NR *Severe* 1 (0.5) 5 (2.4) NR	*Possible ischemic stroke* 1 (0.5) 2 (1) NR *TIA* 2 (0.9) 3 (1.4) NR

Appendix E Table 1. Results of Included Randomized, Controlled Trials for KQs 4 and 5

First Author, Year Trial Name	G1 (N) G2 (N) G3 (N)	All-Cause Mortality G1 N (%) G2 N (%) ES (95% CI)	Stroke-Related or CV-Related Mortality G1 N (%) G2 N (%) ES (95% CI)	Any Stroke G1 N (%) G2 N (%) ES (95% CI)	Cardioembolic or Ischemic Stroke G1 N (%) G2 N (%) ES (95% CI)	Stroke-Related Morbidity G1 N (%) G2 N (%) ES (95% CI)	Other G1 N (%) G2 N (%) ES (95% CI)
Stroke Prevention in Atrial Fibrillation Investigators, 1990 & 1991 Stroke Prevention in Atrial Fibrillation Investigators, 1990 & 1991[86, 87] SPAF I	*Group 1 (anti-coagulation candidates)* Warfarin, adjusted dose (210) Aspirin 325 mg/day (206) Placebo (211) *Group 2 (non-anticoagulation candidates)* Aspirin 325 mg/day (346) Placebo (357)	*Total mortality warfarin vs. placebo (Group 1)* Warfarin: 6 (2.2%/year) Placebo: 8 (3.1%/year) Risk reduction: 0.25 (-1.11 to .73), p=0.56 *Total mortality aspirin vs. placebo (Groups 1 and 2 combined)* Aspirin: 39 (5.3%/year) Placebo: 50 (6.5%/year) Risk reduction: 0.20 (-0.20 to 0.46), p=0.37	*Fatal ischemic stroke (Group 1)* Warfarin: 0 Placebo: 0 NA *Fatal ischemic stroke (Groups 1 and 2 combined)* Aspirin: 3 (0.5) Placebo: 2 (0.4) NR *Vascular death (Group 1)* Warfarin: 3 (1.4) Placebo: 5 (2.4) NA *Vascular death (Groups 1 and 2 combined)* Aspirin: 18 (3.3) Placebo: 19 (3.3) NR *Probable vascular death (Group 1)* Warfarin: 1 (0.5) Placebo: 2 (0.9) NA *Probable vascular death (Groups 1 and 2 combined)* Aspirin: 5 (0.9) Placebo: 8 (1.4) NR	NR	*Ischemic stroke or systemic embolism warfarin vs. placebo (Group 1)* Warfarin: 6 (2.3%/year) Placebo: 18 (7.4%/year) Risk reduction: 0.67 (0.27 to 0.85), p=0.01 *Ischemic stroke or systemic embolism vs. placebo (Groups 1 and 2 combined)* Aspirin: 26 (3.6%/year) Placebo: 46 (6.3%/year) Risk reduction: 0.42 (-0.09 to 0.63), p=0.02	*Minimally disabling ischemic stroke (Group 1)* Warfarin: 4 (1.9) Placebo: 10 (4.7) NA *Minimally disabling ischemic stroke (Groups 1 and 2 combined)* Aspirin: 10 (1.8) Placebo: 24 (4.2) NR *Moderate to severely disabling ischemic stroke (Group 1)* Warfarin: 2 (1.0) Placebo: 7 (3.3) NA *Moderate to severely disabling ischemic stroke (Groups 1 and 2 combined)* Aspirin: 10 (1.8) Placebo: 16 (2.8) NR	*TIA without ischemic stroke or systemic embolism (Group 1)* Warfarin: 3 (1.1%/year) Placebo: 4 (1.6%/year) NR *TIA without ischemic stroke or systemic embolism (Group 2)* Aspirin: 7 (1.0%/year) Placebo: 13 (1.7%/year) Risk reduction: 0.45 (-0.32 to 0.77), p=0.19 *Myocardial infarction (Group 1)* Warfarin: 2 (0.8%/year) Placebo: 2 (0.8%/year) NR *Myocardial infarction (Group 2)* Aspirin: 7 (0.9%/year) Placebo: 12 (1.6%/year) Risk reduction: 0.40 (-0.46 to 0.75), p=0.29 *Primary event or death Warfarin vs. placebo (Group 1)* Warfarin: 10 (3.8%/year) Placebo: 24 (9.8%/year) Risk reduction: 0.58 (0.20 to 0.78), p=0.01 *Primary event or death aspirin vs. placebo (Groups 1 and 2 combined)* Aspirin: 57 (7.9%/year) Placebo: 86 (11.8%/year) Risk reduction: 0.32 (0.07 to 0.50), p=0.02

Appendix E Table 1. Results of Included Randomized, Controlled Trials for KQs 4 and 5

First Author, Year Trial Name	G1 (N) G2 (N) G3 (N)	All-Cause Mortality G1 N (%) G2 N (%) ES (95% CI)	Stroke-Related or CV-Related Mortality G1 N (%) G2 N (%) ES (95% CI)	Any Stroke G1 N (%) G2 N (%) ES (95% CI)	Cardioembolic or Ischemic Stroke G1 N (%) G2 N (%) ES (95% CI)	Stroke-Related Morbidity G1 N (%) G2 N (%) ES (95% CI)	Other G1 N (%) G2 N (%) ES (95% CI)
Connolly, 1991 [78] CAFA	Warfarin, adjusted dose (187) Placebo (191)	*All-cause mortality* NR *Other deaths & vascular deaths* (Efficacy analysis) 7 4) 6 (3) (ITT analysis) 10 (5) 8 (4)	*Vascular death* (Efficacy analysis) 6 (3.2) 6 (3.1) NR (ITT analysis) 9 (4.8) 6 (3.1) NR	NR	*Lacunar stroke* (Efficacy analysis) 1 (0.5) 0 (0) NR (ITT analysis) 1 (0.5) 0 (0) NR *Non-lacunar stroke* (Efficacy analysis) 4 (2.1) 9 (4.7) NR (ITT analysis) 5 (2.7) 9 (4.7) NR	*Severe non-lacunar stroke* (ITT analysis) 2 (1.1) 4 (2.1) NR *Mild non-lacunar stroke* (ITT analysis) 3 (1.6) 5 (2.6) NR	*TIA* (Efficacy analysis) 1 (0.5) 2 (1.0) NR (ITT analysis) 2 (1.1) 2 (1.0) NR *Non-CNS embolic event* (Efficacy analysis) 1 (0.5) 2 (1.0) NR (ITT analysis) 1 (0.5) 2 (1.0) NR
Ezekowitz et al., 1992 [79] SPINAF	Warfarin 4 mg/day and adjusted to meet PT ratios (260) Control (265)	15 (5.8) (3.3%/year) 22 (8.3) (5.0%/year) Risk reduction: 0.31 (-0.29 to 0.63) p=0.19	*Cardiac cause (not related to cerebral outcome)* 7 (2.7) 6 (2.3) ES NR *Fatal stroke* 1 (0.4) 1 (0.4) ES NR	4 (1.5) (0.9%/year) 19 (7.2) (4.3%/year) Risk reduction: 0.79 (0.52 to 0.90) p=0.001	4 (1.5) (0.9%/year) 19 (7.2) (4.3%/year) Risk reduction: 0.79 (0.52 to 0.90) p=0.001	*Stroke with no impairment* 0 9 (3.4) NR *Stroke with minor impairment* 3 (1.2) 7 (2.6) NR *Stroke with major impairment* 0 (0) 2 (0.8) NR	*Cerebral infarction or death* 19 (7.3) (4.2%/year) 41 (15.5) (9.3%/year) Risk reduction: 0.53 (0.24 to 0.71) p=0.003 *Thrombotic vascular events* 9 (3.5) (2.0%/year) 16 (6.0) (3.6%/year) Risk reduction: 0.43 (-0.22 to 0.74) p=0.16

