AMERICAN ACADEMY OF FAMILY PHYSICIANS
STRONG MEDICINE FOR AMERICA

UPDATED CLINICAL PRACTICE GUIDELINE

Pharmacologic Management of Newly Detected Atrial Fibrillation

AAFP BOARD APPROVED APRIL 2017

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All costs associated with the development of this guideline came exclusively from the operating budget of the American Academy of Family Physicians (AAFP).

CONFLICTS OF INTEREST

There were no conflicts of interest declared.

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DISCLAIMER

These recommendations are provided only as assistance for clinicians making clinical decisions regarding the care of their patients. As such, they cannot substitute for the individual judgment brought to each clinical situation by the patient's family physician. As with all clinical reference resources, they reflect the best understanding of the science of medicine at the time of publication, but they should be used with the clear understanding that continued research may result in new knowledge and recommendations. All AAFP guidelines are scheduled for a review five years after completion or sooner if new evidence becomes available.

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ABSTRACT

Purpose

To review the evidence and provide clinical recommendations for the pharmacologic management of atrial fibrillation.

Methods

This guideline is based on two systematic reviews of published randomized controlled trials (RCTs) and prospective and retrospective observational studies from 2000 to 2012. An updated literature search was performed to identify new studies from 2012 to December 31, 2015. The target audience for the guideline includes all primary care clinicians, and the target patient population includes adults who have nonvalvular atrial fibrillation that is not due to a reversible cause. This guideline was developed using a modified version of GRADE to evaluate the quality of the evidence and make recommendations based on the balance of benefits and harms.

RECOMMENDATIONS

Recommendation 1

The AAFP strongly recommends rate control in preference to rhythm control for the majority of patients who have atrial fibrillation (strong recommendation, moderate-quality evidence). Preferred options for rate-control therapy include non-dihydropyridine calcium channel blockers and beta blockers. Rhythm control may be considered for certain patients based on patient symptoms, exercise tolerance, and patient preferences (weak recommendation, low-quality evidence).

Recommendation 2

The AAFP recommends lenient rate control (<110 beats per minute resting) over strict rate control (<80 beats per minute resting) for patients who have atrial fibrillation (weak recommendation, low-quality evidence).

Recommendation 3

The AAFP recommends that clinicians discuss the risk of stroke and bleeding with all patients considering anticoagulation (good practice point). Clinicians should consider using the continuous $CHADS_2$ or continuous CHA_2DS_2-VASc for prediction of risk of stroke (weak recommendation, low-quality evidence) and HAS-BLED for prediction of risk for bleeding (weak recommendation, low-quality evidence) in patients who have atrial fibrillation.

Recommendation 4

The AAFP strongly recommends that patients who have atrial fibrillation receive chronic anticoagulation unless they are at low risk of stroke ($CHADS_2$ <2) or have specific contraindications (strong recommendation, high-quality evidence). Choice of anticoagulation therapy should be based on patient preferences and patient history. Options for anticoagulation therapy may include warfarin, apixaban, dabigatran, edoxaban, or rivaroxaban.

Recommendation 5

The AAFP strongly recommends against dual treatment with anticoagulant and antiplatelet therapy in most patients who hav atrial fibrillation (strong recommendation, moderate-quality evidence).

Abbreviations

ACC = American College of Cardiology; ACP = American College of Physicians; AF = atrial fibrillation; AHA = American Heart Association; AHRQ = Agency for Healthcare Research and Quality; ASA = acetylsalicylic acid; ATRIA = Anticoagulation and Risk factors in Atrial Fibrillation; BRI = Bleeding Risk Index; CHADS2 = Congestive heart failure, Hypertension, Age 75+, Diabetes mellitus, prior Stroke, transient ischemic attack or thromboembolic event; CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age 75+, Diabetes mellitus, prior Stroke, transient ischemic attack or thromboembolic event, Vascular disease, Age 65-74, Sex category; CHPS = Commission on Health of the Public and Science; CI = confidence interval; COI = conflict of interest; FDA = U.S. Food and Drug Administration; GDG = guideline development group; GRADE = Grading of Recommendations, Assessment, Development and Evaluation; HAS-BLED = Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (>65 years), Drugs/alcohol concomitantly; HEMORR2HAGES = Hepatic or renal disease, Ethanol abuse, Malignancy, Older (>75), Reduced platelet count or function, Re-bleeding risk (2 points), Hypertension (uncontrolled), Anemia, Genetic factors, Excessive fall risk, Stroke; HR = hazard ratio; HRS = Heart Rhythm Society; NNH = number needed to harm; NNT = number needed to treat; OR = odds ratio; RCT = randomized controlled trial; RR = relative risk ratio; TIA = transient ischemic attack; VKA = vitamin K antagonist.

