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

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Structured Abstract

Purpose: To review the evidence on screening for atrial fibrillation (AF) in older adults for populations and settings relevant to primary care in the United States.

Data Sources: MEDLINE, the Cochrane Library, and trial registries through October 5, 2020; bibliographies from retrieved articles, outside experts, and surveillance of the literature through October 31, 2021.

Study Selection: Two investigators independently selected English-language studies using a priori defined criteria. We included trials that evaluated the benefits or harms of screening for AF in adults age 50 years or older without known symptoms, diagnosis of AF, or previous stroke compared with no screening or usual care. We included studies of screening with devices feasible or referable from primary care settings. For treatment benefits and harms, we included trials of anticoagulation treatment for primary stroke prevention (warfarin or direct oral anticoagulants [DOACs]) compared with placebo or no treatment among persons with AF. Eligible outcomes included diagnostic yield, test accuracy, all-cause mortality, stroke, stroke-related morbidity, quality of life, and harms from screening or treatment. We also included systematic reviews reporting on anticoagulation benefits or harms and observational studies reporting harms. We excluded studies with poor methodological quality and studies conducted in developing countries.

Data Extraction and Analysis: One investigator extracted data and a second checked accuracy. Two reviewers independently rated methodological quality for all included studies using predefined criteria. When at least three similar studies were available, we conducted meta-analyses.

Data Synthesis: We included 26 studies (in 33 publications). One randomized, controlled trial (RCT) designed to evaluate health outcomes randomized all residents aged 75 or 76 years within two geographic regions (N=28,768) to twice-daily ECG screening for 2 weeks or to no screening. Of those invited to screening, 51.3 percent participated. At a median followup of 6.9 years, the rate of composite endpoint events (ischemic stroke, hemorrhagic stroke, systemic embolism, all-cause mortality, and bleeding leading to hospitalization) was significantly lower in the invitation-to-screening group (5.45 events/100 person years) compared with the control group (5.68 event/100 person years) with an unadjusted hazard ratio (HR) of 0.96 (95% confidence interval [CI], 0.92 to 1.00; p=0.045). No significant differences were observed between the invitation-to-screening group and the control group for any of the individual outcomes contributing to the composite endpoint. Two additional RCTs reported health outcomes, but data were limited.

In eight RCTs (n=86,145) evaluating various ECG screening strategies, more cases of AF were detected when compared with no screening (risk difference range 0.06% to 4.8% over 4 to 12 months); statistically significant larger differences between groups were observed for studies using intermittent or continuous ECG compared with one-time testing approaches. No differences in cases detected were observed in two RCTs (n=12,867) comparing one-time ECG screening to pulse palpation reminders. In seven studies of test accuracy (n=4,497) for various one-time screening strategies (single- or 12-lead ECG, oscillometric blood pressure monitors

with AF detection algorithms), sensitivity ranged from 0.80 to 1.00, and specificity ranged from 0.76 to 1.00 when compared with a 12-lead ECG interpreted by one or more cardiologists. In a population of 1,000 persons with a 1.3 percent prevalence of previously unknown AF, this would result in between 0 to 9 false-negative tests and 0 to 237 false-positive tests.

Four RCTs (N=43,633) and one cohort study (n=5,214) reported potential harms of screening. Increased detection of non-AF arrhythmias (1 RCT, 1 cohort) and increased initiation of anticoagulation, antiarrhythmics, and procedures were observed (2 RCTs, 1 cohort) for screening compared with no screening, but the clinical consequences of these findings are not known. Skin irritation from continuous ECG patch ranged from 1.2 to 1.5 percent of participants (2 RCTs). Limited data exist regarding the impact of screening on anxiety (1 RCT) and bleeding outcomes (2 RCTs) compared with no screening.

Warfarin was associated with a reduced risk of ischemic stroke (pooled risk ratio [RR], 0.32 [95% CI, 0.20 to 0.51]; 5 RCTs; n=2,415) and all-cause mortality (pooled RR, 0.68 [95% CI, 0.50 to 0.93]) compared with placebo over a mean of 1.5 years in populations with clinical, mostly persistent AF that was not screen detected. For a population of 1,000 adults with an annual stroke risk of 4 percent, this translates to an absolute reduction of 28 ischemic strokes and 16 deaths per year. DOACs were also associated with lower incidence of stroke (adjusted odds ratios [ORs] ranged from 0.32 to 0.44) in indirect comparisons with placebo or no treatment. The pooled RR for major bleeding for warfarin compared with placebo was 1.8 (95% CI, 0.85 to 3.7; 5 RCTs; 2,415 participants), and the adjusted ORs for major bleeding for DOACs compared with placebo or no treatment ranged from 1.38 to 2.21 but did not exclude a null effect. In one observational study of 26,628 participants, the adjusted hazard ratio for time to first bleeding event for participants receiving anticoagulation over 2 years was 1.7 (95% CI, 1.3 to 2.3) compared with those not receiving anticoagulation.

Limitations: The only study designed to assess the direct benefits and harms of screening had poor fidelity, did not exclude persons with known AF at baseline, and had some risk of bias due to outcome ascertainment. Trials of warfarin treatment were focused on persons with clinical and persistent AF and were limited to 1.5 years. No studies of anticoagulation treatment focused on screen-detected populations were identified. We did not assess the comparative effectiveness or harms of various anticoagulation treatments.

Conclusions: The available direct evidence for health outcomes has numerous limitations, precluding a definitive conclusion about screening benefits and harms. Screening with intermittent or continuous ECG strategies in primary care settings can detect more cases of previously unknown AF compared with no screening, but spot one-time ECG screening may not detect more cases than pulse palpation reminders. In low-prevalence settings, spot one-time screening tests may generate more false-positive than true-positive results. In persons with clinically detected AF, warfarin and DOACs reduce the risk of first stroke and all-cause mortality compared with placebo; the evidence also suggests they increase the risk of major bleeding, although estimates for this harm are imprecise. No trials have assessed the benefits and harms of anticoagulation treatment among screen-detected populations.

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Chapter 1. Introduction

Purpose

This report will be used by the United States Preventive Services Task Force (USPSTF) to update its 2018 statement on screening for atrial fibrillation (AF) with electrocardiography (ECG).[1] At that time, the USPSTF concluded that the current evidence was insufficient (I statement) to assess the balance of benefits and harms of screening for AF with ECG. The USPSTF made the 2018 recommendation based on a 2018 systematic review conducted by the RTI–University of North Carolina Evidence-based Practice Center (EPC).[2] In 2018, the USPSTF found inadequate direct evidence assessing the benefit of screening on health outcomes and inadequate evidence for the detection of AF with ECG compared with usual care. The USPSTF found adequate evidence that anticoagulation treatment reduces stroke and adequate evidence of small to moderate harms for screening and anticoagulation treatment. This 2020 report systematically evaluates the current evidence on screening for AF in populations and settings relevant to primary care in the United States.

Condition Definition

AF is a common supraventricular tachyarrhythmia characterized by structural or electrophysiological abnormalities leading to alteration of atrial tissue and resulting in abnormal impulse formation, or propagation, or both.[3-5] Electrocardiographic features of AF include (1) "irregularly irregular" R-R intervals (intervals from the onset of one R wave to the onset of the next one, one complete cardiac cycle), meaning they follow no repetitive pattern, and (2) no distinct P waves (the waves on an ECG associated with atrial depolarization).[5, 6] Recent 2020 guidelines from the European Society of Cardiology define *clinical AF* as symptomatic or asymptomatic ECG tracing of AF on a surface ECG of at least 30 seconds duration.[7] *Paroxysmal*, *persistent*, and *permanent* are helpful labels to describe clinical AF. Paroxysmal AF terminates spontaneously or with intervention within 7 days of onset; episodes may recur and last from seconds, to minutes, to days. Persistent AF is continuous AF for more than 7 days, and permanent AF is when the clinician and patient make a joint decision to stop further attempts to restore sinus rhythm.[3] In addition to these labels, the increased use of implantable and wearable devices has resulted in the term *subclinical AF*, which refers to episodes of device-detected atrial tachyarrhythmia, that are not clinically apparent because they do not result in symptoms but that may be confirmed as clinical AF by clinician review of the intracardiac electrograms or by surface ECG.[7-9]

Etiology, Natural History, and Risk Factors

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.[10, 11] 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.[12, 13] 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.[14-16] However, some patients have AF with no obvious symptoms.[17] In addition, persons may attribute mild, nonspecific symptoms of AF (e.g., fatigue) to other causes.

AF reduces cardiac blood flow, which, along with changes in blood composition involving platelets, other coagulation proteins, and inflammatory cytokines, predisposes patients to thrombus formation, particularly in the left atrial appendage, which confers an increased risk of stroke and systemic thromboembolism in patients with AF.[18] Before widespread anticoagulant use, AF was associated with a fivefold increase in the risk of stroke, after adjustment for other factors.[19] Although stroke is a major potential complication resulting from AF, the Randomized Evaluation of Long-Term Anticoagulation Therapy clinical trial that compared dabigatran with warfarin reported that stroke accounted for only 7 percent of deaths among persons with AF; sudden cardiac death accounted for 22.3 percent, progressive heart failure for 15.1 percent, and noncardiovascular death for 35.8 percent.[20]

Risk factors for AF include diabetes, previous cardiothoracic surgery, smoking, prior stroke, advanced age, underlying heart disease, hypertension, sleep apnea, obesity, alcohol/drug use, electrocardiographic features such as left ventricular hypertrophy and left atrial enlargement, and hyperthyroidism.[5, 9] Several large longitudinal study cohorts have contributed to externally validated models that aim to predict the risk of future AF, including the Atherosclerosis Risk in Communities (ARIC) Study,[21] the Framingham Heart Study (FHS),[22] and the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE-AF).[23] Such models include 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.

Prevalence and Burden of Disease

Prevalence

AF is the most common arrhythmia.[24] In the United States, estimates of the number of persons with clinical AF ranged from 2.7 million to 6.1 million in 2010.[24] The estimated prevalence of clinical AF among U.S. Medicare beneficiaries in 2016 was 8.6 million.[25] As part of Contextual Question (CQ) 1 (**Appendix A**), we estimated the prevalence of unknown AF as 1.3 percent based on 34 studies using one-time screening approaches conducted among persons without a preexisting diagnosis of AF. We estimated the prevalence as three to four percent based on 13 studies when intermittent or continuous approaches to screening were used.

Based on data from the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study of 1.89 million adult California health plan members, in the 1990s, prevalence was shown to increase 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 with a higher prevalence in men compared with women (**Appendix A Table 1**).[26] A recent cohort study of over 500,000 patients from an integrated

health care delivery system in Pennsylvania reported significantly increased AF incidence between 2006 (4.74 cases per 1,000 person-years) and 2018 (6.82 cases per 1,000 person-years) with increases observed across all age groups and for both sexes but with the largest increases occurring in the age group 85 years or older.[27] During 50 years of observation in the Framingham Heart Study, researchers observed a fourfold increase in the age-adjusted prevalence of AF.[28] This rising prevalence is likely related to changes in diagnostic tools and strategies in routine medical care that result in more AF case finding.

Whether AF prevalence differs by race/ethnicity is uncertain. The ATRIA study identified differences in AF prevalence based on race using available ICD-9 codes from clinical databases containing Kaiser Permanente of Northern California health plan member data. Although African American and White patients ages 50 to 59 years had similar prevalence of AF, higher prevalence was reported among White patients compared with African Americans in older age groups: 1.8 percent vs. 1.3 percent in patients ages 60 to 69 years, 5.2 percent vs. 4.4 percent in patients ages 70 to 79 years, and 9.9 percent vs. 7.7 percent in patients age 80 years or older.[26] A 2019 analysis reported by the ARIC study used 48-hour ambulatory ECG to estimate AF prevalence.[29] The mean age in this analysis was 78 years, and 62 percent of the enrolled population was African American. The authors reported a lower adjusted AF prevalence among African Americans (2.7%) compared with White persons (5.0%); these estimates were adjusted for gender, coronary heart disease, diabetes, hypertension, and age. A 2020 analysis reported by the MESA study, a community-based cohort of 6,814 Americans, mean age 74 years, found higher prevalence of clinically detected AF among Whites compared with African Americans, Hispanics, and Chinese after 14.4 years of followup: 11.3 percent vs. 6.6 percent, 7.8 percent, and 9.9 percent, respectively.[30] However, when the same individuals from the MESA cohort were screened with 14-day ambulatory ECG the prevalence differences among race/ethnic groups (White, African American, Hispanic, and Chinese) were no longer statistically significant in both unadjusted and adjusted analyses: 7.1 percent vs. 6.4 percent, 6.9 percent, and 5.2 percent, respectively.[30] Based on these findings, the role of clinical bias in differential detection of AF by race/ethnicity warrants further investigation.

About 25 percent of AF is paroxysmal. Thus, assessing the overall prevalence of AF—particularly paroxysmal AF—is challenging because episodes of arrhythmia may be brief and undetected.[31] Further, the increased use of implantable cardiac devices has resulted in more awareness regarding device-detected, subclinical AF.[8, 32] In a 2019 study conducted in Denmark, the prevalence of AF was assessed with an implantable loop recorder over 40 months in persons age 70 years or older considered high risk for AF (i.e., comorbid hypertension, diabetes, heart failure, previous stroke).[33] The cumulative incidence of AF in this study was 5.7 percent for AF episodes lasting longer than 24 hours and 33.8 percent for AF episodes lasting 6 minutes or longer.[33]

Burden of Disease

In 2017, AF was the underlying cause of death for 26,077 persons with the age-adjusted mortality rate of 6.6 per 100,000 persons.[24] According to Medicare and MarketScan databases from 2004 through 2006, persons with clinical AF were approximately twice as likely to be hospitalized as age- and sex-matched control individuals (37.5% vs. 17.5%) and more likely to die during hospitalization (2.1% vs. 0.1%) than were similar patients without AF.[24] Furthermore,

in 2014, among the 3,865,447 inpatient stays with any diagnosis of AF, 398,890 stays had AF listed as a principal reason for the inpatient stay (10.3%).[24] This analysis also revealed that care for AF adds approximately $8,700 per year to the cost of a patient's healthcare (compared with a patient without AF) and accounts for $26 billion in U.S. healthcare expenditures annually.[24]

Increasing age is an independent predictor of stroke in persons with AF. Age is associated with an increased risk of stroke 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.[34] 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.[35-37] Approximately 30 percent of patients with AF who have a stroke die within 1 year of the stroke, and up to 30 percent of survivors are permanently disabled.[38]

The clinical importance of asymptomatic AF, including subclinical AF and paroxysmal AF, with respect to the risk of stroke is uncertain. We discuss this in detail in **Appendix B (CQ 2)**. Briefly, four cohort studies suggest a similar or possibly higher incidence of stroke among persons with asymptomatic AF compared with symptomatic AF, but these studies have many limitations, precluding a definitive conclusion.[39-42] Three studies, including one systematic review, reported a somewhat lower risk of stroke among persons with paroxysmal AF compared with permanent AF.[43-45] The risk of stroke for persons with paroxysmal AF may be related to AF burden, which refers to time spent in AF relative to time not spent in AF. There is some evidence that patients with high AF burden may have increased stroke risk compared with persons with low AF burden.[46-49] However, there is little consensus about how to define AF burden and what constitutes high vs. low burden. Although there are early indications that patients with subclinical AF episodes of at least 24 hours' duration may have increased stroke risk, there is less clarity for subclinical AF episodes of shorter duration. However, data related to subclinical AF comes largely from persons with implanted cardiac devices who likely represent a very small proportion of persons with AF, and about whom outcomes and observations may differ because of the underlying conditions which prompted the need for an implanted device.

Rationale for Screening and Screening Strategies

The primary rationale for screening for AF is to identify asymptomatic persons before a thromboembolic event occurs. 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.[50-52] No guidelines recommend the use of rate or rhythm control in asymptomatic persons, except in persons with a resting heart rate over 110 beats per minute because prolonged increased ventricular rates may increase the risk of cardiomyopathy.[53, 54] A trial published in October 2020 of early rhythm control in persons with AF with either medication or ablation suggests a lower risk of a composite outcome (death, stroke, hospitalization with worsening heart failure, hospitalization for acute coronary syndrome) compared with usual care (3.9 events per 100 person-years vs. 5.0 events per 100 person-years; hazard ratio [HR], 0.79 (96% CI, 0.66 to 0.94) but with a somewhat higher risk of serious adverse events of special interest related to rhythm-control therapy (4.9% vs. 1.4%).[55] Thus, other rationale for screening may exist.

Although AF is common, important to the consideration of screening for AF is the prevalence of AF among persons without symptoms and without a prior history of stroke who do not already carry a diagnosis of AF, which provides an estimate of the potentially preventable burden that might be identified through screening. In **Appendix B (CQ 1**), we describe studies that used various approaches to estimate the prevalence of AF among population- or community-based samples and clinic-based samples of persons not already known to have a diagnosis of AF. The studies providing these estimates did not include control groups and thus overestimate the potential yield of screening because cases may also be detected through usual medical care. We address the comparative diagnostic yield of screening compared with no screening as key question 2 (KQ 2) in this review. Among 35 studies using a one-time testing approach (e.g., a one-time single- or 12-lead ECG), the pooled prevalence was 1.3 percent among both clinic- and community-based samples. Among 12 studies using continuous or intermittent ambulatory ECG tests, where diagnosis of AF was defined as greater than 30 seconds of AF in all but one study, the prevalence ranged from 2.7 to 3.7 percent, likely reflecting the identification of more cases of paroxysmal AF. One additional study of an insertable cardiac monitor over 588 days (N=82) yielded a 21 percent prevalence based on AF episodes greater than 2 minutes or longer; however, these may reflect incident as well as prevalent cases.[56]

Approaches to screening vary; they include a one-time, standard 12-lead ECG, in-office devices that record fewer than 12 leads, pulse oximetry and blood measure monitors with automated AF detection algorithms, ambulatory heart rate and rhythm monitors (e.g., continuous Holter monitoring, intermittent looping memory monitors, mobile cardiac telemetry units, patch monitors), and pulse palpation. Since the previous review for the USPSTF, several consumer-directed, "wearable" devices and smartphone applications have become available. These devices rely on traditional ECG technology (i.e., capturing electrical signals across various numbers of sensors) or photoplethysmography, which relies on optical sensors to detect changes in peripheral blood volume to infer heart rate and rhythm. Some of these devices have received U.S. Food and Drug Administration (FDA) 510(k) medical device clearance to be marketed for use as an ECG device or for the detection of arrhythmias, including AF.

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 (sensitivity: 0.92; specificity: 0.82).[57] Healthcare professionals, including medical assistants, nurses, and physicians, often perform pulse measurement or palpation using automated or manual approaches during routine or acute care encounters. 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. A 2020 systematic review and meta-analysis of physician interpretation of ECG under controlled, educational test settings suggest a median accuracy of 68.5 percent for practicing physicians and 74.9 percent for cardiologists.[58] Although a 12-lead ECG interpreted by one or more cardiologists is likely sufficient to serve as a reference standard for determining the accuracy for diagnosing persistent AF, determining the accuracy of tests for diagnosing paroxysmal AF requires the use of continuous ambulatory ECG monitoring as a reference standard.

Treatments/Interventions

Oral anticoagulant medications can prevent thromboembolic events in AF patients by reducing the formation of clots in the left atrium and atrial appendage.[59] Oral anticoagulants to prevent stroke and reduce all-cause mortality in persons with AF include warfarin (a vitamin K antagonist [VKA]) and the newer target-specific anticoagulants, also known as direct oral anticoagulants (DOACs).[3] 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®).[3, 60, 61] Antiplatelet agents are not recommended as a stroke prevention option for persons with AF.[4, 62] Individualized assessment of the balance of potential benefits (i.e., risk reduction in stroke or embolism) vs. potential harms (i.e., risk increase in major bleeding) is recommended when choosing a therapeutic strategy. This assessment is aided by the use of validated risk prediction tools for stroke risk (**Appendix A Table 2**), which include the CHA_2DS_2-VASc score (***C***ongestive heart failure, ***H***ypertension, ***A***ge ≥75 years [doubled], ***D***iabetes mellitus, prior ***S***troke or transient ischemic attack [TIA] or thromboembolism [doubled], ***V***ascular disease, ***Age*** 65-74 years, ***S***ex ***C***ategory. Several prediction tools for bleeding risk (**Appendix A Table 3**) are also available and include the HAS-BLED (***H***ypertension, ***A***bnormal renal and liver function, ***S***troke, ***B***leeding, ***L***abile international normalized ratios, ***E***lderly, ***D***rugs or alcohol, and $HEMORR_2HAGES$ (***H***epatic or renal disease, ***E***thanol abuse, ***M***alignancy, ***O***lder age, ***R***educed platelet count or function, ***R***ebleeding risk, ***H***ypertension, ***A***nemia, ***G***enetic factors, ***E***xcessive fall risk, ***S***troke).[3] These tools were developed to aid in the assessment of stroke and bleeding risk, which is complicated because many risk factors for anticoagulation-related bleeding are also risk factors for stroke in patients with AF. The stroke risk prediction tools (specifically CHA_2DS_2-VASc) were developed and validated primarily in populations (some hospitalized) with clinical AF; thus, their applicability to screen-detected populations is uncertain. Although most guidelines recommend the use of stroke risk prediction tools for informing decisions about anticoagulation, most have modest predictive ability. Based on a 2018 AHRQ Effective Health Care Program Systematic Review of stroke prevention in AF, the most commonly recommended approach (categorical CHA_2DS_2-VASc score) was found to have a c-statistic of 0.64 (95% CI, 0.58 to 0.70) based on 13 studies of 496,683 patients.[63]

In patients with a high risk for stroke who may not be candidates for long-term anticoagulation, left atrial appendage closure is an available option for treatment. An FDA-approved device, the WATCHMAN™, offers a nonpharmacologic alternative to oral anticoagulation.[64] This catheter-delivered heart implant is designed to reduce the risk of thromboembolism by closing off the left atrial appendage, which is the primary site of clot formation in patients with AF. Other devices are under development.[65] The 2019 joint guidelines from the American Heart Association (AHA), the American College of Cardiology, and the Heart Rhythm Society state that percutaneous left atrial appendage occlusion may be considered in patients with AF at increased risk of stroke who have contraindications to long-term anticoagulation, but that oral anticoagulation remains the preferred therapy for stroke prevention for most patients with AF and increased stroke risk.[4] The proportion of persons with screen-detected AF with contraindications to long-term anticoagulation who would be candidates for left atrial appendage closure is not definitively known but is likely low.

Current Clinical Practice

In recent years, several U.S. and international professional organizations have issued recommendations for AF screening and management (**Appendix A Table 4**). Multiple organizations recommend active screening for AF with pulse palpation (and confirming the diagnosis with ECG) in persons age 65 years or older, including the AF-SCREEN International Collaboration,[66] the European Primary Care Cardiovascular Society,[67] the European Society of Cardiology (ESC) in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS) and European Heart Rhythm Association (EHRA),[7] the United Kingdom (U.K.) National Screening Committee (NSC),[68] the World Heart Foundation,[69] the National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand (NHFA CSANZ),[70] and the AHA in collaboration with the American Stroke Association.[71]

Several of these organizations also advocate for the use of screening approaches other than pulse palpation.[7, 66, 68, 70] Specifically, the ESC/EACTS/EHRA,[7] AF-SCREEN,[66] and NHFA CSANZ[70] each support the use of opportunistic ECG (rhythm strip or single lead) for adults age 65 or older as an alternative to pulse palpation, and the first two[7, 66] suggest considering systematic ECG screening for patients age 75 years or older or those at high stroke risk. The 2019 U.K. NSC guidelines mentioned earlier recommend modified blood pressure monitors (if available) administered by nurses in primary care settings in addition to pulse palpation as appropriate screening tests.[68]

Professional organizations have consistently recommended the use of risk prediction tools to guide the appropriate use of stroke prevention therapy in patients with AF. Recent guidelines recommend using the CHA_2DS_2-VASc score to assess stroke risk.[4] In general, guidelines recommend no therapy for those at lowest risk of stroke (based on the CHA_2DS_2-VASc score) and recommend anticoagulant therapy for those at high risk (e.g., CHA_2DS_2-VASc score ≥ 2 for males and ≥ 3 for females).[4, 72] DOACs are recommended over warfarin in the most recent guidelines for those without contraindications.[3, 4, 7, 66, 70, 73, 74] Antiplatelet agents, such as aspirin, are no longer recommended as a primary strategy for stroke prevention in AF.[4, 7]

Chapter 2. Methods

Key Questions and Analytic Framework

The EPC investigators, USPSTF members, and the Agency for Healthcare Research and Quality (AHRQ) Medical Officers developed the scope and KQs for this review.

The analytic framework illustrates the KQs that guided the review (**Figure 1**).

1. Does screening for AF with selected tests improve health outcomes (i.e., reduce all-cause mortality, reduce morbidity or mortality from stroke, or improve quality of life) in asymptomatic older adults?
   a. Does improvement in health outcomes vary for subgroups defined by stroke risk (e.g., based on CHA_2DS_2-VASc score), age, sex, or race/ethnicity?
2. Does systematic screening for AF with selected tests identify older adults with previously undiagnosed AF more effectively than usual care?
3. What is the accuracy of selected screening tests for diagnosing AF in asymptomatic adults?
4. What are the harms of screening for AF with selected tests in older adults?
   a. Do the harms of screening vary for subgroups defined by stroke risk (e.g., based on CHA_2DS_2-VASc score), age, sex, or race/ethnicity?
5. What are the benefits of anticoagulation therapy on health outcomes in asymptomatic, screen-detected older adults with AF?
   a. Do the benefits of anticoagulation vary for subgroups defined by stroke or bleeding risk (e.g., based on CHA_2DS_2-VASc or HAS-BLED score), age, sex, race/ethnicity, or AF burden (i.e., number of episodes, duration of episodes, and proportion of time spent in AF)?
6. What are the harms of anticoagulation therapy in asymptomatic, screen-detected older adults with AF?
   a. Do the harms of anticoagulation therapy vary for subgroups defined by stroke risk or bleeding risk (e.g., based on CHA_2DS_2-VASc or HAS-BLED score), age, sex, race/ethnicity, or AF burden?

In addition to our KQs, we also looked for evidence related to two CQs.

1. What is the prevalence of previously unrecognized or undiagnosed AF in unselected or explicitly asymptomatic adults? Does the prevalence vary by age, primary care vs. community setting, method of diagnosis (e.g., single electrocardiogram vs. ambulatory ECG monitoring), sex, or race/ethnicity?
2. What is the stroke risk for the following populations?
   - Asymptomatic older adults with previously unrecognized or undiagnosed AF
   - Older adults with paroxysmal vs. persistent AF
   - Older adults with paroxysmal AF who have a lower vs. higher AF burden

We do not show these questions in the analytic framework because they were not analyzed using the same systematic review process as the KQs. They are intended to provide additional background information. Findings related to the CQs are summarized in **Appendix B**.

Data Sources and Searches

We searched for English-language articles published through October 5, 2020, in MEDLINE® via PubMed, the Cochrane Library, and the following clinical trial registries: Cochrane Central Register of Controlled Trials, clinical trials.gov, and the World Health Organization International Clinical Trials Registry Platform, which consolidates many non-U.S. clinical trials registries. Our literature search also included websites for the National Institute for Health and Care Excellence, the National Institutes of Health, the Centers for Disease Control and Prevention, the National Institute for Health Research (United Kingdom), and websites of relevant professional societies. We used Medical Subject Headings as search terms when available and keywords when appropriate, focusing on terms to describe relevant populations and interventions. **Appendix C1** describes the search strategies in detail. To supplement electronic searches, we reviewed the reference lists of pertinent review articles and studies meeting our inclusion criteria. We also manually reviewed all literature suggested by peer reviewers or Federal partners and, if appropriate, incorporated studies into the final review.

Since October 2020, we conducted active surveillance of the literature through article alerts and targeted searches of journals to identify major studies published in the interim that may affect the conclusions or understanding of the evidence and the related USPSTF recommendation. We contacted study authors of ongoing studies relevant to KQ 1 to ascertain study completion status. The last surveillance was conducted on October 31, 2021, and four potentially relevant studies were identified through surveillance. Two of these studies have been incorporated into this report because we considered them essential to understanding the evidence and the related USPSTF recommendation.[75-78] The third study was a phase 3 RCT comparing lower-dose (15 mg) edoxaban with placebo in elderly Japanese persons with AF who were not candidates for typical doses of oral anticoagulation.[79] Findings from this study were similar to those reported by other studies of anticoagulation included in this report and did not change conclusions or the strength of evidence for the KQs on the benefits or harms of treatment (KQs 5 and 6). We deemed the fourth study not eligible for inclusion for an ineligible population and intervention;[80] however, its findings offer contextual information regarding overdiagnosis, and the results are briefly summarized in the discussion section of this report.

Study Selection

We developed inclusion and exclusion criteria for selecting studies based on populations, interventions, comparators, outcomes, timing, settings, and study designs; these are described in detail in **Appendix C2**. Based on public comments on the draft research plan for this update and discussions with the USPSTF, we expanded inclusion and exclusion criteria for this update in the following ways compared with the prior evidence report:[2]

- We expanded the eligible population to include adults age 50 years or older because some persons between ages 50 and 65 years would likely be eligible for stroke prevention if they had AF.
- We expanded the eligible screening approaches to non-ECG-based technologies, for example, photoplethysmography and AF-detection algorithms designed for use with oscillometric blood pressure monitors. We also specified that consumer-directed devices would be eligible for inclusion.
- We added diagnostic test accuracy studies, described eligible index tests and reference test comparators, and specified accuracy outcomes.
- We removed antiplatelet agents from the list of eligible treatments because this class of drugs is not recommended for treatment of AF to prevent strokes.

We included English-language studies conducted in countries categorized as *very high* on the Human Development Index.[81] We excluded studies focused on adults with a history of stroke or TIA. For KQs 1, 2, and 4, we focused on unselected or explicitly asymptomatic adults age 50 years or older without known AF. For these KQs, we included randomized, controlled trials (RCTs) or nonrandomized, controlled trials of screening for AF (compared with no screening or nonsystematic screening) that reported health outcomes (KQ 1) including mortality, stroke, stroke-related morbidity and quality of life, comparative diagnostic yield (KQ 2), or harms (KQ 4). For the KQ on accuracy (KQ 3), we excluded diagnostic case-control study designs because of high risk of spectrum bias and excluded studies for which persons who were symptomatic or had known AF comprised 50 percent or more of the study population. For KQs 1 through 4, we included test accuracy studies or systematic reviews assessing index tests feasible for use in or referable from primary care including single-point-in-time tests typically conducted in an office setting (e.g., single- or 12-lead ECG, rhythm assessment via photoplethysmography or algorithms built into oscillometric blood pressure monitors), intermittent ambulatory strategies using ECG or other technologies, and two-stage screening approaches involving a single test followed by a second test. Pulse palpation and other components of a standard physical examination (e.g., heart auscultation) were not eligible as test strategies. For KQs 1 and 2, we required a no-screening or usual care (which could include pulse palpation) comparator. For KQ 3, we required studies to use one of the following reference tests: 12-lead ECG interpreted by cardiologist, continuous ambulatory ECG interpreted by cardiologist, or implantable cardiac monitor. For the KQs on treatment effectiveness and harms, we included RCTs and controlled trials or systematic reviews of RCTs comparing anticoagulation with placebo or no treatment that reported health outcomes (KQ 5) or harms (KQ 6). For the KQs on harms of screening and treatment, we also included large prospective cohort studies (i.e., enrolling >500 patients) or systematic reviews of prospective cohort studies. We excluded studies performed in emergency department, inpatient, and preprocedural settings.

Two independent reviewers screened titles and abstracts and then full-text articles for selection; disagreements were resolved by discussion or by a third reviewer. We included studies that we rated as fair or good methodological quality. We reassessed studies included in the prior 2018 review[2] against the study selection and criteria for this update.

Quality Assessment and Data Extraction

For each included study, one reviewer extracted relevant study characteristics (i.e., population, intervention, comparator) and data for eligible outcomes into a structured form. A second reviewer checked all data for completeness and accuracy, and the lead investigator reviewed all extracted information for consistency across included studies. We contacted study authors to clarify study data when needed.

Two senior reviewers independently assessed each study's methodological quality using the Cochrane ROB 2.0 instrument[82] and the predefined criteria developed by the USPSTF (**Appendix C3**),[83] which uses study methodological quality ratings of poor, fair, and good. In addition to assessing the methodological quality of any newly identified studies, we reassessed the methodological quality of all previously included studies to ensure consistency of the approach. Disagreements in study quality ratings were resolved through discussion.

Data Synthesis and Analysis

We synthesized data in tabular and narrative formats. For each KQ, we assessed whether a quantitative synthesis was appropriate by evaluating the number of studies available and the clinical and methodological heterogeneity present among available studies based on established guidance, which includes evaluating the similarities in study population, medication, dose, and frequency and similarities in timing and specification of outcomes.[84] For KQ 2, too few studies were available for each screening strategy and comparison to conduct meta-analyses; therefore, we did not pool data from multiple studies, but we calculated absolute risk differences (ARDs) and risk ratios (RRs) for the comparative detection of previously undiagnosed AF. For KQs 5 and 6, we conducted quantitative synthesis with random-effects models using the inverse-variance weighted method (DerSimonian and Laird) to estimate pooled effects.[85] We calculated RRs and 95 percent confidence intervals (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. Statistical significance was assumed when 95 percent CIs of pooled results did not cross the null. All testing was two sided. We calculated a number needed to treat (NTT) for statistically significant pooled results based on the RR.[86] For KQs 5 and 6, the I^2 statistic was calculated to assess statistical heterogeneity in effects between studies.[87, 88] 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.[87, 88] We conducted all quantitative analyses using Stata version 16 (StataCorp).

We assessed the overall strength of evidence (SOE) as high, moderate, low, or insufficient based on the consistency of results between studies, precision of findings, study limitations, and reporting bias for each comparison and major outcome of interest, using methods developed for the USPSTF (and the EPC program).[89] We also assessed the applicability of the findings to U.S. primary care populations and settings. Two senior investigators independently developed initial SOE and applicability assessments for each relevant outcome; discrepancies were resolved through discussion and consultation with a third senior investigator. We evaluated the

consistency domain by visually inspecting the forest plot and with the I^2 statistic for pooled outcomes and by assessing the range of estimates and CIs of individual studies when pooling was not possible. We also assessed whether any inconsistencies could be explained by study population or study design characteristics. We evaluated the precision domain for bodies of RCT evidence by calculating the optimal information size (i.e., sample size needed in a single adequately powered trial required to generate a precise estimate) and by evaluating whether the CIs around estimates crossed clinically meaningful thresholds of benefit or harm.

Expert Review and Public Comment

A draft research plan for this topic was posted on the USPSTF website for public comment from March 26, 2020, to April 22, 2020. In response, we added language to clarify the populations of interest and subgroups, specifically the age of eligible populations (which was decreased to age 50 years). We also provided additional detail to specify eligible index and reference tests and removed "with electrocardiography" from the title, analytic framework, and KQs to reflect the use of technologies other than ECG for screening. The final version of the research plan was posted on the USPSTF website on July 16, 2020.[90] A draft report was reviewed by five content experts, three representatives of Federal partners, USPSTF members, and AHRQ Medical Officers and was revised based on comments received. In response to these comments, we provided additional information regarding the rationale for screening, clarified limitations of included studies, and expanded the future research needs section. The draft evidence report was posted on the USPSTF website for public comment from April 20, 2021, to May 17, 2021. We reviewed all citations submitted for consideration. As a result, we updated one of the CQs with additional findings, and we confirmed the relevance of one study that was published shortly before the draft report was posted and the relevance of an additional study pending publication. Both additional studies have been incorporated into this final report.

USPSTF Involvement

This review was funded by AHRQ. Staff of AHRQ 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

We screened 5,963 titles and abstracts and 242 full-text articles to identify 26 unique studies from 33 publications (N=113,784) for inclusion (**Figure 2**).[56, 59, 75-78, 91-117] Twelve of these studies were new to this update.[56, 75-77, 109-118] The list of articles excluded during full-text review is in **Appendix D,** and quality assessments are in **Appendix E**. We identified three RCTs reporting on the benefits of screening (KQ 1); eight RCTs reporting the diagnostic yield of screening compared with no screening or nonsystematic screening (KQ 2), nine studies reporting on the accuracy of various index screening strategies compared with a reference test (KQ 3), four RCTs and 1 cohort study reporting on the harms of screening (KQ 4), 10 studies reporting on the health benefits of treatment with anticoagulation (KQ 5), and 12 studies reporting on the harms of treatment with anticoagulation (KQ 6).

KQ 1. Does Screening for AF With Selected Tests Improve Health Outcomes in Asymptomatic Older Adults?

Three RCTs randomized persons to screening vs. no screening and reported health outcomes; however, only one of these studies was designed and powered for evaluating health outcomes such as stroke.[76-78] The other two RCTs were powered for evaluating differences in the detection of AF (a KQ 2 outcome) but did report a limited amount of information related to health outcomes.[75, 108] Study, population, and intervention characteristics are described in detail in **Appendix F Tables 1** through **3**.

The STROKESTOP RCT randomized all adults age 75 or 76 years living in two regions of Sweden to an invitation to screening (n=14,387) or to a control group that did not receive an invitation to screening (n=14,381).[76-78] A similar number of participants in both groups died or emigrated before the study started, resulting in 13,979 participants analyzed in the invitation-to-screening group and 13,996 in the control group. Because study participants were identified through civic registers, study authors applied no clinical inclusion or exclusion criteria. At baseline, 12.1 percent of the intervention group and 12.8 percent of the control group had known AF. Further, approximately 11 percent of both groups had a history of stroke, TIA, or systemic embolism, and 9 percent had been dispensed an oral anticoagulant within 6 months before study enrollment. The mean CHA_2DS_2VASC score across the population was 3.5. Of those invited to screening, 51.3 percent participated in the screening intervention, which was 2 weeks of twice-daily intermittent single-lead ECG monitoring with a handheld device for 30 seconds.

We assessed the STROKESTOP study as fair quality. The intervention was not blinded to participants. Outcome ascertainment was through national health registries, and persons retrieving data from these health registries were not formally blinded to group allocation. Diagnoses representing outcomes in the health registries were from data collected during routine care and were not centrally adjudicated. Further, providers assigning diagnoses were also not formally blinded, although the only way they would know the group allocation is if the participant disclosed it. Lastly, the primary outcome was originally specified as ischemic stroke in 2012 but was changed in 2017 before any data analysis to a composite endpoint that included ischemic stroke, hemorrhagic stroke, systemic embolism, bleeding leading to hospitalization, and

all-cause mortality. The authors justified this change because of a 40 percent decrease in stroke incidence over this period attributed to increased stroke prevention with DOACs and because a "net benefit" composite outcome that combined benefits with harms was deemed a more clinically relevant outcome.[76-78]

At a median followup of 6.9 years, the rate of composite endpoint events in STROKESTOP for the intent-to-treat analysis was significantly lower in the invitation-to-screening group (5.45 events/100 person-years) compared with the control group (5.68 events/100 person-years) with an unadjusted hazard ratio (HR) of 0.96 (95% CI, 0.92 to 1.00; p=0.045).[76-78] For the outcome of ischemic stroke or system thromboembolism, the HR was 0.92 (95% CI, 0.84 to 1.02). No significant differences were observed between the invitation-to-screening group and the control group for any of the individual outcomes contributing to the composite endpoint or for any other combined outcomes reported by study authors (**Appendix F Table 4**). In a post hoc analysis comparing persons who participated in screening with those in the control group, the adjusted HR was 0.72 (95% CI, 0.68 to 0.76) for ischemic stroke or systemic thromboembolism. However, this *as-treated* analysis should be interpreted with caution because study authors reported significantly fewer comorbidities and medications and more favorable sociodemographic characteristics for those who participated in screening compared with those who were invited but did not participate.

One fair-quality RCT of 1,001 participants with a primary outcome of time to diagnosis of AF (a KQ 2 outcome) reported limited information on health outcomes among secondary outcomes but was not designed or powered to evaluate them.[108] The Assessment of ***RE***mote ***HEA***rt ***R***hythm ***S***ampling using the AliveCor heart monitor to scr***E***en for ***A***trial ***F***ibrillation (REHEARSE-AF) compared twice-weekly 30-second single-lead ECG using a handheld device (n=500) with no screening (n=501) for 12 months; this trial is described in more detail in the KQ 2 section. For all-cause mortality, the authors reported three deaths in the screening group and five in the no-screening group (p=0.51). For a composite of stroke, TIA, and systemic embolism, there were 6 vs. 10 events, respectively (hazard ratio [HR], 0.6 [95% CI, 0.2 to 1.7]; p=0.34).

Lastly, one fair-quality RCT of 856 participants with a primary outcome of AF detection (a KQ 2 outcome) also reported limited information on health outcomes. The SCREEN-AF RCT compared two 2-week intervals of continuous patch ECG monitoring and twice-daily home blood pressure monitoring with AF detection to no screening.[75] After 6 months of followup, two ischemic strokes and one TIA occurred in the screening group and zero occurred in the control group; one death (cardiovascular related) occurred in the control group and zero occurred in the screening group.

As of October 2021, six ongoing trials are assessing the direct benefits of screening for AF; a summary of these studies is included in **Appendix H Table 1**. Three studies are evaluating intermittent ECG with a handheld device (over 2 to 4 weeks) or continuous ECG (with patch monitor over 2 weeks), two are evaluating one-time ECG screening with a handheld device, and one is using a PPG-based screening with ECG patch, but it is unclear whether the approach is one-time, intermittent, or continuous.

KQ 2. Does Systematic Screening for AF With Selected Tests Identify Older Adults With Previously Undiagnosed AF More Effectively Than Usual Care?

We included eight fair-quality RCTs (described in 14 articles, N=86,590).[75-78, 91-95, 105, 108, 109, 111, 116] Five of the RCTs were new in this update.[75-78, 109, 111, 116] Detailed study, population, and intervention characteristics are provided in **Appendix F Table 1** through **Appendix F Table 3**.

Study Characteristics

The characteristics of the included trials are summarized in **Table 1**. Three trials were conducted in the United Kingdom,[91, 105, 108, 109] two in the Netherlands,[111, 116] one in Sweden,[76-78] one in the United States,[109] and one that enrolled participants from both Canada and Germany.[75] All trials enrolled persons at least age 65 years or older; the mean age of participants was 72 to 80 years, and the percentage of enrolled females ranged from 39 percent to 59 percent. None of the trials reported information about the race or ethnicity of participants.

Six studies enrolled participants from primary care practices.[75, 91-95, 105, 108, 111, 116] Of the other two studies, one study[109] was a siteless trial that recruited participants via mail or email from a large health insurance plan roster, and the other study used population registers to randomize all persons ages 75 or 76 living in a specific geographic region of the country, regardless of baseline symptom status or presence of known AF.[76-78] All of the other studies excluded persons with known AF from participation. In one trial,[111] all participants in the intervention group completed a questionnaire screening for symptoms potentially related to AF in the previous month before screening. The other studies did not report methods of ascertaining asymptomatic status before screening. One study[75] required all participants to have hypertension, and the prevalence of hypertension in the four other studies reporting this characteristic at baseline ranged from 36 percent to 77 percent.[76-78, 108, 109, 111, 116] No studies explicitly excluded persons with a history of TIA or stroke; the prevalence of these conditions in the five studies reporting this at baseline ranged from[108, 111, 116] 6.5 percent to 11 percent.[76-78, 108, 109, 111, 116] Two of these studies also reported the baseline prevalence of heart failure (1.4% and 4.0%).[108, 116] Five studies[75-78, 108, 109, 111] reported baseline mean or median CHA_2DS_2-VASc stroke risk scores, which ranged from 3 to 4.

Of the included trials, all of them assessed screening strategies that used ECG. Seven trials compared screening with no screening, but the frequency of screening differed among trials.[75-78, 91-95, 108, 109, 111, 116] Three trials evaluated a one-time ECG.[91-95, 111, 116] The ***S***creening for ***A***trial ***F***ibrillation in the ***E***lderly (SAFE) study was a cluster randomized trial (14,802 participants) that randomized 50 primary care practices to screening vs. no screening with 1-year followup.[91-95] Within the 25 practices randomized to screening, individual participants were then further randomized to ECG screening or pulse palpation reminders. Those in the ECG screening arm were invited by mail to attend a nurse-led screening clinic where their radial pulse was palpated, and a limb-lead, thoracic-lead, and a 12-lead ECG were performed. For the practices assigned to either screening group, primary care physicians and other members of the healthcare team attended educational days covering the importance of detecting AF and available treatment

options. The ***I***mproving ***DE***tection of ***A***trial Fibri***L***lation in Primary Care with the ***M***y***D***iagnostick (IDEAL-MD) study was a cluster randomized trial that randomized 31 general practices (8,526 participants) to ECG screening or no screening with 1-year followup.[111] Within the 15 practices randomized to ECG screening, eligible patients were identified and screened during practice visits with a single-lead ECG using a handheld device. The 16 control practices were informed of the study aim, but no specific intervention was assigned. The ***D***etecting and ***D***iagnosing ***A***trial ***F***ibrillation (D2AF) was a cluster-randomized RCT within 96 primary care practices (17,976 participants) that evaluated a combined strategy of three tests: pulse palpation, oscillometric BP measurement with automated AF detection, and handheld single-lead ECG with automated AF detection compared with usual care over 1-year followup.[116]

Two trials evaluated screening with intermittent hand-held ECG.[76-78, 108] The ***RE***mote ***HEA***rt ***R***hythm ***S***ampling using the AliveCor heart monitor to scr***E***en for ***A***trial ***F***ibrillation (REHEARSE-AF) trial randomized 1,001 participants with a CHA_2DS_2-VASc score of 2 or more recruited from general practices to twice-weekly screening with a single-lead ECG using a handheld device or to no screening for a 1-year duration; followup was also 1 year.[108] STROKESTOP randomized over 28,000 persons age 75 or 76 identified from the population registries of two geographic regions.[76-78] Of those who were randomized to the invitation to the screening program, 51.3 percent enrolled and received an index ECG at baseline followed by 2 weeks of intermittent handheld single-lead ECG monitoring; followup was a median of 6.9 years. Those with AF at baseline who were not already taking direct oral anticoagulants (DOACs) and those with newly identified AF were offered structured followup with a cardiologist.

Two trials evaluated screening with continuous ECG.[75, 109] The ***m***Health ***S***creening ***to P***revent ***S***trokes (mSToPS) trial randomized 2,659 participants recruited by email or mail from a large health insurance plan to screening with a 14-day continuous ambulatory ECG monitoring with a patch initiated immediately after enrollment and again in 3 months or to delayed monitoring 4 months after enrollment (i.e., no screening).[109] Outcomes were reported after 4 months followup from baseline. SCREEN-AF randomized 856 participants to a similar intervention, with the addition of a home blood pressure monitor with automated AF detection to be used twice daily during each 2-week ECG monitoring period.[75] Followup in this study was 6 months.

Two trials compared ECG screening with pulse palpation chart reminders.[91-95, 105] The SAFE trial, previously described, used paper or computer flags placed in patient medical records to encourage providers to conduct pulse palpation; those with an irregular pulse were invited to attend a screening clinic and have an ECG performed. The second trial, Morgan et al, randomized 3,001 participants from four primary care practices to ECG screening or pulse palpation reminders.[105] Those in the ECG screening group were invited by mail to attend a nurse-led screening clinic where their radial pulse was palpated and a lead II ECG rhythm strip was performed. Those unable to attend the clinic were offered screening at home. For those in the other group, a reminder flag was placed in their medical records. 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.

Results of Included Trials

All trials reported on detection of AF cases for the screening intervention groups compared with control groups (either no screening or pulse palpation reminders). Detailed results are provided in **Appendix F Table 4**. Followup lasted 1 year for SAFE, REHEARSE-AF, IDEAL-MD, and D2AF; 4 months for mSToPS; and 6 months for SCREEN-AF, STROKESTOP, and the Morgan et al trial. In SAFE, two cardiologists masked to allocation assessed whether ECGs showed AF in the screening arms; a third arbitrated any disagreements. Medical records were reviewed for participants in the control group to identify new cases of AF.[91, 93] The Morgan et al trial reported AF ascertainment by a single observer (masking not reported) who reviewed medical records of participants for new diagnoses, investigations, and treatment.[105] In REHEARSE-AF, an unmasked study cardiologist confirmed all AF diagnoses made in the intervention group; participants in the control group were diagnosed by local clinicians with validation by a study cardiologist.[108] In STROKESTOP, study authors defined AF as at least one 30-second episode of AF or at least two episodes between 10 and 29 seconds during the 2-week screening period for persons randomized to the screening intervention.[76-78] However; the proportion with AF reported 6 months after baseline and at later followup time points was based on health registry data derived from clinical records.[76] In mSToPS, rhythms from 14-day continuous ECG monitoring were analyzed using an FDA-approved algorithm, and these results underwent additional technical review for report generation and quality assurance after which the report was independently reviewed by the principal investigator.[109] New AF was defined as 30 seconds or more of AF or atrial flutter detected by device or a new clinical diagnosis recorded in claims data. In SCREEN-AF, devices from the continuous ECG monitoring were centrally interpreted with results then provided back to the participants' primary care physicians.[75] New clinical diagnoses were ascertained during study visits, with central adjudication based on ECG tracings and hospital records. In IDEAL-MD, AF was confirmed by a general practitioner (GP) and research cardiologist, and AF was considered newly diagnosed whether screen detected or diagnosed otherwise.[111] In D2AF, AF diagnoses were ascertained by extraction of diagnosis information from the electronic medical records of participants randomized.[116]

Findings are summarized in **Figure 3**. Of the studies using one-time approaches to screening (D2AF, IDEAL-MD, SAFE), risk differences (RDs) ranged from 0.06 to 0.60 percentage points and risk ratios (RR) ranged from 1.04 to 1.58 compared with no screening; findings were only statistically significant in the SAFE trial. Fidelity with respect to the proportion of participants randomized to receive screening that were screened was low to modest in these trials (D2AF, 45%; IDEAL-MD, 11%, SAFE, 53%). The two trials comparing one-time ECG screening with pulse palpation reminders did not find a statistically significant difference in new cases of AF between study arms.[91, 105] The fidelity of pulse palpation among participants randomized to pulse palpation reminders was also low to modest in these trials (Morgan et al,[105] 29%; SAFE, 69%). However, more cases of AF were detected in the SAFE trial when comparing pulse palpation reminders with no screening.[91]

Relative to one-time ECG screening, more cases of AF were detected with intermittent ECG compared with no screening. In REHEARSE-AF, 19 (3.8%) persons had AF detected from screening twice daily for 12 months compared with 5 (1.0%) in the no-screening group (ARD 2.8%; 95% CI, 0.9% to 4.7%). Notably, 11 (58%) of the new AF cases reported symptoms at the time of diagnosis compared with all of the new AF cases in the no-screening group.[108] In

STROKESTOP, which evaluated twice-daily screening for 2 weeks, 1,991 (14.5%) cases of AF were detected by 6 months after baseline compared with 1,850 (13.4%) cases in the no-screening group. The ARD for new cases of AF was 1.0 percent (95% CI, 0.2% to 1.9%).[76-78] As previously noted, most of the cases of AF in both groups were known at baseline.

Relative to one-time screening, more cases of AF were also detected for continuous ECG screening over two 2-week intervals. In mSToPS, by 4 months followup, 53 (3.9%) cases of AF were detected with screening compared with 12 (0.9%) in the control group (ARD 3.0% [95% CI, 1.8% to 4.1%]).[109] Notably, 12 (17%) participants who had AF during monitoring recalled symptoms potentially associated with AF when prompted.[109] The mSToPS trial reported a median time to first detection of AF of 2.0 days (interquartile range [IQR], 1.0 to 5.0) and median AF burden (percentage of monitored time in AF) of 0.9% (IQR, <1% to 4%).[109] Of 109 new cases of AF in the monitored cohort group (immediate or delayed groups) reported at 1 year, 65 (60%) were first found to have AF by ECG patch (as opposed to a clinical diagnosis prior to or after monitoring).[109] The trial reported that the longest individual episode of AF was less than 5 minutes in 7.2 percent and was 5 minutes to 6 hours in 55 percent, was 6 to 24 hours in 25 percent, and was more than 24 hours in 13 percent. In SCREEN-AF, by 6 months followup, 23 (5.4%) AF cases were detected in the screening group compared with two (0.5%) in the no-screening group (ARD, 4.8% [95% CI, 2.6% to 7.0%]; number needed to screen 21).[75] Of the 23 cases detected in the screening group, 20 cases (18 paroxysmal, 2 persistent) were detected through screening, and three presented clinically. Among those in the screening group, the median duration of the longest episode of AF was 5.7 hours (IQR, 2.9 to 12.9) with 50 percent of cases spending more than 6 hours in AF and 15 percent spending more than 24 hours in AF.

Subgroup Findings

The SAFE trial reported subgroup analyses by sex and age for ECG screening or pulse palpation reminders compared with no screening.[91] The subgroup analyses reported that screening may not increase detection of new cases among females. Males in the ECG (44 vs. 16; OR, 2.68 [95% CI, 1.52 to 4.73]) and pulse palpation reminder groups (38 vs. 16; OR, 2.33 [95% CI, 1.30 to 4.15]) had greater odds of having AF diagnosed than males in the no-screening group. The odds were not significantly increased for females 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 years had similar odds of having AF diagnosed in both the ECG 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 pulse palpation reminder groups (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. The other trials included for KQ 2 did not report any subgroup analyses.

KQ 3. What Is the Accuracy of Selected Tests for Diagnosing AF in Asymptomatic Adults?

We identified nine studies reported in 13 articles (N=4,978) on the accuracy of primary-case feasible screening tests (**Table 2**).[56, 75, 91, 112-117] All are new to this update because this KQ was

not included in the previous report. Detailed study, population, and screening test characteristics are provided in **Appendix F Table 5** through **Appendix F Table 7**.