Appendix E Table 1. Results of Included Randomized, Controlled Trials for KQs 4 and 5

First Author, Year Trial Name	G1 (N) G2 (N) G3 (N)	All-Cause Mortality G1 N (%) G2 N (%) ES (95% CI)	Stroke-Related or CV-Related Mortality G1 N (%) G2 N (%) ES (95% CI)	Any Stroke G1 N (%) G2 N (%) ES (95% CI)	Cardioembolic or Ischemic Stroke G1 N (%) G2 N (%) ES (95% CI)	Stroke-Related Morbidity G1 N (%) G2 N (%) ES (95% CI)	Other G1 N (%) G2 N (%) ES (95% CI)
Sato et al., 2006[85] JAST	Aspirin 150–200 mg/day (426) Control (445)	*Cardiovascular death* 3 (.7) 3 (.67) p=1.00 *Noncardiovas-cular death* 7 (1.6) 6 (1.35) p=0.720	NR	17 (4) 18 (4.04) p=0.967	NR	NR	*TIA* 7 (1.64) 2 (.45) p=0.101 *Cardiogenic embolism* 14 (3.29) 12 (2.70) p=0.609 *Peripheral emboli* 0 (0) 1 (.22) p=1.000 *Thrombotic infarction* 3 (.70) 2 (.45) p=0.959 *Lacunar infarction* 0 (0) 4 (.9) p=0.135

Abbreviations: AFASAK=Copenhagen Atrial Fibrillation, Aspirin and Anticoagulation study; BAATAF=Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA=Canadian Atrial Fibrillation Anticoagulation study; CI=confidence interval; CNS=central nervous system; CV=cardiovascular; ES=effect size; G=group; ITT=intent to treat; JAST=Japan Atrial Fibrillation Stroke Trial; KQ=key question; N=sample size; NA=not applicable; NR=not reported; PT=prothrombin time; SPAF=Stroke Prevention in Atrial Fibrillation Study; SPINAF=Stroke Prevention in Atrial Fibrillation study; TIA=transient ischemic attack.

Appendix E Table 2. Results of Included Studies for KQ 5: Harms of Treatment

First Author, Year Trial Name	G1 (N) G2 (N)	Major Bleeding G1 N (%) G2 N (%) ES (95% CI)	Major Gastro-intestinal Bleeding G1 N (%) G2 N (%) ES (95% CI)	Allergic Reaction G1 N (%) G2 N (%) ES (95% CI)	Hemorrhagic Stroke G1 N (%) G2 N (%) ES (95% CI)	Subarachnoid Hemorrhage G1 N (%) G2 N (%) ES (95% CI)	Intracerebral Hemorrhage G1 N (%) G2 N (%) ES (95% CI)	Subdural Hemorrhage/ Hematoma G1 N (%) G2 N (%) ES (95% CI)	Minor Bleeding G1 N (%) G2 N (%) ES (95% CI)	Other Harms G1 N (%) G2 N (%) ES (95% CI)
Petersen, 1989[83] The Copenhagen AFASAK Study	Warfarin dose adjusted per subject (335) Aspirin 75 mg 1x daily (336) Placebo (336)	*Bleeding (non-fatal) causing withdrawal from study* 21 (6.3) 2 0 *Respiratory tract bleeding* 4 (1.2) 1 (0.3) 0 (0) NR *Urogenital bleeding* 6 (1.8) 0 (0) 0 (0) NR *Other bleeding* 0 (0) 2 (0.6) 0 (0) NR	GI bleeding 4 (1.2) 1 (0.3) 0 (0) NR	0 (0) 2 (0.6) 0 (0) NR	NR	NR	1 (0.3) NR NR	NR	All bleeding reported in other columns (no definitions of severity)	*GI discomfort* 0 (0) 4 (1.2) 3 (0.9) NR
The Boston Area Trial for Atrial Fibrillation Investigators, 1990[88] Boston Area Anticoagula-tion Trial for Atrial	Warfarin, low dose NR (212) Control (208)	2 (0.9) 1 (0.5) NR	1 (0.5) 0 (0) NR	NR	NR	NR	0 (0) 0 (0) NR	NR	Total 38 (17.9) 21 (10.1) Incidence Ratio: 1.62 (95% CI, 0.95 to 2.74) Leading to hospitali-zation	Transient Monocular Vision Loss 2 (0.9) 1 (0.5) NR Fatal pulmonary hemorrhage 0 (0) 1 (0.5)