GUIDELINE SCOPE AND PURPOSE

The purpose of this guideline is to provide recommendations for primary care-relevant pharmacologic treatments of patients who have nonvalvular atrial fibrillation. While other treatments were deemed outside the scope of this guideline, family physicians should be aware of the full range of options and discuss these with their patients. The target audience is family physicians and other primary care clinicians. The target patient population is adults who have atrial fibrillation, as defined by electrocardiographic evidence of atrial fibrillation with or without symptoms. All frequencies and durations of atrial fibrillation (paroxysmal, persistent, and permanent) are included. This guideline does not apply to patients who have atrial fibrillation due to a reversible cause (post-operative, post-myocardial infarction, or due to hyperthyroidism) or patients who have atrial fibrillation due to valvular disease.

DIFFERENCES FROM PREVIOUS GUIDELINE

This guideline updates and replaces an earlier guideline published in 2003 from the AAFP and the American College of Physicians, which was reaffirmed by the AAFP in 2008.[1] The topic was nominated to the Agency of Healthcare Research and Quality (AHRQ) for an updated evidence review in 2011. Changes in the methodology and scope of the guideline include the following:

- Adding a consumer/patient representative
- Including evidence for new direct oral anticoagulants
- Including evidence on strict versus lenient rate control
- Narrowing the scope of the guideline to focus solely on pharmacologic management
- Adding a recommendation on risk assessment for stroke
- Adding shared decision-making tools to compare treatment options for rate control and anticoagulation

INTRODUCTION

Atrial fibrillation (AF) is one of the most common types of arrhythmia in adults worldwide, with an estimated 2.7-6.1 million people affected in the United States.[2] Because AF is more common in adults older than 65 years of age, this figure will continue to rise as the population ages.[2] AF presents as a change in heart rate with an irregular pattern, with symptoms that may worsen/change over time. AF can occur as episodes (paroxysmal) or continuously (persistent). Symptom presentation can vary among patients, with some being asymptomatic and others complaining of irregular heart rate, heart palpitations, lightheadedness, extreme fatigue, shortness of breath, anxiety, and chest pain. In addition to an increase in mortality, myocardial infarction, heart failure exacerbation, and cardiomyopathy,[3-6] patients who have AF have a significantly increased risk of stroke; almost a quarter of all strokes in the elderly are related to AF.[7] Symptoms and complications due to AF result in more than 750,000 hospitalizations and 130,000 deaths each year and cost the United States $6 billion each year. Individual health care costs are approximately $8,000 higher per year for patients who have AF than those who do not have AF.[2]

Management options for AF involve rate control, rhythm control, and prevention of thromboembolic events. Options include medications to slow the heart rate, medications to achieve and maintain a regular rhythm, electrical cardioversion, ablation, and other surgical interventions. Stroke prophylaxis is a mainstay of management for individuals with AF who have additional risk factors for stroke. Until recently, the main treatment for stroke prophylaxis was Vitamin K antagonists (VKAs) such as warfarin. Newer direct oral anticoagulants offer an alternative to VKAs for prevention of stroke in patients who have AF.

Bleeding risk can also be assessed for patients treated with anticoagulants or aspirin. The HAS-BLED scale is the most studied and most commonly used. Scores for this tool can range from zero to nine, with a score of three or greater indicating an increased risk for bleeding.[8] Many of the risk factors for bleeding are the same as those for stroke, making it challenging to estimate the trade-off between stroke risk and risk of bleeding.

METHODS

Systematic Review

In 2013, AHRQ published two comparative effectiveness reviews. The first report, *Treatment of Atrial Fibrillation: Comparative Effectiveness Review No. 119,* reviewed the evidence for pharmacologic and surgical treatment of atrial fibrillation.[9] The second review, *Stroke Prevention in Atrial Fibrillation: Comparative Effectiveness Review No. 123,* reviewed the evidence for different anticoagulation strategies for patients with atrial fibrillation. These reports were based on literature searches from January 1, 2000, to August 14, 2012.