Study Characteristics

We rated five studies as good methodological quality[56, 75, 91, 112, 115] and four studies as fair methodological quality.[113, 114, 116, 117] One study was conducted in the United States,[114] one study was conducted in Canada and Germany,[75] and the rest were conducted in various European countries. One study was conducted over the years 2000 through 2003,[91] and rest were conducted in 2011 or later. Five studies enrolled participants from general practices,[75, 91, 112, 113, 116] while the others enrolled participants from outpatient specialty clinics (e.g., cardiology, diabetes and hypertension clinics). The mean age of study participants ranged from 66 to 80 years, and the percentage of participants who were female ranged from 37 to 59 percent. The proportion of participants with known AF at enrollment ranged from 0 to 27 percent. Only two studies reported on predicted stroke or bleeding risk at baseline; in these studies, the median CHA_2DS_2-VASc score was 4.[56, 75]

The screening tests evaluated in these studies varied. Four studies evaluated the accuracy of oscillometric blood pressure monitors with automated irregular pulse/AF detection features against a reference standard of a 12-lead ECG interpreted by one or more cardiologists[113-115] or against a reference standard of continuous patch ECG for two 2-week intervals (total 4 weeks).[75] Two studies evaluated single-lead ECG devices with AF detection features against a reference standard of a 12-lead ECG interpreted by two independent cardiologists.[112, 113] One study evaluated a six-lead ECG automated diagnostic report produced using a custom algorithm compared with a reference standard of a 12-lead ECG interpreted by cardiology.[117] One study evaluated GP interpretation of a 12-lead ECG conducted in a primary care office setting against interpretation by two independent cardiologists.[91] This study also evaluated the accuracy of GP-interpreted single limb or thoracic leads against the same reference standard (i.e., cardiologist interpretation). One study evaluated the accuracy of a combined test with three components: pulse palpation, oscillometric BP with automated AF detection, single-lead ECG with automated AF detection compared with a reference standard of 12-lead ECG interpreted by cardiology. Of note, in this study, only a 10% random sample of persons with negative index test received the reference standard. Lastly, one study evaluated the accuracy of a two-channel, 72-hour Holter monitor adjudicated by two cardiologists against a reference standard of an insertable cardiac monitor interpreted by two electrophysiologists.[56]

Results of Included Studies

Accuracy results are summarized in **Table 3** with additional details in **Appendix F Table 8**. Across the included tests, we estimate that in a population of 1,000 persons with a prevalence of undiagnosed AF of 1.3 percent (based on CQ 1), the number of true-positive tests would range from 4 to 13, false-positive tests would range from 0 to 237, false-negative tests would range from 0 to 9, and true-negative tests would range from 750 to 987.

Oscillometric BP Monitor With AF Detection vs. 12-Lead ECG Cardiology Interpretation

In four comparisons of two devices reported across three studies, sensitivity ranged from 0.92 to 1.0.[113-115] In a fifth comparison reported by one of the studies, sensitivity for one of the two devices evaluated was reported as 0.3 (95% CI, 0.15 to 0.49).[114] This estimate differed markedly from the sensitivity reported by the other monitor reported in the same study and from the same monitor used in a different study.[115] We note the author of this study disclosed that he holds a patent for the AF detection algorithm for the device that demonstrated a higher sensitivity in his study.[114] We could not identify any other characteristics that might explain this outlying finding. Specificity across all five comparisons ranged from 0.90 to 0.97.

Oscillometric BP Monitor With AF Detection vs. Continuous ECG

In the one study reporting the comparison of intermittent twice-daily oscillometric blood pressure monitor with AF detection feature and a reference continuous ECG monitored for a total of 4 weeks , the sensitivity was 0.35 (95% CI, 0.15 to 0.59) and the specificity was 0.81 (95% CI, 0.77 to 0.85).[75] The lower sensitivity observed for this comparison is likely because of the use of a different reference standard, which is better suited for identifying paroxysmal AF than a one-time 12-lead ECG.

Single-Lead ECG With AF Detection vs. 12-Lead ECG Cardiology Interpretation

In one study,[112] the sensitivity was 0.88 (95% CI, 0.47 to 1.0) and the specificity was 1.0 (95% CI, 0.96 to 1.0), while in a second study,[113] the sensitivity was 0.99 (95% CI, 0.93 to 1.0) and specificity was 0.76 (95% CI, 0.73 to 0.79). These studies used different single-lead ECG devices and varied by population enrolled (one study included only persons age 18 years or older from general practices with nonacute indications for 12-lead ECG,[112] while the other study enrolled persons age 75 years or older without other inclusion criteria).

Six-Lead ECG With AF Detection vs. 12-Lead ECG Cardiology Interpretation

In one study,[117] the sensitivity was 0.95 and the specificity was 0.99 (95% CI NR). The study used a six-lead ECG device and enrolled participants (mean age 66) from outpatient cardiology clinics for routine ECG or other appointments.

GP ECG Interpretation vs. 12-Lead ECG Cardiology Interpretation

In the SAFE trial, interpretation of ECGs by GPs at each of the 25 participating intervention practices was compared with 12-lead ECG interpretation by a cardiologist.[91, 94] The sensitivity of GP-interpreted ECG compared with 12-lead ECG interpreted by a cardiologist ranged from 0.80 to 0.85 depending on whether the index test was a 12-lead, single-limb lead or a single thoracic-lead ECG. The specificity ranged from 0.86 to 0.92. Combining GP interpretation with interpretive software increased the sensitivity (0.92 [95% CI, 0.87 to 0.97]) but specificity was similar (0.91 [95% CI, 0.90 to 0.93]). The accuracy of individual GP interpretation varied greatly; sensitivity ranged from 0.5 to 1.0, and the proportion of false-positive readings for individual GPs ranged from 0 to 0.44.

Combined Strategy of Pulse Palpation, Oscillometric BP Measurement, and Single-Lead ECG With AF Detection

In the D2AF trial, a separate analysis of the screening intervention group evaluated the accuracy of combined strategy of pulse palpation with oscillometric BP measurement with automated AF detection and single-lead ECG with automated AF detection.[116] The index test was considered positive if any one component of the test was positive. Of the 4,106 participants screened, 488 has a positive index text and of those 448 had a 12-lead ECG reference standard performed. Of those 448, 26 were confirmed to have AF. Of the 294 randomly sampled persons with negative index tests, zero were confirmed to have AF on 12-lead ECG. We were unable to calculate the sensitivity and specificity of the screening approach based on how the study was designed and reported. However, we calculated the positive predictive value of this screening approach to be six percent, and the negative predictive value to be 100 percent.

Holter Monitor vs. Insertable Cardiac Monitor

One study evaluated a two-channel, 72-hour continuous Holter monitoring compared with an insertable cardiac monitor.[56] The Holter monitor was administered approximately 1 month after the insertable cardiac monitor was placed. Two cases of paroxysmal, but subclinical (i.e., no symptoms), AF were detected by Holter monitoring; these cases were also detected by the insertable cardiac monitor, suggesting a sensitivity of 1.0 when only considering the same 72-hour monitoring period covered by both devices. Over the entire duration of insertable cardiac monitoring (mean 588 days), an additional 15 cases of subclinical paroxysmal AF were detected for an overall sensitivity of 0.12. It is unclear whether these additional cases were prevalent cases of paroxysmal AF missed by the 72-hour Holter monitoring window or new onset paroxysmal AF cases. The specificity of Holter monitoring was 1.0. For those with newly identified AF, the median time to first AF episode based on insertable cardiac monitoring was 91 days (IQR, 41 to 251).

KQ 4. What Are the Harms of Screening for AF in Older Adults?

We identified four RCTs that reported harms of screening; all were described in the KQ 1 and KQ 2 sections of this report and are in **Table 1**. One of them (SAFE[91]) was included in the prior review for the USPSTF, and three (mSToPS,[109] STROKESTOP,[77, 78, 119] SCREEN-AF[75]) are new to this update. The mSToPS study also included a prospective cohort component that reports outcomes relevant to this KQ. Detailed study characteristics are provided in **Appendix F Table 9**.

Study Characteristics

In brief, the SAFE trial randomized 50 practices to screening or no screening and further randomized participants at the screening practices to invitations to attend a nurse-led screening clinic with pulse palpation and single- and 12-lead ECG or chart reminders encouraging clinician pulse palpation.[91] The mSToPS trial randomized 2,659 participants to screening with two rounds of a 14-day continuous ambulatory ECG patch or delayed monitoring (i.e., no screening).[109]

After 4 months, the delayed monitoring group received the intervention. Parallel to the RCT component of mSToPS, study authors assembled an observational cohort consisting of 5,318 participants matched to participants in the RCT component. Participants in all components (immediate monitoring, delayed monitoring, matched controls with no monitoring) were followed over 1 year in a prospective cohort study. STROKESTOP randomized 28,768 participants to an invitation to twice-daily intermittent ECG screening with a handheld device or to a control group.{, #11220;, #8;, #55} Lastly, SCREEN-AF randomized 856 participants to continuous ECG for a total of 4 weeks, with the addition of a home blood pressure monitor with automated AF detection to be used twice daily during each 2-week ECG monitoring period.{, #11215}

Results of Included Studies

Outcomes reported by studies varied. SAFE reported anxiety, STROKESTOP and SCREEN-AF reported bleeding outcomes, mSToPS and SCREEN-AF reported frequency of non-AF arrhythmias and skin irritation from the ECG patch, and mSToPS, STROKESTOP, and SCREEN-AF reported subsequent procedures or medication use. Detailed results are provided in **Appendix F Table 10**. No eligible studies were identified that assessed labeling or consequences of subsequent procedures or interventions initiated because of screening with ECG, or harms related to false-positive results. We remind readers that diagnostic accuracy, including the estimated number of false-positive results, is reported in the KQ 3 results section of this report.

Anxiety

The SAFE study assessed anxiety using the Spielberger Six-Item Anxiety Questionnaire (S6AQ), a measure of general anxiety, but did not collect anxiety data from patients within the no-screening arm of the study.[91] The study evaluated anxiety in the invitation for ECG screening and pulse palpation reminder screening groups at three different time points among 750 patients (out of more than 9,000 in the screening groups) before randomization, 1,940 patients immediately after ECG screening, and 535 patients 17 months after baseline.[91, 120] Anxiety levels were not significantly different between the groups at baseline, immediately after screening, or at 17 months after adjusting for baseline scores (**Appendix F Table 10**). 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), and most participants did not have clinically meaningful levels of anxiety symptoms (i.e., greater than 39 to 40); thus, the clinical importance of the difference is likely low.[91]

Bleeding Outcomes

In STROKESTOP, the rate of hemorrhagic stroke was 0.16 events per 100 person-years in the invitation-to-screening group compared with 0.18 in the control group (HR 0.88 [95% CI, 0.70 to 1.11]).[76] The rate of hospitalization for major bleeding was 1.71 events per 100 person-years in the invitation-to-screening group compared with 1.74 in the control group (HR 0.98 [95% CI, 0.91 to 1.06]). In SCREEN-AF, authors reported zero intracranial hemorrhages.[75] Further,

among those with AF or who were prescribed oral anticoagulations, zero major bleeding events were observed.

Frequency of Non-AF Arrhythmias

The mSToPS trial reported potentially actionable arrhythmias other than AF in 70 participants (2.6%), including nonsustained ventricular tachycardia, prolonged or symptomatic supraventricular tachycardia, significant pause or high-degree atrioventricular block, and very frequent ectopy.[109] The study did not report whether identification of those arrhythmias led to subsequent benefits or harms. Similarly, SCREEN-AF reported the frequency of various non-AF arrythmias, which ranged from 0 percent to 3.9 percent depending on the type of arrhythmia (**Appendix F Table 10**).[75] Similar to mSToPS, the arrhythmias identified would likely be considered clinically actionable, but it is not known whether further action led to benefit or harm.

Subsequent Procedures or Interventions

The mSToPS cohort study reported the number of treatments and procedures over the course of 12 months for the combined screening groups (1,738 participants in the immediate and delayed intervention group) and matched controls (3,476 participants; matched on age, sex, and CHA_2DS_2-VASc) with 12 month followup data but did not report on benefits or harms from those treatments or procedures. The study authors also do not report whether those undergoing further treatment or procedures were diagnosed clinically or were screen detected through patch monitoring.[109] Participants in the combined screening groups had higher rates of initiation of anticoagulation for AF, antiarrhythmic medication use, cardioversion procedures, cardiac ablations, pacemaker or defibrillator placements, and outpatient cardiology visits compared with matched controls who did not receive any screening intervention.(**Appendix F Table 10**). In the SCREEN-AF trial, no statistically significant differences were reported for ED visits, hospitalizations, or pacemaker implantations, although all of these events were rare in both the screening and control groups.[75] A significantly higher number of participants initiated oral anticoagulant therapy in the screening group compared with the control group (ARD 3.2% [95% CI, 1.1 to 5.3]; RR 4.4 [95% CI, 1.5 to 2.8]). In STROKESTOP, a numerically higher number of participants initiated oral anticoagulants in the invitation-to-screening group at all time points through 7 years of followup (e.g., 11.3% vs. 10.8% at 1-year followup), but these differences were not statistically significant.[76]

Skin Irritation

The mSToPS trial reported that 40 participants (1.5%) had skin irritation from wearing an ECG patch. Of those, 32 discontinued wearing the patch, and two sought medical attention and received topical therapy. In SCREEN-AF, five participants (1.2% [95% CI, 0.5% to 2.7%]) reported skin irritation from the patch.[75] The methods of ascertainment of skin irritation were not reported in either trial, and it is unclear whether participants were systematically asked about or evaluated for skin irritation.

Subgroup Findings

We did not find eligible studies reporting whether harms of screening differed for subgroups defined by stroke risk (e.g., based on CHA_2DS_2-VASc score), age, sex, or race/ethnicity.

KQ 5. What Are the Benefits of Anticoagulation Therapy on Health Outcomes in Asymptomatic, Screen-Detected Older Adults With AF?

We found no new trials or systematic reviews that addressed this KQ. For the current review, this KQ was updated to reflect the current standard of care for stroke prevention, which includes anticoagulation but not antiplatelet therapy. Therefore, this section has been revised from the prior review to remove evidence pertaining solely to antiplatelet therapy. In our prior review, our meta-analysis of four trials of aspirin vs. no aspirin found no statistically significant differences in all-cause mortality, cardiovascular mortality, all ischemic stroke, disabling stroke, and ischemic stroke or intracranial hemorrhage.[2]

Although we aimed to determine the benefits of treatment for screen-detected older adults with AF, we found no trials or systematic reviews that focused solely on this population. We included five RCTs of persons who were not screen detected;[97-102] most had long-standing, persistent nonvalvular AF; few had a history of TIA or stroke (<8%); and prevalence of baseline or past symptoms (e.g., palpitations, dyspnea) was generally not reported. Three trials evaluated warfarin[97, 99, 100] and two (described in three articles) evaluated both warfarin and aspirin.[98, 101, 102] The characteristics of the included RCTs are summarized in **Tables 4** and **5**, and the results are summarized in **Figure 4** and **Appendix F Table 11.**

In addition to the included RCTs, we included five systematic reviews comparing warfarin to placebo (**Appendix F Table 13**): two were traditional systematic reviews with meta-analyses,[59, 104] two were meta-analyses of individual patient data,[96, 107] and one was a network meta-analysis.[106] The systematic reviews included a total of 38 unique studies (including the 5 RCTs in our review). Many of the studies included in other systematic reviews were not eligible for this review because they evaluated secondary prevention (i.e., evaluated treatments for persons with a history of TIA or stroke in addition to addressing primary prevention) or because they compared one active treatment to another active treatment (most of the 21 studies included in the network meta-analysis were such studies).

Study Characteristics of Included RCTs

Five trials (described in 6 articles) evaluated warfarin.[97-102] All trials were rated fair quality. Four of the five trials compared warfarin with a placebo (***A***trial ***F***ibrillation, ***AS***pirin, and ***A***nti***K***oagulation study [AFASAK I],[102] ***C***anadian ***A***trial ***F***ibrillation ***A***nticoagulation [CAFA],[99] ***S***troke ***P***revention in ***A***trial ***F***ibrillation [SPAF I],[98, 101] ***S***troke ***P***revention in ***N***onrheumatic ***A***trial ***F***ibrillation [SPINAF][97]) and one (***B***oston ***A***rea ***A***nticoagulation ***T***rial for ***A***trial ***F***ibrillation [BAATAF])[100] 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 non-White 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 before 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.[106]

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).

Results of Included RCTs

In our meta-analysis, warfarin treatment over an average of 1.5 years was associated with reductions in all-cause mortality (pooled RR, 0.68 [95% CI, 0.50 to 0.93]; I^2=0%; 5 trials; 2,415 participants), ischemic stroke (pooled RR, 0.32 [95% CI, 0.20-0.51]; I^2=0%), and moderately to severely disabling stroke (pooled RR, 0.38 [95% CI, 0.19 to 0.78]; I^2=0%) compared with controls (**Figure 4**). For a population with baseline annual stroke risk of 4 percent, such as patients with CHA_2DS_2-VASc scores between 3 and 4, the results indicate that warfarin was associated with a NTT of 24 (95% CI, 17 to 36) to prevent one ischemic stroke over 1.5 years. For a population of 1,000 adults age 65 years or older with an annual stroke risk of 4 percent, this translates to an absolute reduction of 28 ischemic strokes per year and an absolute reduction of 16 deaths per year. Our meta-analyses found no statistically significant difference between groups for cardiovascular-related mortality or TIA, but trials reported relatively few events for those outcomes and CIs were wide (**Figure 4** and **Appendix G Figure 1**).

Results of Previously Published Systematic Reviews and Meta-Analyses

Results of previously published systematic reviews[59, 96, 104, 106, 107] were consistent with our findings and are summarized in **Appendix F Table 13**. 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 DOACs.

One systematic review from the Cochrane collaboration evaluated warfarin compared with placebo for primary prevention.[104] 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: they reported OR, 0.69 (95% CI, 0.50 to 0.94) for all-cause mortality vs. our pooled RR, 0.68 (95% CI, 0.50 to 0.93).

Subgroup Findings

Two individual patient data meta-analyses used the Atrial Fibrillation Investigators database from clinical trials evaluating warfarin.[96, 107] That database included all five warfarin trials described in this report (AFASAK I, CAFA, SPAF I, SPINAF, BAATAF). One evaluated subgroups based on sex and history of hypertension for warfarin,[107] and one evaluated whether benefits vary by age for warfarin.[96]

The individual patient data meta-analysis that evaluated subgroups based on sex and history of hypertension[107] used the same five RCTs evaluating warfarin that we included in our analysis. It reported that the efficacy of warfarin was consistent across subgroups. Warfarin was associated with a reduction in stroke for both males and females, without a statistically significant difference between them (relative risk reduction, 60% [35% to 76%] and 84% [55% to 95%], respectively).

The individual patient data meta-analysis that evaluated subgroups based on age[96] used the same five RCTs evaluating warfarin that we included in our analysis, but also included a secondary prevention trial (EAFT, which involved 439 participants treated with warfarin or placebo).[121] Warfarin was associated with a reduced risk of ischemic stroke (compared with placebo/control) for all ages; for the assessment of relative benefit with increasing age, the interaction did not reach statistical significance (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, interaction of age and warfarin, p=0.07).

Previously Published Network Meta-Analysis

The one included network meta-analysis used 21 RCTs (96,017 participants) of treatment for nonvalvular AF.[106] It was not limited to primary prevention populations, but most of the data were 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 the European Atrial Fibrillation Trial (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 to 1.5 combined with aspirin 325 mg once daily vs. adjusted-dose warfarin with target INR, 2.0 to 3.0). The percentage of participants with a history of stroke or TIA was less than 10 percent 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 (VKAs, all four DOACs) reduced the risk of the primary and secondary efficacy outcomes compared with placebo/control (**Appendix F Table 13**). Effect sizes for VKAs compared with placebo/control were nearly identical to those from our pairwise meta-analyses for warfarin compared with placebo or no treatment. For the four DOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) included in the analysis, the authors reported statistically significant associations with reduction in the primary outcome compared with placebo (unadjusted ORs from 0.27 to 0.38; adjusted ORs from 0.32 to 0.44), but no statistically significant differences for the four DOACs in comparison with one another. In adjusted analyses, the DOACs were not statistically different from VKAs for either efficacy outcome.

KQ 6. What Are the Harms of Anticoagulation Therapy in Asymptomatic, Screen-Detected Older Adults With AF?

We did not identify any studies focused exclusively on asymptomatic, screen-detected older adults with AF. The five RCTs reported for KQ 5 among persons with clinical, mostly persistent AF also reported on harms.[97-102] We also included six systematic reviews (5 were also included for KQ 5): three were traditional systematic reviews with meta-analyses,[59, 103, 104] two were individual patient data meta-analyses,[96, 107] and one was a network meta-analysis.[106] For this update, we identified one new cohort study that reported harms.[110] We remind readers that harms of anticoagulation therapy apply to persons with accurately diagnosed AF, but also to persons treated with anticoagulation because of a false-positive screening test that was either not confirmed with an appropriate diagnostic test or who may have received an inaccurate diagnosis even after subsequent diagnostic testing. Screening test accuracy including estimates of false-positive screening test are described in the KQ 3 section of this report.

Study Characteristics

The five RCTs included for this KQ were previously described in the KQ 5 section and are summarized in **Tables 4** and **5.** The included cohort study, GARFIELD-AF, is a fair-quality, ongoing, prospective, patient registry of newly diagnosed nonvalvular AF from 1,048 primary and specialty clinics across 32 countries (n=28,628).[110] Participants were 18 years or older with at least one stroke risk factor. Median age (IQR) was 71 years (63 to 78 years), and 44 percent were female. Participants received warfarin, DOACs, antiplatelet agents, combination therapies or no treatment. Results are reported for 2 years of followup. Study characteristics are detailed in **Appendix F Table 12**.

Results of Included RCTs

Major Bleeding

Across trials, 31 major bleeding events occurred, 20 in warfarin groups and 11 in placebo/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 nine 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 G Figure 2**).

Results of Observational Studies

In GARFIELD-AF, major bleeding was reported in 1.3 percent of participants (0.71 events per 100 person-years [95% CI, 0.64 to 0.79]). Nonmajor bleeding was reported in 1.8 percent of participants (n=500). Of all bleeding events, 6.9 percent (n=60) were fatal. The adjusted HR for first occurence of major bleeding was 1.73 (95% CI, 1.33 to 2.25) for participants receiving treatment compared with participants receiving no treatment. This estimate was adjusted for age, race/ethnicity other than Caucasian/Hispanic/Latino, smoking, diabetes, history of stroke, TIA or systemic embolism, history of bleeding, cardiac failure, renal disease, nonparoxysmal AF, and vascular disease (**Appendix F Table 12**).

Results of Previously Published Systematic Reviews and Meta-analyses

Results of six previously published systematic reviews[59, 96, 103, 104, 106, 107] were consistent with our findings and are summarized in **Appendix F Table 13**. 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 active treatment comparisons, including comparisons with DOACs.

One systematic review from the Cochrane collaboration evaluated warfarin for primary prevention.[104] 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, they reported OR for intracranial hemorrhage 2.38 [95% CI, 0.54 to 10.5] vs. our pooled RR result, 1.94 [95% CI, 0.56 to 6.68]).

Subgroups

Two of the individual patient data meta-analyses provided information about whether the risk of harms varies for subgroups.[96, 107] Both used the Atrial Fibrillation Investigators database of clinical trials evaluating warfarin or aspirin. That database included all five warfarin compared with placebo/control trials described in this report (AFASAK I, CAFA, SPAF I, SPINAF, BAATAF).

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.[107] 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. 141/83 mm 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-value 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).[96] The analyses used the same five RCTs evaluating warfarin that we included, but also included a secondary prevention trial

(EAFT). They found that warfarin did not interact significantly with patient age for serious hemorrhage (data not reported by study; shown in figures only).

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 5.[106] 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 compared with placebo/control were nearly identical to those from our pairwise meta-analyses for warfarin compared with placebo/control (**Appendix F Table 13**). Similarly, for the four DOACs (apixaban, dabigatran, edoxaban, and rivaroxaban), the authors reported adjusted ORs ranging from 1.38 to 2.21 for major bleeding in indirect comparisons to placebo/no treatment controls; the CIs were wide and findings were not statistically significant (**Appendix F Table 13**). Further, there were no statistically significant differences between any of the four DOACs with respect to bleeding. Compared with VKAs, three of the DOACs (apixaban, dabigatran, and edoxaban) were associated with a lower odds of bleeding (range of adjusted ORs from 0.64 to 0.85, but the difference was only statistically significant for edoxaban (adjusted OR, 0.64 [95% CI, 0.46 to 0.90]). For rivaroxaban compared with VKAs, the odds of major bleeding was higher but not statistically significant (adjusted OR, 1.03 [95% CI, 0.68 to 1.57]).

Chapter 4. Discussion

Summary of Evidence

We identified some direct evidence evaluating the benefits (KQ 1) or harms (KQ 4) of screening for AF, but study limitations and applicability concerns may preclude definitive conclusions from this evidence. We identified evidence related to comparative diagnostic yield (KQ 2) and test accuracy (KQ 3) with heterogeneity in findings largely based on screening test strategy used. We identified no new evidence for benefits of treatment with anticoagulation (KQ 5) and identified one new observational study in addition to existing RCTs offering evidence for harms of anticoagulation (KQ 6). **Table 6** summarizes the evidence synthesized in this report by KQ and provides our EPC's assessment of the consistency, precision, study limitations, SOE, and applicability.

Benefits of Screening (KQ 1)

STROKESTOP is the only included trial that was designed and powered to evaluate health outcomes such as stroke. Authors reported a small but statistically significant, difference favoring the screening group in the intention-to-treat analysis using a composite endpoint that included both benefit and harm outcomes, despite uptake of screening by only half of those randomized to the invitation to screening. Although the *as-treated* analysis reported for ischemic strokes and systemic thromboembolism can partially mitigate the bias resulting from poor uptake in the intention-to-treat analysis, the *as-treated* analysis is observational, and those who participated in screening were slightly younger and healthier than those who were invited but did not participate. Extrapolating findings from participants to nonparticipants is challenging because the characteristics that make someone likely to benefit from anticoagulation also increase bleeding risk from anticoagulation. Thus, understanding the benefits and harms across the full spectrum of the population is critical to drawing conclusions about the net benefit of an intervention. We also note that 12 percent of persons randomized in this study had known AF at baseline, limiting the applicability of this study to asymptomatic populations without known AF. Some of the benefit observed may be attributable to engaging persons with already known AF in care. The other two studies reporting health outcomes from screening compared with no screening were not powered for such outcomes; events were rare or absent in these studies, and they cannot contribute meaningfully to our understanding. We also note the potential for reporting bias for this KQ because one of the studies reporting KQ 2 outcomes (IDEAL-MD) had major cardiovascular events and all-cause mortality designated as secondary outcomes, but these have not been reported.[111] For all of these reasons, we assessed the SOE for this KQ as insufficient for establishing the direct benefit of screening asymptomatic persons with known AF.

Diagnostic Yield, Test Accuracy, and Harms of Screening (KQs 2, 3, and 4)

We found that screening with various ECG strategies can identify more cases of AF compared with no screening, but the difference in detection rate varied with method of screening used. Intermittent or continuous tests yielded more cases than one-time testing strategies, likely due to the identification of paroxysmal AF episodes. However, when one-time ECG screening was compared with pulse palpation reminders, no difference in cases identified was observed, though fidelity was quite low in the pulse palpation reminder group in one of the two studies.[105] The studies using pulse palpation reminders included flags in the patient's medical record encouraging providers (physicians and nurses) to conduct pulse palpation. Whether more instances of pulse palpation occurred in the pulse palpation reminder groups beyond usual vital sign measurement and physical exam in usual practice is not known. We rated the evidence for comparative diagnostic yield as consistent but imprecise and assessed the SOE as moderate for increased detection for screening with various ECG strategies compared with no screening. Our certainty is greater for intermittent and continuous screening strategies than for one-time screening approaches.

Critical to the identification of new cases of AF is the accuracy of tests used for screening: interpreting AF rhythms as normal results in false negatives (a reflection of a test's sensitivity) and interpreting normal rhythms as AF results in false positives (a reflection of a test's specificity). We found that the sensitivity and specificity of various one-time screening strategies based on ECG technology or based on oscillometric blood pressure monitoring with automated AF detection features varied in comparison to a reference standard of a 12-lead ECG interpreted by a cardiologist or a reference standard of continuous patch ECG. This variation may be the result of differences in the underlying populations tested, differences in thresholds used for defining positive index or reference tests, or fidelity with which screening was conducted in accordance with device manufacturer instructions. Further, the clinical importance of the variation within and across screening strategies is uncertain. We assessed the SOE as moderate for oscillometric blood pressure with automated AF detection features, six-lead ECG with automated detection features, and GP-interpreted ECGs and as low for single-lead ECG with automated AF detection features. Based on our findings from CQ 1 (**Appendix B**), if we assume the prevalence of undiagnosed AF in the population is 1.3 percent, then among 1,000 persons screened, the number of false-negative tests ranges from zero to nine, the number of false-positive tests ranges from zero to 237, the number of true positives ranges from four to 13, and the number of true negatives ranges from 750 to 987 depending on the strategy used. Given the relatively low prevalence of undiagnosed AF, screening may generate many more false positives relative to true positives and relative to false negatives. Estimates of true positives, true negatives, false positives, and false negatives for lower- and higher-prevalence settings are provided in **Appendix H Table 2**.

Potential harms of screening (KQ 4) include misinterpretation of ECGs leading to false reassurance (i.e., consequences of false-negative results) and false alarms (i.e., consequences of false-positive results) that lead to anxiety, further testing, and possible initiation of unnecessary treatment (e.g., ablation for rhythm control in asymptomatic persons) or known risks of appropriate treatment (i.e., bleeding from anticoagulation). Data from SCREEN-AF and

STROKESTOP suggest no increased risk of serious bleeding events including hemorrhagic stroke, but such events were rare, and estimates were imprecise, precluding a definitive conclusion about bleeding harms from screening.

We identified one RCT that showed anxiety was not significantly different between participants who received ECG screening and those participants whose providers received pulse palpation reminders, but a direct comparison of screened to not screened participants was not reported. Although our review identified evidence to estimate the potential number of screening tests with inaccurate results (i.e., false positives and false negatives), evidence is limited with respect to the consequences of those inaccurate screening results. Whether false reassurance resulting from a false negative is clinically important depends on the benefits of treatment in screen-detected persons with AF. We also lack robust evidence on the consequences of false alarms resulting from false-positive results. False-positive results may result in patient anxiety; further testing; and, in some cases, initiation of unnecessary anticoagulation that confers a risk of major bleeding if positive screening results are not confirmed. A 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 ECGs from 382 patients (35%) had been misinterpreted; physicians did not correct the computerized misinterpretation and initiated inappropriate and potentially harmful treatments, and they pursued unnecessary additional testing for 92 patients (8.5%).[122]

Findings unrelated to the target condition are another potential result of screening. Based on the mSToPS study, the detection of medically actionable non-AF arrythmias was 2.6 percent among those screened with two rounds of 14-day continuous ambulatory ECG monitoring and was between 0 and 3.9 percent in the SCREEN-AF study. Whether these findings required further diagnostic testing, treatment, or both was not reported.[109] Further, whether additional findings unrelated to AF result in benefits or harms is uncertain. Another evidence review for the USPSTF on screening for cardiovascular disease risk with ECG (not limited to use of ECG to screen for AF) found that the frequency of ECG abnormalities on resting 12-lead ECGs ranged from 31 to 55 percent across studies; the studies did not report how often the identified abnormalities resulted in additional testing or treatments.[123] Potential harms could result from, for example, unnecessary stress tests and angiographies initiated to follow up on ECG abnormalities suggestive of ischemia (but determined to be false positives). However, potential benefits could result from appropriate care provided for off-target conditions (e.g., non-AF arrhythmias, ischemia) identified through screening.

Another potential harm of screening is overdiagnosis (i.e., diagnosis of a condition that never would have caused any symptoms or problems), particularly with respect to the identification of brief episodes of paroxysmal AF or subclinical AF. Whether all AF that is identified through screening will benefit from treatment is uncertain. In the mSToPS trial, 60 percent of participants in the screening group had AF detected through the two rounds of 14-day patch monitoring, while the rest had AF diagnosed clinically, either before or after the monitoring episodes. Of those detected by patch monitoring, the longest individual run of AF (defined as 30 seconds or longer) was less than 5 minutes in 7.2 percent and was less than 6 hours in 62 percent of participants. In SCREEN-AF, 87 percent of AF cases in the screening group were detected from screening, and nearly all were paroxysmal AF. The median duration of the longest episode was 5.7 hours, and 15 percent had an episode of AF that lasted 24 hours or longer. Studies reported higher rates of initiation of anticoagulation treatment, antiarrhythmics, and procedures compared

with persons who were not screened, although estimates for some were imprecise and whether similar rates of initiation occurred in screen-detected vs. clinically detected cases is unknown. In overdiagnosed cases, this treatment may be unnecessary and result in harms. The recently published Atrial Fibrillation Detected by Continuous ECG Monitoring Using Implantable Loop Recorder to Prevent Stroke in High-Risk Individuals (LOOP) offers some context for this issue but was not eligible for inclusion in this review because 25 percent of the enrolled population had a prior history of stroke, TIA, or embolism and because this screening approach may not be feasible for primary care settings.[124] In this study, detection of AF in the group randomized to the implantable monitor for 3 years was 31.8 percent and was 12.2 percent in the control group (HR, 3.17 [95% CI, 2.81 to 3.59]). However, no statistically significant differences were observed in stroke or systemic embolism (4.5% vs. 5.6%; HR, 0.80 [95% CI, 0.61 to 1.05]), all-cause death (11.2% vs. 11.3%; HR, 1.00 [95% CI, 0.84 to 1.19]), hemorrhagic stroke (0.8% vs. 0.8%; HR, 0.97 [95% CI, 0.49 to 1.92]), or major bleeding (4.3% vs. 3.5%; HR 1.26 [95% CI, 0.95 to 1.69]).[80] These findings suggest overdiagnosis and highlight the need for more research to understand the benefits and harms of treating screen-detected AF.

Benefits and Harms of Anticoagulation Treatment (KQs 5 and 6)

Among trials enrolling persons with clinical AF, we found consistent evidence that compared with placebo anticoagulation reduces the risk of stroke and all-cause mortality for persons with AF who do not have a history of stroke or TIA (i.e., for primary prevention). For a population with baseline annual stroke risk of 4 percent (e.g., such as those with CHA_2DS_2-VASc scores of 3 to 4), 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 years or older with an annual stroke risk of 4 percent, the results translate to an absolute reduction of approximately 28 ischemic strokes per year and an absolute reduction of 16 deaths per year compared with placebo. A previously published network meta-analysis[106] included in our review also found that DOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) were more effective compared with placebo and not statistically different from VKAs for a composite outcome (any stroke and systemic embolism) or for all-cause mortality. Further, our surveillance of the literature after the search was completed also identified a recent study comparing low-dose edoxaban with placebo among elderly persons with AF that reported findings consistent with the included evidence.[79] We assessed the evidence on benefits of anticoagulation as consistent and precise with moderate SOE that anticoagulation offers benefits. Although we aimed to determine the benefits of treatment for screen-detected older adults with AF without prior history of TIA or stroke, we found no trials or systematic reviews that focused on this population, and it is uncertain whether benefits of anticoagulation for clinical AF can be applied to those who are screen detected.

Based on evidence from KQ 2, screening is likely to detect more cases of AF compared with no screening, and many of those cases are likely to be paroxysmal cases. Screening for AF may also occur unwittingly through wearable or implanted devices. The AHA, the Canadian Cardiovascular Society (CCS), and the European Society of Cardiology (ESC) have commented on subclinical AF (**Appendix B CQ 2**) in scientific statements; however, we note these statements and the studies that informed them are based on persons with implanted cardiac

devices (i.e., defibrillators and pacemakers) who have underlying cardiac conditions. They may not be applicable to primary care practice populations with screen-detected AF or persons with AF detected through wearable monitors. The CCS guidelines recommend that patients with subclinical AF longer than 24 hours with at least one stroke risk factor should receive OAC.[74] Additionally, patients with subclinical AF of shorter duration who are at high risk should also be considered for OAC. In contrast, the AHA statements currently recommend mainly using vascular risk factors (e.g., CHA_2DS_2-VASc score) when deciding to use OAC for stroke prevention in AF.[8, 125] The AHA cited concerns that cutoffs for length of AF episodes in studies were arbitrary and not empirically derived; the effect of brief AF episodes is unknown; the lack of correlation between clinical burden of AF (e.g., symptoms and impact on quality of life) and AF burden as measured by time spent in AF during long-term monitoring, and some studies did not differentiate participants with AF vs. atrial flutter.[8] However, the AHA statements indicate that the duration of AF may be a consideration in the decision to anticoagulate.[8] Although the ESC has recognized that AF burden may influence stroke risk, they conclude that the current evidence is weak and AF burden should not be a major factor in decision making related to stroke prevention treatment.[7] However, they suggest consideration for use in selected patients at high risk when AF diagnosis can be verified and a net clinical benefit is present.[7]

With respect to harms of anticoagulation treatment, the evidence from trials and systematic reviews of trials suggests warfarin and DOACs are associated with a higher risk of major bleeding when compared with placebo; however, these results were imprecise and did not exclude a null effect. However, the one new study identified for this report (GARFIELD-AF cohort of over 26,000 persons) also suggests an association between treatment and bleeding, and its estimate was more precise and excluded a null effect (HR, 1.73 [95% CI, 1.33 to 2.25]). Further, a dose-response effect (persons with higher INRs experience more bleeding) and evidence outside of this review suggesting increased risk of bleeding from anticoagulation for conditions other than AF led us to assess the evidence as having moderate strength that anticoagulation increases the risk of major bleeding compared with placebo.

Limitations of the Evidence

The only study designed and powered to assess the direct benefits of screening (STROKESTOP) had numerous limitations. First, nearly half of those invited to participate in screening declined. Second, the outcomes evaluated were diagnosed through routine clinical care without formal masking and were not based on standard diagnostic criteria with central, blinded adjudication, as is typical for large trials involving vascular outcomes. Third, the trial protocol was amended to specify a composite endpoint combining both benefit and harm events that cannot be interpreted without evaluating the individual outcomes contributing to the composite, all of which were imprecise and not statistically significant. Whether benefit and harm endpoints should be combined into a "net benefit" composite is an area of debate and violates standard assumptions required for the use of composite endpoints.[126-128] Lastly, this study enrolled persons with known AF, many of whom were already taking oral anticoagulants. Although the proportion of overall participants with known AF was relatively low (about 12%), the applicability of findings to asymptomatic persons without known AF is unclear because part of any benefit observed may be attributable to connecting persons with known AF to further care.

The studies of screening other than STROKESTOP that reported on detection of AF excluded persons with known AF; however, some persons with prior stroke or TIA or with unrecognized or unreported symptoms were included. For example, one trial included for KQ 2 (mSToPs) that recruited participants directly from a health plan only enrolled 2,820 participants of the 102,000 that were eligible and invited to enroll; whether persons that were symptomatic at baseline may have enrolled at higher rates compared with those without symptoms is not known. Thus, the applicability of the current evidence is for persons with undetected or undiagnosed AF as studies did not routinely assess for and exclude persons with possible symptoms. Some studies assessing whether one-time screening approaches can identify more cases of AF were conducted 10 to 15 years ago, and changes in technology and overall awareness of the condition may limit the usefulness of their findings. Further, the fidelity of the screening intervention was poor to modest in the studies evaluating one-time approaches to screening.

Trials of warfarin treatment were limited to 1.5 years of followup and estimates of the benefits of longer-term use are not available. We do not have direct evidence for the effectiveness of DOACs compared with no treatment because such trials would not be ethical. Further, treatment trials enrolled participants with clinical, persistent AF, and the applicability of treatment benefits and harms to screen-detected populations, including those with paroxysmal AF and subclinical AF, are not known.

Future Research Needs

The STROKESTOP study was an important contribution to the evidence base related to screening for AF, but limitations prevent drawing definitive conclusions about the benefits and harms of screening on health outcomes solely based on it. Additional randomized trials of asymptomatic persons without known AF comparing screening for AF with no screening that report important health outcomes, such as stroke incidence, acute coronary syndrome, heart failure, all-cause mortality, and major bleeding, are needed to fully evaluate the benefits and harms of screening. Currently, six RCTs (**Appendix H Table 1**) are ongoing that will offer this additional direct evidence. Three studies are evaluating intermittent ECG with a handheld device or continuous ECG; these studies are more likely to detect cases of paroxysmal or subclinical AF compared with the RCTs that are evaluating a one-time ECG test strategy. In addition to providing direct evidence about screening, differences in outcomes across studies using these two different approaches to screening may offer evidence to help quantify overdiagnosis resulting from the identification of subclinical AF and brief episodes of paroxysmal AF.

Research related to new consumer devices marketed for heart rhythm monitoring and their role in screening for AF may also be warranted given their increased marketing to and use by consumers for monitoring overall health and wellness. Such tools increase the opportunity for AF detection, but management based on detection through these tools is not yet defined.[129] The Heartline Study, a collaboration between Johnson & Johnson and Apple, is an example of a virtual, randomized controlled study designed to directly enroll consumers to evaluate the use of iPhone applications and the Apple Watch for the early detection of AF, impact on medication adherence for OACs in persons previously diagnosed with AF, and supporting other analyses to identify and prevent other medical conditions beyond those involving the heart.[130]

The Apple Heart Study, published in 2019, is another example. This study was an uncontrolled, siteless, pragmatic trial sponsored by Apple that used photoplethysmography, an optical sensor-based technology, embedded in the Apple Watch (Series 3 and earlier), synched to an Apple iPhone, with an algorithm to detect possible AF.[131] The study recruited participants age 22 years or older from among persons downloading the Apple Watch application from the Apple App Store, and 67,259 (16%) were age 55 years or older. Participants with previously known AF or who were current users of OACs were excluded. Among participants age 55 years or older, 1,331 (2.0%) received an irregular pulse notification, which based on the study protocol was triggered if at least five of six consecutive tachograms were irregular, generally equivalent to at least an hour or more of an irregular rhythm. However, only 295 (22.2%) of those receiving a notification returned the confirmatory ECG patch monitor. Of those who returned the patch monitor, 110 (37.3%) were confirmed to have AF. Extrapolating the confirmation rate of 37 percent back to all participants age 55 years or older who received an irregular pulse notification suggests 492 cases of previously unknown AF for a prevalence of 0.7 percent. This prevalence is lower than what we calculated in our pooled estimates (CQ 1, **Appendix A**) and may reflect a population with fewer AF risks than a general community or clinic-based population but also a longer threshold of abnormal rhythm for triggering the initial notification. Similar to the Apple Heart Study, the Huawei Heart Study was also designed to investigate general population screening using a smartphone device–based photoplethysmography among persons in China.[132, 133] We note a recently published retrospective analysis of patients who presented for clinical evaluation related to receiving an abnormal pulse detection from their Apple Watch (Series 4 and earlier) at a large health system located across five states over a 5-month period spanning 2018 to 2019. Of the 264 patients presenting for evaluation, 22 percent had preexisting diagnosis of AF and only 33 had self-recorded ECG, a feature only available on the Series 4 model. Of the 264 patients, 33 percent reported experiencing no symptoms. A clinically actionable cardiovascular diagnosis was established in 30 patients (11.4%), of which 13 (4.9%) were AF.

In addition to direct evidence for screening benefits and harms, more research is needed to evaluate the benefit of early treatment. Specifically, more research related to anticoagulation among persons with subclinical AF or brief episodes of paroxysmal AF because the existing evidence regarding treatment benefits and harms is focused on persons with clinical AF that was not screen detected. Two RCTs (**Appendix H Table 1**) are ongoing that are evaluating a DOAC compared with standard of care (aspirin or placebo) among participants with cardiac implantable electronic devices. These trials include exploratory and subgroup analyses that will report on differences in health outcomes (stroke, major bleeding) based on duration and pattern of subclinical AF and atrial high-rate episodes. These analyses may inform our understanding of the benefits and harms of treating screen-detected AF and the threshold of AF burden at which to initiate OAC, although the patient population (persons with implanted cardiac devices) may not be representative of a general primary care population. Two other RCTs (**Appendix H Table 1**) are evaluating DOACs compared with standard-of-care AF treatment among persons with a low or intermediate risk of stroke; one of these (BRAIN-AF) includes neurocognitive decline as an endpoint in addition to stroke, death, and bleeding events.

In addition, more research on the benefits of early rate and/or rhythm control in screen-detected, asymptomatic persons with AF is required. Most guidelines recommend rate and/or rhythm control to manage symptoms. And previous studies of rhythm control did not find better outcomes compared with rate control alone. However, these studies largely included persons

with long-standing AF and relied mostly on antiarrhythmic medication. The recently published EAST-AFNET trial of early rhythm control suggests a potential cardiovascular benefit of this strategy, but with some additional harms from increased serious adverse events related to rhythm control therapy.[58] Unlike previous trials that largely included persons with long standing AF and relied only on medication, this trial included persons with AF without symptoms (30% of enrolled). The median number of days from diagnosis was 36 and a majority of persons had either first episode AF or paroxysmal AF. Further, this trial offered ablation as one of the available interventions and nearly one in five participants assigned to the intervention group received ablation.

Limitations of the Review

This review was limited to studies published in English and conducted in very highly developed countries that we rated as fair or good methodological quality. We only considered screening approaches that were feasible to conduct in primary care settings or referable from primary care settings. Further, we limited our evaluation of health outcomes to stroke, stroke-related mortality, and cardiovascular outcomes. Outcomes related to cognitive decline and dementia, frailty, and noncardiovascular outcomes might be considered in future studies. For this review, we considered non-AF findings and treatment and procedures of false-positive AF results as potential harms (e.g., because procedures have inherent disutility, inconvenience, and costs). We acknowledge that treatment offered for medically actionable non-AF findings may offer benefit for some persons. Such benefits may be captured in studies designed to address the direct benefit of screening (KQ 1). Lastly, we did not evaluate the comparative effectiveness of anticoagulation treatments.

Conclusions

The available direct evidence for health outcomes has numerous limitations, precluding a definitive conclusion about screening benefits and harms. Screening with intermittent or continuous ECG strategies in primary care settings can detect more cases of previously unknown AF compared with no screening, but spot one-time ECG screening may not detect more cases than pulse palpation reminders. In low-prevalence settings, spot one-time screening tests may generate more false-positive than true-positive results. In persons with clinically detected AF, warfarin and DOACs reduce the risk of first stroke and all-cause mortality compared with placebo; the evidence also suggests they increase the risk of major bleeding, although estimates for this harm are imprecise. No trials have assessed the benefits and harms of anticoagulation treatment among screen-detected populations.

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Figure 1. Analytic Framework

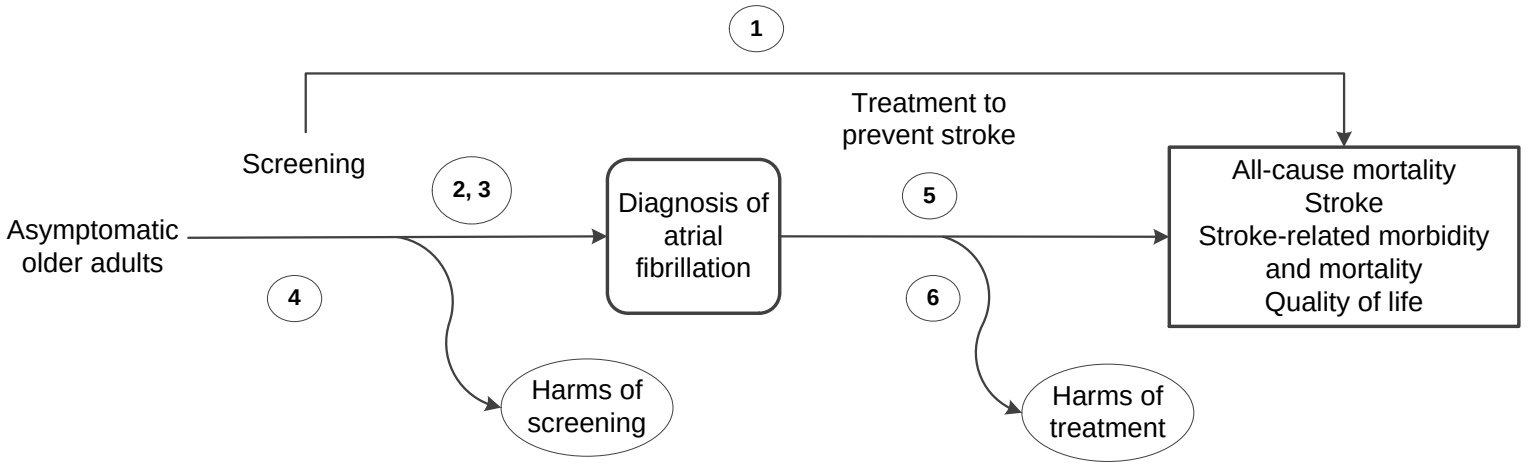
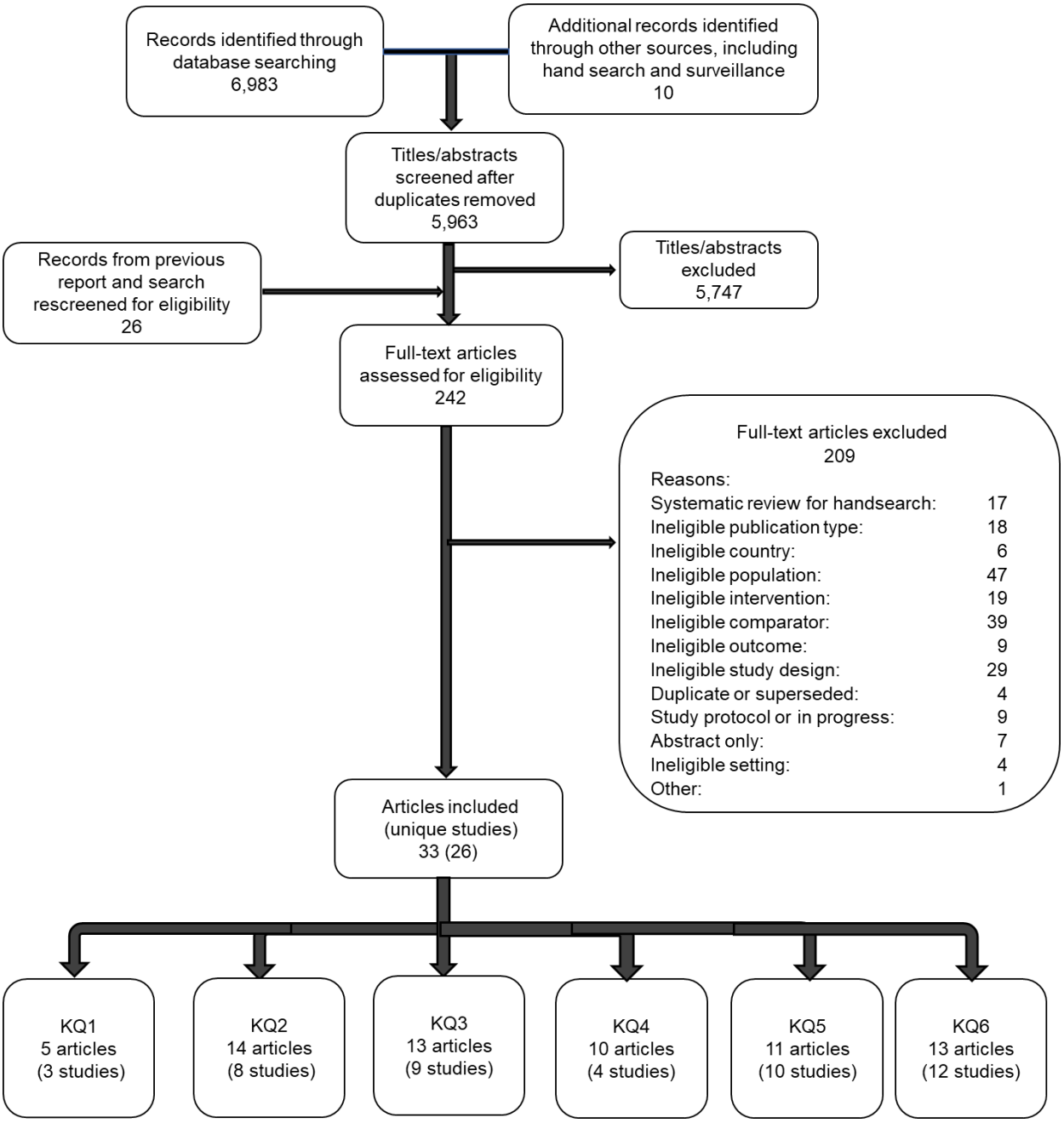


Figure 2. Literature Flow Diagram for Systematic Review of Screening for Atrial Fibrillation



Abbreviation: KQ =key question

Figure 3. Comparative Diagnostic Yield From Randomized, Controlled Trials of Screening for Atrial Fibrillation (KQ 2)

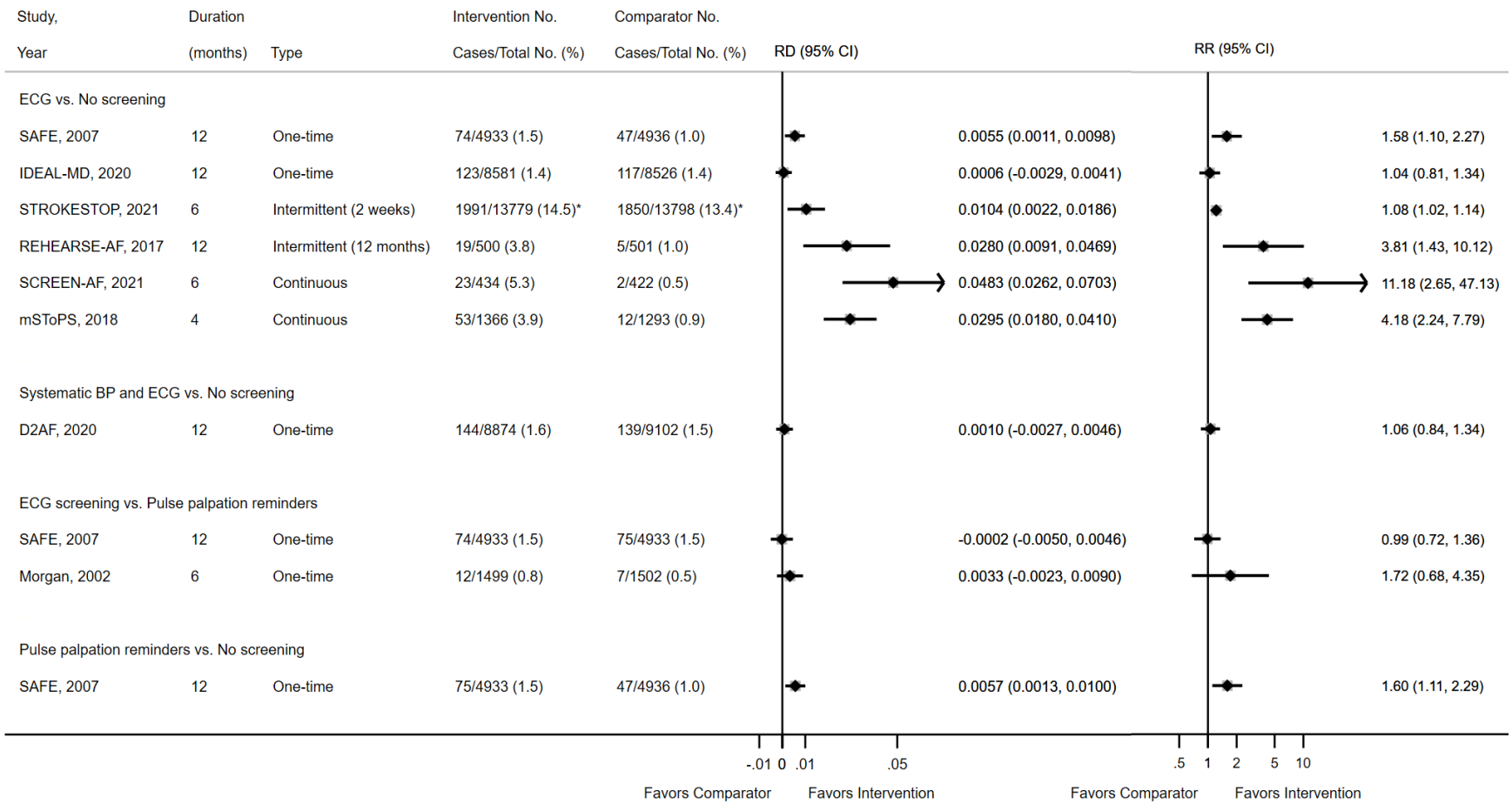


Figure Note: To calculate the ARD in percentage points, multiply value by 100 (e.g., 0.0010 multiplied by 100=0.1 percentage points).