Appendix E Table 2. Results of Included Studies for KQ 5: Harms of Treatment

First Author, Year Trial Name	G1 (N) G2 (N)	Major Bleeding G1 N (%) G2 N (%) ES (95% CI)	Major Gastro-intestinal Bleeding G1 N (%) G2 N (%) ES (95% CI)	Allergic Reaction G1 N (%) G2 N (%) ES (95% CI)	Hemorrhagic Stroke G1 N (%) G2 N (%) ES (95% CI)	Subarachnoid Hemorrhage G1 N (%) G2 N (%) ES (95% CI)	Intracerebral Hemorrhage G1 N (%) G2 N (%) ES (95% CI)	Subdural Hemorrhage/ Hematoma G1 N (%) G2 N (%) ES (95% CI)	Minor Bleeding G1 N (%) G2 N (%) ES (95% CI)	Other Harms G1 N (%) G2 N (%) ES (95% CI)
Fibrillation (BAATAF)									4 (1.9) 6 (2.9) NR Leading to transfusion 2 (0.9) 1 (0.5) NR	NR Fatal intracranial hemorrhage (due to loss of consciousness then falling) 1 (0.5) 0 (0) NR
Stroke Prevention in Atrial Fibrillation Investigators, 1990 & 1991[86, 87] Stroke Prevention in Atrial Fibrillation (SPAF) Study	*Group 1 (anti-coagulation candidates)* Warfarin-adjusted dose (210) Aspirin 325 mg/day (206) Placebo (211) *Group 2 (non-anticoagu-lation candidates)* Aspirin 325 mg/day (346) Placebo (357)	*Major bleeding complications intention to treat population (Group 1)* Warfarin: 4 (1.5%/year) Placebo: 4 (1.6%/year) NR *(Groups 1 and 2)* Aspirin: 10 (1.4%/year) Placebo: 14 (1.9%/year) NR *Major bleeding complications relevant bleeding (Group 1)* Warfarin: 3 (1.4) Placebo: 1 (0.5) NR	NR	*Severe allergic reactions* 0 (0) 0 (0) NR	NR	NR	*Group 1* Warfarin: 1 (0.5) Placebo: 0 (0) NR *Group 1 and 2* Aspirin: 1 (0.2) Placebo: 0 (0) NR	*Subdural hematoma (Group 1)* Warfarin: 1 (0.5) Placebo: 2 (0.9) NR *Subdural hematoma (Groups 1 and 2)* Aspirin: 1 (0.2) Placebo: 2 (0.4) NR	*Minor bleeding leading to therapy withdrawal* *(Group 1)* Warfarin: 4 (1.9) Placebo: 1 (0.5) NR *(Groups 1 and 2)* Aspirin: 0 (0) Placebo: 2 (0.4) NR	Intracerebral Fatal Hemorrhage Warfarin: 1 Placebo: 0 *(Groups 1 and 2)* Aspirin: 1 Placebo: 0

Appendix E Table 2. Results of Included Studies for KQ 5: Harms of Treatment

First Author, Year Trial Name	G1 (N) G2 (N)	Major Bleeding G1 N (%) G2 N (%) ES (95% CI)	Major Gastro-intestinal Bleeding G1 N (%) G2 N (%) ES (95% CI)	Allergic Reaction G1 N (%) G2 N (%) ES (95% CI)	Hemorrhagic Stroke G1 N (%) G2 N (%) ES (95% CI)	Subarachnoid Hemorrhage G1 N (%) G2 N (%) ES (95% CI)	Intracerebral Hemorrhage G1 N (%) G2 N (%) ES (95% CI)	Subdural Hemorrhage/ Hematoma G1 N (%) G2 N (%) ES (95% CI)	Minor Bleeding G1 N (%) G2 N (%) ES (95% CI)	Other Harms G1 N (%) G2 N (%) ES (95% CI)
		(Groups 1 and 2) Aspirin: 5 (0.9) Placebo: 4 (0.7) NR								
Connolly, 1991[78] Canadian Atrial Fibrillation Anticoagula-tion (CAFA) Study[72]	Warfarin dose adjusted per subject (187) Placebo (191)	*Life-threatening or major bleeding* 5 (2.7) 1 (0.5) NR Other major bleeding after permanent discontinuation of medication 0 1	NR	NR	NR	NR	NR	NR	30 (16) 18 (9.4) NR	*Intracranial hemorrhage* (Efficacy analysis) 1 (0.5) 0 (0) NR (Intention to treat analysis) 1 (0.5) 0 (0) NR *Other fatal hemorrhage* (Efficacy analysis) 1 (0.5) 0 (0) NR (Intention to treat analysis) 1 (0.5) 0 (0) NR *Annual rate of fatal or major hemorrhage* 2.5%/year 0.5%/year NR

Appendix E Table 2. Results of Included Studies for KQ 5: Harms of Treatment

First Author, Year Trial Name	G1 (N) G2 (N)	Major Bleeding G1 N (%) G2 N (%) ES (95% CI)	Major Gastro-intestinal Bleeding G1 N (%) G2 N (%) ES (95% CI)	Allergic Reaction G1 N (%) G2 N (%) ES (95% CI)	Hemorrhagic Stroke G1 N (%) G2 N (%) ES (95% CI)	Subarachnoid Hemorrhage G1 N (%) G2 N (%) ES (95% CI)	Intracerebral Hemorrhage G1 N (%) G2 N (%) ES (95% CI)	Subdural Hemorrhage/ Hematoma G1 N (%) G2 N (%) ES (95% CI)	Minor Bleeding G1 N (%) G2 N (%) ES (95% CI)	Other Harms G1 N (%) G2 N (%) ES (95% CI)
Ezekowitz et al., 1992[79] Veterans Affairs Cooperative Study SPINAF	Patients without previous cerebral infarction: Warfarin: 4 mg/day and adjusted to meet PT ratios (260) Control (265) Patients with previous cerebral infarction: Warfarin: 4 mg/day and adjusted to meet PT ratios (21) Control (25)	Without previous cerebral infarction: Major hemorrhage 6 (2.3) (1.3%/year) 4 (1.5) (0.9%/year) Risk reduction: -0.53 (-4.22 to 0.55) p=0.54 With previous cerebral infarction: 0 (0) 0 (0)	Without previous cerebral infarction: Major hemorrhage 6 (2.3) (1.3%/year) 4 (1.5) (0.9%/year) Risk reduction: -0.53 (-4.22 to 0.55) p=0.54 With previous cerebral infarction: 0 (0) 0 (0)	NR	NR	NR	Without previous cerebral infarction: Cerebral hemorrhage 1 (0.4) 0 (0) ES NR With previous cerebral infarction: Cerebral hemorrhage 0 (0) 0 (0)	NR	Without previous cerebral infarction: Minor hemorrhage 64 (24.6) (14.0%/year) 46 (17.4) (10.5%/year) Risk reduction: -0.42 (-0.98 to -0.02) p=0.04 With previous cerebral infarction: Minor hemorrhage 3 (14.3) (9.2%/year) 7 (28.0) (16.2%/year) Risk reduction: 0.49 (-0.53 to 0.83) p=0.31	NR
Sato et al., 2006[85] Japan Atrial Fibrillation Stroke Trial (JAST)	Aspirin 150–200 mg/day (426) Control (445)	Major bleeding 7 (1.64) 2 (0.45) p=0.101	NR	NR	NR	NR	NR	NR	NR	Intracranial bleeding 4 (0.94) 2 (0.45) NR

AFASAK did not specify bleeding severity and was therefore not included in this analysis. It reported bleeding events leading to withdrawal from study, 21 for warfarin and 0 for placebo.