The scope of the AHRQ reports was reviewed, and the panel chose to focus on the following key questions that they considered most relevant to primary care practice:

Treatment of Atrial Fibrillation

KQ1: What are the comparative safety and effectiveness of pharmacological agents used for ventricular rate control in patients with atrial fibrillation? Do the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest?

KQ2: What are the comparative safety and effectiveness of a strict rate-control strategy versus a more lenient rate-control strategy in patients with atrial fibrillation? Do the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest?

KQ6: What are the comparative safety and effectiveness of rate-control therapies compared with rhythm-control therapies in patients with atrial fibrillation? Do the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest?

Stroke Prevention in Atrial Fibrillation

KQ1: In patients with nonvalvular atrial fibrillation, what are the comparative diagnostic accuracy and impact on clinical decision making (diagnostic thinking, therapeutic, and patient outcome efficacy) of available clinical and imaging tools for predicting thromboembolic risk?

KQ2: In patients with nonvalvular atrial fibrillation, what are the comparative diagnostic accuracy and impact on clinical decision making (diagnostic thinking, therapeutic, and patient outcome efficacy) of clinical tools and associated risk factors for predicting bleeding events?

KQ3: What are the comparative safety and effectiveness of specific anticoagulation therapies, antiplatelet therapies, and procedural interventions for preventing thromboembolic events:

a. In patients with nonvalvular atrial fibrillation?

b. In specific subpopulations of patients with nonvalvular fibrillation?

The sections of the AHRQ evidence reports relevant to these key questions were reviewed and used as the foundation for the AAFP's recommendations.

Updated Literature Search

A targeted, updated literature search using the same search criteria outlined in the AHRQ reports[9,10] was completed by the AAFP's medical librarian. The updated search resulted in 217 articles spanning the time from the completion of the AHRQ reports in 2012 through December 31, 2015. The search strategy is outlined in Appendix A. Two reviewers independently examined citations and abstracts using the same inclusion and exclusion criteria that were used in the AHRQ evidence reports.[9,10] A full text article was reviewed if at least one reviewer thought it should be included. This resulted in the review of 91 full text articles. Following exclusion of 48 articles, the remaining 43 articles underwent assessment for risk of bias and study quality. Each relevant study was rated for quality (good, fair, poor) by at least two independent reviewers using the approach outlined by the AHRQ *Methods Guide for Effectiveness and Comparative Effectiveness Reviews.*[11] In keeping with the AHRQ methods, only studies that were rated as good or fair were included for consideration. Studies rated as poor were not included. For this updated evidence review, 16 articles were included (see Appendix B). The updated literature search resulted in the inclusion of one additional RCT with a new medication (edoxaban) that was not addressed in the AHRQ report on stroke prevention.[10] This RCT was used to inform Recommendation 4 on options for chronic anticoagulation. The other studies found in the updated search were observational and secondary analyses of RCTs included in the AHRQ reports. These additional studies did not change the conclusions from the original AHRQ evidence reports. However, these analyses were considered by the panel in determining the recommendations and are discussed in the guideline text as appropriate.

Constructing the Guideline

The AAFP's Commission on Health of the Public and Science appointed a guideline development group (GDG) to update the guideline. Specifics on the guideline development panel and process can be found in the AAFP *Clinical Practice Guideline Manual*.[12] The GDG reviewed the 2003 guideline and the two AHRQ evidence reports. The panel evaluated each recommendation from the guideline and determined those that would be included in the update. The GDG determined that the recommendations for pharmacologic treatment of atrial fibrillation and anticoagulation were the most relevant for family physicians.

Table 1. American Academy of Family Physicians Grading System†

Recommendation*	Definition	Quality of Evidence**
Strong	High confidence in the net benefit for patient-oriented outcomes. Most informed patients would choose recommended option.	High
		Moderate
Weak	Lower confidence in the net benefit for patient-oriented outcomes. Patient choices may vary based on values and preferences.	Moderate
		Low

†The AAFP uses a modified version of Grading of Recommendations Assessment, Development and Evaluation (GRADE)

*Recommendations can be either for or against an intervention or testing modality.

**The strength of the recommendation should be consistent with the quality of the evidence such that strong recommendations are based on high-quality evidence, whereas weak recommendations are based on low- to moderate-quality evidence. Very low-quality evidence should be considered insufficient for a recommendation unless there are highly unusual circumstances and the benefits would greatly outweigh the harms.