* This study enrolled participants from a population registry without regard to AF status; at baseline, 12.1% of the intervention group and 12.8% of the control group had known AF.

Abbreviations: ARD=absolute risk difference; CI=confidence interval; ECG=electrocardiograph; D2AF=Detecting and Diagnosing Atrial Fibrillation; ECG=electrocardiograph; IDEAL-MD=Improving DEtection of Atrial FibriLlation in Primary Care with the MyDiagnostick; KQ=key question; mSToPS=mHealth Screening to Prevent Strokes; No.=number; RD=risk difference; REHEARSE-AF=REmote HEArt Rhythm Sampling using the AliveCor heart monitor to scrEen for Atrial Fibrillation; RR=risk ratio; SAFE=Screening for Atrial Fibrillation in the Elderly.

Figure 4. Benefits and Harms of Warfarin Compared With Placebo/Control

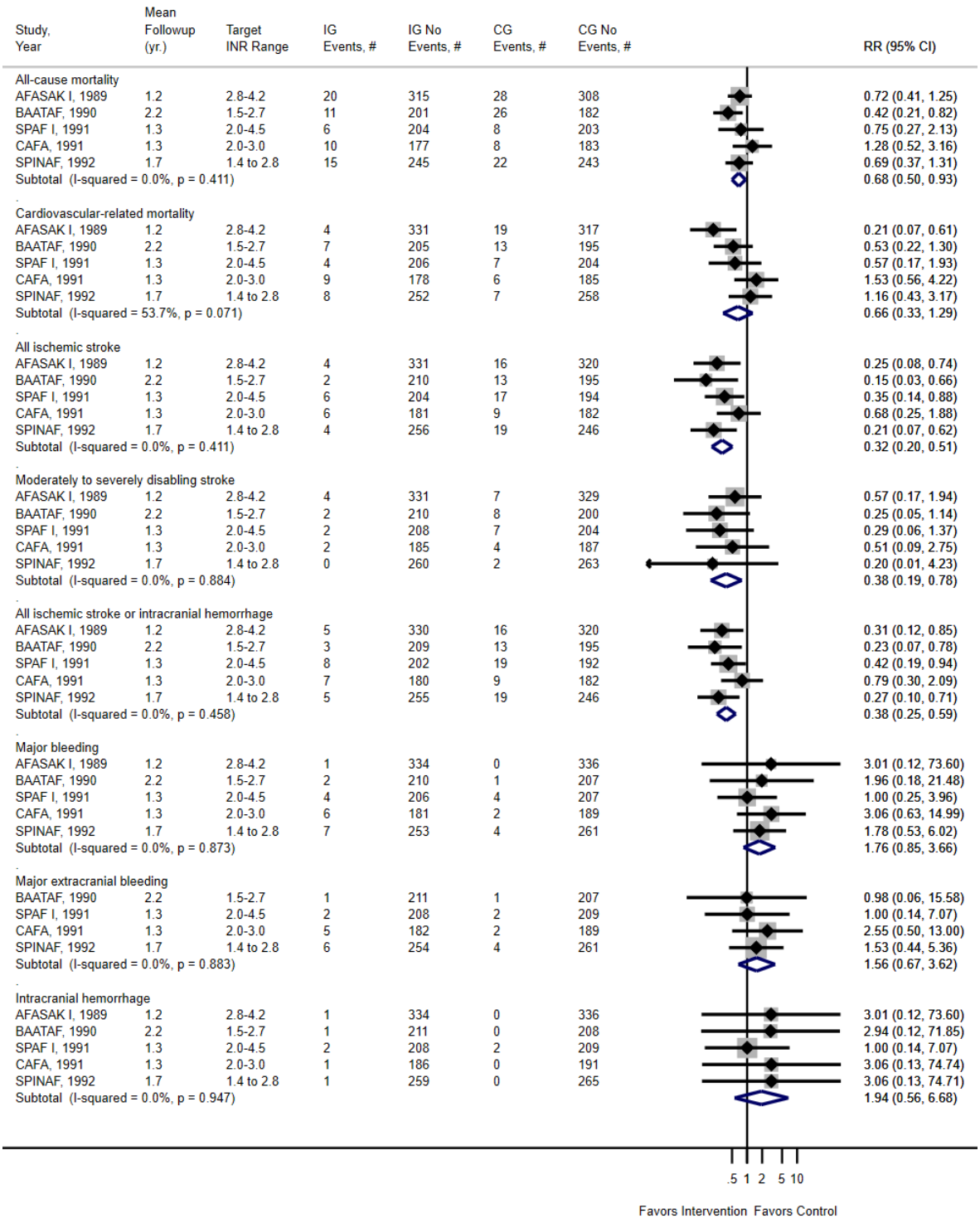


Figure Notes: All-cause mortality: SPINAF includes only those without a history of stroke. AFASAK includes data from a previously published meta-analysis that they obtained data from the original study authors.

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 the 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

Figure 4. Benefits and Harms of Warfarin Compared With Placebo/Control

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=Atrial Fibrillation, ASpirin, and AntiKoagulation; 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 Nonrheumatic Atrial Fibrillation study.

Table 1. Summary of Characteristics of Included Randomized, Controlled Trials of Screening for Atrial Fibrillation (KQ 1 and KQ 2)

Author, Year Trial Name, Registry No.	Study Design	Country	Recruitment Setting	Mean age (SD) in years	N (%) Female	Intervention Groups (N randomized)	Study Duration	Study Quality
Gladstone et al, 2021[75] SCREEN-AF NCT02392754	Parallel-group RCT	Canada and Germany	Primary care clinics	80 (4.0)	487 (57)	No screening, care as usual (422) A single-lead adhesive patch continuous ECG (Zio XT, iRhythm Technologies) worn for 2 weeks at baseline and again at 3 months for a total of 4 weeks; automated home BP monitor with automated AF detection used twice daily during each of the 2-week ECG monitoring periods (434)	6 months	Fair
Halcox et al 2017[108] REHEARSE-AF ISRCTN10709813	Parallel-group RCT	U.K.	General practices (number unknown)	72.6 (5.4)	535 (53)	No screening, care as usual (501) Twice-weekly 30-second, single-lead ECG using a handheld device (AliveCor Heart Monitor), plus additional recordings if symptomatic for 12 months (500)	1 year	Fair
Hobbs et al 2005[91] Fitzmaurice et al, 2007;[93] Fitzmaurice et al, 2014;[92] Mant et al, 2007;[94] Swancutt et al, 2004[95] SAFE ISRCTN19633732	Cluster-group RCT	U.K.	50 primary care practices (25 intervention and 25 control)	75.3 (7.2)	8,500 (57.4)	No screening, care as usual (4,936) Reminder flag was placed in the chart encouraging clinicians to record pulse during routine visits; patients with irregular pulses invited to attend a nurse-led screening clinic and have 12-lead ECG (4,933) Patients invited by letter to attend a nurse-led screening clinic where their radial pulse was palpated, and a 12-lead ECG was performed (4,933)	1 year	Fair
Kaasenbrood et al 2020[111] IDEAL-MD	Cluster-group RCT	The Nether-lands	31 general practices (15 intervention and 16 control)	Intervention: 74.3 (7.3) Control: 74.5 (7.3)	Intervention: 4,680 (54.5) Control: 4,610 (54.1)	No screening, care as usual (8,526) Intervention practices instructed to screen all persons age 65 years without a diagnosis of AF during visits to the practice over the course of the study using a single-lead ECG device, which registers lead one for 1 minute and indicates whether an irregular rhythm is detected. Implementation left to the discretion of practices (8,581).	1 year	Fair
Morgan et al 2002[105]	Parallel-group RCT	U.K.	4 general practices	75.5 (NR)	1,756 (58.8)	Reminder flag was placed in the notes for a 6-month period. Nurses and physicians were encouraged to record pulse during routine visits; if pulse was suspicious for AF, they decided whether to request ECG depending on the history and clinical context (1,502). Patients invited by letter to attend a nurse-led screening clinic where their radial pulse was palpated, and a single lead II rhythm strip was performed (1,499)	6 months	Fair

Table 1. Summary of Characteristics of Included Randomized, Controlled Trials of Screening for Atrial Fibrillation (KQ 1 and KQ 2)

Author, Year Trial Name, Registry No.	Study Design	Country	Recruitment Setting	Mean age (SD) in years	N (%) Female	Intervention Groups (N randomized)	Study Duration	Study Quality
Steinhubl et al 2018[109] mSToPS NCT02506244	Parallel-group RCT	U.S.	Site-less clinical trial involving a large health insurance plan's members Individuals were recruited by email or direct mail.	72.4 (7.3)	1,026 (38.6)	Delayed monitoring using same screening as below but initiated 4 months after enrollment date (1,293) Single-use, 14-day, ambulatory ECG monitoring skin patch. Participants wore an initial patch upon enrollment for 2 weeks and a second patch 3 months later for another 2 weeks (1,366).	4 months	Fair
Svennberg et al 2021[76-78] STROKESTOP NCT01593553	Parallel-group RCT	Sweden	Population registers in two regions	75- and 76-year-olds only	15,273 (54.6)	No invitation to screening (14,381 randomized/13,996 enrolled) Invitation to screening: index ECG at study entry, if NSR then single-lead handheld ECG recorder twice daily for 30 seconds over 14 days (14,387 randomized/13,979 enrolled)	Median 6.9 years	Fair
Uittenbogaart et al, 2020[116] D2AF NL4776	Cluster-group RCT	The Nether-lands	96 primary care practices (47 intervention, 49 control)	Intervention: 75.2 (6.8) Control: 75.0 (6.9)	10,248 (53.4)	No screening, care as usual (9,789) Reminder in chart of 200 eligible patients randomly selected at each practice to conduct pulse palpation, oscillometric blood pressure monitor with AF detection feature, and single-lead handheld ECG with optional Holter monitoring if all three index tests were negative (9,400)	1 year	Fair

Abbreviations: AF=atrial fibrillation; BP=blood pressure; D2AF=Detecting and Diagnosing Atrial Fibrillation; ECG=electrocardiograph; IDEAL-MD=Improving DEtection of Atrial fibriLlation in Primary Care With the MyDiagnostick; KQ=key question; mSToPS=mHealth Screening to Prevent Strokes; N=number of participants; NR=not reported; NSR=normal sinus rhythm; RCT=randomized, controlled trial; REHEARSE-AF=REmote HEArt Rhythm Sampling using the AliveCor heart monitor to scrEen for Atrial Fibrillation; SAFE=Screening for Atrial Fibrillation in the Elderly; SD=standard deviation; U.K.=United Kingdom; U.S.=United States.

Table 2. Summary of Characteristics of Included Test Accuracy Studies (KQ 3)

Author, Year Trial Name Registry No.	Recruitment Setting (Total N)	Inclusion Criteria	Mean age (SD)	N (%) Female	Index Test(s) Description	Reference Test(s) Description	Study Quality
Gladstone et al, 2021[75] SCREEN-AF NCT02392754	Primary care clinics in Canada and Germany (399)	Age ≥75 years who are not receiving OAC with a history of HTN, in sinus rhythm	79.8 (3.8)	255 (58.8)	Oscillometric BP monitor (Micfolife WatchBP-Home A) with automated AF detection used twice daily during each of the 2-week ECG monitoring periods. Test is considered positive if at least 2 of the 3 readings are positive for AF.	Single-lead adhesive patch continuous ECG; worn at baseline for 2 weeks and again at 3 months for a total of 4 weeks. AF defined as ≥1 episode of continuous AF or atrial flutter lasting more than 5 minutes on cECG or by a single 12-lead ECG	Good
Himmelreich et al, 2019[112]	10 general practices in the Netherlands (106)	Age ≥18 years with 12-lead ECG ordered by their primary care physician for nonacute indications	69.3 (10.7)	62 (58)	Single lead, handheld ECG (KardiaMobile) smartphone-connected device with automated AF detection during an office visit for 30s*	12-lead-ECG independently interpreted by two cardiologists, disagreements resolved by a third cardiologist	Good
Hobbs et al, 2005[91] SAFE ISRCTN-19633732	25 general practices in the U.K. (1,452)	Age ≥ 65 years	75.3 (7.2)†	8,500 (57.4)	1) GP interpreted 12-lead ECG 2) GP interpreted limb-lead II ECG 3) GP interpreted thoracic-lead ECG	12-lead ECG independently interpreted by 2 cardiologists	Good
Kearley et al, 2014[113]	6 general practices in the U.K.(999)	Age ≥75 years	79.7 (NR)	507‡ (50.7)‡	1) Modified oscillometric BP monitor (Microlife WatchBP); device flashes for irregular pulse during automatic BP measurement during an in-office visit§ 2) Single-lead ECG with autoanalysis function (OMRON model HCG-801) for unspecified duration during an office visit; in addition to the ECG recording, generates a text indicating the presence of possible AF‖	12-lead ECG interpreted by 2 cardiologists, with disagreements resolved by a third cardiologist	Fair
Marazzi et al, 2012[115]	Hypertension clinic in Italy (383)	None specified	67 (10.5)	230 (46)	1) Osciillometric BP monitor (Microlife BP A200 Plus) with automated AF detection based on 3 sequential BP measurements administered during an office visit 2) Oscillometric BP monitor (OMRON M6) with automated AF detection during an office visit	12-lead ECG interpreted by cardiologist	Good

Table 2. Summary of Characteristics of Included Test Accuracy Studies (KQ 3)

Author, Year Trial Name Registry No.	Recruitment Setting (Total N)	Inclusion Criteria	Mean age (SD)	N (%) Female	Index Test(s) Description	Reference Test(s) Description	Study Quality
Philippsen et al, 2017[56] NCT02041832	Hospital-based diabetes and cardiology outpatient clinics in Denmark (82)	Age ≥65 years receiving treatment for diabetes mellitus and hypertension, with stable medications for at least 1 month	71 (4)	30‡ (37)‡	2-channel, 72-hour Holter monitoring analyzed by trained staff and adjudicated by 2 cardiologists. AF defined as ≥1 episode of irregular rhythm without P waves lasting at least 30 seconds	Continuous ECG monitoring with an insertable cardiac monitor over median of 588 days interpreted by 2 electrophysiologists. AF defined as at least 1 episode of irregular rhythm without P waves lasting at least 2 minutes.	Good
Sabar et al, 2019[117] NCT02401451	Outpatient hospital cardiology clinic (632)	Age ≥18 years attending the outpatient cardiology department for routine 12-lead ECGs or other appointments	66 (range 18-97)	384 (51)	6-lead ECG (RhythmPad, Cardiocity) automated diagnostic report produced using a custom detection algorithm after a single 10-second screening	Single 10-second, 12-lead ECG screening (GE MAC550 machine, Chicago, IL) interpreted by two blinded cardiologists	Fair
Uittenbogaart et al, 2020[116] NL4776	96 primary care practices in the Netherlands (742)	Age ≥65 years	75†	NR (53.4†)	Combined approach that included pulse palpation, oscillometric blood pressure monitor with automated AF detection (WatchBP Home A, Microlife) and single lead handheld ECG (MyDiagnostick)	12-lead ECG interpreted by cardiologists (only 10% random sample of index test negative participants received reference test)	Fair
Wiesel et al, 2014[114]	Two outpatient cardiology clinics in the U.S. (148)	Age ≥50 years	74 (NR)	75‡ (41)‡	1) Oscillometric blood pressure monitor (OMRON M6 Comfort) with automated irregular rhythm detection feature during an office visit 2) Oscillometric blood pressure monitor (Microlife BP A 200) with automated AF detection based on 3 sequential BP measurements during an office visit. ¶	12-lead ECG interpreted by a cardiologist	Fair

* Rhythms classified by algorithm as AF, normal, unreadable, or no classification. For this analysis, screening was considered positive for any "possible AF" tracings and was considered negative for all other tracings. The AF classification refers to both atrial fibrillation and atrial flutter.
† For entire study population, not all study participants from the trial were included in the KQ 3 analyses.
‡ Calculated value.
§ Inconclusive results treated as "positive."
‖ "analysis impossible" text messages were counted as positive tests. Inconclusive results treated as "positive."
¶ Test is considered positive if at least 2 of the 3 readings are positive for AF.

Abbreviations: AF=atrial fibrillation; BP=blood pressure; ECG=electrocardiograph; GP=general practitioner; ISRCTN=International Standard Randomised Controlled Trial Number; KQ=key question; NCT=National Clinical Trial Number; N=number; NL=Netherlands Trial Registry; NR=not reported; SAFE=Screening for Atrial Fibrillation in the Elderly; SD=standard deviation; U.K.=United Kingdom; U.S.=United States.

Table 3. Results of Included Test Accuracy Studies (KQ 3)

Study	Sensitivity (95% CI)	Specificity (95% CI)	Per 1,000 tests (1.3% prevalence of AF)	
			No. of false negatives	No. of false positives
Oscillometric BP monitor with automated AF detection vs. 12-lead ECG interpreted by cardiology				
Kearley et al, 2014[113] (Microlife Watch BP Home A device)	0.95 (0.88 to 0.99)	0.90 (0.88 to 0.92)	1	99
Marazzi et al, 2012[115] (Microlife BP A200 device)	0.92 (NR)	Calculated: 0.95 Study reported: 0.97(NR)	1	49
Marazzi et al, 2012[115] (OMRON M6 device)	1.0 (NR)	0.94 (NR)	0	59
Wiesel et al, 2014[114] (Microlife BP A200 device)	1.0 (0.86 to 1.0)*	0.92 (0.86 to 0.96)	0	79
Wiesel et al, 2014[114] (OMRON M6 device)	0.30 (0.15 to 0.49)*	0.97 (0.93 to 0.99)	9	30
Oscillometric BP monitor with automated AF detection vs. continuous ECG monitoring				
SCREEN-AF, 2021[75] (Microlife Watch BP Home A device)	0.35 (0.15 to 0.59)	0.81 (0.77 to 0.85)	9	188
Single-lead ECG with automated AF detection vs. 12-lead ECG interpreted by cardiology				
Himmelreich et al, 2019[112] (KardiaMobile device)	0.88 (0.47 to 1.0)	1.0 (0.96 to 1.0)	2	0
Kearley et al, 2014[113] (OMRON device)	0.99 (0.93 to 1.0)	0.76 (0.73 to 0.79)	<1	237
Six-lead ECG with automated AF detection vs. 12-lead ECG interpreted by cardiology				
Sabar et al, 2019[117] (RhythmPad 6-lead ECG)	0.95 (NR)	0.99 (NR)	1	10
GP-interpreted ECG vs. 12-lead ECG-interpreted by cardiology				
SAFE, 2005[91] (12-lead)	0.80 (0.71 to 0.87)	0.92 (0.90 to 0.93)	3	79
SAFE, 2005[91] (Single limb lead)	0.83 (0.75 to 0.88)	0.88 (0.87 to 0.90)	2	118
SAFE, 2005[91] (Single thoracic lead)	0.85 (0.79 to 0.91)	0.86 (0.84 to 0.88)	2	138
Combined pulse palpation, oscillometric BP and single lead ECG both with automated AF detection vs. 12-lead ECG interpreted by cardiology				
D2AF, 2020[116] (MyDiagnostick device and MIcrolife Watch BP Home A device)	Cannot determine†	Cannot determine†	Cannot determine†	Cannot determine†
72-hour continuous Holter monitoring vs. continuous ECG monitoring with insertable cardiac monitor over median 588 days‡				
Philippsen et al, 2017[56]	Calculated: 0.12	Calculated: 1	NA	NA

* The author of this study disclosed holding a patent for the AF detection algorithm present in the Microlife BP device; we note that the sensitivity of the OMRON oscillometric device was markedly lower in this study when compared with the estimate for Microlife, and when compared with the OMRON device reported in the study by Marazzi et al.[115]

Table 3. Results of Included Test Accuracy Studies (KQ 3)

† The study only performed a 12-lead referent test on a random sample of participants who tested negative on the index screening test; thus data to determine sensitivity and specificity was not available. However, based on data reported, we calculated the positive predictive value to be 6% and the negative predictive value to be 100%; suggesting a test with very high sensitivity, but poor specificity.
ǂ Holter monitoring occurred approximately 1 month after ICM placement. When limited to the same 72-hour monitoring window, sensitivity was 1.0.

Abbreviations: AF=atrial fibrillation; BP=blood pressure; CI=confidence interval; D2AF= Detecting and Diagnosing Atrial Fibrillation; ECG=electrocardiograph; ICM=insertable cardiac monitor; KQ=key question; SAFE=Screening for Atrial Fibrillation in the Elderly.

Table 4. Characteristics of Included Randomized, Controlled Trials for KQ 5 and KQ 6: Part 1

First Author, Year Trial Name	G1 (N) G2 (N) G3 (N)	Source of Patients	Country	Mean Followup, yr	Mean Age	% Female	% Non-White	Study Quality
Petersen et al, 1989[102] 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 (median)	46	NR	Fair
The Boston Area Trial for Atrial Fibrillation Investigators, 1990[100] BAATAF	Warfarin, adjusted dose (212) Control* (208)	32 centers and 3 private medical offices	U.S.	2.2	68	28	NR	Fair
Stroke Prevention in Atrial Fibrillation Investigators, 1990 & 1991[98, 101] SPAF I	Warfarin, adjusted dose (210) Aspirin 325 mg/day (206) Placebo (211)	15 centers	U.S.	1.3	67	29	16	Fair
Connolly et al, 1991[99] CAFA	Warfarin, dose adjusted per subject (187) Placebo (191)	11 centers (hospitals, outpatient laboratories, and direct clinician referrals)	Canada	1.3	68	25	NR	Fair
Ezekowitz et al, 1992[97] SPINAF	Warfarin, adjusted dose (4-mg/day and adjusted to meet PT ratios) (260) Placebo (265)†	16 Department of Veterans Affairs medical centers	U.S.	1.7	67	0	NR	Fair

* Control group was allowed to take aspirin.

† 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=Atrial Fibrillation, ASpirin, and AntiKoagulation; BAATAF=Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA=Canadian Atrial Fibrillation Anticoagulation study; ECG=electrocardiograph; G=group; KQ=key question; N=sample size; NR=not reported; SPAF=Stroke Prevention in Atrial Fibrillation Study; SPINAF=Stroke Prevention in Nonrheumatic Atrial Fibrillation study; U.S.=United States.

Table 5. Characteristics of Included Randomized, Controlled Trials for KQ 5 and KQ 6: Part 2

First Author, Year Trial Name	% TIA % Stroke	% Heart Failure % Heart Valve Disease % Coronary Artery Disease % Hypertension % Diabetes Mellitus	Target INR (PT)	% Time in Therapeutic Range
Petersen et al, 1989[102] AFASAK	2 4	52 NR 8 prior myocardial infarction 32 12	2.8 to 4.2 (NR)	73
The Boston Area Trial for Atrial Fibrillation Investigators, 1990[100] BAATAF	NR 3	26 23 mitral regurgitation >1+ 52 51 15	1.5 to 2.7 (1.2 to 1.5)	83
Stroke Prevention in Atrial Fibrillation Investigators, 1990 & 1991[98, 101] SPAF I	7 stroke or TIA	19 6 mitral valve prolapse 8 prior myocardial infarction 52 16	2 to 4.5 (1.3 to 1.8)	71 within target prothrombin time
Connolly et al, 1991[99] CAFA	4 stroke or TIA	22 NR 13 prior myocardial infarction 39 12	2 to 3 (NR)	44
Ezekowitz et al, 1992[97] SPINAF	NR 8	30 15 mitral regurgitation>1+ 19 prior myocardial infarction 58 18	1.4 to 2.8 (1.2 to 1.5)	56

Abbreviations: AFASAK=Atrial Fibrillation, ASpirin, and AntiKoagulation; BAATAF=Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA=Canadian Atrial Fibrillation Anticoagulation study; INR=international normalized ratio; NR=not reported; PT=prothrombin time; SPAF=Stroke Prevention in Atrial Fibrillation Study; SPINAF=Stroke Prevention in Nonrheumatic Atrial Fibrillation study; TIA=transient ischemic attack.

Table 6. Summary of Evidence, Screening for Atrial Fibrillation

Key Question	No. of Studies Study Designs (No. of Participants)	Summary of Findings	Consistency and Precision	Limitations	Strength of Evidence	Applicability
KQ 1 Benefits of screening	1 RCT (27,975)[76-78] Designed and to address KQ 1 2 RCTs (1,857)[75, 108] Not designed to address KQ 1 but reported some health outcomes	***Intermittent screening ECG twice daily for 2 weeks compared with no screening (1 RCT)***[76-78] Composite benefit/harm endpoint:* Events/100 person-years 5.45 (5.29 to 5.61) vs. 5.68 (5.52 to 5.85); HR 0.96 (95% CI, 0.92 to 1.00; P=0.045); Secondary outcomes HR (95% CI) • Ischemic stroke: 0.92 (0.83 to 1.01) • All-cause mortality: 0.96 (0.92 to 1.01) • Systemic embolism: 1.10 (0.76 to 1.59) • Ischemic stroke or systemic embolism: 0.92 (0.84 to 1.02) as randomized; 0.76 (0.67 to 0.85), as treated† ***Intermittent screening ECG twice weekly for 12 months compared with no screening (1 RCT)***[108] Composite of stroke, TIA, or systemic embolism: 6 (screened) vs. 10 (not screened) events; HR, 0.61; 95% CI, 0.22 to 1.69 ***Continuous ECG for 2 weeks, twice (total 4 weeks) compared with no screening (1 RCT)***[75] 1 death (no screening), 2 ischemic strokes (screening), 1 TIA (screening), 0 systemic embolism	Consistent; imprecise‡	Fair quality studies; in largest trial ~12% had known AF at baseline and only 51.3% of pesons randomized to screening participated, with no formal outcome assessment masking or central adjudication, primary outcome changed to a composite endpoint that included both benefit and harm outcomes; the other two trials were designed for KQ2 and not powered for health outcomes were not masked and had some measurement bias; reporting bias detected (one of the KQ2 studies was also designed to report KQ1 outcomes per trial registry entry but no results published)	Insufficient for addressing question of direct benefits of screening in persons without known AF	Adults with mean age in 70s and 80s with stroke risks in range recommended for anticoagulation if no contraindication; unclear applicability to screening in persons in primary care practice settings given population recruitment in only trial powered for health outcomes with clear differences between participants and nonparticipants that make predicting the bias from poor fidelity challenging

Table 6. Summary of Evidence, Screening for Atrial Fibrillation

Key Question	No. of Studies Study Designs (No. of Participants)	Summary of Findings	Consistency and Precision	Limitations	Strength of Evidence	Applicability
KQ 2 Identifying new cases of AF	7 RCTs (74,386)[75-78, 91-95, 108, 109, 111, 116]	***Various ECG screening compared with no screening:*** One-time (3 RCTs): ARDs 0.06% to 0.6% Intermittent (2 RCTs): ARDs 1.0% and 2.8% Continuous (2 RCTs): ARDs 3.0% and 4.8%	Consistent,[§] imprecise[‖]	Fair quality, study inclusion/exclusion criteria focused on persons without known AF but most did not routinely assess for potential symptoms at study entry; fidelity low to modest in intervention arms	Moderate for increased detection, with higher detection seen with intermittent and continuous approaches	Applicable to older adults[¶] without known AF for various screening modalities (one-time ECG, intermittent ECG, continuous patch ECG, pulse palpation combined with one-time ECG and oscillometric BP with AF detection)
	2 RCTs (12,867)[91-95, 105]	***ECG screening vs. pulse palpation reminders*:** ARD -0.02% in 1 trial and 0.3% in other trial (not statistically significant in either)	Consistent, imprecise	Fair quality; fidelity of pulse assessment was 29% in one trial and 69% in the other trial; fidelity of ECG screening was 73% in one trial and 53% in the other trial	Low for no difference in detection	Applicable to one-time ECG screening only, reminders in either paper charts or electronic records
	1 RCT (9,869)[91-95]	***Pulse palpation reminders vs. no screening**:* ARD 0.6% (95% CI, 0.1% to 1.0%)	Single study, consistency unknown, precise	Fair quality; fidelity of pulse palpation in response to reminders was 69%	Low for increased detection	Older adults, reminders in either paper charts or electronic records
KQ 3 Accuracy of screening tests[#]	7 studies (4,544)[56, 91, 112-117]	Various screening strategies compared with 12-lead ECG interpreted by cardiologist Sensitivity range: 0.80 to 1.0** Specificity range: 0.76 to 1.0.	Consistent** precise	Four studies were fair quality due to concerns about applicability and selection bias related to method of enrollment in two studies, and lack of masking of index and reference test results in other study and reference standard in one study; most studies used one-time reference standards that may underestimate the prevalence of paroxysmal AF	Moderate to low depending on screening approach[††]	Applicable to adults and for the following screening modalities: 6-lead ECG, GP-interpreted ECG (12-lead or less than 12-lead), oscillometric BP monitor with automatic AF detection, single-lead ECG with automatic AF detection
	1 study (399)[75]	Oscillometric BP monitor with AF detection feature compared with continuous ECG (4 weeks) Sensitivity 0.35, specificity 0.81				

Table 6. Summary of Evidence, Screening for Atrial Fibrillation

Key Question	No. of Studies Study Designs (No. of Participants)	Summary of Findings	Consistency and Precision	Limitations	Strength of Evidence	Applicability
KQ 4 Harms of screening	4 RCTs (43,633‡‡)[75-78, 91-95, 109] 1 cohort (5,214)§§	***Anxiety (1 RCT):*** Mean scores not significantly different for invitation to ECG screening compared with pulse palpation reminders	Consistent; imprecise	Fair quality; anxiety scores not reported for comparison of invitation to ECG screening vs. no screening	Insufficient for anxiety	Applicable to older adults for the following screening modalities: GP-interpreted ECG (anxiety), continuous ECG monitoring patch (non-AF arrythmias, initiation of OACs and procedures, and skin irritation), intermittent ECG (initiation of OACs and procedures, bleeding outcomes)
		Bleeding outcomes (2 RCTs) • 0 intracranial hemorrhages or major bleeding events after 6 months in the smaller of the RCTs • In larger RCT after a median followup of 6.9 years, hemorrhagic stroke HR 0.88 (95% CI, 0.70 to 1.11) and hospitalization for major bleeding HR 0.98 (95% CI, 0.91 to 1.06)	Consistency unknown; imprecise	Fair quality; no centralized outcome adjudication, studies underpowered for rare events	Insufficient for bleeding outcomes	
		Non-AF arrhythmias (1 RCT and 1 cohort): detected in 2.6% of participants who received screening in cohort study and between 0 and 3.9% in the RCT depending on the type of arrhythmia; arrythmias were considered clinically actionable in both studies.	Consistent; precise	Fair quality; no masking	Moderate for increased detection, clinical consequences unknown¶¶	
		Initiation of anticoagulation, antiarrhythmics, and procedures (2 RCTs and 1 cohort):‖‖ generally higher among participants who received screening compared with controls who did not get screened but only statistically significant for higher OAC use in 2 of the 3 studies.	Consistent; imprecise	Fair quality, no masking	Low for increased initiation, clinical consequences unknown¶¶	
		Skin irritation from patch (2 RCTs): 1.2% (95% CI, 0.5% to 2.7%) to 1.5% (95% CI, 1.1% to 2.0%) of participants	Consistent, precise	Fair quality; no masking, methods of ascertainment of skin irritation not reported	Moderate for increased skin irritation	

Table 6. Summary of Evidence, Screening for Atrial Fibrillation

Key Question	No. of Studies Study Designs (No. of Participants)	Summary of Findings	Consistency and Precision	Limitations	Strength of Evidence	Applicability
KQ 5: Benefits of anti-coagulation treatment	5 RCTs (2,415)[97-102] 5 SRs[59, 96, 104, 106, 107]	***Warfarin (mean 1.5 years) vs. placebo/control:*** Reduced all-cause mortality: pooled RR, 0.68; 95% CI, 0.50 to 0.93 Reduced ischemic stroke: pooled RR, 0.32; 95% CI, 0.20 to 0.51 ***Previously published SRs:*** Similar findings reported for warfarin compared with placebo. In a network meta-analysis, 4 DOACs[##] were also more effective than placebo/control (adjusted ORs from 0.32 to 0.44).	Consistent, precise	All warfarin trials were fair quality and stopped early; 3 of the 5 trials were open label; 4 of the 5 trials had inadequate or unclear methods of allocation concealment. Reporting bias not detected. Limitations of the network meta-analysis 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 for benefit	Adults with AF and no history of stroke or TIA; uncertain whether the results are applicable to asymptomatic screen-detected persons with AF Most participants had AF for more than a year and few had paroxysmal AF; estimates for lifelong treatment not available
KQ 6: Harms of anti-coagulation treatment	5 RCTs (2,415)[97-102] 6 SRs[59, 96, 103, 104, 106, 107] 1 prospective cohort study (26,628)[110]	***Warfarin (mean 1.5 years) vs. placebo/control*:** Major bleeding: pooled RR, 1.8; 95% CI, 0.85 to 3.7 Intracranial hemorrhage: pooled RR, 1.9; 95% CI, 0.56 to 6.7 ***Previously published SRs:*** Similar findings reported for warfarin compared with placebo. In a network meta-analysis, the adjusted ORs for major bleeding comparing 4 DOACs[##] with	Consistent, imprecise[†††]	All warfarin trials were fair quality and stopped early; 3 of the 5 trials were open label; 4 of the 5 trials had inadequate or unclear methods of allocation concealment; reporting bias not detected.	Moderate for harm[‡‡‡]	Adults with AF and no history of stroke or TIA

Table 6. Summary of Evidence, Screening for Atrial Fibrillation

Key Question	No. of Studies Study Designs (No. of Participants)	Summary of Findings	Consistency and Precision	Limitations	Strength of Evidence	Applicability
		placebo/controls ranged from 1.38 to 2.21; CIs were wide and included the null.*** ***Anticoagulation compared with no antiocagulation over 2 years in cohort study:*** first bleeding event adjusted HR, 1.73 [95% CI, 1.33 to 2.25]		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.		

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

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

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

§ We rated as consistent because of consistency in detection based on duration and intensity of screening strategy.

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

¶ Subgroup findings from one of the studies (SAFE trial)[91] suggested that screening may not increase detection among females; no subgroup findings were reported by the other four studies, all of which included females; thus, this finding is uncertain.

We did not include the Phillippsen et al study when considering SOE; this study compared a 72-hour Holter monitor to an insertable cardiac monitor that was left in place for a median of 588 days; the Holter monitor was placed approximately 1 month after the insertable monitor was placed, and it is uncertain whether AF events occurring after Holter monitoring period were prevalent cases or new onset.

** Consistent for oscillometric BP with automated AF detection algorithm with exception of one study[114] for which sensitivity was reported as 0.30 for one brand of oscillometric monitor and for which study author disclosed conflict of interest. The evidence for single-lead ECG was less consistent, resulting in a low SOE for that strategy.

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

Table 6. Summary of Evidence, Screening for Atrial Fibrillation

‡‡ The number of participants included a subset of 1,940 of the 14,802 participants who were in the SAFE study, although study reporting relating to anxiety outcomes was unclear.
§§ Includes 1,738 participants who were also part of the mSToPS RCT (immediate and delayed monitoring groups combined).[109]
‖‖ Findings were only statistically significantly higher in the cohort study, except for use of OACs, which was also significantly higher in the RCT (RR 4.4 [95% CI, 1.5 to 12.8]).
¶¶ The detection of clinically actionable non-AF arrythmias could be considered a benefit if it results in treatment or intervention that prevents an untoward outcome. However, it could be a harm if additional treatment or procedures (and related side effects or adverse events) were provided for an arrythmia that might never have caused symptoms or issues. Similarly, the initiation of treatments or subsequent procedures could be considered a benefit or harm depending on the health consequences of such actions.
The four direct oral coagulants (DOACs) are apixaban, dabigatran, edoxaban, and rivaroxaban.
*** The network meta-analysis also found no statistically significant differences for the four DOACs in comparison to one another. Compared with VKAs, three of the DOACs (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 to 1.57).
††† Given the event rate in control group (~1%), a properly powered trial to detect a 60 percent increase in major bleeding (RR, 1.6) would require 11,838 participants (two-tailed alpha=.05, power= 0.8).
Although findings were imprecise and quality was fair, we graded the SOE as moderate considering evidence on dose response (with higher INRs increasing bleeding risk) and evidence on treatment of conditions other than AF that shows consistent evidence of bleeding risk.

Abbreviations: AF=atrial fibrillation; BP=blood pressure; CHA_2DS_2=Congestive heart failure, Hypertension, Age >=75 years, Diabetes mellitus, Prior stroke or TIA or thromboembolism; CI=confidence interval; DOAC=direct oral anticoagulant; ECG=electrocardiogram; GP=general practitioner; HR=hazard ratio; KQ=key question; mSToPS=mHealth Screening to Prevent Strokes; NA=not applicable; No.=number; OAC=oral anticoagulant; OIS=optimal information size; OR=odds ratio; RCT=randomized, controlled trial; RD=risk difference; RR=risk ratio; SAFE=Screening for Atrial Fibrillation in the Elderly; SOE=strength of evidence; SR=systematic review; TIA=transient ischemic attack; VKA=vitamin K antagonist; vs.=versus.

Appendix A Table 1. Prevalence of AF by Age and Sex in the ATRIA Study[26]

Prevalence

Based on data from the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study of 1.89 million adult California health plan members, in the 1990s the prevalence of diagnosed AF among the general population was 0.95 percent and was shown to increase dramatically with age (**Appendix A Table 1**).[26]

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

Abbreviations: AF=atrial fibrillation; ATRIA=Anticoagulation and Risk Factors in Atrial Fibrillation.

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

	Stroke Risk Tool				
	CHA_2DS_2-VASc[134,*]	$CHADS_2$[135]	R_2CHADS_2[136]	QStroke[137]	ATRIA[138,†]
Risk Factor Category	**Scoring/Points**				
Congestive Heart Failure	1 (or LV dysfunction)	1 (recent)	1 (recent)	Y/N	1
Hypertension	1	1 (history of)	1 (history of)	Continuous (SBP)	1
Age (years)	1 (65-74) 2 (75+)	1 (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)	

*Addition of African American ethnicity to the CHA_2DS_2-VASc score (CHA_2DS_2-VASc-R) statistically significantly improves stroke prediction in AF patients >65 years of age by a small amount (HR, 1.24 vs. 1.25; C-statistic 0.60 vs. 0.61). NRI 7.6 percent ($p<0.001$)."

†Scored for age categories with/without prior stroke.

Abbreviations: AF=atrial fibrillation; 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; HR=hazard ratio; LV=left ventricular; M/F=male/female; MI=myocardial infarction; NRI=Net Reclassification Improvement; PAD=peripheral artery disease; QStroke=risk prediction algorithm; 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.

Adapted from: Dzeshka, M. S., Lane, D. A., & Lip, G. Y. (2014). Stroke and bleeding risk in atrial fibrillation: navigating the alphabet soup of risk-score acronyms ($CHADS_2$, CHA_2DS_2-VASC, R_2CHADS_2, HAS-BLED, ATRIA, and more). *Clin Cardiol*, 37(10), 634-644. doi: 10.1002/clc.22294

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

	Bleeding Risk Tool		
	HAS-BLED[139]	**HEMORR$_2$HAGES[140]**	**ATRIA[141]**
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., antiplatelet or NSAIDs)	1		

Abbreviations: ATRIA=AnTicoagulation and Risk Factors in Atrial Fibrillation; CYP$_2$C9 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; HEMORR2HAGES=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=nonsteroidal anti-inflammatory drug; SNP=single nucleotide polymorphisms.

Adapted from: Dzeshka, M. S., Lane, D. A., & Lip, G. Y. (2014). Stroke and bleeding risk in atrial fibrillation: navigating the alphabet soup of risk-score acronyms (CHADS$_2$, CHA$_2$DS$_2$-VASC, R$_2$CHADS$_2$, HAS-BLED, ATRIA, and more). *Clin Cardiol*, 37(10), 634-644. doi: 10.1002/clc.22294

Appendix A Table 4. Recent Recommendations (2013 or Newer) on Primary Prevention of Stroke (Including Screening and/or Treatment) in Patients With Atrial Fibrillation

Society or Professional Organization, Year Scope	Screening	Anticoagulation*	Antiplatelet*
ESC/EACTS/EHRA, 2020[7] Management of AF	Age ≥65 years, opportunistic screening by pulse taking or ECG rhythm strip; systematic ECG screening should be considered in patients ≥75 years or those at high stroke risk	DOAC > VKA‡	Not recommended
AHA/ACC/HRS, 2014-2019[3, 4] Management of AF	Not addressed	DOAC > VKA†	Low stroke risk only‡
U.K. NSC, 2019[68] Screening for AF	Age ≥65 years, screening with ECG not recommended; pulse palpation or modified blood pressure monitors (if available) administered by nurses in primary care settings considered appropriate screening tests (followed by a diagnostic 12-lead ECG interpreted by a trained general practitioner in those who screen positive, and referral to a cardiologist/specialist in cases in which the diagnosis is unclear)	Not addressed	Not addressed
ACCP, 2018[73] Antithrombotic therapy for AF	Not addressed	DOAC > VKA†	Not recommended
CCS, 2018[74] Management of AF	Not addressed	DOAC > VKA§	Low stroke risk only
NHFA CSANZ, 2018[70] Screening for and management of AF	Age ≥65 years, case-finding with pulse palpation (and ECG when AF is suspected because of irregular pulse) or ECG rhythm strip in the clinic or community; devices that provide medical-quality ECG trace are the most preferred option for screening	DOAC > VKA‡, ‖	Not recommended
AF-SCREEN International Collaborative, 2017[66] Screening for AF	Age >65 years, pulse then ECG, single-lead ECG, or patient-activated twice-daily intermittent screening for 2 weeks (for age ≥75 years or those at high stroke risk)	DOAC‡	Not recommended
WHF, 2017[69] Management of AF	Age ≥65 years, pulse palpation, with ECG as appropriate	VKA or DOAC‡	Not recommended
EPCCS, 2016[67] Prevention of stroke in AF	Age ≥65 years, case-finding with pulse palpation at least yearly, with ECG as appropriate (alternative approach could use modified sphygmomanometers or single-lead ECG devices if they have been subject to validation with 12-lead ECG)	VKA or DOAC‡	Not recommended
NICE, 2014[142] Management of AF	Screening asymptomatic persons not directly addressed; Age ≥ 18 years pulse palpation if symptoms and ECG when AF is suspected because of irregular pulse (symptomatic or not)	VKA or DOAC‡	Not recommended
AHA/ASA 2014[71] Prevention of stroke	Age ≥65 years, pulse with ECG as appropriate	VKA or DOAC‡ Note: the AHA published updated guidance in the 2019 AHA/ACC/HRS guideline.	Low stroke risk only‖
AAN, 2014[143] Prevention of stroke in NVAF	Not addressed	VKA or DOAC¶	Low stroke risk only‖
CADTH, 2013[144] Antithrombotic agents in AF	Not addressed	VKA or DOAC#	Not addressed
SIGN, 2013[145] Antithrombotic indications	Not addressed	VKA or DOAC§, **	Limited to persons refusing VKA/DOAC

* All treatment recommendations are for patients found to be appropriate candidates for treatment based on risk stratification.

† Recommended for men with CHA_2DS_2-VASc score ≥2 and women with CHA_2DS_2-VASc score ≥3 (ACCP also recommends offering stroke prevention for patients with a single nonsex CHA_2DS_2-VASc risk factor).

Appendix A Table 4. Recent Recommendations (2013 or Newer) on Primary Prevention of Stroke (Including Screening and/or Treatment) in Patients With Atrial Fibrillation

[ǂ] Recommended for patients with CHA_2DS_2-VASc score ≥2 in men and ≥3 in women and should be considered for score=1 in men or score=2 in women.
[§] Recommended for patients ≥ age 65 or with $CHADS_2$ score ≥1.
[ǁ] Consider for patients with CHA_2DS_2-VASc score=1.
[¶] 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.
[#] DOAC for patients with a $CHADS_2$ score ≥1 who are unable to achieve adequate anticoagulation with warfarin.
** Recommended for patients with CHA_2DS_2-VASc score ≥1.

Abbreviations: AAN=American Academy of Neurology; ACC=American College of Cardiology; ACCP=American College of Chest Physicians; AF=atrial fibrillation; AF-SCREEN=acronym not defined; AHA=American Heart Association; ASA=American Stroke Association; CADTH=Canadian Agency for Drugs and Technologies in Health; CCS=Canadian Cardiovascular Society; $CHADS_2$=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; DOAC=direct oral anticoagulants; ECG=electrocardiography; EACTS=European Association of Cardio-Thoracic Surgery; EHRA=European Heart Rhythm Association; EPCCS=European Primary Care Cardiovascular Society; ESC=European Society of Cardiology; HRS=Heart Rhythm Society; NHFA CSANZ=National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand; NICE=National Institute for Health and Care Excellence; NSC=National Screening Committee; NVAF=nonvalvular atrial fibrillation; SIGN=Scottish Intercollegiate Guidelines Network; U.K.=United Kingdom; VKA=vitamin K antagonist; WHF=World Heart Federation.

CQ 1. What is the prevalence of previously unrecognized or undiagnosed AF in unselected or explicitly asymptomatic adults? Does the prevalence vary by age, primary care vs. community setting, method of diagnosis (e.g., single electrocardiogram vs. ambulatory electrocardiography monitoring), sex, or race/ethnicity?

The data provided in this contextual question (CQ) can be viewed as an estimate of the total burden of undiagnosed AF, whereas differences in detection of undiagnosed AF in the context of screening compared with no screening (or usual care) are addressed in KQ 2 of this report.

We identified 52 studies relevant to this CQ that were suitable for using to determine a pooled prevalence; 19 were included in the previous report[146] and the rest are new to this update. These studies are summarized in **Appendix B Table 1**. We stratified this analysis by population-type (clinic based or community based) and screening approach using *metaprop_one* in Stata version 16 (StataCorp, LLC).[147] Note, we did not conduct formal risk of bias assessment on studies included for this CQ.

In addition to the studies we included in the pooled estimates, we report the findings from the Apple Heart Study,[131] a large uncontrolled pragmatic trial, findings from a long-term study using an implanted cardiac monitor,[56] and findings from an individual patient data (IPD) meta-analysis published in 2019 reporting on the prevalence of screen-detected AF.[148]

Characteristics of Studies Used in Pooled Estimates of Unknown AF Prevalence

Participants were recruited from population- or community-based samples in 25 studies used in our pooled estimates. The remaining 27 studies were performed among clinic-based samples. There were 29 uncontrolled trials, three parallel-assignment RCTs, nine cross-sectional studies, seven cohort studies, two diagnostic accuracy study, and two cluster RCTs. Sample sizes ranged from 75 participants[149] to 644,124 participants.[150] Most studies focused on older adults (age 65 years or older), although some studies included younger adults. Most studies excluded participants with known or diagnosed AF; for those studies that included such participants, we only used data from the proportion of participants without known AF. Some studies reported comorbidities of enrolled participants; in a few studies, participants with prior stroke or TIA were enrolled. Studies did not routinely assess whether enrolled participants had symptoms potentially attributed to AF. Thus, the prevalence estimates from these studies reflect prevalence among a population without known AF but some of whom may have risk factors that portend higher risk of AF or whom may have had unrecognized symptoms of AF.

A variety of methods were used for AF diagnosis. Most studies used devices based on standard electrocardiography (ECG) technology; two studies reported prevalence based on more than one approach. Eighteen studies used one-time, single-lead ECG (typically via handheld devices for 10 to 30 seconds) to identify new cases of AF; in more than half of studies, diagnosis was then confirmed with a 12-lead ECG. Twelve studies used a one-time, 12-lead ECG for AF diagnosis. Two studies used one-time ECG, although the number of leads was not reported, and one study

used a three-lead ECG followed by confirmatory 12-lead ECG. Oscillometric blood pressure monitors and devices based on photoplethysmography with automated AF detection algorithms were used alone or in combination with single- or 12-lead ECG to detect new cases of undiagnosed AF in six studies. Various approaches combining a one-time single- or 12-lead ECG followed by 2 to 4 weeks of intermittent ambulatory ECG monitoring were used in seven studies. Continuous monitoring over 24 hours to 2 weeks was used in eight studies. Lastly, one study instructed participants on pulse palpation and asked them to conduct self-pulse palpation three times daily followed by a 30-second single-lead ECG.

Pooled Prevalence of Unknown AF

Appendix B Figure 1 shows the pooled prevalence of previously undiagnosed AF in clinic and community-based samples based on the use of a test at one point in time. The pooled prevalence among clinic-based samples was 1.2 percent (95% CI, 0.9% to 1.5%; 20 studies; 58,213 participants) and was very similar among community-based samples (**Appendix B Figure 2**; pooled prevalence of 1.3% [95% CI, 1.0% to 1.6%]; 17 studies; 102,508 participants). Some heterogeneity in estimates exists but cannot be entirely explained by differences in study population or method of AF detection.

The prevalence of previously undiagnosed AF in clinic- and community-based samples based on intermittent or continuous monitoring varied more than the use of one-time tests (**Appendix B Figure 3**). The pooled prevalence among clinic-based samples was 3.2 percent (95% CI, 1.5% to 4.9%; 7 studies; 3,885 participants) and was 3.5 percent (95% CI, 2.0% to 5.1%; 8 studies; 662,443 participants) among community-based samples. The combined pooled prevalence for continuous or intermittent monitoring among clinic and community-based samples was 3.3 percent (95% CI, 2.3 to 4.3; 15 studies; 666,328 participants). Similar to one-time testing approaches, some heterogeneity exists, but cannot be entirely explained by differences in study population or method of AF detection.

When comparing one-time tests with intermittent or continuous monitoring, we observe that monitoring patients for longer periods of time yields higher detection rates of AF. This is likely due to increased detection of paroxysmal AF missed by one-time approaches to testing.

Additional Information Regarding Prevalence of Unknown AF

We offer additional information related to studies and data not included in the pooled estimates of prevalence above.

The Apple Heart Study, published in 2019, was an uncontrolled, siteless, industry-funded pragmatic trial that used photoplethysmography, an optical sensor-based technology, embedded in the Apple Watch, synched to an Apple iPhone, with an algorithm to detect possible AF.[131] The study recruited 419,093 participants age 22 years or older from among persons who downloaded the Apple Watch application from the Apple App Store, and 67,259 (16%) were age 55 years or older. Participants with previously known AF or who were current users of oral anticoagulants (OACs) were excluded. The study authors were clear that "notification based on an irregular pulse from a photoplethysmography signal should not be used for a definitive diagnosis of atrial fibrillation."[131, p. 1916] Notifications of abnormal rhythm were based on at least five out of six

consecutive abnormal tachograms within a 48-hour period. This equates to more than 1 hour of abnormal rhythm before a notification is triggered. If a participant received a notification of possible AF, they were sent an ECG patch for 7 days of confirmatory monitoring and scheduled for a telemedicine visit. Among participants age 55 years or older, 1,331 (2.0%) received an irregular pulse notification. However, only 295 (22.2%) of those receiving a notification returned the confirmatory ECG patch monitor. Of those who returned the patch monitor, 110 (37.3%) were confirmed to have AF. Extrapolating the confirmation rate of 37 percent back to all participants age 55 years or older who received an irregular pulse notification suggests 492 cases of previously unknown AF for a prevalence of 0.7 percent. This prevalence is lower than what we calculated in our pooled estimates and may reflect a population with fewer AF risks than a general community or clinic-based population and also a longer threshold for abnormal rhythm for the initial notification.

Philippsen et al enrolled 82 participants age 65 years or older without known or suspected AF recruited from hospital outpatient diabetes and cardiology clinics into a long-term study with an implantable cardiac monitor.[56] Patients with CIED, history of stroke, or history of TIAs were excluded. The mean age was 71, and 37 percent were female. Nearly three-quarters took medication for diabetes, the mean number of hypertensive agents was four, and the mean left ventricular ejection fraction was 60 percent. In this study, the mean duration of ICM use was 588 days, and 20.7 percent of participants had AF detected based on one or more episodes of AF rhythm for at least 2 minutes or longer. The much higher prevalence of AF in this study may reflect the much longer duration of monitoring and the identification of incident along with prevalent cases. In addition, the population enrolled may be considered higher risk than a general community or primary care clinic-based population. However, about a month after placement of the ICM, all participants also underwent a 2-channel, 72-hour Holter monitor, and the prevalence of AF detected by Holter monitoring was 2.4 percent (based on AF episodes at least 30 seconds or longer), consistent with pooled estimates we calculated in the previous section for continuous or intermittent monitoring. Thus, it is likely that the much higher prevalence observed from long-term continuous monitoring is because of the longer duration of monitoring and detection of incident cases, rather than population characteristics.