BAATAF, minor bleeding was defined as bleeding that did not include intracranial bleeding, fatal bleeding, or bleeding that required a blood transfusion (four or more units of blood within 48 hours).

SPAF I, minor bleeding defined as bleeding that did not involve the central nervous system, management requiring hospitalization with transfusion and/or surgery, or permanent residual impairment.

CAFA, minor bleeding defined as non-life-threatening bleeding.

SPINAF, minor bleeding defined as bleeding that did not require a blood transfusion, an emergency procedure, removal of a hematoma, or ICU admission.

Abbreviations: AFASAK=Copenhagen Atrial Fibrillation, Aspirin and Anticoagulation study; BAATAF=Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA=Canadian Atrial Fibrillation Anticoagulation study; CI=confidence interval; ES=effect size; G=group; JAST=Japan Atrial Fibrillation Stroke Trial; KQ=key question; N=sample size; NA=not applicable; NR=not reported; PT=prothrombin time; SPAF=Stroke Prevention in Atrial Fibrillation Study; SPINAF=Stroke Prevention in Atrial Fibrillation study.

Appendix E Table 3. Summary of Included Systematic Reviews, Individual Patient Data Meta-analyses, and Network Meta-analyses on Benefits and Harms of Treatment for Atrial Fibrillation

Author, Year Intervention vs. Comparison	Review Type	Total N	Characteristics of Participants	Main Findings
Aguilar, 2009[93] Warfarin vs. Placebo	SR with MA	2,313	Mean age: 69 Female: 26% Nonwhite: NR History of HF: 45% Diabetes: 15% Prior MI: 15% HTN: 45% Prior stroke or TIA: 3 to 8% in published results of the included studies, but they report obtaining the unpublished results without those 3 to 8%	Included same RCTs as our report Odds ratio (95% CI) All strokes (including ischemic and hemorrhagic): 0.39 (0.26 to 0.59) All Ischemic strokes: 0.34 (0.23 to 0.52)[a] Disabling or fatal strokes (including ischemic and hemorrhagic): 0.47 (0.28 to 0.80) MI: 0.87 (0.32 to 2.42) All systemic emboli: 0.45 (0.13 to 1.57) Intracranial hemorrhage: 2.38 (0.54 to 10.5) Major extracranial bleeding: 1.07 (0.53 to 2.12)[b] Vascular death: 0.84 (0.56 to 1.27) Stroke, MI, or vascular death: 0.56 (0.42 to 0.76) All-cause mortality: 0.69 (0.50 to 0.94)
Aguilar, 2011[101] AP vs. Placebo	SR with MA	2,622	Mean age: 70 Female: 38% % nonwhite: NR History of HF: NR Diabetes and prior MI: NR Prior stroke or TIA: NR HTN: NR	Included AFASAK I, SPAF I, and LASAF (not JAST) Odds ratio (95% CI) All strokes (including ischemic and hemorrhagic): 0.70 (0.47 to 1.07) Ischemic strokes: 0.70 (0.46 to 1.07) All disabling or fatal strokes (including ischemic and hemorrhagic): 0.86 (0.50 to 1.49) MI: 0.47 (0.19 to 1.14) Systemic emboli: 0.67 (0.19 to 2.3) Intracranial hemorrhage: 1.32 (0.22 to 7.80) Major extracranial bleeding: 1.14 (0.44 to 2.98) Vascular death: 0.82 (0.54 to 1.25) Composite outcome: all stroke, MI, or vascular death: 0.71 (0.51 to 0.97) All-cause mortality: 0.75 (0.54 to 1.04)
Atrial Fibrillation Investigators, 1997[98] Aspirin vs. Placebo	IPD	2,574	Mean age: 70 Female: 38% Nonwhite: NR History of HF: 28 Diabetes: 14% Prior MI: 10% Prior stroke or TIA: 35% HTN: 46%	Included AFASAK I and SPAF I, and a secondary prevention trial (EAFT). Relative risk reduction (95% CI) Stroke: 21% (0% to 38%); p=0.05 Disabling stroke: 17% (-12% to 38%; p=0.23) Nondisabling stroke occurrence: 27% (-7% to 51%; p=0.10) Subgroups Age: 1.02 (0.99 to 1.05) Age ≤75: 0.73 (0.54 to 0.99) Male: 0.80 (0.58 to 1.11) Female: 0.80 (0.56 to 1.13) SBP>160 mm Hg: 0.75 (0.48 to 1.18)

Appendix E Table 3. Summary of Included Systematic Reviews, Individual Patient Data Meta-analyses, and Network Meta-analyses on Benefits and Harms of Treatment for Atrial Fibrillation

Author, Year Intervention vs. Comparison	Review Type	Total N	Characteristics of Participants	Main Findings
				SBP<160 mm Hg: 0.81 (0.61 to 1.07) History of hypertension: 0.64 (0.46 to 0.89), p=009; interaction NS, p=.08 No history of hypertension: 0.98 (0.70 to 1.39) History of CHF: 0.54 (0.33 to 0.89) No history of CHF: 0.89 (0.68 to 1.16) History of diabetes: 0.60 (0.34 to 1.06) No history of diabetes: 0.84 (0.65 to 1.09) Risk stratification No clinical risk factors: 1.33 (0.66 to 2.68) >1 clinical risk factors: 0.72 (0.56 to 0.93) (interaction between aspirin and risk factor NS, p=0.10) History of hypertension or diabetes but with no previous stroke or TIA: 54% (17% to 74%; p=0.009; interaction term, p=0.02) Except for patients younger than 65 years, the absolute risk of stroke with aspirin therapy did not decrease below 3.0% per year for any of the risk strata
Atrial Fibrillation Investigators, 1994[96] Warfarin vs. Placebo Aspirin vs. Placebo	IPD	4,174	Mean age: 69 Female: 26% Nonwhite: 7% History of HF: 20% Diabetes: 14% Prior MI: 14% Prior stroke or TIA: 6% HTN: 45%	Included same RCTs as our report for warfarin; only included AFASAK and SPAF for aspirin (JAST was not yet published) *Warfarin (1889 patient-years receiving warfarin)* Relative risk reduction (95% CI) Stroke: 68% (50% to 79%); 3.1% Absolute annual reduction, p<0.001 Stroke with residual deficit: 68% (39% to 83%); 1.4% absolute annual reduction, p<0.001 Death: 33% (9% to 51%); p=0.010 Stroke, systemic embolism, or death: 48% (34% to 60%); p<0.001 Annual frequency of major bleeding events: 1.3% (vs. 1.0% for controls). Patients taking warfarin who had intracranial bleeding (n=6) had a higher systolic (p=0.001) and diastolic (p=0.016) blood pressure at entry to study than patients taking warfarin who did not have intracranial bleeding (mean 169/93 vs. 141/83) Mean age of those with and without intracranial bleeding as 73 and 69, NS *Effect of Warfarin on Stroke by Subgroup* Women: 84% (55% to 95%), p<0.001 Men: 60% (35% to 76%), p<0.001 *Aspirin 1,132 (patient-years receiving aspirin)* Relative risk reduction (95% CI) Stroke: 36% (4% to 57%); p=0.03 Stroke with residual deficit: 30% (20% to 60%); NS Rate of death: 17% (20% to 40%); NS Combination of stroke, systemic embolism, or death: 28% (6% to 45%); p=0.02 Annual frequency of major bleeding events: 1.0%

Appendix E Table 3. Summary of Included Systematic Reviews, Individual Patient Data Meta-analyses, and Network Meta-analyses on Benefits and Harms of Treatment for Atrial Fibrillation

Author, Year Intervention vs. Comparison	Review Type	Total N	Characteristics of Participants	Main Findings
				Effect of Aspirin on Stroke by Subgroup History of hypertension: 59% (28% to 77%); p=0.002 No history of hypertension: 10% (40% to 100%); p=0.76 p=0.02 for difference in effectiveness between those with and without hypertension *Effect of Aspirin on Stroke by Subgroup* Women: 23% (40% to 58%), p=0.38 Men: 44% (3% to 68%), p=0.04
Coleman, 2012[95] Warfarin vs. Placebo Aspirin vs. Placebo VKA vs. Aspirin	SR with MA	42,983	Mean age: 65–75 Female: 0–59% % nonwhite: NR History of HF: NR Diabetes and prior MI: NR Prior stroke or TIA: NR Target range of INRs: NA Median followup: 2 years	Combines studies of primary and secondary prevention (participants had a TIA or stroke) and does not provide any analyses separating them, possibly limiting applicability; did not include SPAF-1, CAFA, or LASAF (but those did not report major gastrointestinal bleeding); also included studies of combinations of medications (e.g., aspirin plus low-dose VKA) Major gastrointestinal bleeding odds ratio (95% CI), 4 trials (including EAFT), 2,219 participants Adjusted-dose warfarin vs. placebo/control: 3.21 (1.32 to 7.82) Aspirin vs. placebo/control: 3.23 (0.56 to 18.66); 3 trials (AFASAK I, JAST, and EAFT), 2,325 participants Adjusted-dose VKA vs. aspirin: 1.92 (1.08 to 3.41); 7 trials, 4,819 participants
Hart, 2007[100] Warfarin vs. Placebo Aspirin vs. Placebo Warfarin vs. Aspirin	SR with MA	28,044 (but most of those from secondary prevention trials)	Warfarin Mean age: 69 Female: 29% Prior stroke or TIA: 20% Aspirin Mean age: 69 Female: 37% Prior stroke or TIA: 29% Median followup: 1.6 to 1.7 years overall	Included secondary prevention RCTs in addition to primary prevention RCTs for most analyses; only separated primary prevention results (using the same trials we included) when reporting absolute risk reduction and NNT Warfarin vs. placebo or no treatment for primary prevention: Stroke, ARR: 2.7%/year (vs. 8.4% for secondary prevention); NNT 40 Aspirin vs. placebo or no treatment for primary prevention: Stroke, ARR: 0.8%/year (vs. 2.5% for secondary prevention); NNT 111 Warfarin vs. aspirin for primary prevention: Stroke, ARR: 0.7%/year (vs. 7% for secondary prevention); NNT 81 Safety outcomes included all trials identified (not limited to primary prevention): Warfarin vs. placebo or no treatment Intracranial hemorrhage: 6 vs. 3 events (RR not calculated) Major extracranial hemorrhage: -66 (-235 to 18); -0.3%/year ARR All-cause mortality: 26 (3 to 43); 1.6%/year ARR Aspirin vs. placebo or no treatment Intracranial hemorrhage: 8 vs. 4 events (RR not calculated) Major extracranial hemorrhage: -2 (-98 to 52); -0.2%/year ARR All-cause mortality: 14 (-7 to 31); 0.5 %/year ARR

Appendix E Table 3. Summary of Included Systematic Reviews, Individual Patient Data Meta-analyses, and Network Meta-analyses on Benefits and Harms of Treatment for Atrial Fibrillation