Lastly, Lowres et al conducted an IPD meta-analysis of 19 studies with at least 1,000 participants to report the prevalence of screen-detected AF.[148] Two of the included studies used pulse palpation confirmed by a 12-lead ECG, and three of the included studies were conducted in countries that were not very highly developed per the United Nations Human Development Index. Nearly all included studies used one-time screening approaches. In this analysis, the age- and sex-adjusted AF detection rate in persons age 65 years or older was 1.4 percent (95% CI, 1.2% to 1.8%), consistent with the pooled estimates we calculated in the previous section for one-time screening tests.

Variation by Subgroup

With respect to variation in prevalence by subgroup, our data suggest that prevalence of AF increases as the age of participants increases. For example, in **Appendix B Figure 1**, the three studies reporting prevalence greater than 5 percent, for one-time and two-step tests, had mean age of 75 years or older.[151-153] In the 2019 IPD, the age- and sex-adjusted detection rate in

persons younger than 65 years was 0.41 percent (95% CI, 0.31% to 0.53%), lower than the 1.44 percent prevalence reported for persons older than 65 years.[148]

With respect to variation by sex, few studies report data stratified by sex. For example, in the actively monitored cohort of the mSToPS trial, 7 percent of males and 5 percent of females had a new AF diagnosis at 1 year.[109] Data from Furberg et al[154] indicated a higher prevalence in males than females, 1.9 percent vs. 1.2 percent, respectively. Of note, this study reported a strong association between advanced age in women and AF prevalence ($p < 0.0001$), whereas this relationship was not significant in men.[154] In the 2019 IPD meta-analysis, the proportion of screen-detected AF was higher among males than females across all age groups.[148]

CQ 2. What is the stroke risk for the following populations?

Asymptomatic Older Adults With Previously Unrecognized or Undiagnosed Atrial Fibrillation

We found no new evidence to directly address the question regarding the risk of stroke in asymptomatic older adults with previously unrecognized or undiagnosed AF. Therefore, we have included below the summary from the prior report unchanged.[146]

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.[189] These were not screen detected as far as the article reports but rather seem to have been incidentally detected in the course of usual care. Just over half were treated with OAC therapy with or without antiplatelet therapy. The cohort included people with a history of coronary artery disease (CAD) without myocardial infarction (MI) (10.6%), MI (4.2%), and stroke or transient ischemic attack (TIA) (9.2%). Mean CHA_2DS_2-VASc score was 2.5 (standard deviation [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 International Classification of Diseases (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). Stroke incidence rates per 1,000 were 19.4 (95% CI, 17.1 to 21.9) for those with incidentally detected AF (all ages) and 8.4 (95% CI, 7.7 to 9.1) for the matched controls without AF.

Appendix B. Contextual Questions

Relative Risk of Stroke in Asymptomatic AF vs. Symptomatic AF

We identified five studies addressing this question; one (ORBIT-AF registry) is new to this update.[190] In brief, there was no difference in stroke risk between patients with asymptomatic AF and symptomatic AF. However, results were somewhat imprecise, the risk of bias was high in these studies, and they may not be fully applicable to primary care patients. Study details, findings, and limitations of the five studies we identified are summarized in **Appendix B Table 2**.

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 three of the five 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 most 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. Two studies clearly distinguished asymptomatic from symptomatic patients.[42, 190] Both studies reported no differences in outcomes for symptomatic vs. asymptomatic patients in adjusted analyses.

Predicted Stroke Risk Among Persons With Unrecognized AF

We identified 14 studies (13 primary research studies and 1 meta-analysis) providing data on the predicted risk of stroke among persons with previously unrecognized or undiagnosed AF; four are new to this update.[148, 151, 157, 172] In brief, mean stroke risk prediction scores of persons identified with AF who were asymptomatic and not known to previously have AF typically fall into ranges that would be associated with initiation of anticoagulation (in the absence of contraindications).

Findings from the 13 primary research studies (with a total of 734 people with previously undiagnosed AF) are summarized in **Appendix B Table 3**. Across these studies, the mean predicted stroke risk among studies using CHA_2DS_2-VASc ranged from 2.1 to 4.0. We determined that based on these studies the percentage of persons who would be eligible for anticoagulation (i.e., score $\geq$2 for males) ranges from 56 percent to 94 percent. Some studies in **Appendix B Table 3** only reported mean $CHADS_2$ scores, and we note these scores are not directly comparable to CHA_2DS_2-VASc scores, the latter of which 1) better identifies very low-

risk patients, 2) classifies a lower proportion as moderate risk and more as high risk, and 3) includes additional AF risk factors, all of which were limitations of the original $CHADS_2$ scoring system.[191]

In addition to the 13 primary research studies summarized above, Lowres et al conducted an individual patient-level (IPD) meta-analysis of more than 140,000 participants screened for AF in 19 studies across 14 countries (including 3 conducted in countries not *very highly developed* per the UN Human Development Index).[148] Studies included had at least 1,000 participants, and participants were recruited from community populations (n=7), general practices (n=6), outpatient clinics (n=3), and pharmacies (n=3). Screening methods included pulse palpation (n=2), single-lead ECG (n=12), 12-lead ECG (n=4), and automated blood pressure machine (n=1). Across studies investigators identified 1,369 new AF cases and reported mean (95% CI) CHA_2DS_2-VASc scores in 5-year increments from ages 60 to 85 years (**Appendix B Table 4**). There was a consistent dose-response relationship between age and CHA_2DS_2-VASc score beginning at 1.1 (0.7 to 1.5) for participants younger than age 60 years and peaking at 3.9 (3.6 to 4.4) for those age 85 years or older**.** Although some of the increase in scores can be attributed to the anticipated age-related increases at 65 and 75 years—1 and 2 points, respectively—there still appears to be an increase in scores independent of the CHA_2DS_2-VASc age-based scoring item. Study authors also reported a country effect, with the highest CHA_2DS_2-VASc scores observed in Germany, Hong Kong, and the United States (mean score greater than 3.0) compared with the lowest in India (mean score less than 2.0); results were not affected by setting, method, urban/rural, era screened, or screen age eligibility. Although the authors do not comment further on this finding, it is possible the gradient could be due to country-based differences in access to care and availability of diagnostic services that are central to diagnosing conditions that are included in the CHA_2DS_2-VASc score (e.g., congestive heart failure, hypertension, diabetes, stroke or prior transient ischemic attack, vascular disease).

Older Adults With Paroxysmal vs. Persistent AF

We identified three publications related to the stroke risk in older adults with paroxysmal vs. persistent or permanent AF. Findings are summarized in **Appendix B Table 5**. In general, the risk of stroke in older adults with paroxysmal AF is lower compared with older adults with nonparoxysmal AF, and there appears to be an increasing gradient for stroke risk based on AF type: paroxysmal, persistent, permanent.

Ganesan et al is a systematic review and meta-analysis of 10 RCTs and two prospective cohort studies including almost 100,000 patients with mean ages of 62 to 73 years.[44] Followup ranged from 1 to 2.8 years. The pooled unadjusted risk ratio (RR) for stroke or systemic embolism in nonparoxysmal AF vs. paroxysmal AF was 1.4 (95% CI, 1.2 to 1.8, 12 studies), and the pooled adjusted HR was 1.4 (95% CI, 1.2 to 1.6; 12 studies). Unadjusted estimates for the annualized risk of thromboembolism in nonparoxysmal and paroxysmal AF were 2.2 percent (95% CI, 1.8 to 2.5) and 1.5 percent (95% CI, 1.2 to 1.8), respectively (7 studies, n=58,421). In univariate meta-regression analyses to explore the unadjusted increased thromboembolic risk, none of the study-level covariates (e.g., mean age, sex, hypertension, prior stroke, diabetes, heart failure) was a significant predictor, supporting AF type as an independent predictor of stroke. The study authors considered the overall individual study quality as strong based on the modified Newcastle-Ottawa scale.

Link et al conducted an RCT of edoxaban vs. warfarin (ENGAGE AF-TIMI 48) in over 21,000 patients with AF and a $CHADS_2$ score of 2 or more.[43] In a prespecified analysis, they reported the risk of the composite outcome of stroke or systemic embolic event in paroxysmal AF (1.5%/yr), persistent AF (1.8%/yr), and permanent AF (2.0%/yr). The adjusted HR (aHR) comparing paroxysmal to either persistent or permanent AF was 0.8 (95% CI, 0.7 to 0.9).

Boriani et al identified 2,119 consecutive inpatients and outpatients with incidentally detected AF (regardless of whether they were asymptomatic) who were enrolled in the EORP-AF Pilot General Registry study from 67 European hospitals and medical centers.[45] All patients were screen detected using an ECG recording when they presented to a cardiologist and no later than 12 months before enrollment in the registry. Patients in the registry were followed for 3 years and had a mean age of 69 years. Authors reported the risk of stroke over 3 years: paroxysmal AF (1.4%), persistent AF (1.1%), and permanent AF (3.5%). At baseline entry into the registry, approximately 80 percent of patients were on OAC therapy.

Older Adults With Paroxysmal AF Who Have a Lower vs. Higher AF Burden

In this section, we report concepts related to AF burden, summarize findings from systematic reviews and primary research studies concerning the risk of stroke and AF burden, summarize existing scientific statements and guidelines on this issue, and describe ongoing studies in this area. Overall, higher AF burden appears to be associated with a higher risk of stroke compared with lower AF burden, but no consensus exists regarding how to define AF burden, limiting its applicability for clinical decision making at the present. Additionally, with the exception of one study, Healey et. al,[193] included in the Uittenbogaard meta-analysis,[48] all included studies appeared to enroll patients with preexisting indications for CIEDs. As discussed in the previous section, the risk of stroke for patients with paroxysmal AF appears to be lower compared with those with nonparoxysmal AF. However, there may be a spectrum of stroke risk in paroxysmal AF that could warrant treatment for some paroxysmal AF patients but not others, but it remains unclear where to best draw the line between those who may and may not benefit from treatment.

Stroke risk stratification in AF has largely been approached based on patient characteristics (e.g., CHA_2DS_2-VASc) rather than AF type (i.e., paroxysmal vs. persistent). More recently the concept of AF burden, rather than AF type, has been introduced to quantify AF exposure, but no uniform definition of AF burden exists. For example, AF burden can refer to the duration of the longest AF episode, the number of AF episodes during a discrete monitoring period, or the proportion of time spent in AF during a monitored period.[7, 125] Additionally, the concept of AF density, which adds temporal dispersion of AF burden, has recently been introduced.[194]

In addition to AF burden, two additional concepts are important: atrial high-risk episodes (AHRE) and subclinical atrial fibrillation (SCAF). AHREs are episodes of atrial tachyarrhythmias (e.g., atrial tachycardia [AT], AF, atrial flutter) that are asymptomatic and detected via long-term continuous monitoring by a cardiac implantable electronic devices (CIED). SCAF is the subset of AHRE that excludes AT and atrial flutter. When SCAF is detected, a physician review of the device electrogram or a conventional 12-lead surface ECG with 30 seconds or more of AF rhythm may confirm clinical AF, regardless of whether symptoms are present or absent.[7, 8, 195] AHRE and SCAF, which are detected by CIED, need to

be differentiated from paroxysmal AF, which is most often diagnosed clinically through surface ECG but can be diagnosed based on good quality, saved intracardiac electrogram.[196, 197, 198] Some studies have demonstrated that up to 80 percent of AHRE lasting longer than 5 minutes are AF.[199, 200] Importantly, implantable devices can lead to false-positive diagnoses of AF, especially within the first 3 months after implantation when transient AF is most likely to occur, which has led some researchers to define SCAF as episodes of AHRE of at least 5 minutes.[201]

Mahajan et al conducted a systematic review and meta-analysis of studies evaluating the association between SCAF and stroke risk in patients with CIEDs with implanted atrial leads.[46] SCAF was defined as device-detected AHRE. Although the authors did not report on indications for CIED placement in the included studies, the baseline characteristics of patients included approximately 4% on anticoagulation, 60% with heart failure, and 35% with CAD. Mean study follow up ranged from 1 to 2.5 years. They identified seven studies (n=15,353 patients). Most studies were either retrospective or prospective cohort studies; the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT) was an RCT, and the Stroke preventiOn Strategies based on Atrial Fibrillation Information from Implanted Devices (SOS AF) is a registry. Each study used a separate cut point to define SCAF based on duration of AHRE episodes ranging from at least 5 minutes to 24 hours; most studies, however, used cut points between 5 minutes and 5.5 hours. The annual stroke rate associated with SCAF was 1.89/100 person-years compared with 0.93/100 person-years for persons without SCAF (pooled OR, 2.4 [95% CI, 1.8 to 3.3]). The review authors rated all included studies as low risk of bias. Point estimates of all seven studies were similar with overlapping confidence intervals and low statistical heterogeneity. However, publication bias was not evaluated, and the range of cut points to define SCAF was large.

One of the studies included in the Mahajan et al meta-analysis, ASSERT, provides further breakdown of stroke risk by AF burden.[47] In this study, 2,580 patients age 65 years or older with hypertension and no AF were enrolled after they had received a CIED for nodal dysfunction. Study participants were analyzed in three groups according to the longest episode of SCAF that occurred over a 3-month period: 6 minutes to 6 hours, 6 hours to 24 hours, and longer than 24 hours. Only participants with SCAF longer than 24 hours had increased risk of stroke (aHR, 3.2 [95% CI, 1.5 to 7.0]) compared with participants without SCAF. Participants with SCAF longer than 24 hours had an annual stroke risk of 5 percent, which is similar to the risk in patients with clinical AF. The major limitation of the study was that SCAF was assessed during the 3-month period after device implementation, which could have led to measurement error due to lead implantation causing transient SCAF.

Uittenbogaart et al conducted a systematic review and meta-analysis of observational studies evaluating thromboembolic events and AF burden.[48] They identified seven studies (n=18,947), some of which were included in the Mahajan et al review. Only one study enrolled participants without medical indications for an implantable cardiac monitor.[193] Most studies were rated as moderate risk of bias. All studies defined SCAF as AHRE lasting at least 5 to 14 minutes. Mean followup duration ranged from 1 to 7 years. AF burden was defined as either the duration of the longest episode, accumulated time per year, or maximum daily burden. Pooled analyses of two studies (n=12,734 participants) comparing participants with AHRE with participants with no AHRE demonstrated increased risk of thromboembolism for participants with AHRE longer than 6 minutes (HR, 1.8 [95% CI, 1.3 to 2.5]) and longer than 6 hours (HR, 1.8 [95% CI, 1.2 to 2.6]).[202, 203] A second pooled analysis (n=2,849 participants) comparing participants with AHRE

to participants with no AHRE demonstrated increased risk of thromboembolism for AHRE greater than 24 hours(HR, 3.2 [95% CI, 1.8 to 5.9]) but no difference for AHRE less than 24 hours.[204, 205] Healey et al, the only included study to enroll participants without an indication for a CIED (n=256), recorded no thromboembolic events among participants with paroxysmal AF.[193]

The KP-RHYTHM Study is a retrospective cohort study that evaluated the risk of stroke in patients with paroxysmal AF detected by ambulatory ECG not on anticoagulation.[49] Participants were members of the California Kaiser Permanente integrated healthcare system who were diagnosed with paroxysmal AF by 14-day Zio Patch monitoring (N=1,965) between 2011 and 2016. AF burden was defined as the proportion of time in AF during the monitoring period with a minimum episode duration of 30 seconds. Rate of thromboembolic events (i.e., stroke, TIA, systemic embolic event) was compared by AF burden in tertiles: less than 2 percent, 2 to 11 percent, and greater than 11 percent. Although rate of thromboembolic events rose by tertile (0.7, 1.0, and 2.9 per 100 person-years, respectively), 95 percent CIs were largely overlapping for all three groups. When compared with the combined first and second tertiles, the unadjusted HR for the third tertile was 3.2 (95% CI, 1.5 to 6.6). Adjusted and sensitivity analyses revealed similar conclusions to the primary analysis.

Both the American Heart Association (AHA) and the Canadian Cardiovascular Society (CCS) have issued statements on stroke prevention in SCAF as a result of the studies outlined above. The CCS guidelines recommend that patients with SCAF longer than 24 hours with at least one stroke risk factor should receive OAC.[74] Additionally, patients with SCAF of shorter duration who are at high risk should also be considered for OAC. On the other hand, the AHA guidelines currently recommend mainly using vascular risk factors (e.g., CHA_2DS_2-VASc score) when deciding to use OAC for stroke prevention in AF.[125] The AHA cited concerns that cutoffs for AF burden in all studies were arbitrary and not empirically derived; the effect of brief AF episodes is unknown; and some studies, including ASSERT, did not differentiate participants with AF vs. atrial flutter, which may have a different stroke risk. For patients with high AF burden (e.g., AHRE > 24 hrs) and high stroke risk (e.g., CHA_2DS_2-VASc ≥ 2 for men and ≥ 3 for women), the AHA considers anticoagulation a reasonable option.[125] Although the European Society of Cardiology has recognized that AF burden may influence stroke risk, they conclude that the current evidence is insufficient to guide treatment and should not be a major factor in decision making related to stroke prevention treatment.[7] However, they suggest modifiable stroke risk factors should be identified and managed. Lastly, they advise providers to consider OAC for selected patients with SCAF $\geq$ 24 hours and an estimated high stroke risk based on a validated tool such as the CHA_2DS_2-VASc.

Two trials comparing DOACs vs. aspirin are currently being conducted that will add information on the relationship between AF burden and stroke risk among people with indications for CIEDs: ARTESiA[206] and NOAH-AFNET 6[207] (**Appendix H Table 1**). ARTESiA is a multicenter, double-blind RCT of up to 4,000 patients age 55 years or older with SCAF (i.e., CIED-detected AF $\geq$ 6 minutes duration) and at least one stroke risk factor.[206] Participants will be randomized to apixaban or aspirin with an anticipated mean followup of 36 months. The composite primary outcome is stroke, TIA, and systemic embolism, and the primary safety outcome is overt major bleeding. A planned subgroup analysis will compare participants with longest baseline SCAF greater than vs. less than the median study population value. NOAH-AFNET 6 is a pragmatic,

multicenter, double-blind RCT of 3,400 participants with CIED-detected AHRE longer than 6 minutes, age 65 years or older, and at least one additional stroke risk factor.[207] Participants are randomized to edoxaban or usual care (i.e., aspirin or placebo based on established indications) and followed for up to 3 years. The primary outcome is stroke, systemic embolism, or cardiovascular death, and a major bleeding event is a secondary outcome. Prespecified exploratory analyses will be conducted based on duration and pattern of AHRE. Results from both trials are expected in 2022. However, both trials are enrolling patients with indications for CIED, which may reduce the applicability of their results to asymptomatic, healthy adults.

Appendix B Table 1. Summary of Studies Published Since 2000 Reporting the Prevalence of Previously Undiagnosed Atrial Fibrillation Among Unselected or Asymptomatic Persons

Author, Year Study Name Registry No.	Study Design	Sample Size	Country	Study Population	Method of Detection	Previously Undiagnosed AF Prevalence (95% CI)
Community-Based Samples						
Bacchini et al, 2019[155]	Uncontrolled trial	3,071	Italy	Participants age 50 years or older recruited from 74 community pharmacies Mean age: NR N (%) Female: NR	Oscillometric BP with automated AF detecton algorightm (MicrolifeAFIB)	1.8% (NR)
Berge et al, 2018[156] ACE NCT01555411	Cross-sectional study	3,553	Norway	Longitudinal, population-based cohort recruited from individuals born in 1950 from a single county Mean age: 63.9 (0.7) N (%) Female: 1,807 (49)	12-lead ECG	0.3% (NR)
Busch et al, 2017[157]	Cohort study	1,678	Germany	Participants age 20 to 79 recruited from population registries Mean age: No-AF: 51 (13) Tele-AF: 64 (14) ECG-AF: 69 (6) N (%) Female: 880 (52)	One-time 12-lead ECG followed by intermittent ambulatory single-lead ECG, two recordings of 30 s each daily over 4 weeks plus whenever symptoms (e.g., dizziness, chest pain) occur. Interpreted by trained personnel, with validation of abnormal rhythms by a second interpreter.	Single, 12-lead ECG: 1.3% (0.8% to 1.9%) Intermittent ECG:2.6% (1.9% to 3.4%) 21 new AF cases based on 12 lead; 43 new cases based on intermittent ECG (all were also detected by 12 lead)
Chan et al, 2016[158]	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)
Chan et al, 2018[159] AFINDER	Uncontrolled trial	10,735	Hong Kong	Community residents age 50 or older recruited through advertisements in media and community centers Mean age: 78.6 (8.1) N (%) Female: 8,564(79.8)	Single-lead handheld ECG (Kardia Mobile) for 30 seconds interpreted with algorithm	0.69% (0.54% to 0.84%)

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Author, Year Study Name Registry No.	Study Design	Sample Size	Country	Study Population	Method of Detection	Previously Undiagnosed AF Prevalence (95% CI)
Claes et al, 2012[160]	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)
Diouf et al, 2016[161]	Cohort study	8,273	Australia	Partcipants age 35 years or older from the Australian Diabetes, Obesity and Lifestyle Study Mean age: NR, all participants were age ≥35 N (%) Female: NR	12-lead ECG	1.1% (NR) Unclear whether sample included persons with known AF.
Doliwa et al, 2009[162]	Test 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)
Engdahl et al, 2013[152]	Uncontrolled trial	767	Sweden	Population-based sample of 75- and 76-year-old adults Men: 43% Heart failure: 4% Hypertension: 53% Diabetes: 11% Stroke/TIA: 10%	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)
Frewen et al, 2013[163] TILDA	Cohort study	4,890	Ireland	Population-based sample of community-dwelling adults age 50 years or older from a longitudinal study on aging 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)

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Author, Year Study Name Registry No.	Study Design	Sample Size	Country	Study Population	Method of Detection	Previously Undiagnosed AF Prevalence (95% CI)
Furberg et al, 1994[154]	Cohort study	5,151	U.S.	Population recruited from Medicare eligibility lists of adults age 65 years or older from four U.S. communities. Mean age 73 (NR) Men: 43% White: 94.7%	One time, 12-lead ECG, interpreted centrally	1.5% (NR)
Gudmundsdottir et al, 2020[164]	Parallel-assignment RCT	6315	Sweden	Population-based sample of 75/76-year-olds randomized to control or invited to screening: Congestive heart failure: 2.4% Hypertension: 51.7% Diabetes mellitus: 11.4% Prior stroke or TIA: 8.1% Vascular disease: 6.9%. Mean age: All participants were 75 or 76 years old at study entry N (%) Female: 3,708 (54)	30 second single-lead ECG with handheld device (Zenicor 2 device, Zenicor Medical Systems, Stockholm, Sweden). If sinus rhythm on index test, high-risk group offered two week intermittent ambulatory ECG with handheld device (Zenicor II) 4 x daily.	2.6% (2.2% to 3.0%) All but 1 new case came from group of participants designated as high risk based on BNP levels recorded at baseline. Of the 165 new cases, 29 were made during initial one-time screen and 136 were diagnosed during extended ECG screening. Only high-risk participants were offered extended screening if initial one-time screening showed normal rhythm.

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Author, Year Study Name Registry No.	Study Design	Sample Size	Country	Study Population	Method of Detection	Previously Undiagnosed AF Prevalence (95% CI)
Kim et al, 2020[153]	Uncontrolled trial	5,366	South Korea	Community-based sample of adults age 60 years or older recruited from community senior centers. In a preliminary study (2,422): Hypertension: 50.9% Diabetes: 24.2% Dyslipidemia: 25.0% Thyroid disease: 8.3% Angina pectoris: 5.2% Myocardial infarction: 2.6% AF: 1.2% Heart failure: 0.7% Valvular heart disease: 0.3% Transient ischemic accident: 0.5% Cerebral infarction: 4.1% Cerebral hemorrhage: 1.5% Mean age: 75.5 (6.5) N (%) Female: 1,660 (69)	Automated single-lead ECG with Kardia Mobile (AliveCor, Mountain View, CA, USA). If positive for AF on first test, participants received confirmatory 12-lead ECG interpreted by cardiologist within 20 minutes.	2.6% (2.2% to 3.1%)
Kropp et al, 2020[165]	Uncontrolled trial	250	U.S.	Community sample of walk in customers at two rural pharmacies Congestive heart failure: 3.2%, Hypertension: 75.2% Age greater than: 75, 21.6% Diabetes mellitus: 29.6% Previous stroke or transient ischemic attack: 7.6% Peripheral vascular disease: 4.8% Age 65 to 74: 25.6% Obstructive sleep apnea: 24.8% Obesity 65.2%. Mean age: 61.7(15.3) N (%) Female: 150 (60)	One-time single-lead, wireless, 30 second mobile-ECG (KardiaMobile by Alivecor)	4.0% (NR) Prevalence was 3% after adjudication by 3 electrophysiologists.
Kvist et al, 2019[166]	Cross-sectional study	1,228	Denmark	Men age 65 to 74 years enrolled in the DANCAVAS trial; recruited from the general population Mean age: Median 69 (IQR 67.0 to 71.0) N (%) Female: 0 (0)	12-lead ECG (recorded within 1 hour of single-lead ECG obtained during CT scan) interpreted by cardiologist	0.7% (0.03% to 1.3%)

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Author, Year Study Name Registry No.	Study Design	Sample Size	Country	Study Population	Method of Detection	Previously Undiagnosed AF Prevalence (95% CI)
Lindberg et al, 2016[167]	Uncontrolled trial	200	Sweden	Participants age 60 years or older in a single municipality who were participating in an ongoing national longitudinal study of aging N (%) age groups: Age 66-80: 125 (62.5%) Age >80: 75: (37.5%) N (%) Female: 112 (56)	24-hour ambulatory ECG (ECG-BodyKom, Kiwodk Nordic AB)	11% (NR)
Lowres et al, 2014[168] SEARCH-AF	Uncontrolled trial	1,000	Australia	Community-based sample of adults age 65 years or older recruited from community pharmacies Mean age: 76 (SD 7) Men: 44%	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)
Mandalenakis et al, 2018[169]	Uncontrolled trial	448	Sweden	Population-based sample of 71-year-old men Systolic blood pressure (mmHg): 147 ± 19 Diastolic blood pressure (mmHg): 86 ± 11 Hypertension: 56% Previous myocardial infarction: 10% Congestive heart failure: 3.5% Previous stroke: 8.6% Mean age: 71 (0) N (%) Female: 0 (0)	12-lead ECG followed by thumb ECG (Zenicor) home recording twice daily for 30 seconds (one morning reading and one evening reading) for a 2-week period	1.8% (NR)
Meschia et al, 2010[150]	Cohort study	29,861	U.S.	Racially and ethnically diverse population-based sample of adults age 45 years or older Median age: 74 (IQR 69 to 79) Men: 45% Stroke: 11% Hypertension: 59% Diabetes: 221%	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)

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Author, Year Study Name Registry No.	Study Design	Sample Size	Country	Study Population	Method of Detection	Previously Undiagnosed AF Prevalence (95% CI)
Omboni et al, 2016[170]	Uncontrolled trial	220	Italy	Community-based sample of adults 18 years or older in two small villages. Screening performed in mobile units. History for cardiovascular disease: 11.4%. Previous diagnosis of hypertension: 36.4% Diabetes: 7.7% Dyslipidemia: 27.3% Obesity: 15.0% Current smokers: 17.3% Current drinkers: 43.2%. Mean age: 57.5 (15.3) N (%) Female: 107 (49)	3 back-to-back readings with oscillometric BP monitor (Microlife WatchBP Office AFIB, Microlife AG, Switzerland). Positive results followed by 30-second single-lead ECG with handheld ECG recorder (Cardio-A Palm ECG, Shenzhen Creative Industry Co. Ltd., China)	1.8% (NR)
Schnabel et al, 2012[171]	Cohort study	5,000	Germany	Population-based sample of adults between ages 35 and 74 years Mean age 52: (SD 11) Men: 49.9% Hypertension: 45.4% Diabetes: 6.0% Heart failure: 17.7% Stroke: 1.5%	12-lead ECG; detection based on confirmed AF by two independent cardiologists.	0.5% (NR)
Svennberg et al, 2015[77] STROKESTOP	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)

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Author, Year Study Name Registry No.	Study Design	Sample Size	Country	Study Population	Method of Detection	Previously Undiagnosed AF Prevalence (95% CI)
Steinhubl et al, 2018[109]	Parallel-assignment RCT	1,738 (actively monitored)	U.S.	Recruitment from members of large health insurance plans recruited directly through email or direct mail. Mean age: 73.5 (7.4) N (%) Female: 521 (38.1)	iRhythm Zio ECG patch for 14 days at baseline and again in 3 months; diagnoses by blinded to diagnosis of clinical events adjudication committee. Patch diagnosis based on 30 seconds or more of AF or atrial flutter detected by device and confirmed by investigator.	6.2 (NR) This includes those diagnosed by patch, but also those who developed clinical symptoms and were diagnosed. 65 diagnoses based on patch, 44 were clinical diagnoses, before monitoring, after monitoring completed but without any findings of AF during monitoring.
Zaprutko et al, 2020[172]	Uncontrolled trial	490	Poland	Community-based sample where every patient entering 10 pharmacies who looked to be >65 years was asked to join the study Mean age: 73.7 (6.5) N (%) Female: 358 (68.2)	One-time single-lead ECG for 30-second interval using handheld device with smartphone application (Kardia mobile). Recordings sent to two cardiologists for final interpretation.	Algorithm interpretation: 3.5% (NR) (17 cases) Intepretation by cardiologist: 2.2% (12 cases), of these 7 (1.4%) were new diagnoses
Clinic-Based Samples						
Bury et al, 2015[173]	Uncontrolled trial	566	Ireland	Convenience sample of patients age 70 or older from 25 general practices Mean age 78 (SD NR) Female: 60% Hypertension: 48.2% Diabetes: 10.6% Coronary heart disease: 22.5% Stroke: 2.6% Other heart surgery or cardiac procedures: 3.1%	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)
Chan et al, 2017[174]	Cross-sectional study	5,969	Hong Kong	Patients ≥65 years of age recruited from primary healthcare setting Mean age: 67.2 (11.0) N (%) Female: 3,217 (54)	Three BP measurements were taken using the automatic oscillometric BP monitor with AF detection algorithm. The “Afib” icon flashed when AF was detected. All diagnoses confirmed by standard 12-lead ECG.	1.2% (NR) NR

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Author, Year Study Name Registry No.	Study Design	Sample Size	Country	Study Population	Method of Detection	Previously Undiagnosed AF Prevalence (95% CI)
Chan et al, 2017[175]	Uncontrolled trial	2,054	Hong Kong	Patients ≥65 years of age with hypertension or diabetes mellitus, attending a genreal outpatient clinic Mean age: 67.8 (10.6) N (%) Female: 1,112 (54)	One-time single-lead, mobile-ECG using AliveCor Heart Monitor AND automatic oscillometric BP monitor (the Microlife WatchBP Office AFIB) with AF detection algorithm, followed by 12-lead ECG for positive results.	1.2% (NR)
Chan et al, 2016[176]	Cross-sectional study	990	Hong Kong	Patients with a history of hypertension and/or diabetes mellitus or were ≥65 years of age recruited a general outpatient clinic Mean age: 68.4 (12.2) N (%) Female: 539 (53)	12-lead ECG confirmation by cardiologist after positive screen by either single-lead ECG for 30s with AliveCor heart monitor and 3 PPG waveforms acquired sequentially using Cardio Rhythm application	5.1% (NR)
Clua-Espuny et al, 2013[177]	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)
Deif et al, 2012[178]	Uncontrolled trial	2,802	Australia	Ambulatory adults age 40 years or older undergoing preoperative evaluation for minor procedures or elective surgery Mean age: 65 (SD 13) Men: 50%	"Routine" ECG; detection criteria NR.	All participants: 0.4% (NR) Participants age 65 years or older: 0.7% (NR)
Fitzmaurice et al, 2007[93] SAFE	Cluster RCT	9,137	U.K.	Patients age 65 years or older from 50 general practices Mean age: 75.3 (SD 7.2) Men: 42.8%	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.	Practices allocated to screening: 1.6% Practices allocated to control: 1.0%

Appendix B Table 1. Summary of Studies Published Since 2000 Reporting the Prevalence of Previously Undiagnosed Atrial Fibrillation Among Unselected or Asymptomatic Persons

Author, Year Study Name Registry No.	Study Design	Sample Size	Country	Study Population	Method of Detection	Previously Undiagnosed AF Prevalence (95% CI)
Ghazal et al, 2020[179]	Test accuracy study	1,010	Sweden	Individuals age ≥ 65 years attending 1 of 4 primary care centers for routine care during study period; Median age: 72 N (%) Female: 622 (61)	Instruction to patients for self pulse palpation 3 times daily followed by a 30-second ECG using handled device (Zenicor) over a 2-week period. Abnormal ECGs reviewed and confirmed by cardiologist; patch ECG used for 5 days in cases with unclear or uninterpretable findings.	2.7% (1.8% to 3.9%)
Ghazal et al, 2019[180]	Cross-sectional study	290	Sweden	Individuals registered with a single primary care center who visited the office for any reason during study period. Mean age: All individuals were between 70 and 74 years N (%) Female: NR, but likely at least half based on other data provided in the study.	12-lead ECG plus 30 second single-lead ECG with handheld device (Zenicor) twice a day for at least 2 weeks, with subsequent confirmation and Holter monitoring if needed.	5.5% (NR)
Grubb et al, 2019[151]	Uncontrolled trial	1,805	United Kingdom	Patients 65 years or older from participating practices with at least 1 stroke risk factor including: heart failure, hypertension, diabetes mellitus, previous stroke or transient ischaemic attack, peripheral or carotid arterial disease Mean age: 74.9 (7.1) N (%) Female: 703 (39)	Handheld, smartphone-based ECG recorder (AliveCor) for 30-second interval.	5.1% (NR) Recordings interpreted by a cardiologist, not automated algorithm.
Hill et al, 1987[181]	Uncontrolled trial	819	U.K.	Symptomless patients age 65 years or older from a single general practice Mean age	Single 12-lead ECG in clinic setting. Detection based on interpretation by two clinicians.	1.2% (NR)

Appendix B Table 1. Summary of Studies Published Since 2000 Reporting the Prevalence of Previously Undiagnosed Atrial Fibrillation Among Unselected or Asymptomatic Persons

Author, Year Study Name Registry No.	Study Design	Sample Size	Country	Study Population	Method of Detection	Previously Undiagnosed AF Prevalence (95% CI)
Kaasenbrood et al, 2020[111]	Cluster RCT	17,107	The Nether-lands	Clinic-based sample of 31 general practices. Baseline characteristics collected in a random sample of 10% of study participants. 15 Intervention practices baseline characteristics: Hypertension: 50.9% Type 2 diabetes: 19.8% COPD: 8.1% Prior myocardial infarction: 6.8% Ischemic stroke: 3.9% TIA 4.6%. 16 control practices baseline characteristics: Hypertension: 50.4% Type 2 diabetes: 17.1% COPD: 8.0% Prior myocardial infarction: 6.7% Ischemic stroke: 6.4% TIA: 4.7%. Mean age: Intervention group: 74.3 (7.3). Control arm: 74.5 (7.3) N (%) Female: Intervention group: 4,680 (54.5). Control arm: 4,610 (54.1)	One-time, single-lead ECG performed with handheld device (MyDiagnostic), interpreted by GP, followed by 12-lead ECG, interpreted by cardiologist	1.4% (NR) Followup over 12 months. Only 10.7% (919) of the population in the intervention practices were actually screened; the proportion with AF among this group was .030.
Kaasenbrood, 2016[182]	Uncontrolled trial	3,269	The Nether-lands	Patients age 60 years or older recruited from 10 general practices at the time of yearly flu vaccination Mean age: 69.4 (SD 8.9) Men: 49.0%	One-time single-lead ECG via handheld device for 60 seconds. Detection based on positive signal confirmed by cardiologist(s).	1.1% (NR)
Kearley et al, 2014[113]	Cross-sectional study	890	U.K.	Patients age ≥75 years recruited from six general practices Mean age: 79.7 (NR) N (%) Female: 507 (50.7)	12-lead ECG interpreted by cardiologist	1.3% (NR)

Appendix B Table 1. Summary of Studies Published Since 2000 Reporting the Prevalence of Previously Undiagnosed Atrial Fibrillation Among Unselected or Asymptomatic Persons

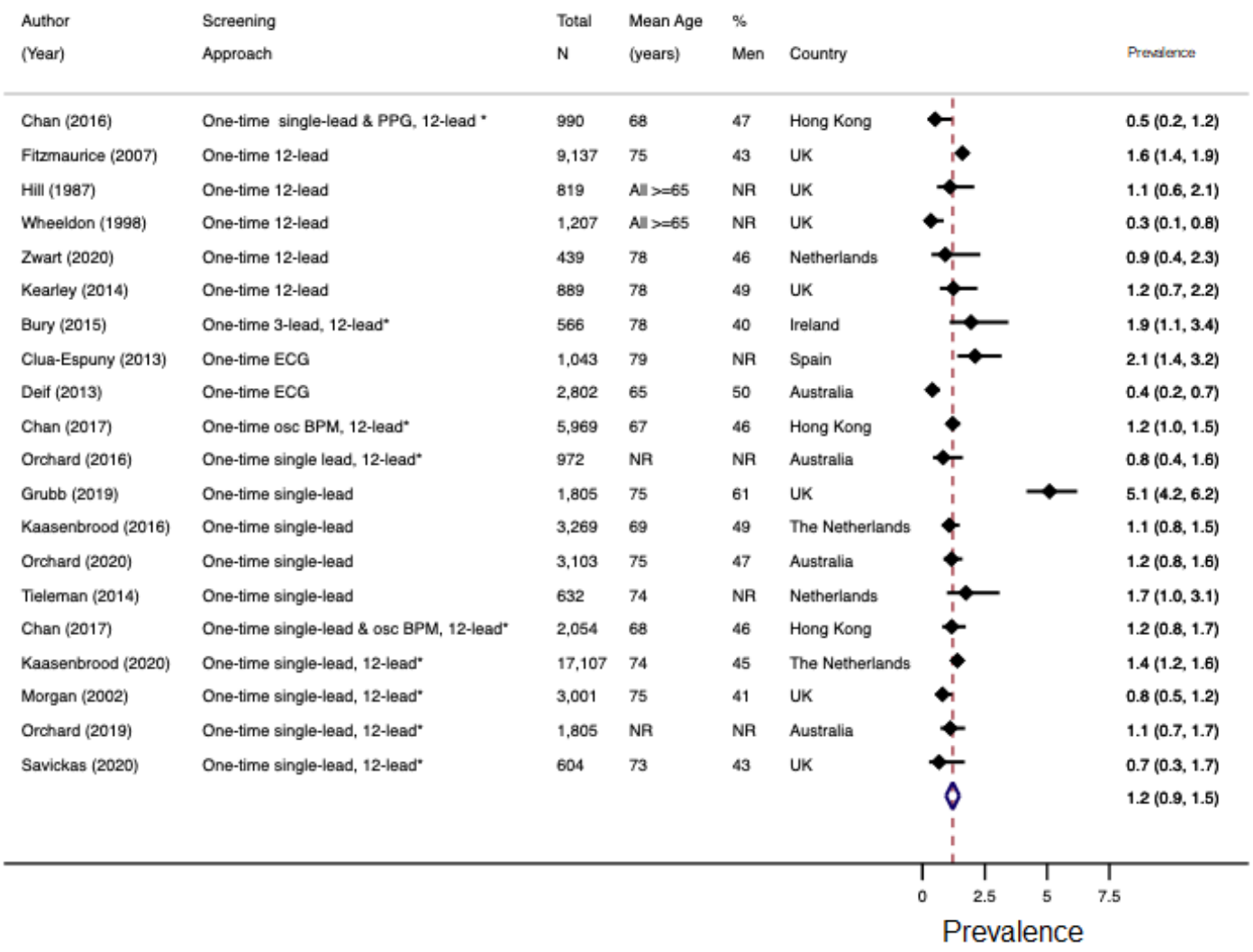
Author, Year Study Name Registry No.	Study Design	Sample Size	Country	Study Population	Method of Detection	Previously Undiagnosed AF Prevalence (95% CI)
Morgan et al, 2002[105]	Parallel assignment RCT with two active comparators	3,001	U.K.	Patients ages 65 to 100 years from four general practices Mean age: 75 (SD NR) Men: 41%	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)
Orchard et al, 2016[183] ACTRN12615000622505	Uncontrolled trial	972	Australia	Participants age 65 years or older recruited from five general practices Mean age: NR N (%) Female: NR	Handheld, single lead ECG (AliveCor), if AF detected or ECG was not able to be classified, then 12-lead ECG used to confirm.	0.8% (NR)
Orchard et al, 2019[184] AF-SMART ACTRN12616000850471	Uncontrolled trial	1,805	Australia	Patients age 65 years or older seen within 8 general practices without known diagnosis of AF Mean age: NR N (%) Female: NR	One-time single lead ECG using AliveCor KardiaMobile smartphone ECG device; results confirmed with 12-lead ECG	1.1% (NR)
Philippsen et al, 2017[56]	Cross-sectional study	82	Denmark	Patients ≥ 65 years of age without known or suspected AF attending the diabetes and cardiology hospital outpatient clinics. Patients with known AF or CIED, history of stroke or TIA were excluded. Mean age: Median: 71.3 (IQR 67.4 to 75.1 years) N (%) Female: 30 (37) N (%) Insulin or oral anitdiabetics: 61 (74) Mean (SD) no. antihypertensives: 4 (0.9) Mean (SD) LVEF, %: 60 (7.0)	2-channel 72-hour Holter monitoring analyzed by trained staff and adjudicated by 2 experienced cardiologists. AF defined as ≥>=1 episode of irregular rhythm without P waves lasting at least 30 seconds.	2.4%
Quinn et al, 2018[185]	Uncontrolled trial	2,054	Canada	Patients age 65 years or older who were attending routine appointments involving 22 primary care clinics Mean age: 73.7 (6.9) N (%) Female: 1,096 (53.4)	Confirmation with 12-lead ECG or 24-hour Holter monitor after pulse check, single-lead ECG, and authomated oscillometric BP measurement with AF detection algorithm	0.6% (NR)

Appendix B Table 1. Summary of Studies Published Since 2000 Reporting the Prevalence of Previously Undiagnosed Atrial Fibrillation Among Unselected or Asymptomatic Persons

Author, Year Study Name Registry No.	Study Design	Sample Size	Country	Study Population	Method of Detection	Previously Undiagnosed AF Prevalence (95% CI)
Salvatori et al, 2015[186]	Uncontrolled trial	274	Italy	Participants age 65 years or older with HTN without known AF or symptoms from 15 general practitioners were randomized to be recruited Mean age: 70 (4) N (%) Female: 127 (46)	48-hour Holter monitoring in participants	2.6% (NR)
Tieleman et al, 2014[187]	Uncontrolled trial	632	The Nether-lands	Patients undergoing influenza vaccination at a two general practice clinics Mean age: 74 (7.1) N (%) Female: NR	One-time single-lead ECG for 60-second interval using handheld device, MyDiagnostick (MyDiagnostick Medical BV). Stored ECG results read by cardiologist for diagnosis.	1.8% (NR)
Turakhia et al, 2015, STUDY-AF[149]	Uncontrolled trial	75	U.S.	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) Men: 100% With hypertension: 95% With heart failure: 17% With coronary artery disease: 77% With diabetes: 56%	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)
Wheeldon et al, 1998[188]	Uncontrolled trial	1,207	U.K.	Patients age 65 years 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)

Abbreviations: ACE=Akershus Cardiac Examination; AF=atrial fibrillation; BNP=NT-proB type natriuretic peptide; BP=blood pressure; CA=California; $CHADS_2$=Congestive heart failure, Hypertension, Age≥75 years, Diabetes mellitus, prior Stroke or TIA or thromboembolism; CHD=coronary heart disease; CHF=congestive heart failure; CI=confidence interval; CIED=cardiac implantable electronic devices; COPD=chronic obstructive pulmonary disease; DM=diabetes mellitus; ECG=electrocardiogram; GP=general practitioner; HTN=hypertension; ICM=insertable cardiac monitor; IQR=interquartile range; LVEF=left ventricular ejection fraction; MI=myocardial infarction; N=number of participants; NR=not reported; PPG=photoplethysmography; RCT=randomized, controlled trial; RR=risk ratio; SAFE=Screening for Atrial Fibrillation in the Elderly; SD=standard deviation; SEARCH-AF=Screening Education and Recognition in Community pHarmacies of Atrial Fibrillation; STUDY-AF=Screening Study for Undiagnosed Atrial Fibrillation; TIA=transient ischemic attack; TILDA=The Irish Longitudinal Study on Ageing; U.K.=United Kingdom; U.S.=United States.

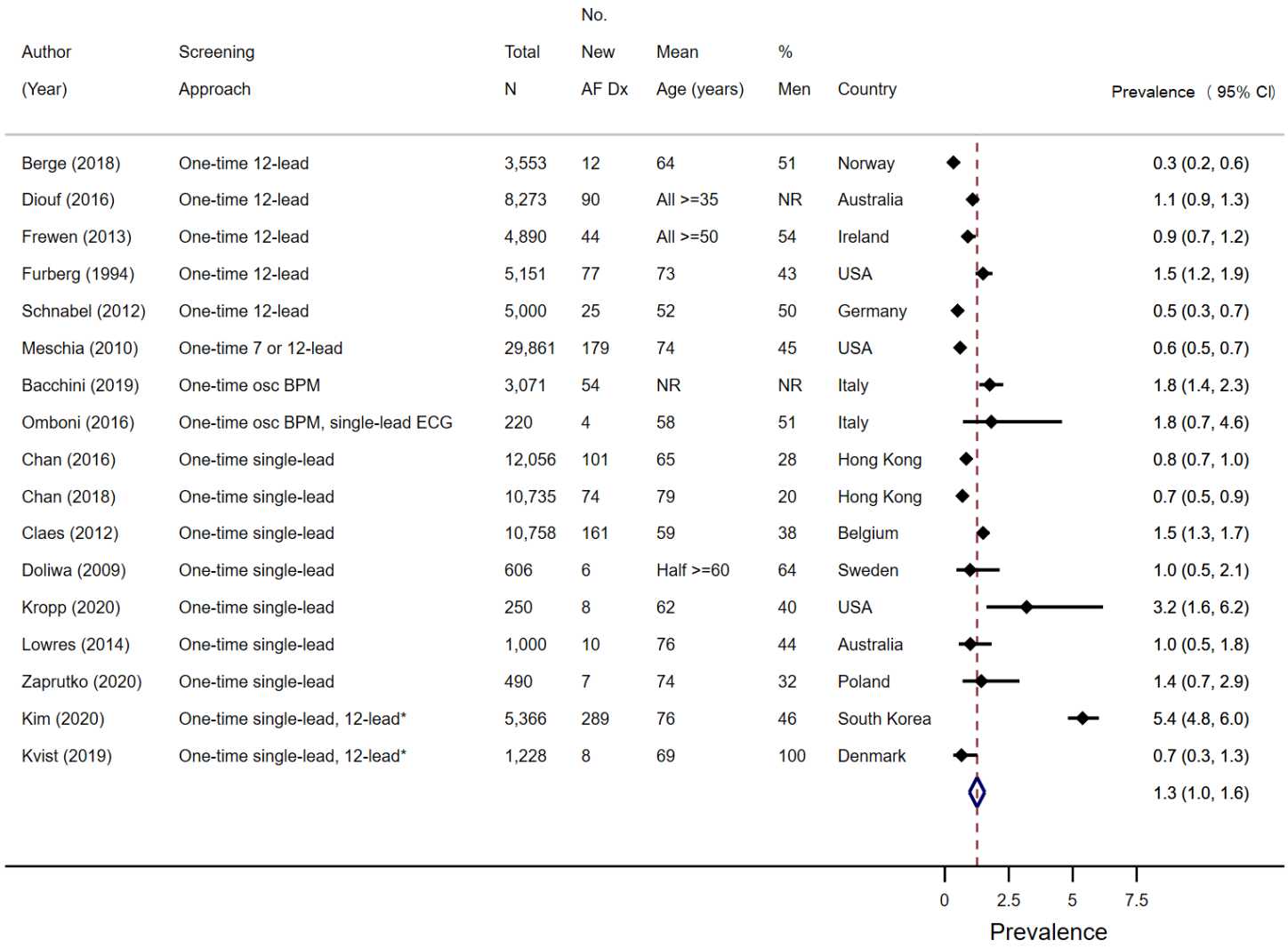
Appendix B Figure 1. Prevalence of Undiagnosed Atrial Fibrillation Based on One-Time Tests in Clinic-Based Populations



* Confirmatory 12-lead ECG

Abbreviations: BPM=blood pressure monitor; CI=confidence interval; ECG=electrocardiography; NR=not reported; osc=oscillometric; PPG=photoplethysmography; UK=United Kingdom.

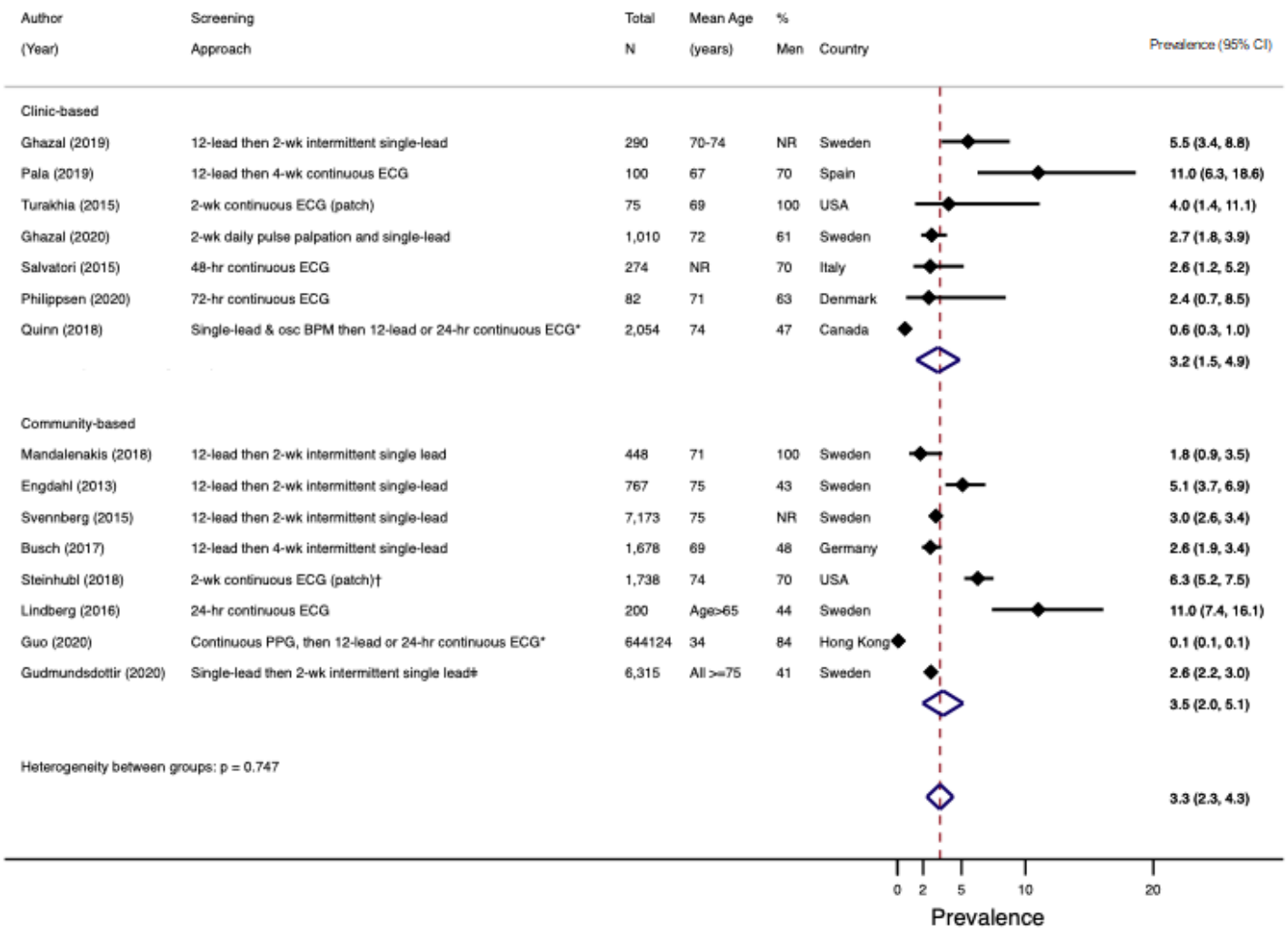
Appendix B Figure 2. Prevalence of Undiagnosed Atrial Fibrillation Based on One-Time Tests in Community-Based Populations



* Confirmatory 12-lead ECG

Abbreviations: BPM=blood pressure monitor; CI=confidence interval; ECG=electrocardiography; NR=not reported; osc=oscillometric; USA=United States of America.

Appendix B Figure 3. Prevalence of Undiagnosed Atrial Fibrillation Based on Continuous or Intermittent Monitoring Tests



* Confirmatory 12-Lead ECG
† Two rounds of 2-week continuous monitoring via ECG patch 3 months apart.
‡ Only persons in the high-risk group as assessed via biomarker received intermittent monitoring.

Abbreviations: CI=confidence interval; ECG=electrocardiography; NR=not reported; osc=oscillometric; UK=United Kingdom; USA=United States of America.