Author, Year Intervention vs. Comparison	Review Type	Total N	Characteristics of Participants	Main Findings
Tereshchenko, 2016[97] All comparisons	NMA	96,017	Mean age: 71.5 Female: 35% Nonwhite: NR Prior stroke or TIA: NR overall, but ranged from 0% to 100%; 4 (of 21) included trials had over 35% secondary prevention; and both trials of rivaroxaban, JROCKET and ROCKET AF, included more than 50% for secondary prevention. Median followup: 1.7 years	Included 21 RCTs of treatment for nonvalvular AF. Not limited to primary prevention. Results below were unadjusted unless otherwise noted (for the major bleeding outcome, unadjusted data were not provided in the published article but were obtained from the author). *VKAs vs. placebo/control odds ratio (95% CI)* Stroke or systemic embolism: 0.38 (0.29 to 0.49) All-cause mortality: 0.69 (0.57 to 0.85) *Placebo/control vs. VKA* Unadjusted; adjusted for population characteristics ($CHADS_2$ scores, TTR, duration of followup) Stroke or systemic embolism: 2.65 (2.03 to 3.46); 2.30 (1.50 to 3.54) All-cause mortality: 1.44 (1.17 to 1.76);1.33 (0.90 to 1.95); Major bleeding: 0.40 (0.24 to 0.68); 0.47 (0.22 to 1.00) *Aspirin vs. placebo/control odds ratio (95% CI)* Unadjusted; adjusted for population characteristics ($CHADS_2$ scores, TTR, duration of followup) Stroke or systemic embolism: 0.75 (0.60 to 0.95); 0.77 (0.53, 1.11) All-cause mortality: 0.82 (0.68 to 0.99); 0.82 (0.57, 1.17) Major bleeding: 1.79 (1.06 to 3.04); 1.65 (0.77 to 3.51) *NOACs vs. placebo/control odds ratio (95% CI) for stroke or systemic embolism* Unadjusted; Adjusted for population characteristics ($CHADS_2$ scores, TTR, duration of followup) Apixaban 0.31 (0.22 to 0.45); 0.35 (0.21 to 0.58) Dabigatran 0.29 (0.20 to 0.43); 0.34 (0.19 to 0.60) Edoxaban 0.38 (0.26 to 0.54); 0.44 (0.25 to 0.77) Rivaroxaban 0.27 (0.18 to 0.42); 0.32 (0.16 to 0.66) *Comparison of NOACs:* no statistically significant differences in effectiveness for each of the 4 NOACs in comparison to one another *NOACs vs. VKA: risk of stroke or systemic embolism; OR (95% CI)* Unadjusted; adjusted for population characteristics ($CHADS_2$ scores, TTR, duration of followup) Apixaban 0.82 (0.62 to 1.10); 0.81 (0.57 to 1.15) Dabigatran 0.78 (0.60 to 1.01); 0.78 (0.53 to 1.14) Edoxaban 1.00 (0.79 to 1.27); 1.01 (0.70 to 1.45) Rivaroxaban 0.72 (0.51 to 1.00); 0.74 (0.42 to 1.31)

Appendix E Table 3. Summary of Included Systematic Reviews, Individual Patient Data Meta-analyses, and Network Meta-analyses on Benefits and Harms of Treatment for Atrial Fibrillation

Author, Year Intervention vs. Comparison	Review Type	Total N	Characteristics of Participants	Main Findings
				NOACs vs. VKA: risk of all-cause mortality; OR (95% CI) Unadjusted; Adjusted for population characteristics ($CHADS_2$ scores, TTR, duration of followup) Apixaban 0.89 (0.80 to 0.99); 0.89 (0.71 to 1.13) Dabigatran 0.90 (0.82 to 0.99); 0.88 (0.70 to 1.12) Edoxaban 0.89 (0.82 to 0.96); 0.90 (0.71 to 1.14) Rivaroxaban 0.84 (0.70 to 1.01); 0.84 (0.48 to 1.48) NOACs vs. VKA: major bleeding Edoxaban 0.61 (0.36 to 1.01); 0.64 (0.46 to 0.90) Only edoxaban was significantly different (adjusted ORs from 0.74 to 0.85 for the others but CIs go up to 1.02 through 1.57 for the various NOACs)
van Walraven, 2008[99] Oral anticoagulant (mostly warfarin)[c] vs. Placebo Antiplatelet (mostly Aspirin) vs. Placebo	IPD	8,932	Mean age: 70.9 for all studies except for BAFTA with was 81.5 Female: 37% History of HF: 20% Diabetes and prior MI: 15 Prior stroke or TIA: 22% HTN: 50% AP dose range: 75 mg to 325 mg daily Median followup: 2.0 years	Included secondary prevention RCTs in addition to primary prevention RCTs; did not separate primary prevention results OAC hazard ratio (95% CI) Ischemic stroke: 0.36 (0.29 to 0.45) Systemic or intracranial hemorrhage: 1.56 (1.03 to 2.37) Cardiovascular event: 0.59 (0.52 to 0.66) Interaction of age and OAC Ischemic stroke: X^2=3.2, p=0.07; trend toward decreasing relative benefit of OAC (HR moved toward 1 as patients age. HR 0.22 [95% CI, 0.11, 0.41] for 50-year-olds and HR 0.53 [0.35, 0.81] for 90-year-olds) Serious hemorrhage: NS Cardiovascular events: NS AP hazard ratio (95% CI) Ischemic stroke: 0.81 (0.72 to 0.90) Systemic or intracranial hemorrhage: 1.03 (0.71 to 1.49) Cardiovascular event: 0.81 (0.75 to 0.88) Interaction of age and AP Ischemic stroke: X^2=6.5, p= 0.01; relative benefit of AP for preventing stroke decreased significantly with age; HR, 0.40; 95% CI, 0.22 to 0.72 at age 50; by age 77, the HR no longer excluded the null; at age 82, the HR exceeded 1. Serious hemorrhage: NS Cardiovascular events: NS

[a] Subgroup analysis was performed for the outcome "ischemic stroke (fatal and nonfatal)." There was no evidence of a difference in the treatment effect between double-blind trials and open-label trials, p=0.92.

[b] In the text, they also report that meta-analysis of data from six trials in which 20% had prior stroke, TIA, or both, major extracranial bleeding was increased in those assigned to OAC (OR 1.80, 95% CI, 1.01 to 3.18), presumably that was by adding EAFT (in which all participants had a history of stroke or TIA).

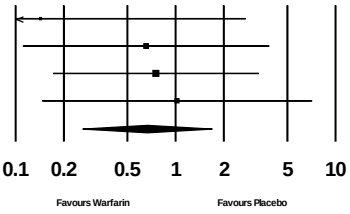
Appendix E Table 3. Summary of Included Systematic Reviews, Individual Patient Data Meta-analyses, and Network Meta-analyses on Benefits and Harms of Treatment for Atrial Fibrillation

[c] Some secondary prevention studies used 4-hydroxycoumarin instead of warfarin.
[d] One secondary prevention study used triflusal.

Abbreviations: AFASAK=Copenhagen Atrial Fibrillation, Aspirin and Anticoagulation study; AP= antiplatelet therapy; ARR=absolute risk reduction; BAFTA=Birmingham Atrial Fibrillation in the Aged; CAFA=Canadian Atrial Fibrillation Anticoagulation study; $CHADS_2$=Congestive heart failure, Hypertension, Age≥75 years, Diabetes mellitus, Prior stroke or TIA or thromboembolism; CHF=cardiac heart failure; CI=confidence interval; EAFT=European Atrial Fibrillation Trial Study Group; G=group; HF=heart failure; Hg=hemoglobin; HR=hazard ratio; HTN: hypertension; INR=International Normalized Ratio, assay used to determine clotting tendency; IPD=individual patient data meta-analysis; JAST=Japan Atrial Fibrillation Stroke Trial; JROCKET=Japanese Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; LASAF=low-dose aspirin, stroke atrial fibrillation trial; MA=meta-analysis; MI=myocardial infarction; N=sample size; NA=not applicable; NR=not reported; NS=not significant; NMA=network meta-analysis; NNT=number-needed-to-treat; NOAC=novel oral anticoagulants; OAC=oral anticoagulant; OR=odds ratio; RCT=randomized, controlled trial; ROCKET AF=Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; RR=relative risk; SBP=systolic blood pressure; SPAF=Stroke Prevention in Atrial Fibrillation Study; SR=systematic review; TIA=transient ischemic attack; TTR=time in therapeutic range; VKA=vitamin K antagonists.

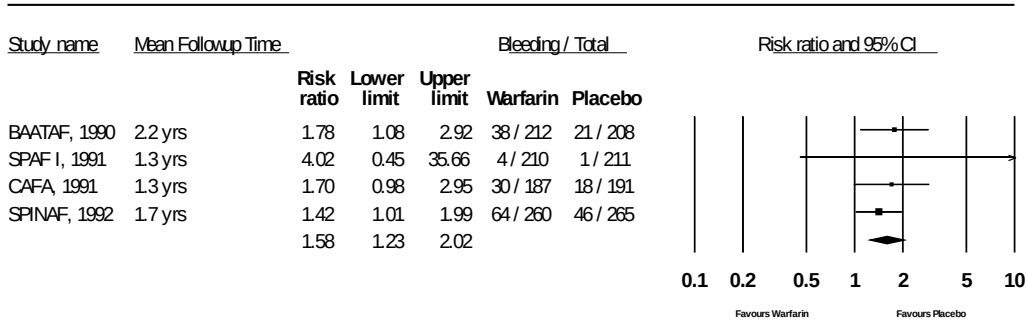
Appendix F Figure 1. Warfarin Versus Placebo/Control, TIA

Study name	Mean Followup Time	Risk ratio	Lower limit	Upper limit	TIA / Total Warfarin	TIA / Total Placebo
AFASAK I, 1989	1.2 yrs	0.14	0.01	2.76	0 / 335	3 / 336
BAATAF, 1990	2.2 yrs	0.65	0.11	3.87	2 / 212	3 / 208
SPAF I, 1991	1.3 yrs	0.75	0.17	3.33	3 / 210	4 / 211
CAFA, 1991	1.3 yrs	1.02	0.15	7.18	2 / 187	2 / 191
		0.66	0.26	1.68		



Q =1.25, df=3, p= 0.74, I-sq= 0.00

Appendix F Figure 2. Warfarin Versus Placebo/Control, Minor Bleeding



Q =1.38, df=3, p= 0.71, I-sq= 0.00

AFASAK did not specify bleeding severity and was therefore not included in this analysis. It reported bleeding events leading to withdrawal from study, 21 for warfarin and 0 for placebo.

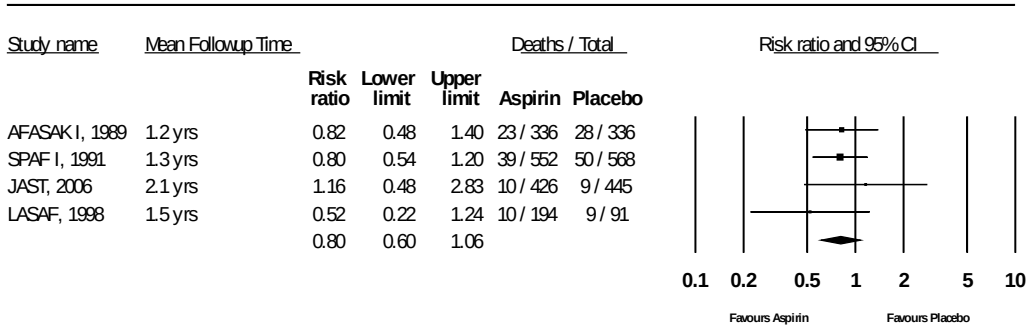
BAATAF, minor bleeding was defined as bleeding that did not include intracranial bleeding, fatal bleeding, or bleeding that required a blood transfusion (four or more units of blood within 48 hours).

SPAF I, minor bleeding defined as bleeding that did not involve the central nervous system, management requiring hospitalization with transfusion and/or surgery, or permanent residual impairment.

CAFA, minor bleeding defined as non-life-threatening bleeding.

SPINAF, minor bleeding defined as bleeding that did not require a blood transfusion, an emergency procedure, removal of a hematoma, or ICU admission.

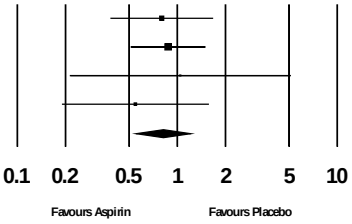
Appendix F Figure 3. Aspirin Versus Placebo/Control, All-Cause Mortality Sensitivity Analyses



Q=1.62, df=3, p= 0.65, I-sq= 0.00; AFASAK, includes data from a previously published meta-analysis that obtained data from the original study authors.