Appendix B Table 2. Stroke Incidence for People With Asymptomatic, Previously Unrecognized AF Compared With Stroke Incidence for People With Symptomatic AF Reported by Observational Studies

Author, Year Country	Study Population and Setting	Stroke Incidence	Study Limitations
Thind et al, 2018[190] U.S.	176 sites enrolled 9319 participants with incident or prevalent AF between 2010 and 2011 from outpatient practices, diagnosed with ECG. Symptom status was assessed at baseline registry (ORBIT-AF) enrollment by clinician and symptom checklist.	Asymptomatic AF, 0.90 per 100 person-years vs. symptomatic AF 1.04 per 100 person-years for stroke or non-CNS embolism over mean followup of 2.6 years Adjusted HR, 0.85 (95% CI, 0.63 to 1.16) comparing asymptomatic to symptomatic AF. Adjusted for a variety of clinical and demographic characteristics including age and use of oral anticoagulation	• High levels of comorbidities may limit applicability to general population (e.g., HTN 83%, DM 30%, CKD 34%, HF 32%, CAD 36%, CVA 15%) • Symptom status assessed at registry enrollment; symptom status at AF diagnosis unknown, which limits applicability to incident asymptomatic AF
Potpara, 2013[39] 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	Asymptomatic AF, 14 (9.6%) vs. symptomatic AF, 44 (4.6%) 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 may not be applicable to general population
Tsang, 2011[40] U.S.	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 before 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[41] U.S.	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.)

Appendix B Table 2. Stroke Incidence for People With Asymptomatic, Previously Unrecognized AF Compared With Stroke Incidence for People With Symptomatic AF Reported by Observational Studies

Author, Year Country	Study Population and Setting	Stroke Incidence	Study Limitations
Boriani, 2015[42] 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 an AF registry from those presenting to cardiology practices from 9 countries. Most asymptomatic patients had valvular heart disease (64.5%), chronic heart failure (44.3%), or CAD (40.1%). (Total cohort=3,119 in the EORP-AF)	Mean followup about 1 year Asymptomatic AF, 112/1064 (10.5%) vs. symptomatic AF, 80/1409 (5.7%) events for a composite incidence of stroke/TIA/peripheral embolism or death higher in asymptomatic AF compared with 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*	• 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 because most participants had known heart disease

*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; CKD=chronic kidney disease; CNS=central nervous system; COPD=chronic obstructive pulmonary disease; CVA= cerebrovascular accident; DM=diabetes mellitus; ECG=electrocardiogram; eGFR=estimated glomerular filtration rate; EORP=EurObservational Research Programme – Atrial Fibrillation; HR=hazard ratio; NR=not reported; ORBIT-AF=Outcomes Registry for Better Informed Treatment of Atrial Fibrillation; TIA=transient ischemic attack; U.S.=United States; vs=versus.

Appendix B Table 3. 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
Bury et al (2015)[173]	12/566 (2.1)	CHA_2DS_2-VASc, median: 4
Chan et al (2016)[158]	101/8,797 (1.1)	CHA_2DS_2-VASc: 3.1 (1.3)
Deif et al (2012)[178]	10/1,459 (0.69)	Among persons age 65 or older CHA_2DS_2-VASc: 3.8 (SD 2.0) $CHADS_2$: 2.2 (1.5)
Grubb et al 2019[151]	92/1,805 (5.1)	CHA_2DS_2-VASc, median (range): 4.0 (2.0 to 7.0)
Kaasenbrood et al (2016)[182]	37/3,269 (1.1)	CHA_2DS_2-VASc: 3.4 (1.9)
Lowres et al (2014)[168]	15/1,000 (1.5)	CHA_2DS_2-VASc: 3.7 (1.1) $CHADS_2$: 1.9 (1.1)
Orchard et al (2020)[192]	36/3,103 (1.2)	CHA_2DS_2-VASc: 3.2
Svennberg et al (2015)[77]	218/7,173 (3.0)	CHA_2DS_2-VASc: 3.5 (1.2)
Turakhia et al (2015)[149]	4/75 (5.3)	CHA_2DS_2-VASc $\geq$2 in all 4 participants
Zaprutko et al (2020)[172]	7/525 (1.3)	CHA_2DS_2-VASc: 2.1 (0.7)
Busch et al (2017)[157]	43/1,678 (2.6)	$CHADS_2$: 2.4 (1.0)
Engdahl et al (2013)[152]	10/767 (1.3)	$CHADS_2$: 1.8 (NR)
Fitzmaurice et al (2014)[92]	149/9137 (1.6)	$CHADS_2$: 1.4 (1.1)

Abbreviations: AF=atrial fibrillation; $CHADS_2$=Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, prior Stroke or TIA or thromboembolism [doubled]; 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; n=number of patients; N/n=number of patients in sample; NR=not reported; SD=standard deviation.

Appendix B Table 4. Predicted Stroke Risk Profile of New AF Cases[148]

Age, years	n	Mean CHA_2DS_2-VASc (95% CI)
<60	251	1.1 (0.7-1.5)
60-64	125	1.4 (1.2-1.6)
65-69	223	2.5 (2.2-2.8)
70-74	240	2.7 (2.4-2.9)
75-79	228	3.8 (3.4-4.1)
80-84	151	3.8 (3.4-4.2)
85+	151	3.9 (3.6-4.4)

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; CI=confidence interval; n=number of patients.

Appendix B Table 5. Stroke Incidence and Predicted Stroke Risk for Older Adults With Paroxysmal AF Compared With Stroke Incidence for People With Persistent or Permanent AF

Author, Year Country	Study Population and Setting	Stroke Incidence	Risk Instrument/ Mean (SD) Predicted Stroke Risk	Study Limitations
Boriani et al, 2018[45] 9 countries (Belgium, Denmark, Greece, Italy, Netherlands, Norway, Poland, Portugal, Romania) Prospective cohort study	Total: 2,119 Paroxysmal AF: 573 Persistent AF: 445 Long-standing persistent AF: 119 Permanent AF: 335	Stroke, n (%) at 3 years followup Paroxysmal AF: 7 (1.4) Persistent AF: 4 (1.1) Permanent AF: 10 (3.5) p=0.14 Calculated RD 0.32 (95% CI, -1.49 to 1.91) paroxysmal vs. persistent Calculated RD -2.07 (95% CI, -4.95 to 0.07) paroxysmal vs. permanent	CHA_2DS_2-VASc: Low risk, n (%) Paroxysmal AF: 71 (12.4) Persistent AF: 28 (6.3) Long-standing persistent AF: 4 (3.4) Permanent AF: 11 (3.3) CHA_2DS_2-VASc: Moderate risk, n (%) Paroxysmal AF: 68 (11.9) Persistent AF: 55 (12.4) Long-standing persistent AF: 7 (5.9) Permanent AF: 16 (4.8) CHA_2DS_2-VASc: High risk, n (%) Paroxysmal AF: 434 (75.7) Persistent AF: 362 (81.3) Long-standing persistent AF: 108 (90.8) Permanent AF: 308 (91.9)	Only included patients presenting to a cardiologist.
Ganesan et al, 2016[44] Systematic review/meta-analysis (n=12 included studies)	99,996 patients from 12 studies (10 RCTs and 2 prospective cohort studies)	Stroke, %: Nonparoxysmal AF: 2.2 (95% CI, 1.8 to 2.5) Paroxysmal AF: 1.5 (95% CI, 1.2 to 1.8) Adjusted* RR of nonparoxysmal vs. paroxysmal AF: 1.4 (95% CI, 1.2 to 1.6), p<0.001, I^2=28.8%	NR	Did not assess if increased thromboembolic risk for nonparoxysmal AF applies uniformly over all $CHADS_2$/CHA_2DS_2-VASc scores.
Link et al, 2017[43] Multiple countries (U.S. and non-U.S.) Prospective cohort study	Total N: 21,105 Paroxysmal AF: 5,366 Persistent AF: 4,868 Permanent AF: 10,865	Stroke or SEE: Paroxysmal AF: 1.5%/yr Persistent AF: 1.8%/yr Permanent AF: 2.0%/yr Adjusted† HR of paroxysmal vs. persistent AF: 0.8 (95% CI, 0.7 to 0.96), p=0.015 Adjusted† HR of paroxysmal vs. permanent AF: 0.8 (95% CI, 0.7 to 0.9), p=0.004	NR	Prespecified secondary analysis of clinical trial data.

* Adjusted for age, gender, hypertension, heart failure, previous thromboembolism, and diabetes mellitus.[44]
† Adjusted for age, sex, hypertension, congestive heart failure, prior stroke or TIA, diabetes mellitus, race, geographic region, BMI, smoking status, alcohol use, coronary artery disease, dyslipidemia, increased risk of falling, hepatic disease, neuropsychiatric disease, prior non-ICH bleed, use of antiplatelet agents at randomization, and creatinine clearance at randomization.[43]

Abbreviations: AF=atrial fibrillation; BMI=body mass index; $CHADS_2$=Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, prior Stroke or TIA or thromboembolism [doubled]; 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; CI=confidence interval; HR=hazard ratio; ICH=intracerebral hemorrhage; n/N=number of patients; NR=not reported; RCT=randomized, controlled trial; RD=risk difference; RR=risk ratio; SD=standard deviation; SEE=systemic embolic event; TIA=transient ischemic attack; U.S.=United States; vs=versus.

Appendix C1. Update Search Strategies

MEDLINE® via PubMed

Main Update Search (5/1/2017 through 2/19/2020)

Search	Query
#1	Search ("Atrial Fibrillation"[Mesh] OR "Atrial Flutter"[Mesh] OR atrial fibril*[tiab] OR atrium fibril*[tiab] OR a-fib[tiab] OR afib[tiab] OR "atrial flutter"[tiab] OR "auricular flutter"[tiab])
#2	Search ("Electrocardiography"[Mesh] OR electrocardiogram*[tiab] OR electrocardiograph*[tiab] OR electrocardiography[tiab] OR EKG[tiab] OR ECG[tiab] OR holter[tiab] OR "mobile cardiac outpatient telemetry"[tiab] OR patch monitor*[tiab] OR single lead[tiab] OR 12-lead[tiab])
#3	Search (#1 AND #2)
#4	Search ("Mass Screening"[Mesh] OR screen*[tiab])
#5	Search (#3 AND #4)
#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])
#7	Search (#5 AND #6)
#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])))
#9	Search (#5 AND #8)
#10	Search (#7 OR #9)
#11	Search (#10 AND Humans[Mesh:NOEXP]) OR (#10 NOT Animals[Mesh:NOEXP])
#12	Search (#10 AND Humans[Mesh:NOEXP]) OR (#10 NOT Animals[Mesh:NOEXP]) Filters: English
#13	Search (#10 AND Humans[Mesh:NOEXP]) OR (#10 NOT Animals[Mesh:NOEXP]) Filters: English; Adult: 19+ years
#14	Search (#10 AND Humans[Mesh:NOEXP]) OR (#10 NOT Animals[Mesh:NOEXP]) Filters: English; Adult: 19+ years; Aged: 65+ years
#15	Search (#10 AND Humans[Mesh:NOEXP]) OR (#10 NOT Animals[Mesh:NOEXP]) Filters: Publication date from 2017/05/01 to 2020/12/31; English; Adult: 19+ years; Aged: 65+ years
#16	Search (#3 AND #4) Filters: Systematic Reviews
#17	Search (#3 AND #4) Filters: Systematic Reviews; Meta-Analysis
#18	Search ((#17 AND Humans[Mesh:NOEXP]) OR (#17 NOT Animals[Mesh:NOEXP]))
#19	Search ((#17 AND Humans[Mesh:NOEXP]) OR (#17 NOT Animals[Mesh:NOEXP])) Filters: English
#20	Search ((#17 AND Humans[Mesh:NOEXP]) OR (#17 NOT Animals[Mesh:NOEXP])) Filters: English; Adult: 19+ years
#21	Search ("Anticoagulants"[Mesh] OR "Dabigatran"[Mesh] OR "Rivaroxaban"[Mesh] OR "Warfarin"[Mesh] OR anticoagulant*[tiab] OR apixaban OR Coumadin OR Dabigatran OR Edoxaban OR Eliquis OR NOAC* OR Pradaxa OR Rivaroxaban OR Savaysa OR "vitamin k agonist"[All Fields] OR "vitamin k agonists"[All Fields] OR VKA OR warfarin OR Xarelto)
#22	Search (#1 AND #21)
#23	Search "Factor Xa Inhibitors"[Mesh] OR "factor xa"[tiab]
#24	Search (#1 AND #23)
#25	Search ("Antithrombins"[Mesh] OR antithrombin*[tiab] OR thrombin inhibit*[tiab])
#26	Search (#1 AND #25)
#27	Search ("Aspirin"[Mesh] OR "Aspirin, Dipyridamole Drug Combination"[Mesh] OR "clopidogrel"[Supplementary Concept] OR "Dipyridamole"[Mesh] OR "acetylsalicylic acid" OR Aggrenox OR anti-platelet* OR antiplatelet* OR ASA[tiab] OR aspirin OR clopidogrel OR Dipyridamole OR Plavix)
#28	Search (#1 AND #27)
#29	Search (#22 OR #24 OR #26 OR #28)
#30	Search (#29 AND Humans[Mesh:NOEXP]) OR (#29 NOT Animals[Mesh:NOEXP])
#31	Search (#29 AND Humans[Mesh:NOEXP]) OR (#29 NOT Animals[Mesh:NOEXP]) Filters: English
#32	Search (#29 AND Humans[Mesh:NOEXP]) OR (#29 NOT Animals[Mesh:NOEXP]) Filters: English; Adult: 19+ years
#33	Search (#29 AND Humans[Mesh:NOEXP]) OR (#29 NOT Animals[Mesh:NOEXP]) Filters: Publication date from 2017/05/01 to 2020/12/31; English; Adult: 19+ years

Appendix C1. Update Search Strategies

Search	Query
#34	Search (#33 AND #6)
#35	Search (#33 AND #8)
#36	Search (#29 AND Humans[Mesh:NOEXP]) OR (#29 NOT Animals[Mesh:NOEXP]) Filters: Systematic Reviews; Publication date from 2017/05/01 to 2020/12/31; English; Adult: 19+ years
#37	Search (#29 AND Humans[Mesh:NOEXP]) OR (#29 NOT Animals[Mesh:NOEXP]) Filters: Systematic Reviews; Meta-Analysis; Publication date from 2017/05/01 to 2020/12/31; English; Adult: 19+ years

Supplemental Search for Emerging Technologies (Inception through 2/19/2020)

Search	Query
#1	Search ("Atrial Fibrillation"[Mesh] OR "Atrial Flutter"[Mesh] OR atrial fibril*[tiab] OR atrium fibril*[tiab] OR a-fib[tiab] OR afib[tiab] OR "atrial flutter"[tiab] OR "auricular flutter"[tiab])
#2	Search ("Fitness Trackers"[Mesh] OR "Mobile Applications"[Mesh] OR “Photoplethysmography"[Mesh] OR “Smartphone"[Mesh] OR “Telemedicine"[Mesh] OR “Wearable Electronic Devices"[Mesh:NOEXP])
#3	Search (#1 AND #2)
#4	Search (“1-lead”[tiab] OR “single lead”[tiab] OR “3-lead”[tiab] OR “three lead” OR AliveCor[tiab] OR app[tiab] OR (apple[tiab] AND watch*[tiab]) OR “digital treatment”[tiab] OR “Cardiio Rhythm”[tiab] OR FibriCheck[tiab] OR Fitbit*[tiab] OR (fitness[tiab] AND tracker*[tiab]) OR “Galaxy Gear”[All Fields] OR “iRhythm Zio”[All Fields] OR KardiaMobile[tiab] OR mHealth[tiab] OR “mobile health”[tiab] OR ((mobile[tiab] AND (app[tiab] OR application*[tiab] OR apps[tiab])) OR Photoplethysmography[tiab] OR PPG[tiab] OR “portable device”[tiab] OR “portable devices”[tiab] OR smartphone*[tiab] OR ((smart[tiab] AND phone*[tiab]) OR (smart[tiab] AND watch*[tiab]) OR smartwatch*[tiab] OR telehealth[tiab] OR telemedicine[tiab] OR verily[tiab] OR wearable*[tiab] OR (“wristband device”[All Fields] OR “wristband devices”[All Fields]))
#5	Search (#1 AND #4)
#6	Search (#3 OR #5)
#7	Search (#6 AND Humans[Mesh:NOEXP]) OR (#6 NOT Animals[Mesh:NOEXP])
#8	Search (#6 AND Humans[Mesh:NOEXP]) OR (#6 NOT Animals[Mesh:NOEXP]) Filters: English
#9	Search (#6 AND Humans[Mesh:NOEXP]) OR (#6 NOT Animals[Mesh:NOEXP]) Filters: Systematic Reviews; English
#10	Search (#6 AND Humans[Mesh:NOEXP]) OR (#6 NOT Animals[Mesh:NOEXP]) Filters: Systematic Reviews; Meta-Analysis; English
#11	Search (#8 NOT #10)

Appendix C1. Update Search Strategies

Supplemental Search for Diagnostic Accuracy (2/1/2014 through 4/22/2020)

Because the KQ on diagnostic accuracy (KQ 3) was new to this update, we conducted supplementary searches focused on screening accuracy (dates: 2/1/2014 to 4/22/2020). We relied on a good-quality systematic review conducted by Welton et al[208] to identify potentially relevant diagnostic accuracy studies conducted before 2014.

Search Number	Query	Filters
1	("Atrial Fibrillation"[Mesh] OR "Atrial Flutter"[Mesh] OR atrial fibril*[tiab] OR atrium fibril*[tiab] OR a-fib[tiab] OR afib[tiab] OR "atrial flutter"[tiab] OR "auricular flutter"[tiab])	
2	("Electrocardiography"[Mesh] OR "continuous ambulatory ECG"[tiab] OR "continuous ambulatory EKG"[All Fields] OR electrocardiogram*[tiab] OR electrocardiograph*[tiab] OR electrocardiography[tiab] OR EKG[tiab] OR ECG[tiab] OR "1-lead"[tiab] OR "single lead"[tiab] OR "3-lead"[tiab] OR "three lead"[tiab] OR "12-lead"[tiab] OR "twelve lead"[tiab] OR "event loop recorder"[tiab] OR Holter[tiab] OR "mobile cardiac telemetry"[tiab] OR patch monitor*)	
3	((apple[tiab] AND watch*[tiab]) OR "digital treatment"[tiab] OR "Cardiio Rhythm"[tiab] OR FibriCheck[tiab] OR Fitbit*[tiab] OR (fitness[tiab] AND tracker*[tiab]) OR "Galaxy Gear"[All Fields] OR "iRhythm Zio"[All Fields] OR KardiaMobile[tiab] OR mHealth[tiab] OR "mobile health"[tiab] OR (mobile[tiab] AND (app[tiab] OR application*[tiab] OR apps[tiab])) OR Photoplethysmography[tiab] OR PPG[tiab] OR "portable device"[tiab] OR "portable devices"[tiab] OR smartphone*[tiab] OR (smart[tiab] AND phone*[tiab]) OR (smart[tiab] AND watch*[tiab]) OR smartwatch*[tiab] OR verily[tiab] OR wearable*[tiab] OR "wristband device"[All Fields] OR "wristband devices"[All Fields])	
4	(#1 AND (#2 OR #3))	
5	("Sensitivity and Specificity"[Mesh] OR "Predictive Value of Tests"[Mesh] OR "ROC Curve"[Mesh] OR "Reproducibility of Results"[Mesh] OR "False Negative Reactions"[Mesh] OR "False Positive Reactions"[Mesh] OR ((pre-test[tw] or pretest[tw]) AND probability[tw]) OR "predictive value"[tw] OR sensitivity[tw] OR specificity[tw] OR accuracy[tw] OR ROC[tw] OR "false positive"[tw] OR "false negative"[tw] OR "likelihood ratio"[tw])	
6	(#4 AND #5)	
7	((diagnos*[tiab] or screening[tiab]) AND (accurate*[tiab] or accuracy[tiab]))	
8	(#4 AND #7)	
9	(diagnos*[tiab] or underdiagnose*[tiab] or detect*[tiab] or identif*[tiab] or screen*[tiab])	
10	(#4 AND #9)	
11	(diagnos*[tiab] or detect*[tiab]) AND (rate[tiab] or yield[tiab] or PAF[tiab])	
12	(#4 AND #11)	
13	("diagnosis" [Subheading] OR "Diagnosis, Computer-Assisted"[Mesh] OR "Early Diagnosis"[Mesh])	
14	(#4 AND #13)	
15	(#6 OR #8 OR #10 OR #12 OR #14)	
16	((#15 AND Humans[Mesh:NOEXP]) OR (#15 NOT Animals[Mesh:NOEXP]))	
17	((#15 AND Humans[Mesh:NOEXP]) OR (#15 NOT Animals[Mesh:NOEXP]))	English

Appendix C1. Update Search Strategies

Search Number	Query	Filters
18	((#15 AND Humans[Mesh:NOEXP]) OR (#15 NOT Animals[Mesh:NOEXP]))	English, Adult: 19+ years
19	(address[pt] OR "autobiography"[pt] OR "bibliography"[pt] OR "biography"[pt] OR "case control"[tw] OR "case report"[tw] OR "case reports"[tw] OR "case series"[tw] OR "comment"[pt] OR "comment on"[All Fields] OR congress[pt] OR "cross-sectional"[tw] OR "dictionary"[pt] OR "directory"[pt] OR "editorial"[pt] OR "festschrift"[pt] OR "historical article"[pt] OR "interview"[pt] OR lecture[pt] OR "legal case"[pt] OR "legislation"[pt] OR letter[pt] "news"[pt] OR "newspaper article"[pt] OR "patient education handout"[pt] OR "periodical index"[pt] OR "retrospective cohort"[tw] OR ("Animals"[Mesh] NOT "Humans"[Mesh]) OR rats[tw] OR cow[tw] OR cows[tw] OR chicken[tw] OR chickens[tw] OR horse[tw] or horses[tw] OR mice[tw] OR mouse[tw] OR bovine[tw] OR sheep OR ovine OR murinae)	English, Adult: 19+ years
20	#18 NOT #19	English, Adult: 19+ years
28	"Evaluation Study" [Publication Type] OR "Validation Study" [Publication Type]	
29	#20 AND #28	
30	("Comparative Study"[pt] OR "Evaluation Study" [Publication Type] OR "Validation Study" [Publication Type] OR "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])))	
31	#20 AND #30	
32	("2014/02/01"[Date - Publication] : "3000"[Date - Publication])	
33	#29 AND #32	

Appendix C1. Update Search Strategies

Cochrane Library

Main Update Search (1/1/2017–2/21/2020)

ID	Search
#1	[mh "Atrial Fibrillation"] OR [mh "Atrial Flutter"] OR atrial fibril*:ti,ab OR atrium fibril*:ti,ab OR a-fib:ti,ab OR afib:ti,ab OR "atrial flutter":ti,ab OR "auricular flutter":ti,ab
#2	[mh "Electrocardiography"] OR electrocardiograph*:ti,ab OR electrocardiogram*:ti,ab OR EKG:ti,ab OR ECG:ti,ab OR holter:ti,ab OR "mobile cardiac outpatient telemetry":ti,ab OR patch monitor*:ti,ab OR "single lead":ti,ab OR "12-lead":ti,ab
#3	#1 AND #2
#4	[mh "Mass Screening"] OR screen*:ti,ab
#5	#3 AND #4
#6	#5 with Publication Year from 2017 to 2020, with Cochrane Library publication date Between May 2017 and Jan 2020, in Trials
#7	#6 NOT "conference abstract":pt
#8	#6 AND "conference abstract":pt
#9	[mh "Anticoagulants"] OR [mh "Dabigatran"] OR [mh "Rivaroxaban"] OR [mh "Warfarin"] OR anticoagulant*:ti,ab OR apixaban OR Coumadin OR Dabigatran OR Edoxaban OR Eliquis OR NOAC* OR Pradaxa OR Rivaroxaban OR Savaysa OR “vitamin k agonist”:ti,ab,kw OR “vitamin k agonists”:ti,ab,kw OR VKA OR warfarin OR Xarelto
#10	#1 AND #9
#11	[mh "Factor Xa Inhibitors"] OR "factor xa":ti,ab
#12	#1 AND #11
#13	[mh "Antithrombins"] OR antithrombin*:ti,ab OR thrombin inhibit*:ti,ab
#14	#1 AND #13
#15	[mh "Aspirin"] OR [mh "Aspirin, Dipyridamole Drug Combination"] OR [mh "Dipyridamole"] OR "acetylsalicylic acid" OR Aggrenox OR anti-platelet* OR antiplatelet* OR ASA:ti,ab OR aspirin OR clopidogrel OR Dipyridamole OR Plavix
#16	#1 AND #15
#17	#10 OR #12 OR #14 OR #16
#18	#17 with Publication Year from 2017 to 2020, in Trials
#19	#18 NOT "conference abstract":pt
#20	#18 AND "conference abstract":pt

Supplemental Emerging Technologies Search (Inception to 2/21/2020)

ID	Search
#1	[mh "Atrial Fibrillation"] OR [mh "Atrial Flutter"] OR atrial fibril*:ti,ab OR atrium fibril*:ti,ab OR a-fib:ti,ab OR afib:ti,ab OR "atrial flutter":ti,ab OR "auricular flutter":ti,ab
#2	[mh "Fitness Trackers"] OR [mh "Mobile Applications"] OR [mh “Photoplethysmography"] OR [mh “Smartphone"] OR [mh “Telemedicine"] OR [mh ^”Wearable Electronic Devices"]
#3	#1 AND #2
#4	"1-lead":ti,ab OR "single lead":ti,ab OR "3-lead":ti,ab OR "three lead":ti,ab OR AliveCor:ti,ab OR app:ti,ab OR (apple:ti,ab AND watch*:ti,ab) OR "digital treatment":ti,ab OR "Cardiio Rhythm":ti,ab OR FibriCheck:ti,ab OR Fitbit*:ti,ab OR (fitness:ti,ab AND tracker*:ti,ab) OR "Galaxy Gear":ti,ab,kw OR "iRhythm Zio":ti,ab,kw OR KardiaMobile:ti,ab OR mHealth:ti,ab OR "mobile health":ti,ab OR (mobile:ti,ab AND (app:ti,ab OR application*:ti,ab OR apps:ti,ab)) OR Photoplethysmography:ti,ab OR PPG:ti,ab OR "portable device":ti,ab OR "portable devices":ti,ab OR smartphone*:ti,ab OR (smart:ti,ab AND phone*:ti,ab) OR (smart:ti,ab AND watch*:ti,ab) OR smartwatch*:ti,ab OR telehealth:ti,ab OR telemedicine:ti,ab OR Verily:ti,ab OR wearable*:ti,ab OR "wristband device":ti,ab,kw OR "wristband devices":ti,ab,kw
#5	#1 AND #4
#6	#3 OR #5
#7	#6 AND "conference abstract":pt
#8	#6 NOT "conference abstract":pt

Appendix C1. Update Search Strategies

Supplemental Diagnostic Accuracy Search (1/1/2014–2/21/2020)

ID	Search
1	[mh "Atrial Fibrillation"] OR [mh "Atrial Flutter"] OR atrial fibril*:ti,ab OR atrium fibril*:ti,ab OR a-fib:ti,ab OR afib:ti,ab OR "atrial flutter":ti,ab OR "auricular flutter":ti,ab
#2	[mh "Electrocardiography"] OR electrocardiogram*:ti,ab OR electrocardiograph*:ti,ab OR EKG:ti,ab OR ECG:ti,ab OR "1-lead":ti,ab OR "single lead":ti,ab OR "3-lead":ti,ab OR "three lead":ti,ab OR "12-lead":ti,ab OR "twelve lead":ti,ab OR "event loop recorder":ti,ab OR Holter:ti,ab OR "mobile cardiac telemetry":ti,ab OR patch monitor*:ti,ab
#3	(apple:ti,ab AND watch*:ti,ab) OR "digital treatment":ti,ab OR "Cardiio Rhythm":ti,ab OR FibriCheck:ti,ab OR Fitbit*:ti,ab OR (fitness:ti,ab AND tracker*:ti,ab) OR "Galaxy Gear":ti,ab,kw OR "iRhythm Zio":ti,ab,kw OR KardiaMobile:ti,ab OR mHealth:ti,ab OR "mobile health":ti,ab OR (mobile:ti,ab AND (app:ti,ab OR application*:ti,ab OR apps:ti,ab)) OR Photoplethysmography:ti,ab OR PPG:ti,ab OR "portable device":ti,ab OR "portable devices":ti,ab OR smartphone*:ti,ab OR (smart:ti,ab AND phone*:ti,ab) OR (smart:ti,ab AND watch*:ti,ab) OR smartwatch*:ti,ab OR Verily:ti,ab OR wearable*:ti,ab OR "wristband device":ti,ab,kw OR "wristband devices":ti,ab,kw
#4	#1 AND (#2 OR #3)
#5	[mh "Sensitivity and Specificity"] OR [mh "Predictive Value of Tests"] OR [mh "ROC Curve"] OR [mh "Reproducibility of Results"] OR [mh "False Negative Reactions"] OR [mh "False Positive Reactions"] OR (("pre-test":ti,ab,kw OR "pretest":ti,ab,kw) AND "probability":ti,ab,kw) OR "predictive value":ti,ab,kw OR "sensitivity":ti,ab,kw OR "specificity":ti,ab,kw OR "accuracy":ti,ab,kw OR "ROC":ti,ab,kw OR "false positive":ti,ab,kw OR "false negative":ti,ab,kw OR "likelihood ratio":ti,ab,kw
#6	#4 AND #5
#7	(diagnos*:ti,ab or screening:ti,ab) AND (accurate*:ti,ab or accuracy:ti,ab)
#8	#4 AND #7
#9	diagnos*:ti,ab or underdiagnose*:ti,ab or detect*:ti,ab or identif*:ti,ab or screen*:ti,ab
#10	#4 AND #9
#11	(diagnos*:ti,ab OR detect*:ti,ab) AND (rate:ti,ab OR yield:ti,ab OR PAF:ti,ab)
#12	#4 AND #11
#13	[mh /DI] OR [mh "Diagnosis, Computer-Assisted"] OR [mh "Early Diagnosis"]
#14	#4 AND #13
#15	#6 OR #8 OR #10 OR #12 OR #14
#16	#15 with Publication Year from 2014 to 2020, in Trials
#17	#16 AND "conference abstract":pt
#18	#16 NOT "conference abstract":pt

Gray Literature Searches (5/1/2017–2/25/2020)

ClinicalTrials.gov

Advanced Search

Limit to

Adults and English

Screening

CONDITION box: "Atrial Fibrillation" OR "Atrial Flutter" OR atrial fibril* OR atrium fibril* OR a-fib OR afib OR "atrial flutter" OR "auricular flutter" AND Other:

Electrocardiograph* OR electrocardiogram* OR EKG OR ECG OR holter OR “mobile cardiac outpatient telemetry” OR patch monitor* OR “single lead” OR 12-lead AND screen*| Adult | Studies updated from 05/01/2017 to 02/24/2020

Appendix C1. Update Search Strategies

Treatment

CONDITION box: "Atrial Fibrillation" OR "Atrial Flutter" OR atrial fibril* OR atrium fibril* OR a-fib OR afib OR "atrial flutter" OR "auricular flutter"

TREATMENT box: Anticoagulants OR Dabigatran OR Rivaroxaban OR Warfarin OR anticoagulant* OR apixaban OR Coumadin OR Dabigatran OR Edoxaban OR Eliquis OR NOAC* OR Pradaxa OR Rivaroxaban OR Savaysa OR “vitamin k agonist” OR “vitamin k agonists” OR VKA OR warfarin OR Xarelto OR "Factor Xa Inhibitors" OR "factor xa" OR Antithrombins OR antithrombin* OR thrombin inhibit* OR Aspirin OR clopidogrel OR Dipyridamole OR "acetylsalicylic acid" OR Aggrenox OR anti-platelet* OR antiplatelet* OR ASA OR aspirin OR Plavix| Adult | Studies updated from 05/01/2017 to 02/24/2020

EXPERT SEARCH STATEMENT: AREA[ConditionSearch] (EXPAND[Concept] "Atrial Fibrillation" OR EXPAND[Concept] "Atrial Flutter" OR atrial fibril* OR atrium fibril* OR a-fib OR afib OR EXPAND[Concept] "atrial flutter" OR EXPAND[Concept] "auricular flutter") AND AREA[InterventionSearch] (Anticoagulants OR Dabigatran OR Rivaroxaban OR Warfarin OR anticoagulant* OR apixaban OR Coumadin OR Dabigatran OR Edoxaban OR Eliquis OR NOAC* OR Pradaxa OR Rivaroxaban OR Savaysa OR “vitamin k agonist” OR “vitamin k agonists” OR VKA OR warfarin OR Xarelto OR "Factor Xa Inhibitors" OR "factor xa" OR Antithrombins OR antithrombin* OR thrombin inhibit* OR Aspirin OR clopidogrel OR Dipyridamole OR "acetylsalicylic acid" OR Aggrenox OR anti-platelet* OR antiplatelet* OR ASA OR aspirin OR Plavix) AND AREA[StdAge] EXPAND[Term] COVER[FullMatch] ("Adult" OR "Older Adult") AND AREA[LastUpdatePostDate] EXPAND[Term] RANGE[05/01/2017, 02/24/2020]

Emerging Technologies

CONDITION box: "Atrial Fibrillation" OR "Atrial Flutter" OR atrial fibril* OR atrium fibril* OR a-fib OR afib OR "atrial flutter" OR "auricular flutter"

OTHER TERMS box: "Fitness Trackers" OR "Mobile Applications" OR Photoplethysmography OR Smartphone OR Telemedicine OR “Wearable Electronic Devices" OR “1-lead” OR “single lead” OR “3-lead” OR “three lead” OR AliveCor OR app OR (apple AND watch*) OR “digital treatment” OR “Cardiio Rhythm” OR FibriCheck OR Fitbit* OR (fitness AND tracker*) OR “Galaxy Gear” OR “iRhythm Zio” OR KardiaMobile OR mHealth OR “mobile health” OR (mobile AND (app OR application* OR apps)) OR Photoplethysmography OR PPG OR “portable device” OR “portable devices” OR smartphone* OR (smart AND phone*) OR (smart AND watch*) OR smartwatch* OR telehealth OR telemedicine OR verily OR wearable* OR “wristband device” OR “wristband devices” | Adult | Studies updated from 05/01/2017 to 02/24/2020

EXPERT SEARCH STATEMENT: EXPAND[Concept] ("Fitness Trackers" OR "Mobile Applications" OR "Photoplethysmography" OR "Smartphone" OR "Telemedicine" OR "Wearable Electronic Devices" OR "1-lead" OR "single lead" OR "3-lead" OR "three lead" OR "AliveCor" OR "app" OR "apple" AND "watch*" OR "digital treatment" OR "Cardiio Rhythm" OR "FibriCheck" OR "Fitbit*" OR "fitness" AND "tracker*" OR "Galaxy Gear" OR "iRhythm Zio" OR "KardiaMobile" OR "mHealth" OR "mobile health" OR "mobile" AND ("app" OR "application*" OR "apps") OR "Photoplethysmography" OR "PPG" OR "portable device" OR "portable devices" OR "smartphone*" OR "smart" AND "phone*" OR "smart" AND "watch*" OR "smartwatch*" OR "telehealth" OR "telemedicine" OR "verily" OR "wearable*" OR "“wristband device”" OR "wristband devices") | EXPAND[Concept] "Atrial Fibrillation" OR EXPAND[Concept] "Atrial Flutter" OR atrial fibril* OR atrium fibril* OR a-fib OR afib OR EXPAND[Concept] "atrial flutter" OR EXPAND[Concept] "auricular flutter" | Adult, Older Adult

Appendix C1. Update Search Strategies

Diagnostic Accuracy Gap Search

CONDITION box: "Atrial Fibrillation" OR "Atrial Flutter" OR atrial fibril* OR atrium fibril* OR a-fib OR afib OR "atrial flutter" OR "auricular flutter"

OTHER TERMS box: ("Electrocardiography" OR “continuous ambulatory ECG” OR “continuous ambulatory EKG” OR electrocardiogram* OR electrocardiograph* OR electrocardiography OR EKG OR ECG OR “1-lead” OR “single lead” OR “3-lead” OR “three lead” OR “12-lead” OR “twelve lead” OR “event loop recorder” OR Holter OR “mobile cardiac telemetry” OR patch monitor* OR (apple AND watch*) OR “digital treatment” OR “Cardiio Rhythm” OR FibriCheck OR Fitbit* OR (fitness AND tracker*) OR “Galaxy Gear” OR “iRhythm Zio” OR KardiaMobile OR mHealth OR “mobile health” OR (mobile AND (app OR application* OR apps)) OR Photoplethysmography OR PPG OR “portable device” OR “portable devices” OR smartphone* OR (smart AND phone*) OR (smart AND watch*) OR smartwatch* OR verily OR wearable* OR “wristband device” OR “wristband devices”) AND ("Sensitivity and Specificity" OR "Predictive Value of Tests" OR "ROC Curve" OR "Reproducibility of Results" OR ((pre-test or pretest) AND probability) OR "predictive value" OR sensitivity OR specificity OR accuracy OR ROC OR "false positive" OR "false negative" OR "likelihood ratio" OR "ROC Curve" OR ((pre-test or pretest) AND probability) OR "predictive value" OR sensitivity OR specificity OR accuracy OR ROC OR "false positive" OR "false negative" OR "likelihood ratio" OR ((diagnos* or screening) AND (accurate* OR accuracy)) OR diagnos* or underdiagnose* or detect* or identif* or screen*)| Adult | Studies updated from 02/01/2014 to 02/24/2020

EXPERT SEARCH STATEMENT: (EXPAND[Concept] "Electrocardiography" OR “continuous ambulatory ECG” OR “continuous ambulatory EKG” OR electrocardiogram* OR electrocardiograph* OR electrocardiography OR EKG OR ECG OR “1-lead” OR “single lead” OR “3-lead” OR “three lead” OR “12-lead” OR “twelve lead” OR “event loop recorder” OR Holter OR “mobile cardiac telemetry” OR patch monitor* OR apple AND watch* OR “digital treatment” OR “Cardiio Rhythm” OR FibriCheck OR Fitbit* OR fitness AND tracker* OR “Galaxy Gear” OR “iRhythm Zio” OR KardiaMobile OR mHealth OR “mobile health” OR mobile AND (app OR application* OR apps) OR Photoplethysmography OR PPG OR “portable device” OR “portable devices” OR smartphone* OR smart AND phone* OR smart AND watch* OR smartwatch* OR verily OR wearable* OR “wristband device” OR “wristband devices”) AND (EXPAND[Concept] "Sensitivity and Specificity" OR EXPAND[Concept] "Predictive Value of Tests" OR EXPAND[Concept] "ROC Curve" OR EXPAND[Concept] "Reproducibility of Results" OR pre-test or pretest AND probability OR EXPAND[Concept] "predictive value" OR sensitivity OR specificity OR accuracy OR ROC OR EXPAND[Concept] "false positive" OR EXPAND[Concept] "false negative" OR EXPAND[Concept] "likelihood ratio" OR EXPAND[Concept] "ROC Curve" OR pre-test or pretest AND probability OR EXPAND[Concept] "predictive value" OR sensitivity OR specificity OR accuracy OR ROC OR EXPAND[Concept] "false positive" OR EXPAND[Concept] "false negative" OR EXPAND[Concept] "likelihood ratio" OR diagnos* or screening AND (accurate* OR accuracy) OR diagnos* or underdiagnose* or detect* or identif* or screen*) | EXPAND[Concept] "Atrial Fibrillation" OR EXPAND[Concept] "Atrial Flutter" OR atrial fibril* OR atrium fibril* OR a-fib OR afib OR EXPAND[Concept] "atrial flutter" OR EXPAND[Concept] "auricular flutter" | Adult, Older Adult | Last update posted from 02/01/2014 to 02/24/2020

WHO ICRTRP Advanced Search (through 2/25/2020)

Screening:

Recruitment status: ALL

Date of registration is between 05/01/2017-02/24/2020

Appendix C1. Update Search Strategies

Condition box: "Atrial Fibrillation" OR "Atrial Flutter" OR atrial fibril* OR atrium fibril* OR a-fib OR afib OR "atrial flutter" OR "auricular flutter"

Title box: Electrocardiograph* OR electrocardiogram* OR EKG OR ECG OR holter OR “mobile cardiac outpatient telemetry” OR patch monitor* OR “single lead” OR 12-lead AND screen*

Treatment:

Recruitment status: ALL

Date of registration is between 05/01/2017-02/24/2020

Condition box: "Atrial Fibrillation" OR "Atrial Flutter" OR atrial fibril* OR atrium fibril* OR a-fib OR afib OR "atrial flutter" OR "auricular flutter"

Intervention box (Due to character limit in search box, split up to two searches to accommodate all intervention terms):

Search 1=Anticoagulants OR Dabigatran OR Rivaroxaban OR Warfarin OR anticoagulant* OR apixaban OR Coumadin OR Dabigatran OR Edoxaban OR Eliquis OR NOAC OR Pradaxa OR Rivaroxaban OR Savaysa OR “vitamin k agonist” OR “vitamin k agonists” OR VKA

Search 2=warfarin OR Xarelto OR "Factor Xa Inhibitors" OR "factor xa" OR antithrombin* OR thrombin inhibit* OR Aspirin OR clopidogrel OR Dipyridamole OR "acetylsalicylic acid" OR Aggrenox OR anti-platelet* OR antiplatelet* OR ASA OR aspirin OR Plavix

Emerging Technologies and Diagnostic Accuracy Supplemental Searches

Recruitment status: ALL

Condition box: "Atrial Fibrillation" OR "Atrial Flutter" OR atrial fibril* OR atrium fibril* OR a-fib OR afib OR "atrial flutter" OR "auricular flutter"

Intervention box: Screening OR Diagnosis OR Electrocardiogram OR Electrocardiograph OR ECG OR EKG OR Smartphone OR Smartwatch OR “Wearable technology” OR “Mobile applications” OR Photoplethysmography

Other Websites Searched (as of 2/25/2020)

AF-Screen International Collaboration

American Academy of Family Physicians

American Academy of Neurology

American Heart Association

American College of Cardiology

American College of Chest Physicians
American College of Physicians

American Stroke Association

Canadian Cardiovascular Society

Appendix C1. Update Search Strategies

Canadian Agency for Drugs and Technologies in Health

Centers for Disease Control and Prevention (United States)

European Heart Rhythm Society

European Society of Cardiology

European Primary Care Cardiovascular Society

Heart Rhythm Society (United States)

National Institutes of Health (United States)

National Institute for Health and Care Excellence (United Kingdom)

National Institute for Health Research (United Kingdom)

Scottish Intercollegiate Guidelines Network

United Kingdom National Screening Committee
World Heart Federation

Appendix C1. Update Search Strategies

Update Searches, October 5–6, 2020

MEDLINE via PubMed, Main Searches (September 19, 2019–October 5, 2020)

Search Number	Query	Filters
1	("Atrial Fibrillation"[Mesh] OR "Atrial Flutter"[Mesh] OR atrial fibril*[tiab] OR atrium fibril*[tiab] OR a-fib[tiab] OR afib[tiab] OR "atrial flutter"[tiab] OR "auricular flutter"[tiab])	
2	("Electrocardiography"[Mesh] OR electrocardiogram*[tiab] OR electrocardiograph*[tiab] OR electrocardiography[tiab] OR EKG[tiab] OR ECG[tiab] OR holter[tiab] OR "mobile cardiac outpatient telemetry"[tiab] OR patch monitor*[tiab] OR single lead[tiab] OR 12-lead[tiab])	
3	(#1 AND #2)	
4	("Mass Screening"[Mesh] OR screen*[tiab])	
5	(#3 AND #4)	
6	((((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])	
7	(#5 AND #6)	
8	("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])))	
9	(#5 AND #8)	
10	(#7 OR #9)	
11	(#10 AND Humans[Mesh:NOEXP]) OR (#10 NOT Animals[Mesh:NOEXP])	
12	(#10 AND Humans[Mesh:NOEXP]) OR (#10 NOT Animals[Mesh:NOEXP])	English
13	(#10 AND Humans[Mesh:NOEXP]) OR (#10 NOT Animals[Mesh:NOEXP])	English, Adult: 19+ years
14	#13 AND ("2019/09/19"[Date - Publication] : "3000"[Date - Publication])	English, Adult: 19+ years
15	(#3 AND #4)	Systematic Review
16	(#3 AND #4)	Meta-Analysis, Systematic Review
17	(#3 AND #4)	Meta-Analysis, Systematic Review, English
18	(#3 AND #4)	Meta-Analysis, Systematic Review, English, Adult: 19+ years
19	(#18 AND Humans[Mesh:NOEXP]) OR (#18 NOT Animals[Mesh:NOEXP])	Meta-Analysis, Systematic Review, English, Adult: 19+ years
20	#19 NOT #14	
21	("Anticoagulants"[Mesh] OR "Dabigatran"[Mesh] OR "Rivaroxaban"[Mesh] OR "Warfarin"[Mesh] OR anticoagulant*[tiab] OR apixaban OR Coumadin OR Dabigatran OR Edoxaban OR Eliquis OR NOAC* OR Pradaxa OR Rivaroxaban OR Savaysa OR "vitamin k agonist"[All Fields] OR "vitamin k agonists"[All Fields] OR VKA OR warfarin OR Xarelto)	
22	(#1 AND #21)	
23	"Factor Xa Inhibitors"[Mesh] OR "factor xa"[tiab]	
24	(#1 AND #23)	
25	("Antithrombins"[Mesh] OR antithrombin*[tiab] OR thrombin inhibit*[tiab])	
26	(#1 AND #25)	

Appendix C1. Update Search Strategies

Search Number	Query	Filters
27	("Aspirin"[Mesh] OR "Aspirin, Dipyridamole Drug Combination"[Mesh] OR "clopidogrel"[Supplementary Concept] OR "Dipyridamole"[Mesh] OR "acetylsalicylic acid" OR Aggrenox OR anti-platelet* OR antiplatelet* OR ASA[tiab] OR aspirin OR clopidogrel OR Dipyridamole OR Plavix)	
28	(#1 AND #27)	
29	(#22 OR #24 OR #26 OR #28)	
30	(#29 AND Humans[Mesh:NOEXP]) OR (#29 NOT Animals[Mesh:NOEXP])	
31	(#29 AND Humans[Mesh:NOEXP]) OR (#29 NOT Animals[Mesh:NOEXP])	English
32	(#29 AND Humans[Mesh:NOEXP]) OR (#29 NOT Animals[Mesh:NOEXP])	English, Adult: 19+ years
33	#32 AND ("2019/09/19"[Date - Publication] : "3000"[Date - Publication])	
34	#33 AND #6	
35	#33 AND #8	
36	#32 AND ("2019/09/19"[Date - Publication] : "3000"[Date - Publication])	Systematic Review
37	#32 AND ("2019/09/19"[Date - Publication] : "3000"[Date - Publication])	Meta-Analysis, Systematic Review
38	(#13 OR #20 OR #32) AND ("retraction"[All Fields] OR "Retracted Publication"[pt] OR Duplicate Publication [PT] OR Erratum[All Fields])	

MEDLINE via PubMed, Emerging Technologies Searches (September 19, 2019–October 5, 2020)

Search Number	Query	Filters
1	("Atrial Fibrillation"[Mesh] OR "Atrial Flutter"[Mesh] OR atrial fibril*[tiab] OR atrium fibril*[tiab] OR a-fib[tiab] OR afib[tiab] OR "atrial flutter"[tiab] OR "auricular flutter"[tiab])	
2	("Fitness Trackers"[Mesh] OR "Mobile Applications"[Mesh] OR "Photoplethysmography"[Mesh] OR "Smartphone"[Mesh] OR "Telemedicine"[Mesh] OR "Wearable Electronic Devices"[Mesh:NOEXP])	
3	(#1 AND #2)	
4	("1-lead"[tiab] OR "single lead"[tiab] OR "3-lead"[tiab] OR "three lead" OR AliveCor[tiab] OR app[tiab] OR (apple[tiab] AND watch*[tiab]) OR "digital treatment"[tiab] OR "Cardiio Rhythm"[tiab] OR FibriCheck[tiab] OR Fitbit*[tiab] OR (fitness[tiab] AND tracker*[tiab]) OR "Galaxy Gear"[All Fields] OR "iRhythm Zio"[All Fields] OR KardiaMobile[tiab] OR mHealth[tiab] OR "mobile health"[tiab] OR ((mobile[tiab] AND (app[tiab] OR application*[tiab] OR apps[tiab])) OR Photoplethysmography[tiab] OR PPG[tiab] OR "portable device"[tiab] OR "portable devices"[tiab] OR smartphone*[tiab] OR ((smart[tiab] AND phone*[tiab]) OR (smart[tiab] AND watch*[tiab]) OR smartwatch*[tiab] OR telehealth[tiab] OR telemedicine[tiab] OR verily[tiab] OR wearable*[tiab] OR ("wristband device"[All Fields] OR "wristband devices"[All Fields]))	
5	(#1 AND #4)	
6	(#3 OR #5)	
7	(#6 AND Humans[Mesh:NOEXP]) OR (#6 NOT Animals[Mesh:NOEXP])	
8	(#6 AND Humans[Mesh:NOEXP]) OR (#6 NOT Animals[Mesh:NOEXP])	English
9	(#6 AND Humans[Mesh:NOEXP]) OR (#6 NOT Animals[Mesh:NOEXP])	Systematic Review, English
10	(#6 AND Humans[Mesh:NOEXP]) OR (#6 NOT Animals[Mesh:NOEXP])	Meta-Analysis, Systematic Review, English
11	#7 AND ("retraction"[All Fields] OR "Retracted Publication"[pt] OR Duplicate Publication [PT] OR Erratum[All Fields])	
12	#7 AND ("2019/09/19"[Date - Publication] : "3000"[Date - Publication])	
13	#10 AND ("2019/09/19"[Date - Publication] : "3000"[Date - Publication])	

Appendix C1. Update Search Strategies

Medline via PubMed Supplemental Search for Diagnostic Accuracy (November 1, 2019–October 5, 2020)

Search Number	Query	Filters
1	("Atrial Fibrillation"[Mesh] OR "Atrial Flutter"[Mesh] OR atrial fibril*[tiab] OR atrium fibril*[tiab] OR a-fib[tiab] OR afib[tiab] OR "atrial flutter"[tiab] OR "auricular flutter"[tiab])	
2	("Electrocardiography"[Mesh] OR "continuous ambulatory ECG"[tiab] OR "continuous ambulatory EKG" OR electrocardiogram*[tiab] OR electrocardiograph*[tiab] OR electrocardiography[tiab] OR EKG[tiab] OR ECG[tiab] OR "1-lead"[tiab] OR "single lead"[tiab] OR "3-lead"[tiab] OR "three lead"[tiab] OR "12-lead"[tiab] OR "twelve lead"[tiab] OR "event loop recorder"[tiab] OR Holter[tiab] OR "mobile cardiac telemetry"[tiab] OR patch monitor*)	
3	((apple[tiab] AND watch*[tiab]) OR "digital treatment"[tiab] OR "Cardiio Rhythm"[tiab] OR FibriCheck[tiab] OR Fitbit*[tiab] OR (fitness[tiab] AND tracker*[tiab]) OR "Galaxy Gear" OR "iRhythm Zio" OR KardiaMobile[tiab] OR mHealth[tiab] OR "mobile health"[tiab] OR (mobile[tiab] AND (app[tiab] OR application*[tiab] OR apps[tiab])) OR Photoplethysmography[tiab] OR PPG[tiab] OR "portable device"[tiab] OR "portable devices"[tiab] OR smartphone*[tiab] OR (smart[tiab] AND phone*[tiab]) OR (smart[tiab] AND watch*[tiab]) OR smartwatch*[tiab] OR verily[tiab] OR wearable*[tiab] OR "wristband device" OR "wristband devices")	
5	#2 OR #3	
6	#1 AND #5	
7	("Sensitivity and Specificity"[Mesh] OR "Predictive Value of Tests"[Mesh] OR "ROC Curve"[Mesh] OR "Reproducibility of Results"[Mesh] OR "False Negative Reactions"[Mesh] OR "False Positive Reactions"[Mesh] OR ((pre-test[tw] or pretest[tw]) AND probability[tw]) OR "predictive value"[tw] OR sensitivity[tw] OR specificity[tw] OR accuracy[tw] OR ROC[tw] OR "false positive"[tw] OR "false negative"[tw] OR "likelihood ratio"[tw])	
8	#6 AND #7	
9	((diagnos*[tiab] or screening[tiab]) AND (accurate*[tiab] or accuracy[tiab]))	
10	#6 AND #9	
11	(diagnos*[tiab] OR underdiagnose*[tiab] OR detect*[tiab] OR identif*[tiab] OR screen*[tiab])	
12	#6 AND #11	
13	(diagnos*[tiab] OR detect*[tiab]) AND (rate[tiab] OR yield[tiab] OR PAF[tiab])	
14	#6 AND #13	
15	("diagnosis" [Subheading] OR "Diagnosis, Computer-Assisted"[Mesh] OR "Early Diagnosis"[Mesh])	
16	#6 AND #15	
17	#8 OR #10 OR #12 OR #14 OR #16	
18	(#17 AND Humans[Mesh:NOEXP]) OR (#17 NOT Animals[Mesh:NOEXP])	
19	(#17 AND Humans[Mesh:NOEXP]) OR (#17 NOT Animals[Mesh:NOEXP])	English
20	(#17 AND Humans[Mesh:NOEXP]) OR (#17 NOT Animals[Mesh:NOEXP])	English, Adult: 19+ years
21	(address[pt] OR "autobiography"[pt] OR "bibliography"[pt] OR "biography"[pt] OR "case control"[tw] OR "case report"[tw] OR "case reports"[tw] OR "case series"[tw] OR "comment"[pt] OR "comment on"[tw] OR congress[pt] OR "cross-sectional"[tw] OR "dictionary"[pt] OR "directory"[pt] OR "editorial"[pt] OR "festschrift"[pt] OR "historical article"[pt] OR "interview"[pt] OR lecture[pt] OR "legal case"[pt] OR "legislation"[pt] OR letter[pt] "news"[pt] OR "newspaper article"[pt] OR "patient education handout"[pt] OR "periodical index"[pt] OR "retrospective cohort"[tw] OR rats[tw] OR cow[tw] OR cows[tw] OR chicken[tw] OR chickens[tw] OR horse[tw] or horses[tw] OR mice[tw] OR mouse[tw] OR bovine[tw] OR sheep OR ovine OR murinae)	
22	#20 NOT #21	
23	"Evaluation Study" [Publication Type] OR "Validation Study" [Publication Type]	
24	#22 AND #23	
25	("Comparative Study"[pt] OR "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 AND (study OR studies)))	