Appendix F Figure 4. Aspirin Versus Placebo/Control, Cardiovascular-Related Mortality Sensitivity Analyses

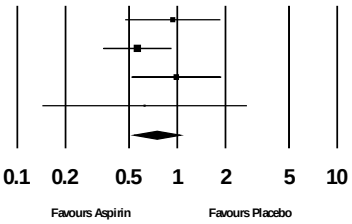
Study name	Mean Followup Time	Risk ratio	Lower limit	Upper limit	Death / Total: Aspirin	Death / Total: Placebo
AFASAK I, 1989	1.2 yrs	0.80	0.38	1.68	12 / 336	15 / 336
SPAF I, 1991	1.3 yrs	0.88	0.51	1.51	23 / 552	27 / 568
JAST, 2006	2.1 yrs	1.04	0.21	5.15	3 / 426	3 / 445
LASAF, 1998	1.5 yrs	0.55	0.19	1.58	7 / 194	6 / 91
		0.81	0.55	1.20		



Q =0.70, df=3, p= 0.87, I-sq= 0.00

Appendix F Figure 5. Aspirin versus Placebo/Control, All Ischemic Stroke

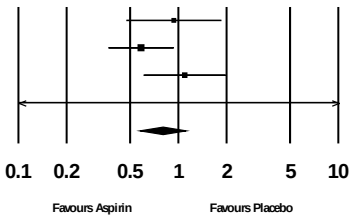
Study name	Mean Followup Time	Risk ratio	Lower limit	Upper limit	Stroke / Total Aspirin	Stroke / Total Placebo
AFASAK I, 1989	1.2 yrs	0.94	0.47	1.87	15 / 336	16 / 336
SPAF I, 1991	1.3 yrs	0.56	0.34	0.92	23 / 552	42 / 568
JAST, 2006	2.1 yrs	0.99	0.52	1.89	17 / 426	18 / 445
LASAF, 1998	1.5 yrs	0.63	0.14	2.74	4 / 194	3 / 91
		0.74	0.53	1.03		



Q =2.42, df=3, p= 0.49, I-sq= 0.00

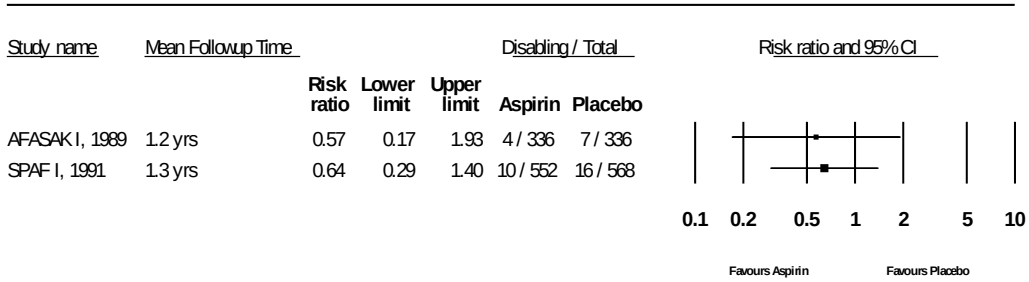
Appendix F Figure 6. Aspirin versus Placebo/Control, All Ischemic Stroke or Intracranial Hemorrhage Sensitivity Analyses

Study name	Mean Followup Time	Risk ratio	Lower limit	Upper limit	Aspirin	Placebo
AFASAK I, 1989	1.2 yrs	0.94	0.47	1.87	15 / 336	16 / 336
SPAF I, 1991	1.3 yrs	0.58	0.36	0.94	25 / 552	44 / 568
JAST, 2006	2.1 yrs	1.10	0.60	1.99	21 / 426	20 / 445
LASAF, 1998	1.5 yrs	1.42	0.06	34.41	1 / 194	0 / 91
		0.79	0.57	1.10		



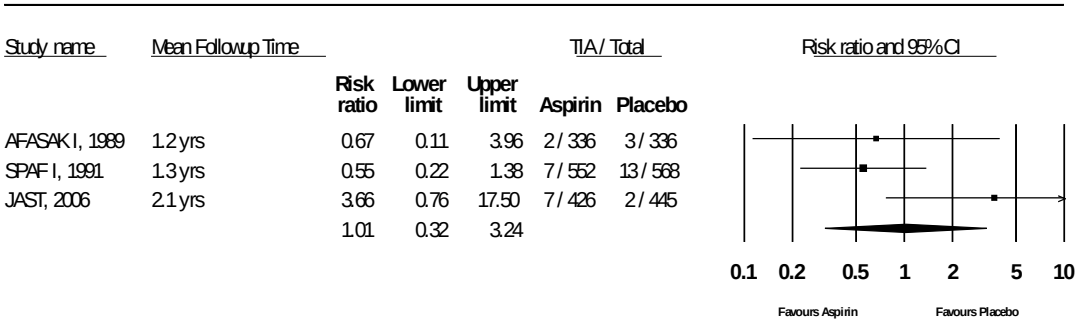
Q =3.06, df=3, p= 0.38, I-sq= 1.81

Appendix F Figure 7. Aspirin Versus Placebo/Control, Moderately to Severely Disabling Stroke



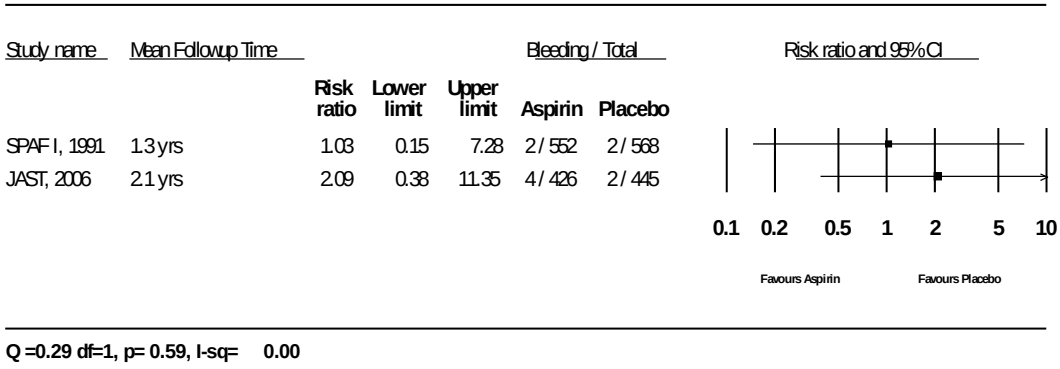
AFASAK reported disabling stroke which was defined as a stroke leaving definite functional disability a month after onset. SPAF I reported moderately to severely disabling stroke which was defined as a stroke requiring assistance to perform basic activities of daily living after onset.

Appendix F Figure 8. Aspirin Versus Placebo/Control, TIA



Q =4.25 df=2, p= 0.12, I-sq= 52.98

Appendix F Figure 9. Aspirin Versus Placebo/Control, Intracranial Bleeding



For AFASAK: zero for aspirin and zero for placebo. For SPAF I: aspirin, one fatal intracerebral hemorrhage and one fatal subdural hematoma; placebo, two subdural hematomas with full recovery.

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