Appendix C1. Update Search Strategies

Search Number	Query	Filters
26	#22 AND #25	
27	#24 OR #26	
28	("2019/11/20"[Date - Publication] : "3000"[Date - Publication])	
29	#27 AND #28	
30	#20 NOT #21	Systematic Review
31	#20 NOT #21	Meta-Analysis, Systematic Review
32	#31 AND #28	
33	#22 AND ("retraction"[All Fields] OR "Retracted Publication"[pt] OR Duplicate Publication [PT] OR Erratum[All Fields]) AND ("2014/02/01"[Date - Publication] : "3000"[Date - Publication])	

Appendix C1. Update Search Strategies

Cochrane Library Main Search, Limited by Entry into Cochrane Library Between November 21, 2019–October 5, 2020

ID	Search
#1	[mh "Atrial Fibrillation"] OR [mh "Atrial Flutter"] OR atrial fibril*:ti,ab OR atrium fibril*:ti,ab OR a-fib:ti,ab OR afib:ti,ab OR "atrial flutter":ti,ab OR "auricular flutter":ti,ab
#2	[mh "Electrocardiography"] OR electrocardiograph*:ti,ab OR electrocardiogram*:ti,ab OR EKG:ti,ab OR ECG:ti,ab OR holter:ti,ab OR "mobile cardiac outpatient telemetry":ti,ab OR patch monitor*:ti,ab OR "single lead":ti,ab OR "12-lead":ti,ab
#3	#1 AND #2
#4	[mh "Mass Screening"] OR screen*:ti,ab
#5	#3 AND #4
#6	#5 NOT "conference abstract":pt
#7	[mh "Anticoagulants"] OR [mh "Dabigatran"] OR [mh "Rivaroxaban"] OR [mh "Warfarin"] OR anticoagulant*:ti,ab OR apixaban OR Coumadin OR Dabigatran OR Edoxaban OR Eliquis OR NOAC* OR Pradaxa OR Rivaroxaban OR Savaysa OR “vitamin k agonist”:ti,ab,kw OR “vitamin k agonists”:ti,ab,kw OR VKA OR warfarin OR Xarelto
#8	#1 AND #7
#9	[mh "Factor Xa Inhibitors"] OR "factor xa":ti,ab
#10	#1 AND #9
#11	[mh "Antithrombins"] OR antithrombin*:ti,ab OR thrombin inhibit*:ti,ab
#12	#1 AND #11
#13	[mh "Aspirin"] OR [mh "Aspirin, Dipyridamole Drug Combination"] OR [mh "Dipyridamole"] OR "acetylsalicylic acid" OR Aggrenox OR anti-platelet* OR antiplatelet* OR ASA:ti,ab OR aspirin OR clopidogrel OR Dipyridamole OR Plavix
#14	#1 AND #13
#15	#8 OR #10 OR #12 OR #14
#16	#15
#17	#15 NOT "conference abstract":pt
#18	#15 AND "conference abstract":pt

Cochrane Library Emerging Technologies Search, Limited by Entry into Cochrane Library Between November 21, 2019–October 5, 2020

ID	Search
#1	[mh "Atrial Fibrillation"] OR [mh "Atrial Flutter"] OR atrial fibril*:ti,ab OR atrium fibril*:ti,ab OR a-fib:ti,ab OR afib:ti,ab OR "atrial flutter":ti,ab OR "auricular flutter":ti,ab
#2	[mh "Fitness Trackers"] OR [mh "Mobile Applications"] OR [mh “Photoplethysmography"] OR [mh “Smartphone"] OR [mh “Telemedicine"] OR [mh ^”Wearable Electronic Devices"]
#3	#1 AND #2
#4	"1-lead":ti,ab OR "single lead":ti,ab OR "3-lead":ti,ab OR "three lead":ti,ab OR AliveCor:ti,ab OR app:ti,ab OR (apple:ti,ab AND watch*:ti,ab) OR "digital treatment":ti,ab OR "Cardiio Rhythm":ti,ab OR FibriCheck:ti,ab OR Fitbit*:ti,ab OR (fitness:ti,ab AND tracker*:ti,ab) OR "Galaxy Gear":ti,ab,kw OR "iRhythm Zio":ti,ab,kw OR KardiaMobile:ti,ab OR mHealth:ti,ab OR "mobile health":ti,ab OR (mobile:ti,ab AND (app:ti,ab OR application*:ti,ab OR apps:ti,ab)) OR Photoplethysmography:ti,ab OR PPG:ti,ab OR "portable device":ti,ab OR "portable devices":ti,ab OR smartphone*:ti,ab OR (smart:ti,ab AND phone*:ti,ab) OR (smart:ti,ab AND watch*:ti,ab) OR smartwatch*:ti,ab OR telehealth:ti,ab OR telemedicine:ti,ab OR Verily:ti,ab OR wearable*:ti,ab OR "wristband device":ti,ab,kw OR "wristband devices":ti,ab,kw
#5	#1 AND #4
#6	#3 OR #5
#7	#6 AND "conference abstract":pt
#8	#6 NOT "conference abstract":pt

Cochrane Library Diagnostic Accuracy Search, Limited by Entry into Cochrane Library Between November 21, 2019–October 5, 2020—No New Results

ID	Search
#1	[mh "Atrial Fibrillation"] OR [mh "Atrial Flutter"] OR atrial fibril*:ti,ab OR atrium fibril*:ti,ab OR a-fib:ti,ab OR afib:ti,ab OR "atrial flutter":ti,ab OR "auricular flutter":ti,ab
#2	[mh "Electrocardiography"] OR electrocardiogram*:ti,ab OR electrocardiograph*:ti,ab OR EKG:ti,ab OR ECG:ti,ab OR "1-lead":ti,ab OR "single lead":ti,ab OR "3-lead":ti,ab OR "three lead":ti,ab OR "12-lead":ti,ab OR "twelve lead":ti,ab OR "event loop recorder":ti,ab OR Holter:ti,ab OR "mobile cardiac telemetry":ti,ab OR patch monitor*:ti,ab
#3	(apple:ti,ab AND watch*:ti,ab) OR "digital treatment":ti,ab OR "Cardiio Rhythm":ti,ab OR FibriCheck:ti,ab OR Fitbit*:ti,ab OR (fitness:ti,ab AND tracker*:ti,ab) OR "Galaxy Gear":ti,ab,kw OR "iRhythm Zio":ti,ab,kw OR KardiaMobile:ti,ab OR mHealth:ti,ab OR "mobile health":ti,ab OR (mobile:ti,ab AND (app:ti,ab OR application*:ti,ab OR apps:ti,ab)) OR Photoplethysmography:ti,ab OR PPG:ti,ab OR "portable device":ti,ab OR "portable devices":ti,ab OR smartphone*:ti,ab OR (smart:ti,ab AND phone*:ti,ab) OR (smart:ti,ab AND watch*:ti,ab) OR smartwatch*:ti,ab OR Verily:ti,ab OR wearable*:ti,ab OR "wristband device":ti,ab,kw OR "wristband devices":ti,ab,kw
#4	#1 AND (#2 OR #3)
#5	[mh "Sensitivity and Specificity"] OR [mh "Predictive Value of Tests"] OR [mh "ROC Curve"] OR [mh "Reproducibility of Results"] OR [mh "False Negative Reactions"] OR [mh "False Positive Reactions"] OR (("pre-test":ti,ab,kw OR "pretest":ti,ab,kw) AND "probability":ti,ab,kw) OR "predictive value":ti,ab,kw OR "sensitivity":ti,ab,kw OR "specificity":ti,ab,kw OR "accuracy":ti,ab,kw OR "ROC":ti,ab,kw OR "false positive":ti,ab,kw OR "false negative":ti,ab,kw OR "likelihood ratio":ti,ab,kw
#6	#4 AND #5
#7	(diagnos*:ti,ab or screening:ti,ab) AND (accurate*:ti,ab or accuracy:ti,ab)
#8	#4 AND #7
#9	diagnos*:ti,ab or underdiagnose*:ti,ab or detect*:ti,ab or identif*:ti,ab or screen*:ti,ab
#10	#4 AND #9
#11	(diagnos*:ti,ab OR detect*:ti,ab) AND (rate:ti,ab OR yield:ti,ab OR PAF:ti,ab)
#12	#4 AND #11
#13	[mh /DI] OR [mh "Diagnosis, Computer-Assisted"] OR [mh "Early Diagnosis"]
#14	#4 AND #13
#15	#6 OR #8 OR #10 OR #12 OR #14
#16	#15 AND "conference abstract":pt
#17	#15 NOT "conference abstract":pt

Gray Literature Search Update

ClinicalTrials.gov, October 6, 2020 (all limited to last update between February 25, 2020–October 6, 2020)

WHO ICTRP searches were not updated due to current unavailability of the database.

Screening

CONDITION box: "Atrial Fibrillation" OR "Atrial Flutter" OR atrial fibril* OR atrium fibril* OR a-fib OR afib OR "atrial flutter" OR "auricular flutter"

AND

Other Terms:

Electrocardiograph* OR electrocardiogram* OR EKG OR ECG OR holter OR “mobile cardiac outpatient telemetry” OR patch monitor* OR “single lead” OR 12-lead AND screen*

Limit to Adult/Older Adult and latest update posted: 02/25/2020 – 10/06/2020

Treatment

Condition box:

"Atrial Fibrillation" OR "Atrial Flutter" OR atrial fibril* OR atrium fibril* OR a-fib OR afib OR "atrial flutter" OR "auricular flutter"

Treatment box:

Anticoagulants OR Dabigatran OR Rivaroxaban OR Warfarin OR anticoagulant* OR apixaban OR Coumadin OR Dabigatran OR Edoxaban OR Eliquis OR NOAC* OR Pradaxa OR Rivaroxaban OR Savaysa OR “vitamin k agonist” OR “vitamin k agonists” OR VKA OR warfarin OR Xarelto OR "Factor Xa Inhibitors" OR "factor xa" OR Antithrombins OR antithrombin* OR thrombin inhibit* OR Aspirin OR clopidogrel OR Dipyridamole OR "acetylsalicylic acid" OR Aggrenox OR anti-platelet* OR antiplatelet* OR ASA OR aspirin OR Plavix

Limit to Adult/Older Adult and latest update posted: 02/25/2020 – 10/06/2020

Expert search statement:

AREA[ConditionSearch] (EXPAND[Concept] "Atrial Fibrillation" OR EXPAND[Concept] "Atrial Flutter" OR atrial fibril* OR atrium fibril* OR a-fib OR afib OR EXPAND[Concept] "atrial flutter" OR EXPAND[Concept] "auricular flutter") AND AREA[InterventionSearch] (Anticoagulants OR Dabigatran OR Rivaroxaban OR Warfarin OR anticoagulant* OR apixaban OR Coumadin OR Dabigatran OR Edoxaban OR Eliquis OR NOAC* OR Pradaxa OR Rivaroxaban OR Savaysa OR “vitamin k agonist” OR “vitamin k agonists” OR VKA OR warfarin OR Xarelto OR "Factor Xa Inhibitors" OR "factor xa" OR Antithrombins OR antithrombin* OR thrombin inhibit* OR Aspirin OR clopidogrel OR Dipyridamole OR "acetylsalicylic acid" OR Aggrenox OR anti-platelet* OR antiplatelet* OR ASA OR aspirin OR Plavix) AND AREA[StdAge] EXPAND[Term] COVER[FullMatch] ("Adult" OR "Older Adult") AND AREA[LastUpdatePostDate] EXPAND[Term] RANGE[02/25/2020, 10/06/2020]

Emerging Technologies

Condition box:

("Atrial Fibrillation" OR "Atrial Flutter" OR atrial fibril* OR atrium fibril* OR a-fib OR afib OR "atrial flutter" OR "auricular flutter")

Other Terms:

Appendix C1. Update Search Strategies

("Fitness Trackers" OR "Mobile Applications" OR Photoplethysmography OR Smartphone OR Telemedicine OR "Wearable Electronic Devices" OR "1-lead" OR "single lead" OR "3-lead" OR "three lead" OR AliveCor OR app OR (apple AND watch*) OR "digital treatment" OR "Cardiio Rhythm" OR FibriCheck OR Fitbit* OR (fitness AND tracker*) OR "Galaxy Gear" OR "iRhythm Zio" OR KardiaMobile OR mHealth OR "mobile health" OR (mobile AND (app OR application* OR apps)) OR Photoplethysmography OR PPG OR "portable device" OR "portable devices" OR smartphone* OR (smart AND phone*) OR (smart AND watch*) OR smartwatch* OR telehealth OR telemedicine OR verily OR wearable* OR "wristband device" OR "wristband devices")

Limit to Adult/Older Adult, Last update posted from 02/25/2020 to 10/06/2020

Expert search statement:

EXPAND[Concept] ("Fitness Trackers" OR "Mobile Applications" OR Photoplethysmography OR Smartphone OR Telemedicine OR "Wearable Electronic Devices" OR "1-lead" OR "single lead" OR "3-lead" OR "three lead" OR AliveCor OR app OR (apple AND watch*) OR "digital treatment" OR "Cardiio Rhythm" OR FibriCheck OR Fitbit* OR (fitness AND tracker*) OR "Galaxy Gear" OR "iRhythm Zio" OR KardiaMobile OR mHealth OR "mobile health" OR (mobile AND (app OR application* OR apps)) OR Photoplethysmography OR PPG OR "portable device" OR "portable devices" OR smartphone* OR (smart AND phone*) OR (smart AND watch*) OR smartwatch* OR telehealth OR telemedicine OR verily OR wearable* OR "wristband device" OR "wristband devices") AND AREA[ConditionSearch] ("Atrial Fibrillation" OR "Atrial Flutter" OR atrial fibril* OR atrium fibril* OR a-fib OR afib OR "atrial flutter" OR "auricular flutter") AND AREA[StdAge] EXPAND[Term] COVER[FullMatch] ("Adult" OR "Older Adult") AND AREA[LastUpdatePostDate] EXPAND[Term] RANGE[02/25/2020, 10/06/2020]

Diagnostic Accuracy Gap Search (shortened Other terms statement to remove duplicate terms and simplify logic)

Condition box:

"Atrial Fibrillation" OR "Atrial Flutter" OR atrial fibril* OR atrium fibril* OR a-fib OR afib OR "atrial flutter" OR "auricular flutter"

Other terms box:

("continuous ambulatory ECG" OR "continuous ambulatory EKG" OR electrocardiogram* OR electrocardiograph* OR electrocardiography OR EKG OR ECG OR "1-lead" OR "single lead" OR "3-lead" OR "three lead" OR "12-lead" OR "twelve lead" OR "event loop recorder" OR Holter OR "mobile cardiac telemetry" OR patch monitor* OR apple watch* OR "digital treatment" OR "Cardiio Rhythm" OR FibriCheck OR Fitbit* OR fitness tracker* OR "Galaxy Gear" OR "iRhythm Zio" OR KardiaMobile OR mHealth OR "mobile health" OR mobile app* OR Photoplethysmography OR PPG OR "portable device" OR "portable devices" OR smartphone* OR smart phone* OR smart watch* OR smartwatch* OR verily OR wearable* OR "wristband device" OR "wristband devices") AND ("Sensitivity and Specificity" OR "Predictive Value of Tests" OR "ROC Curve" OR "Reproducibility of Results" OR pre-test probability OR

pretest probability OR "predictive value" OR sensitivity OR specificity OR accuracy OR ROC OR "false positive" OR "false negative" OR "likelihood ratio" OR diagnos* or underdiagnose* or detect* or identif* or screen*)

Limit to Adult and Older Adult, Last update posted from 02/25/2020 to 10/06/2020

Expert search box:

("continuous ambulatory ECG" OR "continuous ambulatory EKG" OR electrocardiogram* OR electrocardiograph* OR electrocardiography OR EKG OR ECG OR "1-lead" OR "single lead" OR "3-lead" OR "three lead" OR "12-lead" OR "twelve lead" OR "event loop recorder" OR Holter OR "mobile cardiac telemetry" OR patch monitor* OR apple watch* OR "digital treatment" OR "Cardiio Rhythm" OR FibriCheck OR Fitbit* OR fitness tracker* OR "Galaxy Gear" OR "iRhythm Zio" OR KardiaMobile OR mHealth OR "mobile health" OR mobile app* OR Photoplethysmography OR PPG OR "portable device" OR "portable devices" OR smartphone* OR smart phone* OR smart watch* OR smartwatch* OR verily OR wearable* OR "wristband device" OR "wristband devices") AND ("Sensitivity and Specificity" OR "Predictive Value of Tests" OR "ROC Curve" OR "Reproducibility of Results" OR pre-test probability OR pretest probability OR "predictive value" OR sensitivity OR specificity OR accuracy OR ROC OR "false positive" OR "false negative" OR "likelihood ratio" OR diagnos* or underdiagnose* or detect* or identif* or screen*) AND AREA[ConditionSearch] (EXPAND[Concept] "Atrial Fibrillation" OR EXPAND[Concept] "Atrial Flutter" OR atrial fibril* OR atrium fibril* OR a-fib OR afib OR EXPAND[Concept] "atrial flutter" OR EXPAND[Concept] "auricular flutter") AND AREA[StdAge] EXPAND[Term] COVER[FullMatch] ("Adult" OR "Older Adult") AND AREA[LastUpdatePostDate] EXPAND[Term] RANGE[02/25/2020, 10/06/2020]

Appendix C2. Detailed Eligibility Criteria

	Include	Exclude
Condition definition	AF (paroxysmal or persistent)	Other cardiac arrhythmias, non-arrhythmia–related cardiovascular disease (e.g., coronary heart disease, hypertension). Studies reporting atrial flutter will not be excluded as long as the focus is on AF.
Populations	KQs 1, 2, 4: Unselected or explicitly asymptomatic older adults (age ≥50 years) without known AF; older adults selected for increased risk of AF (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. KQ 3: Unselected or explicitly asymptomatic older adults without known AF; mixed populations of asymptomatic and symptomatic persons with and without AF or that include younger adults are eligible if results are reported separately for asymptomatic persons, those without known AF, or the older population, or less than 50% of the population is symptomatic, has known AF, or is younger than age 50 years. KQs 5, 6: Older adults with AF. To approximate screen-detected persons with AF, 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 1–4: Symptomatic adults; adults with known AF; children, adolescents, and adults younger than age 50 years; adults at high(est) risk for AF (including but not limited to those with mitral valve disease or repair/replacement); and adults with history of stroke or transient ischemic attack KQs 5, 6: Adults needing antiplatelet or anticoagulation medications for conditions other than AF; adults with AF and known heart disease, heart failure, and/or previous stroke or transient ischemic attack. Studies that exclusively enroll these populations will be excluded.

Appendix C2. Detailed Eligibility Criteria

	Include	Exclude
Screening test or intervention	KQs 1, 2, 4: Systematic screening using ECG or other technologic approach. Eligible approaches include: One-time 12-lead or less than 12-lead ECG Intermittent or continuous ambulatory ECG such as Holter monitoring, event loop recorders, or patch monitors One-time intermittent or continuous ambulatory photoplethysmography that includes an AF detection algorithm One-time, intermittent, or continuous oscillometric blood pressure measurement devices that include an AF detection algorithm Commercially available technologies directed to consumers (e.g., smartwatches, smartphone apps, heart rate or rhythm monitors) KQ 3: Eligible index tests include: One-time 12-lead or less than 12-lead ECG interpreted by primary care provider, with or without ECG machine algorithm interpretation Intermittent ambulatory ECG such as event loop recorders or patch monitors One-time or intermittent ambulatory photoplethysmography that includes an AF detection algorithm One-time or ambulatory oscillometric blood pressure measurement devices with an AF detection algorithm Two-stage screening tests involving a single initial test followed by a second test KQs 5, 6: Medical treatment with anticoagulants (e.g., apixaban, dabigatran, edoxaban, rivaroxaban, warfarin). Results will be stratified by type of medication.	KQs 1, 2, 4: Physical examination (including one-time in-office pulse palpation or heart auscultation); one-time in-office manual or automated pulse, blood pressure measurement, or pulse oximetry; two-stage approach in which a physical examination component or vital sign measurement is the initial test and only persons with irregular pulse or vital sign receive ECG KQ 3: Same as excluded tests for KQs 1, 2, and 4 plus ECG (any number of leads) interpreted by a cardiologist*; continuous ambulatory ECG monitoring*; and cardiac monitoring with an implantable device* KQs 5, 6: Nonpharmacologic treatment to prevent stroke (e.g., implantable devices), treatment or management of AF for reasons other than prevention of stroke (e.g., rate or rhythm control, cardioversion, ablation), antiplatelet therapy, and combinations of antiplatelet and anticoagulation treatment (e.g., aspirin plus warfarin)
Comparisons	KQs 1, 2, 4: No screening, nonsystematic screening, or usual care (which may include pulse palpation, single manual or automated blood pressure measurement, or cardiac auscultation during a physical examination) KQ 3: For persistent AF, single 12-lead ECG interpreted by one or more cardiologists; for paroxysmal AF, continuous ambulatory ECG monitoring interpreted by one or more cardiologists and implantable cardiac monitor interpreted by one or more cardiologists. Interpretation of ECG can be with or without a device-embedded AF detection algorithm. KQs 5, 6: Placebo, no treatment	KQs 1, 2, 4: No comparison, nonconcordant historical control KQ 3: No reference standard, reference standard other than 12-lead ECG, continuous ambulatory ECG monitoring, or implantable cardiac monitor all interpreted by one or more cardiologists with or without a device-embedded AF detection algorithm KQs 5, 6: Active treatment (i.e., other anticoagulation medications or nonpharmacologic treatment)

Appendix C2. Detailed Eligibility Criteria

	Include	Exclude
Outcomes	KQ 1: All-cause mortality, stroke, stroke-related morbidity or mortality, and quality of life KQ 2: Comparative diagnostic yield (i.e., number of persons diagnosed with AF in one group vs. another [unscreened/nonsystematically screened] group) KQ 3: Sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios, true positives, true negatives, false positives, false negatives KQ 4: Anxiety, labeling, harms of subsequent procedures or interventions initiated as a result of screening (e.g., subsequent ablation with complications), frequency of findings other than AF KQ 5: All-cause mortality, cardioembolic stroke, cardioembolic stroke–related morbidity or mortality, and quality of life KQ 6: Any harms requiring unexpected or unwanted medical attention (e.g., hemorrhagic stroke, major bleeding, allergic reaction)	KQs 4, 6: Nonserious events (e.g., bleeding not requiring or resulting in medical attention)
Study designs	KQ 1, 2, 4–6: RCTs and controlled clinical trials KQ 3: Diagnostic test accuracy studies or systematic reviews of diagnostic test accuracy studies KQ 4: Large prospective cohort studies are also eligible KQ 5: Systematic reviews of relevant trials are also eligible KQ 6: Systematic reviews of relevant trials 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, small prospective cohort studies, and retrospective cohort studies
Setting	KQs 1–4: Studies performed in primary care or primary care–referable settings, community settings KQs 5, 6: Studies performed in primary care or specialty settings	KQs 1–4: Studies performed in specialty settings (including the emergency department), studies of patients undergoing preoperative evaluation, and inpatient settings KQs 5, 6: Studies conducted primarily in inpatient settings
Country	Studies conducted in countries categorized as “Very High” on the 2018 Human Development Index (as defined by the United Nations Development Programme)	Studies conducted in countries that are not categorized as “Very High” on the 2018 Human Development Index
Language	English	Non-English
Study quality	Good or fair	Poor (according to design-specific USPSTF criteria)

* 12-lead ECG and continuous ambulatory ECG interpreted by a cardiologist and implantable cardiac monitoring are excluded from KQ 3 (diagnostic accuracy) because these tests are considered the reference standard. Single-lead ECG interpreted by a cardiologist is not eligible because this review focuses on accuracy of conducting/interpreting tests in a primary care setting.

Abbreviations: AF=atrial fibrillation; ECG=electrocardiography; KQ=key question; RCT=randomized, controlled trial; 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[83]; Harris et al, 2001.[209]

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[83]; Harris et al, 2001.[209]

Appendix D. Excluded Studies

List of Exclusion Codes:

X1: Systematic review used for handsearch

X2: Ineligible publication type

X3: Ineligible country

X4: Ineligible population

X5: Ineligible intervention

X6: Ineligible comparator

X7: Ineligible outcome

X8: Ineligible study design

X9: Duplicate or superseded

X10: Study protocol or in progress

X11: Abstract only

X12: Non-English full text

X13: Other

X14: Poor quality

X15: Ineligible setting

X16: Other

1. ETNA AF-Europe: first 1-year follow-up snapshot analysis of 1,215 AF patients treated with edoxaban in routine clinical practice in Belgium. Acta Clin Belg. 2020;75:4-5. doi: 10.1080/00015385.2020.1705029. PMID: CN-02163896. Exclusion Code: X11.
2. Adderley NJ, Ryan R, Nirantharakumar K, et al. Prevalence and treatment of atrial fibrillation in UK general practice from 2000 to 2016. Heart. 2019 Jan;105(1):27-33. doi: 10.1136/heartjnl-2018-312977. PMID: 29991504. Exclusion Code: X7.
3. Aguilar M, Hart R. Antiplatelet therapy for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. Cochrane Database Syst Rev. 2005 Oct 19(4):CD001925. doi: 10.1002/14651858.CD001925.pub2. PMID: 16235290. Exclusion Code: X5.
4. Alharbi M, Straiton N, Smith S, et al. Data management and wearables in older adults: a systematic review. Maturitas. 2019 Jun;124:100-10. doi: 10.1016/j.maturitas.2019.03.012. PMID: 30910279. Exclusion Code: X6.
5. Al-Kaisey AM, Koshy AN, Ha FJ, et al. Accuracy of wrist-worn heart rate monitors for rate control assessment in atrial fibrillation. Int J Cardiol. 2019doi: 10.1016/j.ijcard.2019.11.120. PMID: CN-02048453. Exclusion Code: X4.
6. Al-Kaisey AM, Koshy AN, Ha FJ, et al. Accuracy of wrist-worn heart rate monitors for rate control assessment in atrial fibrillation. Int J Cardiol. 2020 Feb 1;300:161-4. doi: 10.1016/j.ijcard.2019.11.120. PMID: 31787389. Exclusion Code: X4.
7. An Y, Ogawa H, Yamashita Y, et al. Causes of death in Japanese patients with atrial fibrillation: the Fushimi Atrial Fibrillation Registry. Eur Heart J Qual Care Clin Outcomes. 2019 Jan 1;5(1):35-42. doi: 10.1093/ehjqcco/qcy033. PMID: 30020445. Exclusion Code: X7.

Appendix D. Excluded Studies

8. Ananthan K. The efficacy and feasibility of atrial fibrillation screening using photoplethysmography-based smart devices. J Am Coll Cardiol. 2020 Mar 24;75(11):1365-6. doi: 10.1016/j.jacc.2019.09.074. PMID: 32192669. Exclusion Code: X2.

9. Atrial Fibrillation Investigators. The efficacy of aspirin in patients with atrial fibrillation. Analysis of pooled data from 3 randomized trials. Arch Intern Med. 1997 Jun 9;157(11):1237-40. PMID: 9183235. Exclusion Code: X5.

10. Attia ZI, Noseworthy PA, Lopez-Jimenez F, et al. An artificial intelligence-enabled ECG algorithm for the identification of patients with atrial fibrillation during sinus rhythm: a retrospective analysis of outcome prediction. Lancet. 2019 Sep 7;394(10201):861-7. doi: 10.1016/s0140-6736(19)31721-0. PMID: 31378392. Exclusion Code: X5.

11. Attia ZI, Noseworthy PA, Lopez-Jimenez F, et al. An artificial intelligence-enabled ECG algorithm for the identification of patients with atrial fibrillation during sinus rhythm: a retrospective analysis of outcome prediction. Lancet. 2019 Sep 7;394(10201):861-7. doi: 10.1016/s0140-6736(19)31721-0. PMID: 31378392. Exclusion Code: X9.

12. Auer J, Primus C. A smartwatch to identify atrial fibrillation. N Engl J Med. 2020 Mar 5;382(10):974. doi: 10.1056/NEJMc1916858. PMID: 32130825. Exclusion Code: X2.

13. Badi MK, Vilanilam GK, Gupta V, et al. Pharmacotherapy for patients with atrial fibrillation and cerebral microbleeds. J Stroke Cerebrovasc Dis. 2019 Aug;28(8):2159-67. doi: 10.1016/j.jstrokecerebrovasdis.2019.04.027. PMID: 31103554. Exclusion Code: X8.

14. Bandorski D, Bogossian H, Ecke A, et al. Evaluation of the prognostic value of electrocardiography parameters and heart rhythm in patients with pulmonary hypertension. Cardiol J. 2016;23(4):465-72. doi: 10.5603/CJ.a2016.0044. PMID: 27367480. Exclusion Code: X4.

15. Barrett PM, Komatireddy R, Haaser S, et al. Comparison of 24-hour Holter monitoring with 14-day novel adhesive patch electrocardiographic monitoring. Am J Med. 2014 Jan;127(1):95.e11-7. doi: 10.1016/j.amjmed.2013.10.003. PMID: 24384108. Exclusion Code: X4.

16. Bashar SK, Han D, Hajeb-Mohammadalipour S, et al. Atrial fibrillation detection from wrist photoplethysmography signals using smartwatches. Sci Rep. 2019 Oct 21;9(1):15054. doi: 10.1038/s41598-019-49092-2. PMID: 31636284. Exclusion Code: X4.

17. Bleda AL, Melgarejo-Meseguer FM, Gimeno-Blanes FJ, et al. Enabling heart self-monitoring for all and for AAL-portable device within a complete telemedicine system. Sensors (Basel). 2019 Sep 14;19(18)doi: 10.3390/s19183969. PMID: 31540042. Exclusion Code: X8.

18. Bo M, Li Puma F, Badinella Martini M, et al. Effects of oral anticoagulant therapy in older medical in-patients with atrial fibrillation: a prospective cohort observational study. Aging Clin Exp Res. 2017 Jun;29(3):491-7. doi: 10.1007/s40520-016-0569-7. PMID: 27100358. Exclusion Code: X6.

19. Boriani G, Proietti M, Laroche C, et al. Changes to oral anticoagulant therapy and risk of death over a 3-year follow-up of a contemporary cohort of European patients with atrial fibrillation final report of the EURObservational Research Programme on Atrial Fibrillation (EORP-AF) pilot general registry. Int J Cardiol. 2018 Nov 15;271:68-74. doi: 10.1016/j.ijcard.2018.05.034. PMID: 30001945. Exclusion Code: X6.

20. Brangier A, Ferland G, Rolland Y, et al. Vitamin K antagonists and cognitive decline in older adults: a 24-month follow-up. Nutrients. 2018 May 24;10(6)doi: 10.3390/nu10060666. PMID: 29794977. Exclusion Code: X6.

Appendix D. Excluded Studies

21. Brasier N, Raichle CJ, Dörr M, et al. Detection of atrial fibrillation with a smartphone camera: first prospective, international, two-centre, clinical validation study (DETECT AF PRO). Europace. 2019 Jan 1;21(1):41-7. doi: 10.1093/europace/euy176. PMID: 30085018. Exclusion Code: X8.

22. Busch MC, Gross S, Alte D, et al. Impact of atrial fibrillation detected by extended monitoring-a population-based cohort study. Ann Noninvasive Electrocardiol. 2017 Nov;22(6)doi: 10.1111/anec.12453. PMID: 28440600. Exclusion Code: X6.

23. Caceres BA, Hickey KT, Bakken SB, et al. Mobile electrocardiogram monitoring and health-related quality of life in patients with atrial fibrillation: findings from the iPhone Helping Evaluate Atrial Fibrillation Rhythm Through Technology (iHEART) Study. J Cardiovasc Nurs. 2020 Feb 3doi: 10.1097/jcn.0000000000000646. PMID: 32015256. Exclusion Code: X7.

24. Cai W, Chen Y, Guo J, et al. Accurate detection of atrial fibrillation from 12-lead ECG using deep neural network. Comput Biol Med. 2020 Jan;116:103378. doi: 10.1016/j.compbiomed.2019.103378. PMID: 31778896. Exclusion Code: X5.

25. Camm AJ, Accetta G, Mahmeed WA, et al. Impact of gender on event rates at 1-year in patients with newly diagnosed non-valvular atrial fibrillation: contemporary perspective from the GARFIELD-AF registry. BMJ open. 2017;7(3) (no pagination)doi: 10.1136/bmjopen-2016-014579. PMID: CN-01338615. Exclusion Code: X5.

26. Chan PH, Wong CK, Poh YC, et al. Diagnostic performance of a smartphone-based photoplethysmographic application for atrial fibrillation screening in a primary care setting. J Am Heart Assoc. 2016 Jul 21;5(7)doi: 10.1161/jaha.116.003428. PMID: 27444506. Exclusion Code: X6.

27. Chan PH, Wong CK, Pun L, et al. Diagnostic performance of an automatic blood pressure measurement device, Microlife WatchBP Home A, for atrial fibrillation screening in a real-world primary care setting. BMJ Open. 2017 Jun 15;7(6):e013685. doi: 10.1136/bmjopen-2016-013685. PMID: 28619766. Exclusion Code: X6.

28. Chan PH, Wong CK, Pun L, et al. Head-to-head comparison of the AliveCor Heart monitor and Microlife WatchBP Office AFIB for atrial fibrillation screening in a primary care setting. Circulation. 2017 Jan 3;135(1):110-2. doi: 10.1161/circulationaha.116.024439. PMID: 28028066. Exclusion Code: X6.

29. Chan PH, Wong CK, Pun L, et al. Diagnostic performance of an automatic blood pressure measurement device, Microlife WatchBP Home A, for atrial fibrillation screening in a real-world primary care setting. BMJ Open. 2017 Jun 15;7(6):e013685. doi: 10.1136/bmjopen-2016-013685. PMID: 28619766. Exclusion Code: X9.

30. Chao TF, Lip GYH, Lin YJ, et al. Major bleeding and intracranial hemorrhage risk prediction in patients with atrial fibrillation: Attention to modifiable bleeding risk factors or use of a bleeding risk stratification score? A nationwide cohort study. Int J Cardiol. 2018 Mar 1;254:157-61. doi: 10.1016/j.ijcard.2017.11.025. PMID: 29407081. Exclusion Code: X6.

31. Chen E, Jiang J, Su R, et al. A new smart wristband equipped with an artificial intelligence algorithm to detect atrial fibrillation. Heart Rhythm. 2020 May;17(5 Pt B):847-53. doi: 10.1016/j.hrthm.2020.01.034. PMID: 32354449. Exclusion Code: X3.

32. Cheng W, Liu W, Li B, et al. Relationship of anticoagulant therapy with cognitive impairment among patients with atrial fibrillation: a meta-analysis and systematic review. J Cardiovasc Pharmacol. 2018 Jun;71(6):380-7. doi: 10.1097/fjc.0000000000000575. PMID: 29528873. Exclusion Code: X1.

33. Chon KH, McManus DD. Detection of atrial fibrillation using a smartwatch. Nat Rev Cardiol. 2018 Nov;15(11):657-8. doi: 10.1038/s41569-018-0057-1. PMID: 29985453. Exclusion Code: X2.

34. Christesen AMS, Vinter N, Mortensen LS, et al. Inequality in oral anticoagulation use and clinical outcomes in atrial fibrillation: a Danish nationwide perspective. Eur Heart J Qual Care Clin Outcomes. 2018 Jul 1;4(3):189-99. doi: 10.1093/ehjqcco/qcy011. PMID: 30102321. Exclusion Code: X6.

35. Cunha S, Antunes E, Antoniou S, et al. Raising awareness and early detection of atrial fibrillation, an experience resorting to mobile technology centred on informed individuals. Res Social Adm Pharm. 2019 Aug 20doi: 10.1016/j.sapharm.2019.08.036. PMID: 31473110. Exclusion Code: X4.

36. Cunha S, Antunes E, Antoniou S, et al. Raising awareness and early detection of atrial fibrillation, an experience resorting to mobile technology centred on informed individuals. Res Social Adm Pharm. 2020 Jun;16(6):787-92. doi: 10.1016/j.sapharm.2019.08.036. PMID: 31473110. Exclusion Code: X4.

37. De Silva K, Chow C, Kumar S. A smartwatch to identify atrial fibrillation. N Engl J Med. 2020 Mar 5;382(10):974. doi: 10.1056/NEJMc1916858. PMID: 32130824. Exclusion Code: X2.

38. Desteghe L, Raymaekers Z, Lutin M, et al. Performance of handheld electrocardiogram devices to detect atrial fibrillation in a cardiology and geriatric ward setting. Europace. 2017 Jan;19(1):29-39. doi: 10.1093/europace/euw025. PMID: 26893496. Exclusion Code: X4.

39. Diamantino AC, Nascimento BR, Beaton AZ, et al. Atrial fibrillation detection with a portable device during cardiovascular screening in primary care. Heart. 2020 Feb 4doi: 10.1136/heartjnl-2019-316277. PMID: 32019822. Exclusion Code: X4.

40. Diederichsen SZ, Haugan KJ, Brandes A, et al. Natural history of subclinical atrial fibrillation detected by implanted loop recorders. J Am Coll Cardiol. 2019 Dec 3;74(22):2771-81. doi: 10.1016/j.jacc.2019.09.050. PMID: 31779791. Exclusion Code: X4.

41. Diederichsen SZ, Haugan KJ, Kronborg C, et al. A comprehensive evaluation of rhythm monitoring strategies in screening for atrial fibrillation: insights from patients at risk long-term monitored with implantable loop recorder. Circulation. 2020 Mar 2doi: 10.1161/circulationaha.119.044407. PMID: 32114796. Exclusion Code: X5.

42. Diemberger I, De Caterina R. ETNA-AF-Europe: first 1-year follow-up snapshot analysis of more than 12,500 AF patients treated with edoxaban in routine clinical practice. G Ital Cardiol. 2019;20(12):163S-. PMID: CN-02095102. Exclusion Code: X10.

43. Ding EY, Han D, Whitcomb C, et al. Accuracy and usability of a novel algorithm for detection of irregular pulse using a smartwatch among older adults: observational study. JMIR Cardio. 2019 May 15;3(1):e13850. doi: 10.2196/13850. PMID: 31758787. Exclusion Code: X4.

44. Ding M, Fratiglioni L, Johnell K, et al. Atrial fibrillation and use of antithrombotic medications in older people: A population-based study. Int J Cardiol. 2017 Dec 15;249:173-8. doi: 10.1016/j.ijcard.2017.07.012. PMID: 29121723. Exclusion Code: X7.

45. Diouf I, Magliano DJ, Carrington MJ, et al. Prevalence, incidence, risk factors and treatment of atrial fibrillation in Australia: The Australian Diabetes, Obesity and Lifestyle (AusDiab) longitudinal, population cohort study. Int J Cardiol. 2016 Feb 15;205:127-32. doi: 10.1016/j.ijcard.2015.12.013. PMID: 26730844. Exclusion Code: X6.

46. Doliwa PS, Frykman V, Rosenqvist M. Short-term ECG for out of hospital detection of silent atrial fibrillation episodes. Scand Cardiovasc J. 2009 Jun;43(3):163-8. doi: 10.1080/14017430802593435. PMID: 19096977. Exclusion Code: X6.

47. Dörr M, Nohturfft V, Brasier N, et al. The WATCH AF Trial: SmartWATCHes for detection of atrial fibrillation. JACC Clin Electrophysiol. 2019 Feb;5(2):199-208. doi: 10.1016/j.jacep.2018.10.006. PMID: 30784691. Exclusion Code: X8.

48. Dörr M, Nohturfft V, Brasier N, et al. Reply: Watch out: the many limitations in Smartwatch-driven AF detection. JACC Clin Electrophysiol. 2019 Apr;5(4):526-7. doi: 10.1016/j.jacep.2019.03.001. PMID: 31000111. Exclusion Code: X11.

49. Duarte R, Stainthorpe A, Greenhalgh J, et al. Lead-I ECG for detecting atrial fibrillation in patients with an irregular pulse using single time point testing: a systematic review and economic evaluation. Health Technol Assess. 2020 Jan;24(3):1-164. doi: 10.3310/hta24030. PMID: 31933471. Exclusion Code: X1.

50. Duarte R, Stainthorpe A, Mahon J, et al. Lead-I ECG for detecting atrial fibrillation in patients attending primary care with an irregular pulse using single-time point testing: A systematic review and economic evaluation. PLoS One. 2019;14(12):e0226671. doi: 10.1371/journal.pone.0226671. PMID: 31869370. Exclusion Code: X1.

51. Eerikäinen LM, Bonomi AG, Dekker LRC, et al. Atrial fibrillation episodes detected using photoplethysmography: do we know which are true? J Am Coll Cardiol. 2020 Mar 24;75(11):1365. doi: 10.1016/j.jacc.2019.10.064. PMID: 32192670. Exclusion Code: X2.

52. Eerikainen LM, Bonomi AG, Schipper F, et al. Detecting atrial fibrillation and atrial flutter in daily life using photoplethysmography data. IEEE J Biomed Health Inform. 2019 Nov 4doi: 10.1109/jbhi.2019.2950574. PMID: 31689222. Exclusion Code: X5.

53. Eerikainen LM, Bonomi AG, Schipper F, et al. Detecting atrial fibrillation and atrial flutter in daily life using photoplethysmography data. IEEE J Biomed Health Inform. 2020 Jun;24(6):1610-8. doi: 10.1109/jbhi.2019.2950574. PMID: 31689222. Exclusion Code: X8.

54. Eerikainen LM, Bonomi AG, Schipper F, et al. Comparison between electrocardiogram- and photoplethysmogram-derived features for atrial fibrillation detection in free-living conditions. Physiol Meas. 2018 Aug 8;39(8):084001. doi: 10.1088/1361-6579/aad2c0. PMID: 29995641. Exclusion Code: X8.

55. Frisch DR, Weiss M, Dikdan SJ, et al. Improved accuracy and confidence with multiple-lead recordings from a single-lead mobile electrocardiographic device. Pacing Clin Electrophysiol. 2019 Sep;42(9):1191-6. doi: 10.1111/pace.13775. PMID: 31400010. Exclusion Code: X4.

56. Galarnyk M, Quer G, McLaughlin K, et al. Usability of a wrist-worn smartwatch in a direct-to-participant randomized pragmatic clinical trial. Digit Biomark. 2019 Sep-Dec;3(3):176-84. doi: 10.1159/000504838. PMID: 32095776. Exclusion Code: X7.

57. Gettel C, Goldberg EM. Is the risk of bleeding among older adults with atrial fibrillation lower with antiplatelet compared with oral anticoagulants? Ann Emerg Med. 2018 Nov;72(5):547-9. doi: 10.1016/j.annemergmed.2017.10.011. PMID: 29174831. Exclusion Code: X2.

58. Ghosh SK, Tripathy RK, Paternina MRA, et al. Detection of atrial fibrillation from single lead ECG signal using multirate cosine filter bank and deep neural network. J Med Syst. 2020 May 10;44(6):114. doi: 10.1007/s10916-020-01565-y. PMID: 32388733. Exclusion Code: X8.

59. Giebel GD, Gissel C. Accuracy of mHealth devices for atrial fibrillation screening: systematic review. JMIR Mhealth Uhealth. 2019 Jun 16;7(6):e13641. doi: 10.2196/13641. PMID: 31199337. Exclusion Code: X7.

60. Gilani M, Eklund JM, Makrehchi M. Automated detection of atrial fibrillation episode using novel heart rate variability features. Conf Proc IEEE Eng Med Biol Soc. 2016 Aug;2016:3461-4. doi: 10.1109/embc.2016.7591473. PMID: 28269045. Exclusion Code: X4.

61. Giron NA, Millan CA, Lopez DM. Systematic review on features extracted from PPG signals for the detection of atrial fibrillation. Stud Health Technol Inform. 2019;261:266-73. PMID: 31156128. Exclusion Code: X1.

62. Golive A, May HT, Bair TL, et al. The population-based long-term impact of anticoagulant and antiplatelet therapies in low-risk patients with atrial fibrillation. Am J Cardiol. 2017 Jul 1;120(1):75-82. doi: 10.1016/j.amjcard.2017.03.256. PMID: 28483209. Exclusion Code: X8.

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127. Nct. MyHeartLab free living study. https://clinicaltrials.gov/show/NCT04314947. 2020PMID: CN-02089214. Exclusion Code: X10.

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143. Pastori D, Farcomeni A, Saliola M, et al. Temporal trends of time in therapeutic range and incidence of cardiovascular events in patients with non-valvular atrial fibrillation. Eur J Intern Med. 2018 Aug;54:34-9. doi: 10.1016/j.ejim.2018.04.007. PMID: 29655807. Exclusion Code: X6.

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Appendix E Table 1. Quality Assessment of Randomized, Controlled Trials (KQ 1 and KQ 2): Part 1

Author, Year Trial Name	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	What was the reported intervention fidelity?	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?
Fitzmaurice, 2014;[92] Fitzmaurice, 2007;[93] Mant, 2007;[94] Hobbs, 2005;[91] Swancutt, 2004[95] SAFE	Yes	No	Yes for age and sex; unclear otherwise	53% of patients invited for systematic screening underwent ECG; 69% of those randomized to pulse palpation reminders had pulse assessment recorded.	NR, but not suspected	0.6% missing data	0.1%	No
Gladstone, 2021 SCREEN-AF[75]	Yes	Yes	No	Yes	No	7.4%	NR	No
Halcox, 2017;[108] Halcox, 2018[210] REHEARSE-AF	Unclear, method of sequence generation NR but was centralized process with interactive voice response	NR	Yes	74% submitted single-lead ECG recordings every week; 80% of participants in screening group submitted at least 1 weekly ECG during 90% or more of the study weeks	No	G1: 5/500 (1%) G2: NR	NR	No
Kaasenbrood, 2020[111] NR	Yes	No	Probably yes	10.7% of the eligible population at intervention practice were screened	Probably Yes	NA, cluster RCT	NA, cluster RCT	NA, cluster RCT
Morgan, 2002[105]	Yes	Unclear	Yes for age and sex; unclear otherwise	73% of those invited for screening had ECG, 29% of those assigned to pulse palpation reminders had pulse assessment recorded.	NR	NR	NR	Unclear
Steinhubl, 2018[109] mSToPS	Yes	Probably yes	Yes	34% in the immediate monitoring group and 35% in the delayed monitoring group did not wear a patch	Unclear	NA, cluster RCT	NA, cluster RCT	NA, cluster RCT

Appendix E Table 1. Quality Assessment of Randomized, Controlled Trials (KQ 1 and KQ 2): Part 1

Author, Year Trial Name	Was randomization adequate?	Was allocation concealment adequate?	Were groups similar at baseline?	What was the reported intervention fidelity?	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?
Svennberg, 2021 STROKESTOP[76, 77, 118]	Yes	Probably yes	Yes	51.3% of persons assigned to screening group participated in the intervention	NR	793 (2.8%) died, emigrated, or moved out of region before study start; of those starting study, all were included in the analysis	2.8% in screened group; 2.7% in not screened group	No
Uittenbogaart et al, 2020[116] D2AF NL4776	Yes	Yes	Probably yes	45% of those assigned to intervention practices got screened	Unclear	NA, cluster RCT	NA, cluster RCT	NA, cluster RCT

Abbreviations: D2AF=Detecting and Diagnosing Atrial Fibrillation; ECG=electrocardiogram; G=group; KQ=key question; mSToPS=mHealth Screening to Prevent Strokes; NA=not applicable; NR=not reported; RCT=randomized, controlled trial; REHEARSE-AF=Assessment of REmote HEArt Rhythm Sampling using the AliveCor heart monitor to scrEen for Atrial Fibrillation; SAFE=Screening for Atrial Fibrillation in the Elderly.

Appendix E Table 2. Quality Assessment of Randomized, Controlled Trials (KQ 1 and KQ 2): 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?	Was the method to handle missing data adequate?	Did the study use acceptable statistical methods?	Quality Rating	Comments
Fitzmaurice, 2014;[92] Fitzmaurice, 2007;[93] Mant, 2007;[94] Hobbs, 2005;[91] Swancutt, 2004[95] 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 AF was previously diagnosed
Gladstone, 2021 SCREEN-AF[75]	Yes	Yes	Yes	No	Yes	Yes	Yes	Fair	Blinding of intervention not conducted, but likely minimal impact.
Halcox, 2017;[108] Halcox, 2018[210] REHEARSE-AF	Uncertain but seems that approach to confirming AF may have differed between groups	No	No	No	Yes (for primary outcome of AF detection)	NR	Yes	Fair	Moderate risk of measurement bias with lack of any masking and uncertainty about what workup was done to confirm AF. Underpowered for KQ 1 outcomes.
Kaasenbrood, 2020[111] NR	Probably yes	No	Probably yes	Probably yes	Probably yes	NR	Probably yes	Fair	Clustering did not affect regression results, so not included in final model; poor fidelity of intervention in the screening practices.

Appendix E Table 2. Quality Assessment of Randomized, Controlled Trials (KQ 1 and KQ 2): 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?	Was the method to handle missing data adequate?	Did the study use acceptable statistical methods?	Quality Rating	Comments
Morgan, 2002[105]	Unclear, single observer reviewed medical records	No	No	NR	Unclear (6 months and few new cases of AF)	NR	Yes	Fair	The main outcomes describe total numbers of AF cases detected (inclusive of both previously known AF and newly diagnosed AF), 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 AF, 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 uptake/fidelity; allocation concealment NR; baseline comparison only provided for age and sex.
Steinhubl, 2018[109] mSToPS	Probably yes	Yes	Probably yes	Probably yes	Yes	Probably yes	Yes	Fair	Somewhat poor fidelity in screening group.

Appendix E Table 2. Quality Assessment of Randomized, Controlled Trials (KQ 1 and KQ 2): 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?	Was the method to handle missing data adequate?	Did the study use acceptable statistical methods?	Quality Rating	Comments
Svennberg, 2021 STROKESTOP[76, 77, 118]	Unclear, clinical outcomes based on national registry data based on diagnoses made clinically; diagnoses were not centrally adjudicated as is typical for vascular events in trials	No	Unclear	Unclear whether clinicians making diagnoses or research staff working with registry data were masked	Yes	Not applicable	Yes, but primary outcome was changed part way through the study (authors provided some justification)	Fair	Poor fidelity in the screened group, outcome assessment masking not formalized, outcomes not centrally adjudicated and based on clinical data, primary outcome changed to a composite endpoint (with some author justification because of newer studies suggesting lower risk of stroke than what was used to initially power the study).
Uittenbogaart et al, 2020[116] NL4776	Yes	No	No	Unclear	Yes	Probably yes	Yes	Fair	Poor fidelity in the screening arm.

Abbreviations: AF=atrial fibrillation; KQ=key question; mSToPS=mHealth Screening to Prevent Strokes; NR=not reported; REHEARSE-AF=Assessment of REmote HEArt Rhythm Sampling using the AliveCor heart monitor to scrEen for Atrial Fibrillation; SAFE=Screening for Atrial Fibrillation in the Elderly; vs.=versus.

Appendix E Table 3. Quality Assessment of Randomized, Controlled Trials (KQ 5 and KQ 6): 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?
Connolly et al, 1991[99] 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 et al, 1992[97]	Unclear	Unclear	Yes	NA	NR	NR	4% lost to followup; 16% dropped out	2%; 3%	No
Petersen et al, 1989[102] 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
Stroke Prevention in Atrial Fibrillation Study Group, 1991[98, 101] 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

Appendix E Table 3. Quality Assessment of Randomized, Controlled Trials (KQ 5 and KQ 6): 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?
The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators, 1990[100] 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 AntiKoagulation; BAATAF=Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA=Canadian Atrial Fibrillation Anticoagulation Study; NA=not applicable; NR=not reported; SPAF=Stroke Prevention in Atrial Fibrillation Study Group; vs.=versus.

Appendix E Table 4. Quality Assessment of Randomized, Controlled Trials (KQ 5 and KQ 6): 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
Connolly et al, 1991[99] 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 et al, 1992[97]	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
Petersen et al, 1989[102] 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
Stroke Prevention in Atrial Fibrillation Study Group, 1991[98, 101] SPAF	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 unclear
The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators, 1990[100] 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=Atrial Fibrillation, ASpirin, and AntiKoagulation; ASA=American Society of Anesthesiologists; BAATAF=Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA=Canadian Atrial Fibrillation Anticoagulation Study; DSMB=Data and Safety Monitoring Board; INR=International Normalized Ratio; NA=not applicable; NR=not reported; PT=prothrombin time; SPAF=Stroke Prevention in Atrial Fibrillation Study Group.

Appendix E Table 5. Quality Assessment of Randomized, Controlled Trials: Additional Questions for Studies Reporting Harms (KQ 6)

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
Connolly et al, 1991[99] CAFA study	Yes	Yes	Yes	Yes (mean followup 15.2 months)	Fair	Self-report of bleeding events
Ezekowitz et al, 1992[97]	Yes	Yes	Yes	Yes (mean followup 1.7 to 1.8 years)	Fair	
Petersen et al, 1989[102] AFASAK	Yes	Yes	Yes	Yes	Fair	
Stroke Prevention in Atrial Fibrillation Study Group, 1991[98, 101] SPAF	Yes	Yes	Yes	Yes (mean followup 1.3 years)	Fair	
The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators, 1990[100] BAATAF	Yes	Yes	Yes	Yes (mean followup 2.2 years)	Fair	

Abbreviations: AFASAK=Atrial Fibrillation, ASpirin, and AntiKoagulation; BAATAF=Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA=Canadian Atrial Fibrillation Anticoagulation Study; SPAF=Stroke Prevention in Atrial Fibrillation Study Group.

Appendix E Table 6. Quality Assessment of Diagnostic Test Accuracy Studies (KQ 3): Part 1

Study Author (Year)	Overall Study Quality	Comments
Gladstone et al (2021) [75]	Good	No serious concerns for bias in any domains.
Himmelreich et al (2019)[112]	Good	No serious concerns for bias in any domains.
Hobbs et al (2005)[91]	Good	This analysis was embedded within a larger RCT comparing systematic and opportunistic screening to no screening. All study-related ECGs were used in the accuracy analysis. No serious concerns for bias in any domains.
Kearley et al (2014)[113]	Fair	This study was given a fair rating for the following reasons: (1) the exclusion criteria were vague and could have introduced selection bias by allowing general practitioners to exclude patients considered inappropriate for participation without specifying what those reasons were other than terminal illness; (2) of the 2,673 patients recruited for study involvement, there is no specific description of how many patients were nonresponders; (3) there is no description of how many patients were excluded from the study because the practice discontinued involvement in the study; (4) there is no description of why practices discontinued involvement in the study; 5) nurse palpation vs. 12 lead ECG is included in the patient recruitment flowchart but is not described in the methods or reported in the results; 6) handling of missing triage testing data was not discussed in the methods or results.
Marazzi et al (2012)[115]	Good	
Philippsen et al (2017)[56]	Good	No serious concerns for bias in any domains.
Sabar et al (2019)[117]	Fair	Consecutive patients from outpatient cardiology clinics recruited for participation but no information about clinical status (e.g., existing AF); thus, the applicability is unclear.
Uittenbogaart et al, 2020[116]	Fair	Only intervention practices were instructed to conduct confirmatory ECG for positive screens, so readers of the confirmatory ECGs would conceivably know these participants had screened positive. It appears usual care practices diagnosed patients through a different pathway that did not include the expert ECG readers. Primarily only participants in the screening practices who screened positive received ECG (the reference standard)—a 10% random sample who screened negative also received reference ECG; its unclear which patients in the usual care practices received ECG.
Weisel et al (2014)[114]	Fair	Unclear method of enrollment, unclear whehter test results were masked.

Abbreviations: EECG=electrocardiogram; KQ=key question; RCT=randomized, controlled trial; vs.=versus.

Appendix E Table 7. Quality Assessment of Diagnostic Test Accuracy Studies (KQ 3): Part 2

Study Author(s) (Year(s))	Consider patients evaluated (prior testing, presentation, intended use of index test and setting). Is there concern that the included patients do not match the review question?	Consider index test. Is there concern that the index test, its conduct, or interpretation differ from the review question?	Consider reference test. Is there concern that the target condition as defined by the reference standard does not match the review question?
Gladstone et al (2021)[75]	Yes	No	No
Himmelreich et al (2019)[112]	Yes	No	No
Hobbs et al (2005)[91]	Yes	No	No
Kearley et al (2014)[113]	Yes	No	No
Marazzi et al (2012)[115]	Unclear	No	No
Philippsen et al (2017)[56]	Yes	No	No
Sabar et al (2019)[117]	Unclear	No	No
Uittenbogaart et al, 2020[116]	Yes	No	No
Weisel et al (2014)[114]	Yes	No	No

Abbreviation: KQ=key question.

Appendix E Table 8. Quality Assessment of Diagnostic Test Accuracy Studies (KQ 3): Part 3

Study Author(s) (Year(s))	Was a consecutive or random sample of patients enrolled?	Was a case-control design avoided?	Did the study avoid inappropriate exclusions?	Could the selection of patients have introduced bias?
Gladstone et al (2021)[75]	Yes	Yes	Yes	No
Himmelreich et al (2019)[112]	Yes	Yes	Yes	No
Hobbs et al (2005)[91]	Yes	Yes	Yes	No
Kearley et al (2014)[113]	Yes	Yes	Yes	Yes
Marazzi et al (2012)[115]	Yes	Yes	Yes	No
Philippsen et al (2017)[56]	Unclear	Yes	Yes	No
Sabar et al (2019)[117]	Yes	Yes	Yes	No
Uittenbogaart et al, 2020[116]	Yes	Yes	Yes	No
Weisel et al (2014)[114]	Unclear	Yes	Yes	No

Abbreviations: KQ=key question.

Appendix E Table 9. Quality Assessment of Diagnostic Test Accuracy Studies (KQ 3): Part 4

Study Author(s) (Year)	Were the index test results interpreted without knowledge of the results of the reference standard?	If a threshold was used, was it prespecified?	Could the conduct or interpretation of the index test have introduced bias?
Gladstone et al (2021)[75]	Yes	Yes	No
Himmelreich et al (2019)[112]	Yes	Yes	No
Hobbs et al (2005)[91]	Yes	Unclear	No
Kearley et al (2017)[113]	Yes	Yes	No
Marazzi et al (2012)[115]	Yes	Yes	No
Philippsen et al (2017)[56]	Yes	Yes	No
Sabar et al (2019)[117]	Yes	Yes	No
Uittenbogaart et al, 2020[116]	Yes	Yes	No
Weisel et al (2014)[114]	Unclear	Unclear	No

Abbreviations: KQ=key question.

Appendix E Table 10. Quality Assessment of Diagnostic Test Accuracy Studies (KQ 3): Part 5

Study Author (Year)	Is the reference standard likely to correctly classify the target condition?	Were the reference standard results interpreted without knowledge of the results of the index test?	Could the reference standard, its conduct, or its interpretation have introduced bias?
Gladstone et al (2021)[75]	Yes	Yes	No
Himmelreich et al (2019)[112]	Yes	Yes	No
Hobbs et al (2005)[91]	Yes	Yes	No
Kearley et al (2014)[113]	Yes	Yes	No
Marazzi et al (2012)[115]	Yes	Yes	No
Philippsen et al (2017)[56]	Yes	Yes	No
Sabar et al (2019)[117]	Yes	Yes	No
Uittenbogaart et al, 2020[116]	Yes	Unclear	Yes
Weisel et al (2014)[114]	Yes	Yes	No

Abbreviations: KQ=key question.

Appendix E Table 11. Quality Assessment of Diagnostic Test Accuracy Studies (KQ 3): Part 6

Study Author(s) (Year(s))	Was there an appropriate interval between index test(s) and reference standard?	Did all patients receive a reference standard?	Did all patients receive the same reference standard?	Were all patients included in the analysis?
Gladstone et al (2021)[75]	Yes	No	Yes	No
Himmelreich et al (2019)[112]	Yes	Yes	Yes	No
Hobbs et al (2005)[91]	Yes	Yes	Yes	Yes
Kearley et al (2014)[113]	Yes	Yes	Yes	Yes
Marazzi et al (2012)[115]	Yes	Yes	Yes	Yes
Philippsen et al (2017)[56]	Yes	Yes	Yes	Yes
Sabar et al (2019)[117]	Yes	Yes	Yes	Yes
Uittenbogaart et al, 2020[116]	Yes	No (random sample received it)	Yes	Yes
Weisel et al (2014)[114]	Yes	Yes	Yes	Unclear

Abbreviations: KQ=key question.

Appendix E Table 12. Quality Assessment of Systematic Reviews, Network Meta-Analyses, and IDP Meta-Analyses (KQ 5 and KQ 6)

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[104]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Good
Atrial Fibrillation Investi-gators, 1994[107]	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
Coleman, 2012[103]	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
Hart, 2007[59]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Teresh-chenko, 2016[106]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
van Walraven, 2009[96]	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

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

Appendix E Table 13. Relevance of Systematic Reviews and Meta-Analyses for the Benefits and Harms of Anticoagulation Therapy (KQ 5 and KQ 6)

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 warfarin?	If the review is an NMA, did it include the relevant trials for newer OACs?	Has the review been updated?	Comments
Aguilar, 2009[104]	SR with MA	Yes	Yes	Yes	NA	No	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.
Atrial Fibrillation Investi-gators, 1994[107]	IPD	Yes	Yes	Yes	NA	No	Used the Atrial Fibrillation Investigators database; used only the 5 warfarin trials (2 of those also included ASA)
Coleman, 2012[103]	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 CAFA (but those did not report MGIB)	NA	No	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
Hart, 2007[59]	SR with MA	Yes	No, but separated (primary vs. secondary prevention) results for absolute risk reduction of stroke	Yes	NA	No (it is an update of a 1999 review)[211]	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)
Teresh-chenko, 2016[106]	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	Yes, all the newer relevant trials included (although this excluded phase II trials of DOACs)	No	Includes some contribution of data from people with a history of TIA or stroke. DOAC phase II studies were excluded.

Appendix E Table 13. Relevance of Systematic Reviews and Meta-Analyses for the Benefits and Harms of Anticoagulation Therapy (KQ 5 and KQ 6)

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 warfarin?	If the review is an NMA, did it include the relevant trials for newer OACs?	Has the review been updated?	Comments
van Walraven, 2009[96] 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)	Yes	NA	No	Used the Atrial Fibrillation Investigators database; included head-to-head and placebo-controlled studies

Abbreviations: ASA=American Society of Anesthesiologists; CAFA=Canadian Atrial Fibrillation Anticoagulation study; DOAC=direct oral anticoagulant; EAFT=European Atrial Fibrillation Trial; IPD=Individual patient data; JAST=Journal of Analytical Science and Technology; KQ=key question; LASAF=low-dose aspirin, stroke atrial fibrillation trial; MA=meta-analysis; MGIB=major gastrointestinal bleed; NA=not applicable; NASPEAF=National Study for Prevention of Embolism in Atrial Fibrillation Science; SPAF=Stroke Prevention in Atrial Fibrillation Study; SR=systematic review; TIA=transient ischemic attack.

Appendix E Table 14. Quality Assessment of Observational Cohort Studies Reporting Harms (KQ 6): Part 1

First Author, Year, Study Name	Is there potential for confounding	Was the analysis based on splitting participants' follow up?	Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Use of an appropriate analysis method that controlled for important confounding domains?	Were confounding domains that were controlled for measured validly and reliably?	Control for any post-intervention variables?	Use an appropriate analysis method that adjusted for time-varying confounding?	Were confounding domains that were adjusted for measured validly and reliably?	Bias Due to Confounding	Comment
Bassand, 2018 GARFIELD-AF[110]	Yes	No	NA	Probably no	Probably yes	No	Probably yes	Probably yes	Moderate	Uncertain that all important confounders were included

Abbreviations: GARFIELD-AF=Global Anticoagulant Registry in the FIELD-Atrial Fibrillation; KQ=key question; NA=not applicable.

Appendix E Table 15. Quality Assessment of Observational Cohort Studies Reporting Harms (KQ 6): Part 2

First Author, Year, Study Name	Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	Were the post-intervention variables that influenced selection likely to be associated with intervention?	Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Do start of followup and start of intervention coincide for most participants?	Were adjustment techniques used that are likely to correct for the presence of selection biases?	Bias Due to Selection	Comment
Bassand, 2018 GARFIELD-AF[110]	No			Yes		Low	

Abbreviations: GARFIELD-AF=Global Anticoagulant Registry in the FIELD-Atrial Fibrillation; KQ=key question.

Appendix E Table 16. Quality Assessment of Observational Cohort Studies Reporting Harms (KQ 6): Part 3

First Author, Year, Study Name	Were intervention groups clearly defined?	Was the information used to define intervention groups recorded at the start of the intervention?	Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Bias Due to Classification	Comment
Bassand, 2018 GARFIELD-AF[110]	Yes	Yes	No	Low	

Abbreviations: GARFIELD-AF=Global Anticoagulant Registry in the FIELD-Atrial Fibrillation; KQ=key question.

Appendix E Table 17. Quality Assessment of Observational Cohort Studies Reporting Harms (KQ 6): Part 4

First Author, Year, Study Name	Were there deviations from the intended intervention beyond what would be expected in usual practice?	Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Were important co-interventions balanced across inter-vention groups?	Was the intervention implemented successfully for most participants?	Did study participants adhere to the assigned intervention regimen?	Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	Bias Due to Deviations	Comment
Bassand, 2018 GARFIELD-AF[110]	Probably no	No	No information	No information	No information	No information	No information	

Abbreviations: GARFIELD-AF=Global Anticoagulant Registry in the FIELD-Atrial Fibrillation; KQ=key question.

Appendix E Table 18. Quality Assessment of Observational Cohort Studies Reporting Harms (KQ 6): Part 5

First Author, Year, Study Name	Were outcome data available for all, or nearly all, participants?	Were participants excluded due to missing data on intervention status?	Were participants excluded due to missing data on other variables needed for the analysis?	Are the proportion of participants and reasons for missing data similar across interventions?	Is there evidence that results were robust to the presence of missing data?	Bias Due to Missing Data	Comment
Bassand, 2018 GARFIELD-AF[110]	Yes	No	No	Yes	Yes	Low	

Abbreviations: GARFIELD-AF=Global Anticoagulant Registry in the FIELD-Atrial Fibrillation; KQ=key question.

Appendix E Table 19. Quality Assessment of Observational Cohort Studies Reporting Harms (KQ 6): Part 6

First Author, Year, Study Name	Could the outcome measure have been influenced by knowledge of the intervention received?	Were outcome assessors aware of the intervention received by study participants?	Were the methods of outcome assessment comparable across intervention groups?	Were any systematic errors in measurement of the outcome related to intervention received?	Bias due to Measurement of Outcomes	Comment
Bassand, 2018 GARFIELD-AF[110]	Probably yes	No information	Yes	No information	Moderate	Outcome assessment not specified as blinded to use of OACs.

Abbreviations: GARFIELD-AF=Global Anticoagulant Registry in the FIELD-Atrial Fibrillation; KQ=key question; OAC=oral anticoagulant.

Appendix E Table 20. Quality Assessment of Observational Cohort Studies Reporting Harms (KQ 6): Part 7

First Author, Year, Study Name	Multiple outcome measurements within the outcome domain?	Multiple analyses of the intervention-outcome relationship?	Different subgroups?	Bias Due to Selection of Reported Result	Comment
Bassand, 2018 GARFIELD-AF[110]	No	No	No	Low	

Abbreviations: GARFIELD-AF=Global Anticoagulant Registry in the FIELD-Atrial Fibrillation; KQ=key question.

Appendix E Table 21. Quality Assessment of Observational Cohort Studies Reporting Harms (KQ 6): Part 8

First Author, Year, Study Name	Overall Risk of Bias	Comment
Bassand, 2018 GARFIELD-AF[110]	Moderate	Some risk of bias due to confounding and some concerns over outcome ascertainment because not blinded and ascertainment of bleeding might be more rigorous for participants known to be taking OACs

Abbreviations: GARFIELD-AF=Global Anticoagulant Registry in the FIELD-Atrial Fibrillation; KQ=key question; OAC=oral anticoagulant.

Appendix F Table 1. Study Characteristics of Included Randomized, Controlled Trials Evaluating Benefits and Harms of Screening for Atrial Fibrillation (KQ 1 and KQ 2)

Author, Year Trial Name, Registry No.	Study Design	Country	Study Quality	Total N	Sponsorship
Gladstone et al, 2021[75] SCREEN-AF NCT02392754	Parallel-group RCT	Canada and Germany	Fair	856	Canadian Institutes of Health Research, German Centre for Cardiovascular Research, Boehringer Ingelheim, Microlife Corp, ManthaMed, iRhythm
Halcox et al, 2017[108] REHEARSE-AF ISRCTN10709813	Parallel-group RCT	U.K.	Fair	1,001	Welsh Government Health Technology and Telehealth Fund; AliveCor Inc.
Hobbs et al, 2005[91] Fitzmaurice et al, 2007;[93] Fitzmaurice et al, 2014;[92] Mant et al, 2007;[94] Swancutt et al, 2004[95] SAFE ISRCTN19633732	Cluster-group RCT	U.K.	Fair	9,088*	National Health Service Research & Development Health Technology Assessment Programme
Kaasenbrood et al, 2020[111] IDEAL-MD NCT02270151	Cluster-group RCT	The Netherlands	Fair	17,107	Boehringer Ingelheim
Morgan et al, 2002[105]	Parallel-group RCT	U.K.	Fair	3,001	Wellcome Trust, South and West Regional National Health Service Research and Development Directorate
Steinhubl et al, 2018[109] mSToPS NCT02506244	Parallel-group RCT	U.S.	Fair	2,659	Janssen Pharmaceuticals; National Institutes of Health; Qualcomm Foundation
Svennberg et al 2021[76] Friberg et al 2013[78] Svennberg et al 2015[77] STROKESTOP NCT01593553	Parallel-group RCT	Sweden	Fair	28,768 (randomized)/ 27,975 (enrolled)	Stockholm County Council, the Swedish Heart & Lung Foundation, King Gustav V and Queen Victoria's Freemasons' Foundation, the Klebergska Foundation, the Tornspiran Foundation, the Scientific Council of Halland Region, the Southern Regional Healthcare Committee, the Swedish Stroke Fund, Carl Bennet AB, Boehringer Ingelheim, Bayer, and Bristol Myers Squibb–Pfizer
Uittenbogaart et al, 2020[116] D2AF NL4776	Cluster-group RCT	The Netherlands	Fair	17,976	ZonMw, the Netherlands Organisation for Health Research and Development) and Amsterdam Universities Medical Centres

* Excludes participants with known AF or missing notes from the analysis.

Appendix F Table 1. Study Characteristics of Included Randomized, Controlled Trials Evaluating Benefits and Harms of Screening for Atrial Fibrillation (KQ 1 and KQ 2)

Abbreviations: D2AF=Detecting and Diagnosing Atrial Fibrillation; IDEAL-MD=Improving DEtection of Atrial fibriLlation in Primary Care With the MyDiagnostick; KQ=key question; mSToPS=mHealth Screening to Prevent Strokes; N=number of participants; RCT=randomized, controlled trial; REHEARSE=REmote HEArt Rhythm Sampling using the AliveCor heart monitor to scrEen for Atrial Fibrillation; SAFE=Screening for Atrial Fibrillation in the Elderly; U.K.=United Kingdom; U.S.=United States.

Appendix F Table 2. Population Characteristics of Included Randomized, Controlled Trials Evaluating Benefits and Harms of Screening for Atrial Fibrillation (KQ 1 and KQ 2)

Author, Year Trial Name, Registry No.	Recruitment Setting	Inclusion Criteria	Exclusion Criteria	Mean age (SD)	N (%) Female	Other	Ascertainment of Symptom Status at Enrollment
Gladstone et al, 2021[75] SCREEN-AF NCT02392754	Primary care clinics	Community-dwelling persons age 75 years or older without known AF and who were not receiving OAC but who could be candidates if AF were diagnosed (CHADS2 ≥2 and no contraindications); history of HTN, in sinus rhythm as assessed by 30-second pulse palpation and heart auscultation upon enrollment	History of AF or atrial flutter, pacemaker, defibrillator, or implanted loop recorder	80 (4.0)	487 (57)	Median (IQR) CHA_2DS_2-VASc score: 4 (4 to 5)	NR
Halcox et al, 2017[108] REHEARSE-AF ISRCTN10709813	General practices	>65 years of age with a CHA_2DS_2-VASc score ≥2	Current receipt of OAC therapy, known diagnosis of AF, a known contra-indication to anti-coagulation, or permanent cardiac pacing implantation	72.6 (5.4)	535 (53)	Mean (SD) CHA_2DS_2-VASc score: 3.0 (1.0) N (%) HTN Intervention: 268 (53.6) Control: 272 (54.3) DM Intervention: 129 (25.8) Control: 140 (27.9) Prior stroke/TIA Intervention: 35 (7.0) Control: 28 (5.6) Heart failure Intervention: 5 (1.0) Control: 9 (1.8)	NR 8 (42%) of the new cases in the intervention group experienced symptoms at time of diagnosis; 2 (40%) of the new cases in the control group were symptomatic at time of diagnosis
Hobbs et al, 2005[91] Fitzmaurice et al, 2007;[93] Fitzmaurice et al, 2014;[92] Mant et al, 2007;[94] Swancutt et al, 2004[95] SAFE ISRCTN19633732	50 primary care practices; 25 randomized to intervention and 25 randomized to control	65 years or older	Terminally ill or moved primary care practice	75.3 (7.2)	8, 500 (57.4)	NR	NR

Appendix F Table 2. Population Characteristics of Included Randomized, Controlled Trials Evaluating Benefits and Harms of Screening for Atrial Fibrillation (KQ 1 and KQ 2)

Author, Year Trial Name, Registry No.	Recruitment Setting	Inclusion Criteria	Exclusion Criteria	Mean age (SD)	N (%) Female	Other	Ascertainment of Symptom Status at Enrollment
Kaasenbrood et al, 2020[111] No IDEAL-MD NCT02270151	31 general practices in the Netherlands (15 intervention practices and 16 control practices)	Age ≥65 years without a history of AF	Persons with atrial flutter	Intervention: 74.3 (7.3) Control: 74.5 (7.3)	Intervention: 4,680 (54.5) Control: 4,610 (54.1)	Mean (SD) CHA_2DS_2VASc score screen detected 3.6 (1.6) vs. regular detection 4.0 (1.5) N (%) HTN Intervention: 441 (50.9) Control: 427 (50.4) DM Intervention: 172 (19.8) Control: 145 (17.1) Prior stroke Intervention: 34 (3.9) Control: 54 (6.4) Prior TIA Intervention: 40 (4.6) Control: 40 (4.7)	All participants in intervention group completed a symptoms questionnaire for the previous month
Morgan et al 2002[105]	Four general practices	Patients aged 65 to 100 years	None	75.5 (NR)	1,756 (58.8)	NR	NR
Steinhubl et al 2018[109] No mSToPS NCT02506244	Site-less clinical trial involving a large health insurance plan's members throughout the United States. Individuals were recruited by email or direct mail and directed to a web-based informational website if interested.	75 years or older or a male older than 55 years or female older than 65 years with 1 or more comorbidities. Comorbidities include prior stroke, heart failure, diagnosis of both diabetes and hypertension, mitral valve disease, left ventricular hypertrophy, COPD requiring home oxygen, sleep apnea, history of pulmonary embolism, history of myocardial infarction, or diagnosis of obesity.	Any current or prior diagnosis of AF, atrial flutter, or atrial tachycardia; already prescribed anti-coagulation therapy; implantable pacemaker, defibrillator, or both	72.4 (7.3)	1,026 (38.6)	Median (IQR) CHA_2DS_2-VASc score: 3 (2-4) N (%) HTN Intervention: 1053 (77.1) Control: 993 (76.8) DM Intervention: 529 (38.7) Control: 472 (36.5) Prior stroke Intervention: 187 (13.7) Control: 182 (14.1) Heart failure Intervention: 69 (5.1) Control: 59 (4.6)	NR 12 (17.4%) of the patients diagnosed with AF in the intervention group recalled having symptoms when prompted

Appendix F Table 2. Population Characteristics of Included Randomized, Controlled Trials Evaluating Benefits and Harms of Screening for Atrial Fibrillation (KQ 1 and KQ 2)

Author, Year Trial Name, Registry No.	Recruitment Setting	Inclusion Criteria	Exclusion Criteria	Mean age (SD)	N (%) Female	Other	Ascertainment of Symptom Status at Enrollment
Svennberg et al 2021[76] Friberg et al 2013[78] Svennberg et al 2015[77] STROKESTOP NCT01593553	Residents age 75 or 76 years were identified using their person identification number from population registers and randomized to receive an invitation to screening or to be assigned to the control group	75 or 76 years old living in the Halland and Stockholm regions of the country; no other entry criteria specified	No exclusion criteria specified	Median 76 (IQR 75.5-76.6)	15,273 (54.6)	Based on registry data Mean (SD) CHA2DS2-VASC score: 3.5 (1.3) N (%) AF Intervention: 1,691 (12.1) [959/6,814 (14.1%) of non-participants) vs. 732/7,165 (10.2%) of participants] Control: 1,794 (12.8) Hypertension Intervention: 4,963 (35.5%) Control: 4,980 (35.6%) Stroke or TIA or systemic embolism Intervention: 1,557 (11.1%) Control: 1,513 (10.8%) Heart failure Intervention: 1,045 (7.5%) Control: 1,098 (7.8%) Diabetes Intervention: 2,115 (15.1%) Control: 2,107 (15.1%) OAC dispensed in 6 months prior to baseline Intervention: 1,282 (9.2%) Control: 1,313 (9.4%)	NR

Appendix F Table 2. Population Characteristics of Included Randomized, Controlled Trials Evaluating Benefits and Harms of Screening for Atrial Fibrillation (KQ 1 and KQ 2)

Author, Year Trial Name, Registry No.	Recruitment Setting	Inclusion Criteria	Exclusion Criteria	Mean age (SD)	N (%) Female	Other	Ascertainment of Symptom Status at Enrollment
Uittenbogaart et al, 2020[116] D2AF NL4776	96 primary care practices within networks of the two participating universities and a Primary Care Database (47 intervention practices, 49 control practices)	Age ≥ 65 with no known history of AF in the practice's electronic health record	History of AF, pacemaker or ICD, could not provide informed consent, terminal illness, or could not visit the practice	Intervention: 75.2 (6.8) Usual care: 75.0 (6.9)	10,248 (55)	N(%) Hypertension Intervention: 4,540 (49.6) Usual care: 4,579 (48.7) Stroke or TIA Intervention: 886 (9.7) Usual care: 911 (9.7) Heart failure Intervention: 348 (3.8) Usual care: 362 (3.9) Thromboembolism Intervention: 460 (5.0) Usual care: 431 (4.6) Diabetes Intervention: 1,768 (19.3) Usual care: 1,750 (18.6)	NR

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; COPD=chronic obstructive pulmonary disease; D2AF=Detecting and Diagnosing Atrial Fibrillation; DM=diabetes mellitus; HTN=hypertension; IDEAL-MD=Improving DEtection of Atrial fibriLlation in Primary Care With the MyDiagnostick; IQR=interquartile range; KQ=key question; mSToPS=mHealth Screening to Prevent Strokes; N=number of participants; OAC=oral anticoagulant; REHEARSE=REmote HEArt Rhythm Sampling using the AliveCor heart monitor to scrEen for Atrial Fibrillation; SAFE=Screening for Atrial Fibrillation in the Elderly; TIA=transient ischemic attack; vs.=versus.

Appendix F Table 3. Intervention Characteristics of Included Randomized, Controlled Trials Evaluating Benefits and Harms of Screening for Atrial Fibrillation (KQ 1 and KQ 2)

Author, Year Trial Name Registry No.	Intervention Groups (N randomized)	Study Group Descriptions	Comments on Interventions
Gladstone et al, 2021 SCREEN-AF NCT02392754[75]	No screening (422) Continuous ECG and intermittent BP measurement (434)	Comparator: Standard clinical care with no screening intervention Group 1: A single-lead adhesive patch continuous ECG (Zio XT, iRhythm Technologies) worn on the chest for 2 weeks; worn at baseline and again at 3 months for a total duration of 4 weeks; automated home BP monitor with automated AF detection used twice daily during each of the 2-week ECG monitoring periods	First cECG monitor was worn by 423 participants (97.5%) and second monitor was worn by 344 participants (79.3%)
Halcox et al 2017[108] REHEARSE-AF ISRCTN10709813	No screening (501) ECG screening (500)	Comparator: No specific intervention, received care as usual by their general practitioner Group 1: Twice-weekly 30-second, single-lead ECG using a handheld device (AliveCor Heart Monitor) for 12 months, plus additional recordings if symptomatic	74% of participants did not miss a single week of ECG monitoring
Hobbs et al 2005[91]; Fitzmaurice et al, 2007[93]; Fitzmaurice et al, 2014[92]; Mant et al, 2007[94]; Swancutt et al, 2004[95] SAFE ISRCTN19633732	No screening (4,936) Pulse palpation reminders (4,933) ECG screening (4,933)	Comparator: No screening intervention Group 1: 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 Group 2: Patients invited by letter to attend a nurse-led screening clinic where their radial pulse was palpated, and a 12-lead ECG was performed	
Kaasenbrood et al 2020[111] No IDEAL-MD NCT02270151	Usual care (no screening intervention) (8,526) Single-lead ECG (8,581)	Comparator: Control practices were briefly informed about the aim of the study but no specific intervention assigned. Group 1: Intervention practices instructed to screen all persons age 65 years without a diagnosis of AF during visits to the practice over the course of the study using the MyDiagnostick device, which registers lead 1 for 1 minute and indicates whether an irregular rhythm is detected. Implementation of screening left to the discretion of practices.	Fidelity: Only 10.7% of the eligible population at intervention practice (8,581) were screened
Morgan et al 2002[105]	Opportunistic screening (1,502) ECG screening (1,499)	Comparator: Reminder flag was placed in the notes for a 6-month period. Nurses and physicians were encouraged to record pulse during routine visits; if pulse was suspicious for AF, they decided whether to request ECG depending on the history and clinical context. Group 1: Patients invited by letter to attend a nurse-led screening clinic where their radial pulse was palpated, and a single-lead II rhythm strip was performed.	

Appendix F Table 3. Intervention Characteristics of Included Randomized, Controlled Trials Evaluating Benefits and Harms of Screening for Atrial Fibrillation (KQ 1 and KQ 2)

Author, Year Trial Name Registry No.	Intervention Groups (N randomized)	Study Group Descriptions	Comments on Interventions
Steinhubl et al 2018[109] No mSToPS NCT02506244	Delayed home-based ECG monitoring (1,293) Immediate iRhythmZio home-based ECG monitoring (1,366)	Comparator: Delayed monitoring using same screening as below but initiated 4 months after enrollment date. Group 1: FDA-approved, single-use, water-resistant, 14-day, ambulatory ECG monitoring skin adhesive patch that monitors and retains in memory the wearer's continuous ECG for up to 2 weeks. Participants wore an initial patch upon enrollment for 2 weeks, and a second patch 3 months later for another 2 weeks.	Fidelity: N (%) not wearing patch Immediate monitoring: 458 (34) Delayed monitoring: 459 (35)
Svennberg et al 2021[76] Friberg et al 2013[78] Svennberg et al 2015[77] STROKESTOP NCT01593553	No invitation to screening (14,381 randomized/13,996 enrolled [385 excluded prior to study start, 369 died, 16 emigrated]) Screening (14,387 randomized/13,979 enrolled [408 excluded prior to study start, 362 died, 15 emigrated, 31 moved from the region])	Comparator: No invitation to screening Group 1: Invitation to screening at a study center; at enrollment participants receive an index ECG, those in sinus rhythm were then instructed on use of a single-lead handheld ECG recorder (Zenicor) to use twice daily for 30 seconds over a 14-day duration. Persons with known AF not already on OAC, new AF either on index ECG or on intermittent ECG were offered structured followup with a cardiologist. Participants with inconclusive ECGs were offered conventional 24-hour Holter monitoring.	Fidelity: 51.3% of persons assigned to screening group participated in the intervention

Appendix F Table 3. Intervention Characteristics of Included Randomized, Controlled Trials Evaluating Benefits and Harms of Screening for Atrial Fibrillation (KQ 1 and KQ 2)

Author, Year Trial Name Registry No.	Intervention Groups (N randomized)	Study Group Descriptions	Comments on Interventions
Uittenbogaart et al, 2020[116] D2AF NL4776	Usual care (9,526) Screening (9,218)	Comparator: Usual care as determined by each practice. At the time of the study, guidance from the Dutch College of General Practitioners, which "recommends assessing heart rhythm in every patient with shortness of breath, reduced ability to exercise, palpitations, dizziness, light headedness, syncope, chest pain, and [TIA] or stroke, as part of the usual diagnostic work-up," but not systematic screening. Patients with any of these risk factors could participate in the clinics' structured disease management programs and visit their practices at least once a year, during which they would receive pulse palpation and sometimes ECG. Group 1: 200 patients eligible for screening were randomly selected in each practice and marked as such in the electronic health record. When the treating physician or other practice staff opened the record of a marked patient during the study year, the provider received an alert on their computer screen that the patient had been selected for AF screening. Providers would obtain informed consent and perform systematic serial screening with 3 tests: 1) radial pulse palpation for ≥15 seconds (with any irregularity considered a positive test), 2) electronic BP monitor with AF detection function (WatchBP Home A, Microlife), and 3) handheld single-lead ECG with automated AF detection function (MyDiagnostick, MyDiagnostick Medical) in a preset alternating order. Immediately after serial testing, patients with >=1 positive index test, plus a random sample of patients (10%; generated by the study software) with 3 negative index tests, underwent 12-lead ECG as the reference standard for AF. ECG results were interpreted by an experienced assessor (supervised by a cardiologist), a 2nd cardiologist, and possibly a 3rd cardiologist in the event of disagreement. Patients with no AF detected using 12-lead ECG were invited to undergo continuous Holter recording (multichannel Holter electrocardiograph recorder model H2, Fysiologic) for 2 weeks.	Only 4,106/9,218 (44.5%) of eligible patients in the intention-to-screen group participated in the screening protocol. This proportion screened varied by practice from 6.7% to 65.8%.

Abbreviations: D2AF=Detecting and Diagnosing Atrial Fibrillation; FDA=Food and Drug Administration; IDEAL-MD=Improving DEtection of Atrial fibriLlation in Primary Care With the MyDiagnostick; KQ=key question; mSToPS=mHealth Screening to Prevent Strokes; N=number of participants; NA=not applicable; OAC=oral anticoagulant; REHEARSE=REmote HEArt Rhythm Sampling using the AliveCor heart monitor to scrEen for Atrial Fibrillation; SAFE=Screening for Atrial Fibrillation in the Elderly.

Appendix F Table 4. Results of Included Randomized, Controlled Trials Evaluating Benefits of Screening for Atrial Fibrillation (KQ 1 and KQ 2)

Author, Year Trial, Registry No.	Intervention Groups (N randomized)	Detection of Atrial Fibrillation	Morbidity	Mortality
Gladstone et al, 2021[75] SCREEN-AF NCT02392754	Comparator: No screening (422) Group 1: Continuous ECG and intermittent BP measurement (434)	n/N (%) new cases of AF at 6 months defined as an episode lasting more than 5 minutes on continuous ECG or presenting clinically Screening: 23/434 (5.3%) Usual care: 2/422 (0.5%) RR (95% CI): 11.2 (2.7 to 47.1) ARD (95% CI): 4.8% (2.6% to 7.0%) NNS: 21 20 of 23 cases (87%) detected in the intervention group were detected by screening and 3 presented clinically with symptoms. 1 case was atrial flutter and 19 were AF. Type of AF for screen-detected cases: Paroxysmal: 18 Persistent: 2 40% were detected in the first week and 75% in the second week, 85% detected in the third week, 15% detected in the 4th week Median time in AF: 6.3 hours (IQR 4.2 to 14.0; range 1.3 hours to 28 days) Duration of AF episodes: >1 hr: 95% >4 hrs: 70% >6 hrs: 50% >9 hours: 30% >12 hrs: 25% >24 hrs: 15% Median duration of longest episode: 5.7 hours (IQR 2.9 to 12.9) % new cases of AF at 3 months (based on single cycle of screening) Screening: 4.6% Usual care: 0.2% RR (95% CI): 19.5 (2.6 to 144.3) ARD (95% CI): 4.4% (2.3 to 6.4) NNS: 23	N with ischemic stroke Screening: 2 Usual care: 0 N with TIA Screening: 1 Usual care: 0 N with systemic embolism: 0	N deaths Screening: 0 Usual care: 1 (cardiovascular event)

Appendix F Table 4. Results of Included Randomized, Controlled Trials Evaluating Benefits of Screening for Atrial Fibrillation (KQ 1 and KQ 2)

Author, Year Trial, Registry No.	Intervention Groups (N randomized)	Detection of Atrial Fibrillation	Morbidity	Mortality
Halcox et al 2017[108] REHEARSE-AF ISRCTN10709813	No screening (501) Systematic ECG screening (500)	***Systematic ECG screening vs. no screening*** New cases identified: 19 vs. 5 HR, 3.9 (95% CI, 1.4 to 10.4), p=0.007 ARD 2.8% (95% CI, 0.91% to 4.69%) Paroxysmal AF: 12 vs. 0 Persistent AF: 7 vs. 5 Symptoms at the time of diagnosis: 11 vs. 5 No symptoms at the time of diagnosis: 8 vs. 0	***Systematic ECG screening vs. no screening*** Composite (stroke, TIA, or system embolism): 6 vs. 10 HR, 0.61 (95% CI, 0.22 to 1.69), p=0.34 In screened group: 1 ischemic stroke, 1 hemorrhagic stroke, 4 events of undetermined origin In unscreened group: 2 strokes related to embolization due to AF, 2 due to carotid disease, and 6 of undetermined origin	***Systematic ECG screening vs. no screening*** Deaths: 3 vs. 5 (p=0.51)

Appendix F Table 4. Results of Included Randomized, Controlled Trials Evaluating Benefits of Screening for Atrial Fibrillation (KQ 1 and KQ 2)

Author, Year Trial, Registry No.	Intervention Groups (N randomized)	Detection of Atrial Fibrillation	Morbidity	Mortality
Hobbs et al 2005;[91] Fitzmaurice et al, 2007;[93] Fitzmaurice et al, 2014;[92] Mant et al, 2007;[94] Swancutt et al, 2004[95] SAFE ISRCTN19633732	No screening (4,936) Pulse palpation reminders (4,933) Systematic ECG screening (4,933)	***Systematic ECG screening vs. pulse palpation reminders*** N (%) new AF: Systematic ECG screening: 74 (1.5) Pulse palpation reminders: 75 (1.5) Between group difference: 0.02% (95% CI, -0.5% to 0.5%) RR 0.99 (95% CI, 0.72 to 1.36) ARD –0.02% (95% CI, -0.50% to 0.46%) ***Systematic ECG screening vs. no screening*** N (%) new AF: No screening:47 (1.0) Systematic ECG screening: 74 (1.5) p=0.016 If reported as a percent of those randomized (N=9,866) No screening: 0.95% Systematic ECG screening: 1.5% RR 1.58 (95% CI, 1.10 to 2.27) ARD 0.55% (95% CI, 0.11% to 0.98%) Men: 44 vs. 16; OR, 2.68 (95% CI, 1.52 to 4.73) Women: 30 vs. 31; OR, 0.98 (95% CI, 0.59 to 1.61) Age 65-74 years: 30 vs. 18; OR 1.62 (95% CI, 0.91 to 2.88) Age >74 years: 44 vs. 29; OR, 1.56 (95% CI, 0.98 to 2.49) ***Pulse palpation reminders vs. no screening*** N (%) new AF: No screening:47 (1.0) Pulse palpation reminders: 75 (1.5) p=0.013 If reported as a percentage of those randomized (N=9,866) No screening: 0.95% Pulse palpation reminders: 1.5% RR 1.60 (95% CI, 1.11 to 2.29) ARD 0.0057 (95% CI, 0.0013 to 0.0100) Men: 38 vs. 16; OR, 2.33 (95% CI, 1.30 to 4.15) Women: 37 vs. 31; OR, 1.20 (95% CI, 0.74 to 1.92) Age 65-74 years: 31 vs. 18; OR, 1.63 (95% CI, 0.92 to 2.89) Age >74 years: 44 vs. 29; OR, 1.60 (95% CI, 1.00 to 2.56)	NR	NR

Appendix F Table 4. Results of Included Randomized, Controlled Trials Evaluating Benefits of Screening for Atrial Fibrillation (KQ 1 and KQ 2)

Author, Year Trial, Registry No.	Intervention Groups (N randomized)	Detection of Atrial Fibrillation	Morbidity	Mortality
Kaasenbrood et al 2020[111] No IDEAL-MD NCT02270151	Usual care (no systematic screening) (8,526) Single-lead ECG (8,581)	***Systematic ECG screening vs. no screening*** N (%) diagnosed with AF at 1 year Usual care: 117 (1.4) ECG screening: 123 (1.4) RR 1.04 (95% CI, 0.81 to 1.34) ARD 0.06% (95% CI, -0.29% to 0.41%) Of newly detected cases in intervention practices, 28 (22.8%) were detected by screening and 95 (77.2%) were detected through usual care upon presentation of symptoms or during BP measurement. Mean CHA_2DS_2VASC score among newly detected AF cases: Intervention: 3.6 for screen detected, 4.0 for clinically presenting Control: 3.9	NR	NR
Morgan et al 2002[105]	Pulse palpation reminders (1,502) Systematic ECG screening (1,499)	***Systematic screening vs. pulse palpation reminders*** New cases identified: 7 (0.5) vs. 12 (0.8) RR 1.72 (95% CI, 0.68, 4.35) ARD 0.33% (95% CI, -0.23% to 0.90%) All cases identified: 19 (1.3) vs. 67 (4.5) Between-group difference: 3.2% (2.0% to 4.4%), p<0.001; (Most of these cases had a prior diagnosis of AF)	NR	NR

Appendix F Table 4. Results of Included Randomized, Controlled Trials Evaluating Benefits of Screening for Atrial Fibrillation (KQ 1 and KQ 2)

Author, Year Trial, Registry No.	Intervention Groups (N randomized)	Detection of Atrial Fibrillation	Morbidity	Mortality
Steinhubl et al 2018[109] No mSToPS NCT02506244	Delayed home-based monitoring (wait-list control) (1,293) iRhythmZio home-based ECG monitoring (1,366)	***Systematic ECG monitoring vs. no monitoring*** AF defined by ≥ 30 seconds of AF or flutter detected by device or a new clinical diagnosis recorded in claims data. ITT analysis *N (%) of Incidence of newly diagnosed AF at 4 months*: Delayed monitoring: 12 (0.9) Immediate monitoring: 53 (3.9) RR 4.18 (95% CI, 2.24 to 7.79) ARD 3.0% (95% CI, 1.8% to 4.1%) Per protocol analysis (limited to only those who wore the patch) N/total N (%) for incidence of newly diagnosed AF at 4 months: Delayed monitoring: 5/832 (0.9) Immediate monitoring: 46/906 (5.1) ARD: 4.5% (95% CI, 3.0% to 61%) Characteristics of AF detected: 17.4% who had AF while wearing a patch recalled having some symptoms when prompted; most were mild and did not lead to clinical evaluation. Only 3 participants diagnosed by patch had continuous AF, the rest had self-limited periods of AF with a mean of 9.8 episodes per 2 week period. Of 109 cases of new AF in monitored cohort (immediate and delayed monitoring) at 1 year of followup, 65 (60%) were diagnosed by patch as opposed to clinical diagnosis before or after patch monitoring. 19 (29.2%) of the 65 cases of AF detected through monitoring only had AF on the second patch. Median time to first detection of AF: 2.0 days (IQR, 1.0 to 5.0) Median duration of an individual's longest AF duration: 185.5 minutes (IQR 30.1 to 606) Longest duration: <5 minutes: 7.2% 5 min-6 hours: 55.0% 6 to 24 hours: 24.6% >24 hours: 13.0% Median AF burden (% of monitored time in AF): 0.9% (IQR, <1% to 4%) Median CHA_2DS_2VASC score among persons first diagnosed by patch: 3 (IQR, 2 to 4)	NR	NR

Appendix F Table 4. Results of Included Randomized, Controlled Trials Evaluating Benefits of Screening for Atrial Fibrillation (KQ 1 and KQ 2)

Author, Year Trial, Registry No.	Intervention Groups (N randomized)	Detection of Atrial Fibrillation	Morbidity	Mortality
Svennberg et al 2021[76] Friberg et al 2013[78] Svennberg et al 2015[77] STROKESTOP NCT01593553	Comparator: No screening (4,381 randomized/13,996 analyzed) Screening (14,387 randomized/13,979 analyzed)	***Invitation to screening vs. no invitation to screening*** N (%) with AF diagnosis after screening intervention: Screening: 1,953 (14.0) (262 cases (13% of AF cases were new AF, not previously known) Control: 1,794 (12.8) P=0.005 Calculated ARD (95% CI): 1.89 (1.10% to 2.68%) Calculated RR (95% CI): 1.16 (1.09 to 1.23) N (%) with AF diagnosis after 6 months Screening: 1,991 (14.5%) Control: 1,850 (13.4%) Calculated ARD (95% CI): 1.0 (0.2% to 1.9%) Calculated RR (95% CI): 1.1 (1.02 to 1.1) % with AF after 1 year, 2 years, 3 years, 4 years, 5 years 6 years, 7 years (P value comparing screened to control at timepoint) Screening: 15.1, 16.2, 17.6, 18.9, 20.0, 20.9, 21.3 Control: 14.1 (0.022), 15.5(0.106), 16.7(0.062), 18.0(0.062), 19.0 (0.054), 19.4(0.006), 20.3 (0.282)	At a median followup of 6.9 years (all participants were followed for a minimum of 5.6 years): # events; events/100 person-years (95% CI); HR (95% CI); where indicated, HR adjusted for age, gender, living alone, born abroad, income, education, alcohol use, prior ischemic stroke, TIA, heart failure, vascular disease, diabetes, chronic kidney disease, cancer, dementia, use of beta-blockers, use of ACEI/ARB, use of statins Composite endpoint (ischemic or hemorrhagic stroke, systemic embolism, bleeding requiring major hospitalization, all-cause mortality) Screened: 4,456; 5·45 (5.29 to 5.61) Control: 4,616; 5·68 (5.52 to 5.85) HR 0.96 (0.92 to 1.00; P=0.045); NNS 91 (ITT) aHR 0.72 (0.68 to 0.76) (as treated participants vs. control) Ischemic stroke Screened: 766; 0.90 (0.84 to 0.97) Control: 830; 0.98 (0.92 to 1.05) HR 0.92 (0.83 to 1.01) (ITT) aHR 0.83 (0.73 to 0.94) (as treated participants vs. control) Systemic embolism Screened: 60; 0.07 (0.05 to 0.09) Control: 54; 0.06 (0.05 to 0.08) HR 1.10 (0.76 to 1.59) Ischemic stroke or systemic thromboembolism (Screened: 812; 0.96 (0.89 to 1.02) Control: 874;1.03 (0.97 to 1.11) HR 0·92 (0.84 to 1.02) (ITT) aHR 0.76 (0.67 to 0.85) (as treated participants vs. controls)	# events; events/100 person-years (95% CI); All-cause mortality Screened: 3,177; 3.65 (3.53 to 3.78) Control: 3,287; 3.79 (3.67 to 3.93) HR 0·96 (95% CI, 0.92 to 1.01)

Appendix F Table 4. Results of Included Randomized, Controlled Trials Evaluating Benefits of Screening for Atrial Fibrillation (KQ 1 and KQ 2)

Author, Year Trial, Registry No.	Intervention Groups (N randomized)	Detection of Atrial Fibrillation	Morbidity	Mortality
Svennberg et al 2021[76] Friberg et al 2013[78] Svennberg et al 2015[77] STROKESTOP NCT01593553 (continued)			New clinical diagnosis of dementia Screening: 1,164; 1.38 (1.30 to 1.46) Control: 1,217; 1.45 (1.37 to 1.54) HR 0v95 (0.88 to 1.03) Cardiovascular death Screening: 1,211; 1·39 (1·32 to 1·47) Control: 1,197; 1·38 (1·31 to 1·46) HR 1·01 (0·93 to 1·09) Cardiovascular hospitalization Screening: 3,633; 4.76 (4.61 to 4.92) Control: 3,659; 4.82 (4v67 to 4.98) HR 0.99 (0.94 to 1.04) Primary endpoint with the addition of cardiovascular hospitalization Screening: 6,101; 8.21 (8.01 to 8v42) Control: 6,191; 8.38 (8.18 to 8.60) HR 0·98 (0.95 to 0.01) Ischemic or hemorrhagic stroke or dementia Screening: 1,981; 2.48 (2.37 to 2.59) Control: 2,077; 2.61 (2.50 to 2.72) HR 0.95 (0.89 to 1.01) Pulmonary embolism or venous thromboembolism Screening: 577; 0.68 (0.63 to 0.74) Control: 564; 0.67 (0.61 to 0.72) HR 1.02 (0.91 to 1.15)	

Appendix F Table 4. Results of Included Randomized, Controlled Trials Evaluating Benefits of Screening for Atrial Fibrillation (KQ 1 and KQ 2)

Author, Year Trial, Registry No.	Intervention Groups (N randomized)	Detection of Atrial Fibrillation	Morbidity	Mortality
Uittenbogaart et al, 2020[116] D2AF NL4776	Comparator: Usual care (9,526) Screening (9,218)	***Intention-to-screen vs. usual care*** Modified ITT analysis (excluding those lost to followup) Intention-to-screen: 144/8,874 (1.62%) Usual care: 139/9,102 (1.53%) Adjusted OR (95% CI): 1.06 (0.84 to 1.35) adjusted for clustering and stratification variables (prevalence of AF and region) Multiple imputation OR (95% CI): 1.04 (0.82 to 1.31) (imputation with group, age, sex, and stratification variables) Per-protocol analysis limited to those actually screened with the intervention protocol Intention-to-screen: 48/4,085 (1.2%) Usual care: 139/9102 (1.53%) Adjusted OR (95% CI): 0.86 (0.61 to 1.20) adjusted for clustering stratification variables (prevalence of AF and region), age (in years), sex (male or female), and history of HTN, diabetes mellitus, stroke (TIA or stroke), thromboembolism, and HF No change to OR (95% CI) after multiple imputation with group, age, sex, and stratification variables No significant difference in time to detection for either the modified ITT or per-protocol analysis.	NR	NR

Abbreviations: ACEI=angiotensin converting enzyme inhibitor; AF=atrial fibrillation; aHR=adjusted hazard ratio; ARB=angiotensin receptor blocker; ARD=absolute risk difference; BP=blood pressure; 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; CI=confidence interval; D2AF=Detecting and Diagnosing Atrial Fibrillation; ECG=electrocardiograph; HF=heart failure; HR=hazard ratio; HTN=hypertension; IQR=interquartile range; IDEAL-MD=Improving DEtection of Atrial fibriLlation in Primary Care With the MyDiagnostick; ITT=intention to treat analysis; KQ=key question; mSToPS=mHealth Screening to Prevent Strokes; N=number; NNS=number needed to screen; NR=not reported; OR=odds ratio; REHEARSE-AF=REmote HEArt Rhythm Sampling using the AliveCor heart monitor to scrEen for Atrial Fibrillation; RR=risk ratio; SAFE=Screening for Atrial Fibrillation in the Elderly; TIA=transient ischemic attack; vs.=versus.

Appendix F Table 5. Study Characteristics of Included Test Accuracy Studies (KQ 3)

Author, Year Study Name Registry No.	Study Design	Country	Years Conducted	Study Sponsor
Gladstone et al, 2021[75] SCREEN-AF NCT02392754	Cross-sectional diagnostic test accuracy study	Canada and Germany	2015 to 2019	Canadian Institutes of Health Research, German Centre for Cardiovascular Research, Boehringer Ingelheim, Microlife Corp, ManthaMed, iRhythm
Himmelreich et al, 2019[112]	Cross-sectional diagnostic test accuracy study	The Netherlands	2017-2018	Organization for Health Research and Development.
Hobbs et al, 2005[91] SAFE ISRCTN19633732	Cross-sectional diagnostic test accuracy study within a randomized, controlled trial for KQ 2 and cost-effectiveness study	U.K.	2000-2003	Department of Health
Kearley et al, 2014[113]	Cross-sectional diagnostic test accuracy study	U.K.	2011-2012	National Institute for Health Research and its School for Primary Care Research
Marazzi et al, 2012[115]	Cross-sectional diagnostic test accuracy study	Italy	NR	NR
Philippsen et al, 2017[56] NCT02041832	Cross-sectional diagnostic test accuracy study	Denmark	2013-2015	University of Southern Denmark; Department of Cardiology, Hospital of Southern Jutland; Department of Cardiology, Odense University Hospital; A.P. Møller Foundation for the Advancement of Medical Science, Copenhagen, Denmark; Knud and Edith Eriksen's Memorial Foundation, Sønderborg, Denmark; and Brødrene Hartmann's Foundation, Copenhagen, Denmark
Sabar et al, 2019[117]	Cross-sectional diagnostic test accuracy study	U.K.	2014-2016	Cardiocity Limited, Lancaster, UK
Uittenbogaart et al, 2020[116] D2AF NL4776	Cross-sectional diagnostic test accuracy study within a randomized, controlled trial for KQ 2	The Netherlands	2015-2018	ZonMw, the Netherlands Organisation for Health Research and Development) and Amsterdam Universities Medical Centres
Wiesel et al, 2014[114]	Cross-sectional diagnostic test accuracy study	U.S.	2014	Microlife Corporation

Abbreviations: D2AF=Detecting and Diagnosing Atrial Fibrillation; KQ=key question; NR=not reported; SAFE=Screening for Atrial Fibrillation in the Elderly; U.K.=United Kingdom; U.S.=United States.

Appendix F Table 6. Population Characteristics of Included Test Accuracy Studies (KQ 3)

Author, Year Study Name NCT Number	Recruitment Setting	Total N	Inclusion and Exclusion Criteria	Mean Age (SD)	N (%) Female	N (%) with known AF Stroke Risk Score Bleeding Risk Score	N (%) With Other Comorbidities
Gladstone et al, 2021[75] SCREEN-AF NCT02392754	Primary care clinics	399	*Inclusion:* Age ≥75 years who were not receiving OAC with a history of HTN, in sinus rhythm as assessed by 30-second pulse palpation and heart auscultation upon enrollment *Exclusion:* History of AF or atrial flutter, pacemaker, defibrillator, or implanted loop recorder	79.8 (3.8)	255 (58.8)	0 (0) *Stroke risk:* CHA_2DS_2-VASc median (IQR): 4.0 (4.0 to 5.0) *Bleeding risk*: NR	CAD: 72 (16.7) DM: 102 (23.7) HTN: 434 (100) CHF: 16 (3.7) Valvular HD: 4 (0.9) Previous stroke: NR Previous TIA: NR Previous stroke or TIA: 40 (9.3)
Himmelreich et al, 2019[112]	10 general practices	106	*Inclusion:* 18 years or older with 12-lead ECG order by their primary care clinician for nonacute indications. *Exclusion:* Pacemaker, order for ECG due to an acute indication (e.g., acute coronary syndrome).	69.3 (10.7)	62 (58)	10 (9.4) *Stroke risk:* NR *Bleeding risk:* NR	CAD: 17 (16.0) DM: 56 (52.8) HTN: 56 (52.8) CHF: 3 (2.8) Valvular HD: 3 (2.8) Previous stroke: NR Previous TIA: NR Previous stroke or TIA: 7 (6.6)
Hobbs et al, 2005[91] SAFE ISRCTN19633732	25 general practices cluster randomized to the intervention arm of a trial of screening	1,452	*Inclusion:* Age 65 years or older and belonging to participating general practices *Exclusion:* Terminally ill, died during study period, or moved practices	75.3 (7.2)*	8,500 (57.4)*	1,068 (7.2)* *Stroke risk:* NR *Bleeding risk:* NR	CAD: NR DM: NR HTN: NR CHF: NR Valvular HD: NR Previous stroke: NR Previous TIA: NR
Kearley et al, 2014[113]	Six general practices	999	*Inclusion:* Patients aged ≥75 years *Exclusion:* Patients with implanted pacemakers or defibrillators, unable to give informed consent, or for whom it was deemed inappropriate to participate	79.7 (range 75.1-99.8)	507 (50.7)†	110 (11) *Stroke risk:* NR *Bleeding risk:* NR	CAD: NR DM: 122 (12.2) HTN: 533 (53.3) CHF: 31 (3.1) Valvular HD: NR Previous stroke: 31 (3.1) Previous TIA: 65 (6.5) N (%) of participants with potential AF symptoms in 4 weeks before screening: 50 (5%) (of these 16 were known cases of AF, 3 were new cases of AF, and the rest did not have AF)

Appendix F Table 6. Population Characteristics of Included Test Accuracy Studies (KQ 3)

Author, Year Study Name NCT Number	Recruitment Setting	Total N	Inclusion and Exclusion Criteria	Mean Age (SD)	N (%) Female	N (%) with known AF Stroke Risk Score Bleeding Risk Score	N (%) With Other Comorbidities
Marazzi et al, 2012[115]	Hypertension clinic	383	*Inclusion:* None specified *Exclusion:* Age <18 years, presence of a pacemaker, implanted defibrillator, or difference of BP values >5 mmHg between arms	67 (10.5)	230 (46)	101 (20.7), of these approximately half were known at enrollment; the others were newly detected during this study. *Stroke risk:* NR *Bleeding risk:* NR	CAD: NR DM: NR HTN: 503 (100) CHF: NR Valvular HD: NR Previous stroke: NR Previous TIA: NR
Philippsen et al, 2017[56] NCT02041832	Diabetes and cardiology hospital outpatient clinics	82	*Inclusion:* Patients ≥65 years of age without known AF receiving treatment for diabetes mellitus and hypertension, with stable medications for at least 1 month. *Exclusion:* Any other risk factors for AF besides diabetes or hypertension or meeting ≥1 of the following exclusion criteria: known AF; ongoing OAC treatment; LVEF <45%; significant valve disease needing intervention; implanted pacemaker or implantable cardioverter-defibrillator; known IHD, stroke, TIA, or peripheral artery disease; thyrotoxicosis; end-stage renal failure; or severe obesity expected to compromise ECG and ICM signal	71 (4)	30 (37)†	0 *Stroke risk:* CHA_2DS_2-VASc median (IQR): 4 (3-4) *Bleeding risk:* NR	CAD: 0 DM: 82 (100) HTN: 82 (100) CHF: NR Valvular HD: NR Previous stroke: 0 Previous TIA: 0
Sabar et al, 2019[117]	Outpatient hospital cardiology clinic		*Inclusion:* Age ≥18 years old attending the outpatient cardiology department for routine 12-lead ECGs or other appointments *Exclusion:* Allergies to Velcro or metal used in the RhythmPad leads; medical condition affecting the wrists that may be interfered with by the attachment of the RhythmPad (e.g., a fractured limb with a cast); those with pacemakers or other ICDs that would interfere with the ECG recording	66 (range 18-97)	384 (51)	NR	NR

Appendix F Table 6. Population Characteristics of Included Test Accuracy Studies (KQ 3)

Author, Year Study Name NCT Number	Recruitment Setting	Total N	Inclusion and Exclusion Criteria	Mean Age (SD)	N (%) Female	N (%) with known AF Stroke Risk Score Bleeding Risk Score	N (%) With Other Comorbidities
Uittenbogaart et al, 2020[116] D2AF NL4776	96 general practices	742	*Inclusion:* Age ≥ 65 with no known history of AF in the practice's electronic health record *Exclusion:* NR	75.2 (6.	NR (53.4)	9.7% (in overall screening arm) *Stroke risk:* NR *Bleeding risk:* NR	% with comorbidities from overall screening arm of main trial: Hypertension; 49.6 Stroke or TIA: 9.7 Jeart failure: 3.8 Thromboembolism: 5.0 Diabetes: 19.3
Wiesel et al, 2014[114] NR	Two outpatient cardiology clinics	148	*Inclusion:* Age 50 years or older *Exclusion:* Pacemaker or defibrillators	74 (range 50-100)	75 (41)†	50 (27) *Stroke risk:* NR *Bleeding risk:* NR	CAD: 76 (41) DM: 45 (25) HTN: 168 (92) CHF: 32 (17) Valvular HD: NR Previous stroke: 11 (6) Previous TIA: NR

*Overall population, including control group participants
†Calculated value

Abbreviations: AF=atrial fibrillation; BP=blood pressure; CAD=coronary heart disease; 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; CHF=congestive heart failure; DM =diabetes mellitus; D2AF=Detecting and Diagnosing Atrial Fibrillation; ECG=electrocardiograph; HD=heart disease; HTN=hypertension; ICM=insertable cardiac monitor; IHD=ischemic heart disease; IQR=interquartile range; KQ=key question; LVEF=left ventricular ejection fraction; N=number; NR=not reported; OAC=oral anticoagulants; SAFE=Screening for Atrial Fibrillation in the Elderly; SD=standard deviation; TIA=transient ischemic attack.

Appendix F Table 7. Test Characteristics of Included Test Accuracy Studies (KQ 3)

Author, Year Study Name Registry Number	Index Test(s) Description	Reference Test(s) Description
Gladstone et al, 2021[75] SCREEN-AF NCT02392754	WatchBP-Home A oscillometric BP monitor (Microlife) with automated AF detection used twice daily during each of the 2-week ECG monitoring periods. Test is considered positive if at least 2 of the 3 readings are positive for AF.	A single-lead adhesive patch continuous ECG (Zio XT, iRhythm Technologies) worn on the chest for 2 weeks; worn at baseline and again at 3 months for a total duration of 4 weeks. Results interpreted by participants' primary care physician. AF defined as ≥1 episode of continuous AF or atrial flutter lasting more than 5 minutes on cECG or by a single 12-lead ECG.
Himmelreich et al, 2019[112]	Single-lead ECG using KardiaMobile (AliveCor, Inc.) handheld smartphone-connected device with AF detection algorithm: administered during in-office visit for 30 s. Rhythms classified by algorithm as AF, normal, unreadable, or no classification. For this analysis, screening was considered positive for any “possible AF” tracings and was considered as negative for all other tracings. The AF classification refers to both AF or atrial flutter.	Single 12-lead-ECG independently interpreted by 2 cardiologists, with disagreements resolved by a third cardiologist.
Hobbs et al, 2005[91] SAFE ISRCTN19633732	GP-interpreted 12-lead ECG obtained from Biolog machine GP-interpreted limb-lead II ECG obtained from Biolog machine GP-interpreted thoracic-lead ECG obtained from Biolog machine	12-lead ECG obtained from Biolog machine interpreted independently by 2 cardiologists
Kearley et al, 2014[113]	WatchBP modified oscillometric BP monitor (Microlife, Switzerland): device flashes when it detects an irregular pulse during automatic BP measurement administered during an in-office visit. Inconclusive results treated as “positive.” OMRON single-lead ECG with a text and tracing autoanalysis function (model HCG-801, Omron Healthcare Europe, the Netherlands): placed on bare chest and right index finger for unspecified duration, administered during single in-office visit, generates a text message, in addition to the ECG recording, that indicates the presence of possible AF. "Irregular" or "analysis impossible" text messages were counted as positive tests. Inconclusive results treated as “positive.”	Single 12-lead ECG interpreted by a panel of 2 cardiologists, with a third cardiologist to resolve uncertainty and disagreement

Appendix F Table 7. Test Characteristics of Included Test Accuracy Studies (KQ 3)

Author, Year Study Name Registry Number	Index Test(s) Description	Reference Test(s) Description
Marazzi et al, 2012[115]	Microlife BP A200 Plus oscillometric BP measurement device(Microlife AG, Widnau, Switzerland): oscillometric self-measurement device intended for home use that measures BP at the arm level and also detects AF during routine BP measurements using a specifically dedicated algorithm that analyzes pulse rate irregularity. An irregularity index was calculated by dividing the standard deviation by the mean of the last 10 pulse time intervals (minus intervals that were 25% greater or less than the mean) during cuff deflation. Rhythms were considered irregular if the index exceeded a threshold value of 0.06. OMRON M6 automatic oscillometric BP measurement device (OMRON Healthcare Co., Kyoto, Japan): oscillometric self-measurement device intended for home use that measures BP at the arm level and also detects pulse rate irregularity during routine BP measurement. An irregularity index was calculated by dividing the standard deviation by the mean of the last 10 pulse time intervals (minus intervals that were 25% greater or less than the mean) during cuff deflation. Rhythms were considered irregular if the index exceeded a threshold value of 0.066.	12-lead ECG interpreted by board-certified cardiologist
Philippsen et al, 2017[56] NCT02041832	2-channel 72-hour Holter monitoring (Lifecard CF, SpaceLabs Healthcare, Snoqualmie, WA) analyzed by trained staff and adjudicated by 2 experienced cardiologists. AF defined as ≥1 episode of irregular rhythm without P waves lasting at least 30 seconds. Holter monitoring occurred about 1 month after placement of ICM.	Continuous ECG monitoring with an insertable cardiac monitor (Reveal XT, Medtronic, Minneapolis, MN) interpreted by 2 experienced electrophysiologists. AF defined as at least 1 episode of irregular rhythm without P waves lasting at least 2 minutes. Median duration of monitoring 588 days (IQR 453 to 712).
Sabar et al, 2019[117]	RhythmPad 6-lead ECG (Cardiocity, Lancaster, UK) automated diagnostic report produced using a custom algorithm after a single 10-second screening.	Single 10-second, 12-lead ECG screening (GE MAC550 machine, Chicago, IL) interpreted by two blinded cardiologists
Uittenbogaart et al, 2020[116] D2AF NL4776	Pulse palpation of radial pulse by clinician plus single-lead ECG using handeld device with automated AF detection (MyDiagnostick, MyDiagnostick Medical) plus oscilllometric BP with automated AF detection (WatchBP Home A, Microlife).	12-lead ECG interpreted by experienced assessor supervised by a cardio9logist and all ECG re-reviewed by a 2nd cardiologist., with a third cardiologist adjudicating any differences
Wiesel et al, 2014[114]	Oscillometric blood pressure monitor, OMRON M6 Comfort (Omron Healthcare Co., Ltd., Kyoto, Japan) with irregular rhythm detection feature: administered once during in-office visit Oscillometric blood pressure monitor, Microlife BP A 200 (Microlife) with AF detection feature based on 3 sequential BP readings; administered once during in-office visit. Test is considered positive if at least 2 of the 3 readings are positive for AF.	12-lead ECG interpreted by cardiologist

Abbreviations: AF=atrial fibrillation; BP=blood pressure; D2AF=Detecting and Diagnosing Atrial Fibrillation; ECG=electrocardiograph; GP=general practitioner; KQ=key question; IQR=interquartile range; MN=Minnesota; SAFE=Screening for Atrial Fibrillation in the Elderly.

Appendix F Table 8. Results of Included Test Accuracy Studies (KQ 3)

Author, Year Study Name Registry No.	Comparison	Total N	TP	FP	TN	FN	Sensitivity (95% CI)	Specificity (95% CI)	Other Accuracy Results (95% CI)
Gladstone et al, 2021[75] SCREEN-AF NCT02392754	WachBP oscillometric BP monitor (automated AF detection) vs. continuous ECG monitoring (Zio XT Patch)	399	7	72	307	13	0.35 (0.15 to 0.59)	0.81 (0.77 to 0.85)	PPV: 0.09 (0.05 to 0.16) NPV: 0.96 (0.95 to 0.97)
Himmelreich et al, 2019[112]	KardiaMobile (AliveCor) single-lead ECG with automated AF detection vs. cardiology-interpreted 12-lead ECG	106	7	0	98	1	0.88 (0.47 to 1.0)	1.0 (0.96 to 1.0)	PLR: infinite NLR: 0.12 (0.02 to 0.78) PPV: 1.0 NPV: 0.99 (0.94 to 1.0)
Hobbs et al, 2005[91] SAFE ISRCTN19633732	GP-interpreted 12-lead ECG vs. cardiologist-interpreted 12-lead ECG	1,452	79	114	1,239	20	0.80 (0.71 to 0.87)	0.92 (0.90 to 0.93)	PPV: 0.41 (0.34 to 0.48) NPV: 0.98 (0.98 to 0.99)
	GP-intepreted limb lead II ECG vs. cardiologist-intepreted 12-lead ECG	1,476	104	156	1,194	22	0.83 (0.75 to 0.88)	0.88 (0.87 to 0.90)	PPV: 0.40 (0.34 to 0.46) NPV: 0.98 (0.97 to 0.99)
	GP-interpreted thoracic lead ECG vs. cardiologist-interpreted 12-lead ECG	1,452	112	180	1,141	19	0.85 (0.79 to 0.91)	0.86 (0.84 to 0.88)	PPV: 0.38 (0.33 to 0.44) NPV: 0.98 (0.98 to 0.99)
Kearley et al, 2014[113]	Microlife WatchBP oscillometric BP with automated AF detection vs. cardiologist-interpreted 12-lead ECG	999	75	95	825	4	0.95 (0.88 to 0.99)	0.90 (0.88 to 0.92)	PLR: 9.2 (7.6 to 11.2) NLR: 0.057 (0.02 to 0.15) PPV:0.44 (0.37 to 0.52) NPV: 1.0 (0.99 to 1.0)
	OMRON single-lead ECG (automated AF detection) vs. cardiologist-interpreted 12-lead ECG	999	78	219	701	1	0.99 (0.93 to 1.0)	0.76 (0.73 to 0.79)	PLR: 4.2 (3.7 to 4.7) NLR: 0.02 (0.002 to 0.12) PPV: 0.26 (0.21 to 0.32) NPV: 1.0 (0.99 to 1.0)
Marazzi et al, 2012[115]	Microlife BP A200 (Microlife) with automated AF detection vs. cardiologist-interpreted 12-lead ECG	503	93	19	383	8	0.92 (NR)	*Calculated:* 0.95 *Study reported:* 0.97(NR)	NR
	OMRON M6 oscillometric BP with automated AF detection vs. cardiologist-interpreted 12-lead ECG	503	101	23	379	0	1.0 (NR)	0.94 (NR)	NR

Appendix F Table 8. Results of Included Test Accuracy Studies (KQ 3)

Author, Year Study Name Registry No.	Comparison	Total N	TP	FP	TN	FN	Sensitivity (95% CI)	Specificity (95% CI)	Other Accuracy Results (95% CI)
Philippsen et al, 2017[56] NCT02041832	72-hour continuous Holter monitoring vs. continuous ECG monitoring with insertable cardiac monitor	82	2	0	65	15	When limited to the same 72-hour monitoring window, sensitivity is 1.0. *Calculated:* 0.12 over median 588 days (IQR 453 to 712) duration of reference standard monitoring	*Calculated:* 1	Median time to first AF episode per ICM among those with AF: 91 days (IQR: 41 to 251). All patients denied symptoms at the time of their initial AF episode.
Sabar et al, 2019[117]	RhythmPad 6-lead ECG automated diagnostic report vs. 12-lead ECG interpreted by cardiologists	632	63	6	560	3	0.95 (NR)	0.99 (NR)	PPV: 0.90 NPV: 0.99
Uittenbogaart et al, 2020[116] D2AF NL4776	Pulse palpation, oscillometric BP monitor with automated AF detection (WatchBP Home A, Microlife) and single-lead handheld ECG (MyDiagnostick) vs. 12-lead ECG interpreted by cardiologists	742	CD	CD	CD	CD	CD	CD	PPV: .06 NPV: 1.0
Wiesel et al, 2014[114]	OMRON M6 Comfort oscillometric BP withautomated AF detection vs. cardiologist-interpreted 12-lead ECG	183	9	5	148	21	0.30 (0.15 to 0.49)	0.97 (0.93 to 0.99)	Accuracy: 0.86 (0.80 to 0.91)
	Microlife BP A200 oscillometric BP with automated AF detection) vs. cardiologist-interpreted 12-lead ECG	183	30	12	141	0	1.0 (0.86 to 1.0)	0.92 (0.86 to 0.96)	Accuracy: 0.93 (0.89 to 0.96)

Abbreviations: AF=atrial fibrillation; BP=blood pressure; CD=cannot determine; CI=confidence interval; D2AF=Detecting and Diagnosing Atrial Fibrillation; ECG=electrocardiograph; FP=false positives; FN=false negatives; GP=general practitioner; ICM=insertable cardiac monitor; IQR=interquartile range; KQ=key question; N=number; NLR= negative likelihood ratio; NPV=negative predictive value; NR=not reported; PLR=positive likelihood ratio; PPV=positive predictive value; TN=true negative; TP=true positive; vs.=versus.

Appendix F Table 9. Study and Population Characteristics of Included Studies Evaluating Harms of Screening for Atrial Fibrillation (KQ 4)

Author, Year Trial Name Registry No.	Study Design	Study Quality	Country	Setting	Number of Participants	Mean age (SD), years	N (%) Female	Inclusion and Exclusion
Gladstone et al[75] SCREEN-AF NCT02392754	Parallel-group RCT	Fair	Canada and Germany	Primary care clinics	856	80 (4.0)	487 (57)	I*nclusion:* Age 75 years without known AF but with history of HTN; excluded *Exclusion:* History of AF or atrial flutter, pacemaker, defibrillator, or implanted loop recorder
Hobbs et al, 2005[91-95] SAFE ISRCTN19633732	Cluster RCT and cross-sectional test accuracy study	Fair	U.K.	50 primary care practices	14,802	75.3 (7.2)	8,500 (57.4)	*Inclusion:* Age 65 years or older and belonging to participating general practices *Exclusion:* Terminally ill, died during study period, or moved practices
Steinhubl et al, 2018[109] mSToPS NCT02506244	Parallel-group RCT and prospective matched cohort study	Fair	U.S.	Site-less clinical trial involving a large health insurance plan's members throughout the United States. Individuals were recruited by email or direct mail.	2,659 in the RCT; 5,214 in the cohort study	72.4 (7.3) in the RCT; 73.7 (7.0) in the cohort study	1,026 (38.6); 2,112 (40.5)	*Inclusion:* 75 years or older; or a male older than 55 years or female older than 65 years with 1 or more comorbidities (prior stroke, heart failure, diagnosis of both diabetes and hypertension, mitral valve disease, left ventricular hypertrophy, COPD requiring home oxygen, sleep apnea, history of pulmonary embolism, history of myocardial infarction, or diagnosis of obesity) *Exclusion:* Any current or prior diagnosis of AF, atrial flutter, or atrial tachycardia; already prescribed anticoagulation therapy; implantable pacemaker, defibrillator, or both
Svennberg et al 2021[76] Friberg et al 2013[78] Svennberg et al 2015[77] STROKESTOP NCT01593553	Parallel-group RCT	Fair	Sweden	Recruitment from population register in two regions	27,975	Median 76 (IQR 75.5-76.6)	15,273 (54.6)	No criteria other than age 75 or 76 living in two regions

Abbreviations: AF=atrial fibrillation; COPD=chronic obstructive pulmonary disease; HTN=hypertension; IQR=interquartile range; KQ=key question; mSToPS=mHealth Screening to Prevent Strokes; N=number of participants; RCT=randomized, controlled trial; SAFE=Screening for Atrial Fibrillation in the Elderly; U.K.=United Kingdom; U.S.=United States.

Appendix F Table 10. Results of Included Studies Reporting Harms of Screening for Atrial Fibrillation (KQ 4)

Author, Year Study Name Registry No.	Interventions (N randomized or enrolled)	Outcomes
Gladstone et al [75] SCREEN-AF NCT02392754	Comparator: No screening (422) Continuous ECG and intermittent BP measurement over a total of 4 weeks (434)	**Followup at 6 months** Intracranial hemorrhage: 0 Major bleeding events: 0 (among those with AF or those prescribed OAC) Adverse skin reaction requiring premature discontinuation of monitoring: 5/434 (1.2%, 95% CI, 0.5% to 2.7%) N (%, 95% CI) Non-AF arrhythmias detected in screened group 3rd degree AV block or Mobitz type 2 second degree AV block: 13 (3%, 1.8% to 5.1%) Pauses ≥5 seconds: 4 (0.9%, 0.4% to 2.3%) Heart rate < 40 bpm for ≥30 seconds: 17 (3.9%, 2.5% to 6.2%) Heart rate >160 bpm for ≥30 seconds: 3 (0.7, 0.2% to 2.0%) Ventricular tachycardia > 100 bpm for ≥30 seconds: 0 Polymorphic ventricular tachycardia or ventricular fibrillation of any duration: 0 **Screening vs. No screening;** health care use at 6 months ED visits Screening: 5 Usual care: 2; p>0.99 Hospitalizations Screening: 5 Usual care: 3; p=0.48 Pacemaker implantations Screening: 3 Usual care: 2; p>0.99 OAC therapy Intervention: 18/434 (4.1%) Usual care: 4/422 (0.9%) RR (95% CI): 4.4 (1.5 to 12.8) ARD (95% CI): 3.2% (1.1 to 5.3)

Appendix F Table 10. Results of Included Studies Reporting Harms of Screening for Atrial Fibrillation (KQ 4)

Author, Year Study Name Registry No.	Interventions (N randomized or enrolled)	Outcomes
Hobbs et al, 2005[91-95] SAFE ISRCTN19633732	Systematic screening with single and 12-lead ECGs (4,933) Opportunistic screening (chart note encouraging pulse palpation) (4,933) No screening (4,936) Note: For the anxiety outcome assessments, the no screening group was not assessed, and the number of participants was limited to a subset of those screened (750 at baseline, 2,595 post screening, and 777 after 17 months)	**Systematic screening vs. opportunistic screening** *Anxiety assessed using the Spielberger Six-Item Anxiety Questionnaire* Baseline mean anxiety score 35.78 (95% CI, 33.80 to 37.76) vs. 36.44 (95% CI, 34.35 to 38.53); p=0.695; response rate: of 750 questionnaires sent to patients before randomization, 620 (83%) were returned and 493 (66%) were completed. Postscreening mean anxiety score 28.77 (95% CI, 28.27 to 29.26) vs. 28.25 (95% CI, 26.78 to 29.73); p=0.732 (unadjusted); response rate: 2,595 patients who underwent ECG screening were given the questionnaire immediately after screening and 1,940 were returned (75%). After 17 months mean anxiety score 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; response rate: of 777 questionnaires sent to patients 17 months after baseline, 535 were returned (69%). 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
Steinhubl et al, 2018[109] mSToPS NCT02506244	For the RCT: Control-delayed monitoring (1,293) iRhythmZio ECG monitoring (1,366) For the cohort study: Combined immediate and delayed monitoring group (1,738) Matched controls (3,476)	**Monitoring vs. delayed monitoring (RCT results after 4 months)** *Skin irritation associated with wearing ECG patch*: 40 (1.5% [95% CI, 1.1% to 2.0%]). Of these, 32 discontinued wearing the patch and 2 sought medical attention and received topical therapy. *Potentially actionable arrhythmias other than A*F: 70 (2.6% [95% CI, 2.1% to 3.3%]) Nonsustained ventricular tachycardia more than 5 beats: 24 participants Prolonged or symptomatic supraventricular tachycardia: 22 participants Significant pause or high-degree atrioventricular block: 25 participants Very frequent ectopy: 1 participant **Combined monitoring groups vs. matched controls (cohort study results for 1 year),** *Number per 100 person-years; AD (95% CI)* Initiation of anticoagulation 5.7 vs. 3.7; AD 2.0 (1.29 to 2.2) Initiation of anticoagulation specifically for AF 2.4 vs. 1.3; AD 1.1 (1.0 to 1.2) Cardioversion procedures 0.24 vs. 0.19; AD 0.05 (0.03 to 0.08) Cardiac ablation 0.3 vs. 0.1; AD 0.2 (0.18 to 0.24) Placement of pacemaker or defibrillator 0.79 vs. 0; AD 0.79 (0.75 to 0.84) Participants with at least 1 outpatient visit to a cardiologist 33.5 vs. 26.0; AD 7.5 (7.2 to 7.9)

Appendix F Table 10. Results of Included Studies Reporting Harms of Screening for Atrial Fibrillation (KQ 4)

Author, Year Study Name Registry No.	Interventions (N randomized or enrolled)	Outcomes
Svennberg et al 2021[76] Friberg et al 2013[78] Svennberg et al 2015[77] STROKESTOP NCT01593553	No screening (14,381 randomized/13,996 analyzed) Screening (4,387 randomized/13,979 analyzed)	**Screening vs. no screening (median followup 6.9 years)** N (%) with OAC use After 6 months Screening: 1,455 (10.6) Control: 1,403 (10.2); p=0.286 % with OAC use after 1, 2, 3, 4, 5, 6, and 7 years, respectively Screening: 11.3, 12.2, 13.3, 14.7, 16.2, 17.9, 18.5 Control: 10.8, 11.6, 12.8, 14.1, 15.8, 17.2, 18.1 p>0.089 at all time points Number of events; events/100 person-years (95% CI); HR (95% CI) Hemorrhagic stroke Screened: 137; 0.16 (0.13 to 0.19) Control: 155; 0.18 (0.15 to 0.21) HR 0.88 (0.70 to 1.11) Hospitalization for major bleeding Screened: 1,431; 1.71 (1.63 to 1.81) Control: 1,448; 1.74 (1.66 to 1.83) HR 0.98 (0.91 to 1.06)

Abbreviations: AD=absolute difference; AF=atrial fibrillation; CI=confidence interval; ECG=electrocardiograph; G=group; HR=hazard ratio; KQ=key question; mSToPS=mHealth Screening to Prevent Strokes; N=number; RCT=randomized, controlled trial; SAFE=Screening for Atrial Fibrillation in the Elderly; vs.=versus.

Appendix F Table 11. Results of Included Randomized, Controlled Trials for Benefits of Anticoagulation (KQ 5)

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 et al, 1989[102] AFASAK	Warfarin, adjusted dose (335) Placebo (336)	71 total deaths Mortality by group NR	Stroke-related mortality 1 (0.3) 4 (1.2) NR Vascular deaths 3 (0.9) 15 (4.5) p<0.02	NR	Cumulative incidence of thromboembolic related complications 5 (1.5) 16 (6.3) p<0.05 Annual incidence of thromboembolic complications 2.0%/year (0.6% to 4.8%) 5.5%/year (2.9% to 9.4%)	Minor stroke 0 (0) 2 (0.6) NR Nondisabling stroke 0 (0) 3 (0.9) NR Disabling stroke 4 (1.2) 7 (2.1) NR	TIA 0 (0) 3 (0.9) NR Visceral emboli 0 (0) 2 (0.6) NR Emboli in both extremities 0 (0) 0 (0) NR
The Boston Area Trial for Atrial Fibrillation Investiga-tors, 1990[100] 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 F Table 11. Results of Included Randomized, Controlled Trials for Benefits of Anticoagulation (KQ 5)

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[98, 101] SPAF I	Warfarin, adjusted dose (210) Placebo (211)	Total mortality Warfarin: 6 (2.2%/year) Placebo: 8 (3.1%/year) Risk reduction: 0.25 (-1.11 to 0.73), p=0.56	Fatal ischemic stroke Warfarin: 0 Placebo: 0 NA Vascular death Warfarin: 3 (1.4) Placebo: 5 (2.4) NA Probable vascular death Warfarin: 1 (0.5) Placebo: 2 (0.9) NA	NR	Ischemic stroke or systemic embolism Warfarin: 6 (2.3%/year) Placebo: 18 (7.4%/year) Risk reduction: 0.67 (0.27 to 0.85), p=0.01	Minimally disabling ischemic stroke Warfarin: 4 (1.9) Placebo: 10 (4.7) NA Moderate to severely disabling ischemic stroke Warfarin: 2 (1.0) Placebo: 7 (3.3) NA	TIA without ischemic stroke or systemic embolism Warfarin: 3 (1.1%/year) Placebo: 4 (1.6%/year) NR Myocardial infarction Warfarin: 2 (0.8%/year) Placebo: 2 (0.8%/year) NR Primary event or death Warfarin: 10 (3.8%/year) Placebo: 24 (9.8%/year) Risk reduction: 0.58 (0.20 to 0.78), p=0.01

Appendix F Table 11. Results of Included Randomized, Controlled Trials for Benefits of Anticoagulation (KQ 5)

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 et al, 1991[99] 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 Nonlacunar stroke (efficacy analysis) 4 (2.1) 9 (4.7) NR (ITT analysis) 5 (2.7) 9 (4.7) NR	Severe nonlacunar stroke (ITT analysis) 2 (1.1) 4 (2.1) NR Mild nonlacunar 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

Appendix F Table 11. Results of Included Randomized, Controlled Trials for Benefits of Anticoagulation (KQ 5)

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)
Ezekowitz et al, 1992[97] SPINAF	Warfarin 4 mg/day and adjusted to meet PT ratios (260) Placebo (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

Abbreviations: AFASAK=Atrial Fibrillation, ASpirin, and AntiKoagulation; 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; 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 Nonrheumatic Atrial Fibrillation study; TIA=transient ischemic attack.

Appendix F Table 12. Results of Included Studies for Harms of Anticoagulation (KQ 6)

Author, Year Study 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 et al, 1989[102] AFASAK	Warfarin dose adjusted per subject (335) Placebo (336)	Bleeding (nonfatal) causing withdrawal from study 21 (6.3) 0 NR Respiratory tract bleeding 4 (1.2) 0 (0) NR Urogenital bleeding 6 (1.8) 0 (0) NR Other bleeding 0 (0) 0 (0) NR	GI bleeding 4 (1.2) 0 (0) NR	0 (0) 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) 3 (0.9) NR

Appendix F Table 12. Results of Included Studies for Harms of Anticoagulation (KQ 6)

Author, Year Study 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)
The Boston Area Trial for Atrial Fibrillation Investigators, 1990[100] BAATAF	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 4 (1.9) 6 (2.9) NR Leading to transfusion 2 (0.9) 1 (0.5) NR	Transient monocular vision loss 2 (0.9) 1 (0.5) NR Fatal pulmonary hemorrhage 0 (0) 1 (0.5) NR Fatal intracranial hemorrhage (due to loss of consciousness then falling) 1 (0.5) 0 (0) NR

Appendix F Table 12. Results of Included Studies for Harms of Anticoagulation (KQ 6)

Author, Year Study 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)
Stroke Prevention in Atrial Fibrillation Investigators, 1990 & 1991[98, 101] SPAF	Warfarin-adjusted dose (210) Placebo (211)	Major bleeding complications intention to treat population Warfarin: 4 (1.5%/year) Placebo: 4 (1.6%/year) NR Major bleeding complications relevant bleeding Warfarin: 3 (1.4) Placebo: 1 (0.5) NR	NR	Severe allergic reactions 0 (0) 0 (0) NR	NR	NR	Warfarin: 1 (0.5) Placebo: 0 (0) NR	Subdural hematoma Warfarin: 1 (0.5) Placebo: 2 (0.9) NR	Minor bleeding leading to therapy withdrawal‡ Warfarin: 4 (1.9) Placebo: 1 (0.5) NR	Intracerebral fatal hemorrhage Warfarin: 1 Placebo: 0

Appendix F Table 12. Results of Included Studies for Harms of Anticoagulation (KQ 6)

Author, Year Study 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)
Connolly et al, 1991[99] CAFA	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 (ITT) 1 (0.5) 0 (0) NR Other fatal hemorrhage (efficacy analysis) 1 (0.5) 0 (0) NR (ITT) 1 (0.5) 0 (0) NR Annual rate of fatal or major hemorrhage 2.5%/year 0.5%/year NR

Appendix F Table 12. Results of Included Studies for Harms of Anticoagulation (KQ 6)

Author, Year Study 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[97] 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

Appendix F Table 12. Results of Included Studies for Harms of Anticoagulation (KQ 6)

Author, Year Study 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)
Bassand et al, 2018[110] GARFIELD-AF Registry	Warfarin (9,947) Antiplatelet agents (6,905) Direct thrombin inhibitors (1,499) Factor Xa inhibitors (2,300) Combi-nation treatment (4,126) No treatment (3,444)	Total major bleeding 366 (1.3) Adjusted HR for first occurrence of major bleeding: 1.73 (95% CI, 1.33 to 2.25) for anticoagulation compared with no treatment	NR	NR	Total primary hemorrhagic stroke 66 (0.2); NR by groups	Total subarachnoid hemorrhage 5 (0.02); NR by groups	Total intracerebral hemorrhage 41 (0.1); NR by groups	NR	Nonmajor clinically relevant bleeding 500 (1.7); NR by groups	NR

* 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.
† 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).
‡ 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.
§ Minor bleeding defined as non-life-threatening bleeding.
‖ Minor bleeding defined as bleeding that did not require a blood transfusion, an emergency procedure, removal of a hematoma, or ICU admission.

Abbreviations: AFASAK=Atrial Fibrillation, ASpirin, and AntiKoagulation; BAATAF=Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA=Canadian Atrial Fibrillation Anticoagulation study; CI=confidence interval; ES=effect size; G=group; GARFIELD-AF=Global Anticoagulant Registry in the FIELD-Atrial Fibrillation; HR=hazard ratio; ICU=intensive care unit; ITT=intention to treat analysis; 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 Nonrheumatic Atrial Fibrillation study.

Appendix F Table 13. 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[104] Warfarin vs. Placebo	SR with MA	2,313	Mean age: 69 Female: 26% Non-White: 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) * 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)† 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)
Atrial Fibrillation Investigators, 1994[107] Warfarin vs. Placebo	IPD	4,174	Mean age: 69 Female: 26% Non-White: 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 Warfarin (1,889 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
Coleman, 2012[103] Warfarin vs. Placebo	SR with MA	42,983	Mean age: 65–75 Female: 0–59% % non-White: 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)

Appendix F Table 13. 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
Hart, 2007[59] Warfarin vs. placebo	SR with MA	28,044 (but most of those from secondary prevention trials)	Warfarin Mean age: 69 Female: 29% Prior stroke or TIA: 20% 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 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

Appendix F Table 13. 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[106] VKA vs. placebo DOACs vs. placebo DOACs vs. warfarin	NMA	96,017	Mean age: 71.5 Female: 35% Non-White: 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. Adjusted results were adjusted for $CHADS_2$ scores, time in therapeutic range, and duration of followup. 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)‡ Unadjusted; adjusted Stroke or systemic embolism: 0.38 (0.29 to 0.49); 0.43 (0.28 to 0.67) All-cause mortality: 0.69 (0.57 to 0.85); 0.75 (0.51 to 1.11) Major bleeding: 2.50 (1.47 to 4.17); 2.13 (1.00 to 4.55) DOACs vs. placebo/control odds ratio (95% CI) for stroke or systemic embolism Unadjusted; adjusted 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 DOACs: no statistically significant differences in effectiveness for each of the 4 DOACs compared with one another DOACs vs. placebo/control adjusted odds ratio (95% CI) for major bleeding Unadjusted; adjusted Apixaban 1.84 (0.88 to 3.85); 1.59 (0.71 to 3.54) Dabigatran 2.14 (1.03 to 4.46); 1.82 (0.81 to 4.07) Edoxaban 1.50 (0.72 to 3.13); 1.38 (0.60 to 3.15) Rivaroxaban 2.34 (1.09 to 5.05); 2.21 (0.92 to 5.26) DOACs vs. VKA: risk of stroke or systemic embolism; OR (95% CI) Unadjusted; adjusted 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 F Table 13. 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[106] (continued)				DOACs vs. VKA: risk of all-cause mortality; OR (95% CI) Unadjusted; adjusted 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) DOACs vs. VKA: major bleeding; OR (95% CI) Unadjusted: adjusted Apixaban 0.74 (0.42 to 1.31); 0.74 (0.54 to 1.02) Dabigatran 0.86 (0.52 to 1.44); 0.85 (0.65 to 1.11) Edoxaban 0.61 (0.36 to 1.01); 0.64 (0.46 to 0.90) Rivaroxaban 0.95 (0.54 to 1.65); 1.03 (0.68 to 1.57)
van Walraven, 2008[96] Oral anticoagulant (mostly warfarin)§ vs. Placebo	IPD	8,932	Mean age: 70.9 for all studies except for BAFTA, which 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 vs. placebo; 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: 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

* 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.

† In the text, they also report that meta-analysis of data from six trials in which 20 percent 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).

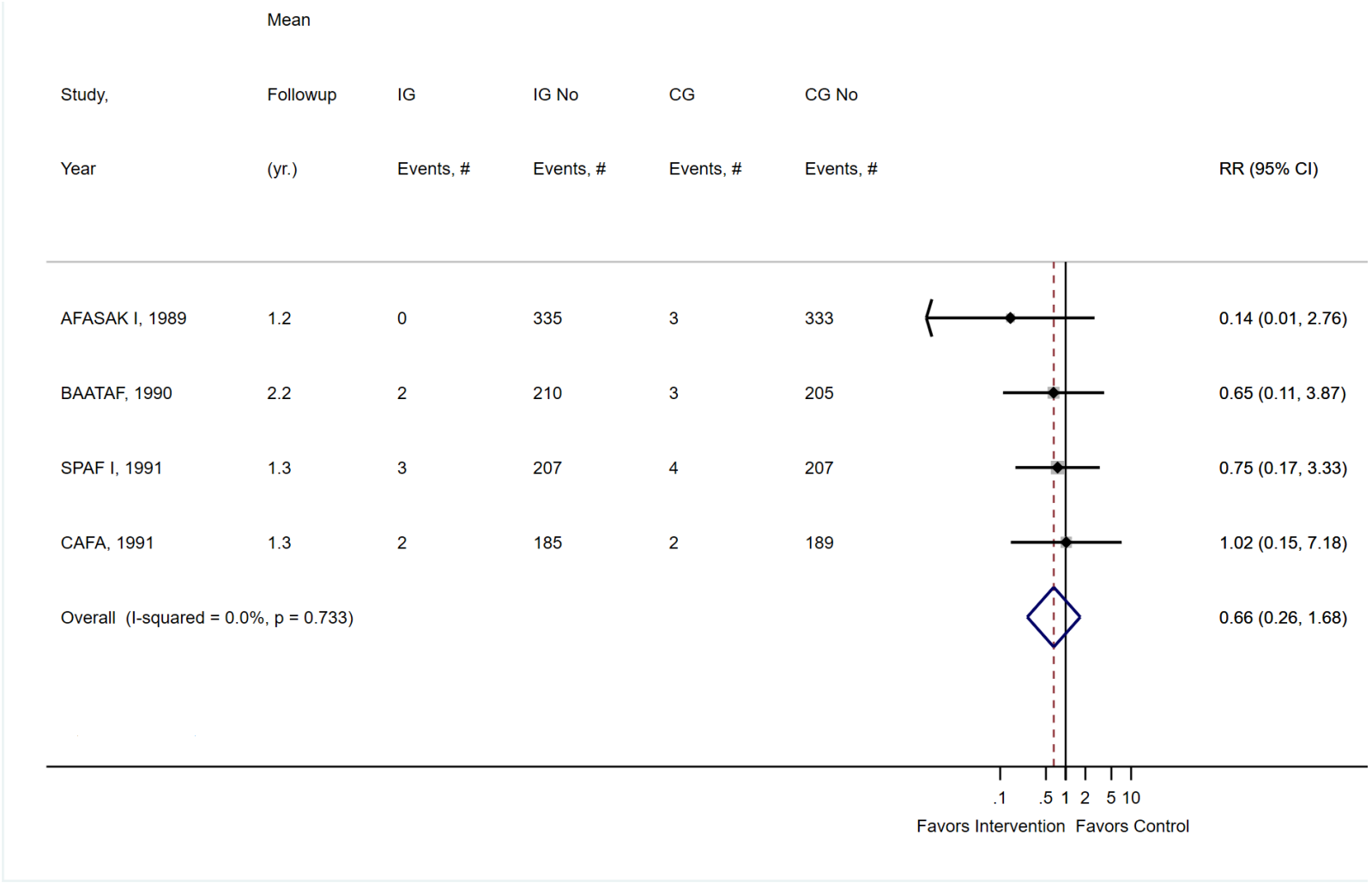
ǂ This study presented results as placebo vs. VKA; we have transformed the reported study results for consistency with how results are presented in other parts of this report (VKA vs. placebo as the referent group).

§ Some secondary prevention studies used 4-hydroxycoumarin instead of warfarin.

Abbreviations: AP=antiplatelet therapy; ARR=absolute risk reduction; BAFTA=Boston 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; CI=confidence interval; DOAC=direct oral anticoagulants; EAFT=European Atrial Fibrillation Trial Study Group; G=group; HF=heart failure; HR=hazard ratio; HTN: hypertension; INR=International Normalized Ratio, assay used to determine clotting tendency; IPD=individual patient data meta-analysis; 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; NS=not

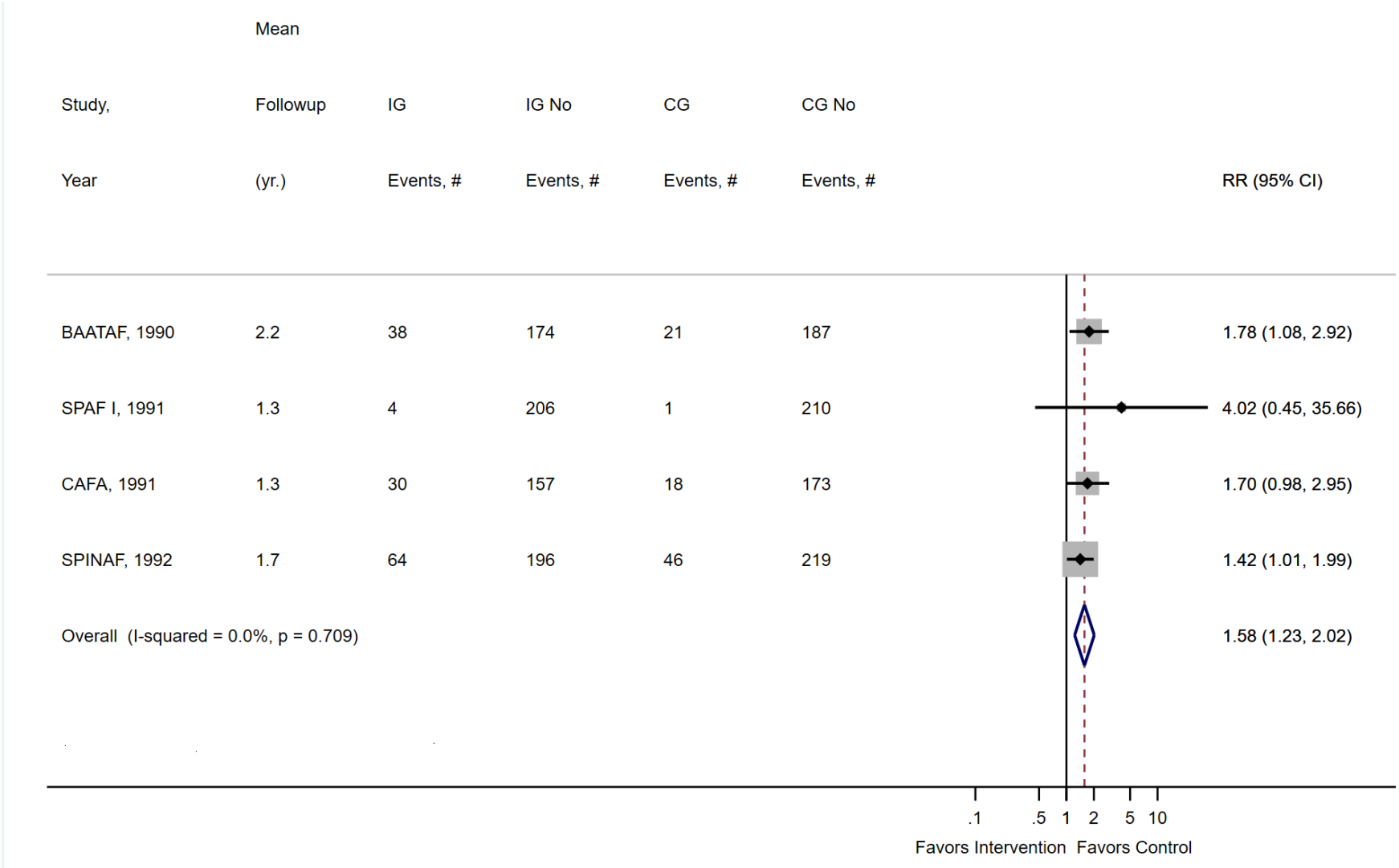
statistically significant; OAC=oral anticoagulant; OR=odds ratio; RCT=randomized, controlled trial; ROCKET AF=Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; RR=risk ratio; SPAF=Stroke Prevention in Atrial Fibrillation Study; SR=systematic review; TIA=transient ischemic attack; VKA=vitamin K antagonists; vs.=versus.

Appendix G Figure 1. Meta-Analysis of Warfarin vs. Placebo/Control for Transient Ischemic Attack



Abbreviations: AFASAK=Atrial Fibrillation, ASpirin, and AntiKoagulation; BAATAF=Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA=Canadian Atrial Fibrillation Anticoagulation study; CG=control group; CI=confidence interval; IG=intervention group; RR=risk ratio; SPAF=Stroke Prevention in Atrial Fibrillation Study.

Appendix G Figure 2. Meta-Analysis of Warfarin vs. Placebo/Control for Minor Bleeding



Abbreviations: BAATAF=Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA=Canadian Atrial Fibrillation Anticoagulation study; CG=control group; CI=confidence interval; IG=intervention group; RR=risk ratio; SPAF=Stroke Prevention in Atrial Fibrillation Study; SPINAF=Stroke Prevention in Nonrheumatic Atrial Fibrillation study.

Appendix H Table 1. Summary of Relevant Ongoing Studies

Trial Name Registry No. Design	Population Enrolled	Intervention and Comparator	Status and Estimated Completion Date	Outcomes	Results Published
Potentially relevant direct evidence (KQ 1) studies					
GUARD-AF NCT04126486 RCT	Age ≥70 years in primary care; N=52,000	• Ambulatory ECG (Zio XT patch monitor) for 2 weeks • Standard care	Recruiting 6/2021 (estimated)	Incidence of all strokes and bleeding leading to hospitalization within 24 months (primary endpoint)	No
Potentially relevant direct evidence and comparative diagnostic yield (KQ 1 and KQ 2) studies					
VITAL-AF NCT03515057 Cluster RCT	Age ≥65 years in primary care; N=35,308	• One time single-lead handheld ECG during primary care clinic visit • Standard care	Active, not recruiting 10/2021 (estimated)	Incident AF over 12 months, ischemic stroke or major hemorrhage over 2 years	No for main results, preliminary KQ 2 results presented at an AHA conference in Nov 2020.
eBRAVE-AF NCT04250220 RCT	Age ≥50 years and a policy holder of a large health insurance company; N=4,400	• PPG-based screening using a smartphone and ECG patch • Symptom based AF-screening	Recruiting 03/2021 (estimated)	Newly detected AF at 6 months, newly prescribed oral anticoagulation, stroke, and thromboembolic events.	No
The Effect of a Case-finding App on the Detection Rate of Atrial Fibrillation in Primary Care Patients NCT04545723 cluster-RCT	Age≥65 years in primary care; N=8,765	• FibriCheck app-based screening during a primary care clinic visit • Standard opportunistic screening with pulse palpation and a 12-lead ECG when a irregular rhythm is found	Not yet recruiting 05/2022 (estimated)	Newly detected AF at 4 weeks, thromboembolic complications, death, and compliance.	No
STROKESTOP II NCT02743416 Unclear whether RCT or cohort	Age 75 or 76 years in primary care; N=8,000	• Initial screening with NT-proBNP • If NT-proBNP >125 ng/L (high risk group): intermittent ECG recordings twice daily for 2 weeks • If NT-proBNP<125 ng/L (low risk group): one initial single-lead ECG • Standard care	Active, not recruiting 4/2023 (estimated)	Incidence of stroke in low-risk group compared with control group at 5 years (primary endpoint); also evaluating detection of AF	No for main results, several ancillary and baseline enrollment papers have been published.
SAFER ISRCTN16939438 Cluster RCT	Age≥65 years in primary care; Feasibility study: N=4,800 RCT: N=126,000	• Intermittent single-lead ECG at home over 2 to 4 weeks • Standard care	Feasibility study 3/2021 (estimated) Full RCT 9/2026 (estimated)	Stroke, MI, all-cause mortality, risk of serious bleeding, cost-effectiveness	No

Appendix H Table 1. Summary of Relevant Ongoing Studies

Trial Name Registry No. Design	Population Enrolled	Intervention and Comparator	Status and Estimated Completion Date	Outcomes	Results Published
Potentially relevant treatment benefits and harms (KQs 5 and 6) studies					
NOAH-AFNET 6 NCT02618577 EudraCT (2015-003997-33), and ISRCTN (17309850) RCT	Age ≥65 years with CIED for any reason, AHRE ≥180 beats/min and ≥6 min. At least 1 additional stroke risk factor; N=3,400	• Edoxaban • Standard care (ASA or placebo)	3/2022	Composite of stroke, systemic embolism, or cardiovascular death; major bleeding events; exploratory analyses by duration or pattern of AHRE.	No
ARTESiA NCT01938248 RCT	Age ≥55 years with CIED, SCAF ≥175 beats/min and ≥6 min but <24 hrs. At least 1 additional stroke risk factor; N=4,000	• Apixaban • Aspirin	12/2022	Composite of stroke or systemic embolism; major bleeding; subgroup analysis of long vs. short SCAF episodes.	No
BRAIN-AF RCT	Age ≥30 to ≤62 years with nonvalvular atrial fibrillation and low-risk of stroke N=3,250	• Rivaroxaban • Standard of care	02/2022	Composite endpoint of stroke, TIA, and neurocognitive decline; death; systemic embolic events; neurocognitive decline; and hospitalization for cardiovascular or bleeding event.	No
SINGLE-AF NCT04437654 RCT	Age 19-80 years with CHA2DS2-VASc score 1 for male or 3 for female among nonvalvular atrial fibrillation patients; N=1,800	• Apixaban • Standard of care except anticoagulation	07/2026	Composite of stroke or systemic embolism, major bleeding, and death.	No

Abbreviations: AF=atrial fibrillation; AHRE=atrial high rate episodes; ARTESiA=Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation; ASA=American Stroke Association; CABG=coronary artery bypass graft; CIED=cardiac implanted electronic device; ECG=electrocardiograph; IDEAL-MD=Improving DEtection of Atrial fibriLlation in Primary Care With the MyDiagnostick; GUARD-AF=reducing Stroke by Screening for UndiaAgnosed atrial Fibrillation in Elderly inDividuals; KQ=key question; mSToPS=mHealth Screening to Prevent Strokes; N=number of participants; NOAH-AFNET 6=Non-vitamin K Antagonist Oral Anticoagulants in Patients with Atrial High Rate Episodes; NT-proBNP=N-terminal pro beta type natriuretic peptide; PCA=primary coronary angioplasty; RCT=randomized, controlled trial; SCAF=subclinical atrial fibrillation; TIA=transient ischemic attack; VITAL-AF=Screening for Atrial Fibrillation Among Older Patients in Primary Care Clinics.

Appendix H Table 2. Estimates of True Positives, False Positives, True Negatives, and False Negatives per 1,000 Tests Based on Sensitivity and Specificity of Various Screening Strategies Reported in KQ 3 for Prevalence of Undiagnosed Atrial Fibrillation of 0.5%, 1.3%, and 4%

Study	Sensitivity	Specificity	TP			FP			TN			FN		
AF Prevalence			0.5%	1.3%	4%	0.5%	1.3%	4%	0.5%	1.3%	4%	0.5%	1.3%	4%
Oscillometric BP monitor with automated AF detection vs. 12-lead ECG interpreted by cardiology														
Kearley et al, 2014[113] (Microlife)	0.95	0.90	5	12	38	100	99	96	896	888	864	0	1	2
Marazzi et al, 2012[115] (Microlife)	0.92	0.95	5	12	37	50	49	48	945	938	912	0	1	3
Marazzi et al, 2012[115] (OMRON)	1.0	0.94	5	13	40	60	59	58	935	928	902	0	0	0
Wiesel et al, 2014[114] (Microlife)	1.0	0.92	5	13	40	80	79	77	915	908	883	0	0	0
Wiesel et al, 2014[114] (OMRON)	0.30	0.97	2	4	12	30	30	29	965	957	931	4	9	28
Oscillometric BP monitor with automated AF detection vs. continuous ECG														
Gladstone et al, 2021[75] (Microlife)	0.35	0.81	2	5	14	189	188	182	806	799	778	3	9	26
Single-lead ECG with automated AF detection vs. 12-lead ECG interpreted by cardiology														
Himmelreich et al, 2019[112] (KardiaMobile)	0.88	1.0	4	11	35	0	0	0	995	987	960	1	2	5
Kearley et al, 2014[113] (OMRON)	0.99	0.76	5	13	40	239	237	230	756	750	730	0	0	0
Six-lead ECG with automated AF detection vs. 12-lead ECG interpreted by cardiology														
Sabar et al, 2019[117] (RhythmPad 6-lead ECG)	0.95	0.99	5	12	38	10	10	10	985	977	950	0	1	2
GP-interpreted ECG vs. 12-lead ECG interpreted by cardiology														
Hobbs et al, 2005[91] SAFE (12-lead)	0.80	0.92	4	10	32	80	79	77	915	908	883	1	3	8
Hobbs et al, 2005[91] SAFE (Single-limb lead)	0.83	0.88	4	11	33	119	118	115	876	869	845	1	2	7
Hobbs et al, 2005[91] SAFE (Single-thoracic lead)	0.85	0.86	4	11	34	139	138	134	856	849	826	1	2	6
Combined pulse palpation, oscillometric BP monitor and single lead ECG both with automated AF detection vs. 12 lead ECG interpreted by cardiology														
*Uittenbogaart et al, 2020[116] D2AF	CD	CD	CD	CD	CD	CD	CD	CD	CD	CD	CD	CD	CD	CD

* The study only performed a 12-lead reference test on a random sample of participants who tested negative on the index screening test; thus data to determine sensitivity and specificity was not available. However, based on data reported, we calculated the positive predictive value to be 6% and the negative predictive value to be 100%; suggesting a test with very high sensitivity, but poor specificity.

Abbreviations: AF=atrial fibrillation; BP=blood pressure; CD=cannot determine since referent 12-lead ECG only performed on a random sample of persons screening negative on index test; D2AF=Detecting and Diagnosing Atrial Fibrillation; ECG=electrocardiograph; FN=false negatives; FP=false positives; GP=general practitioner; SAFE=Screening for Atrial Fibrillation in the Elderly; TN=true negative; TP=true positive; vs.=versus.