The evidence from the systematic reviews was evaluated using a modified version[12] of the GRADE[13] system to rate the quality of the evidence for each outcome and the overall strength of each recommendation. GRADE uses the term "strength of recommendation" to rate the extent to which one can be confident that the desirable effects of an intervention outweigh the undesirable effects and reflect the degree to which there is evidence of improved patient-oriented health outcomes (Table 1). The GRADE system also provides opportunities to issue guideline recommendations without a rating when appropriate (e.g., those that will be helpful to a clinician but for which there is no direct evidence to support the recommendation). These statements are labeled by the AAFP as "good practice points."[13,14]

Guideline recommendations were finalized based on consensus of the GDG. Patient-oriented outcomes were prioritized in the guideline recommendations. Outcomes assessed included maintenance of ventricular rate and sinus rhythm; symptom relief; quality of life; all-cause and cardiovascular mortality; stroke; systemic embolism; cardiovascular events; hospitalizations; major and minor bleeding; and other adverse events due to medications. The recommendations were worded to reflect the strength and direction of the recommendation, and the quality of the evidence was listed parenthetically. Quantitative risk information was also included in the supporting text using data from the AHRQ reports and individual studies, as appropriate. The number needed to treat/harm was calculated from these data. Evidence tables were created using the GRADEpro Guideline Development Tool [Software]. McMaster University, 2015 (developed by Evidence Prime, Inc.). Available at gradepro.org.

Peer Review

The guideline was peer-reviewed by relevant external stakeholders. All comments and any modifications based on those comments were documented. The AAFP Commission on Health of the Public and Science (CHPS) and Board of Directors reviewed and approved the final guideline.

Conflict of Interest

Conflicts of interest (COI) were solicited in writing at the beginning of the guideline process and updated verbally at each subsequent call. No panel member disclosed any COI.

RECOMMENDATIONS

Recommendation 1: The AAFP strongly recommends rate control in preference to rhythm control for the majority of patients with atrial fibrillation (strong recommendation, moderate-quality evidence). Preferred options for rate-control therapy include non-dihydropyridine calcium channel blockers and beta blockers. Rhythm control may be considered for certain patients based on symptoms, exercise tolerance, and patient preferences (weak recommendation, low-quality evidence).

Strategies to control heart rate or maintain sinus rhythm can improve symptoms in patients with AF. Moderate-quality evidence showed similar outcomes between rate-control and rhythm-control strategies for cardiovascular mortality, stroke, and all-cause mortality (AHRQ Evidence Table–Rate versus Rhythm Control). High-quality evidence showed that rate-control strategies are superior to rhythm-control strategies in reducing cardiovascular hospitalizations (OR 0.25, 95% CI 0.14-0.43). Antiarrhythmic medications can be associated with significant risks and side effects, including proarrhythmia. Given the benefit of reduced cardiovascular hospitalizations with rate control, and the potential harms associated with antiarrhythmic medications, a rate-control strategy should be initiated for most patients with AF.

Rate control can be achieved with one of several medications, including beta blockers (e.g., metoprolol, carvedilol), non-dihydropyridine calcium channel blockers (e.g., diltiazem, verapamil), and digoxin.[15] Beta blockers and calcium channel blockers consistently outperform digoxin for rate control, so digoxin is not recommended as first-line management (ARHQ Evidence Table–Rate Control).

The AAFP's prior guideline on management of atrial fibrillation recommended specific rate-control therapies. However, the recent AHRQ report showed insufficient evidence to support the superiority of individual calcium channel blockers and beta blockers. The subsequent updated literature search revealed only one additional study of fair quality that showed a benefit of calcium channel blockers over beta blockers for reduction of symptom frequency and severity. This study was limited by a very small number of subjects (n = 60) and short duration of follow-up (three weeks).[16]

Rhythm control is an option for treatment of AF for patients whose symptoms are not managed by rate control. Low-quality evidence showed a potential, nonsignificant benefit of rhythm control for reduction in heart failure symptoms (OR 0.78, 95% CI 0.42-1.44). There are a wide variety of pharmacologic and procedural strategies available to maintain a regular rhythm, which makes it difficult to ascertain the comparative effectiveness and safety of these different drugs and procedures. Pharmacologic agents used for rhythm control include amiodarone, dronedarone, propafenone, and sotalol.[15]

Recommendation 2: The AAFP recommends lenient rate control (<110 beats per minute resting) over strict rate control (<80 beats per minute resting) for patients with atrial fibrillation (weak recommendation, low-quality evidence).

The degree of rate control (strict versus lenient) is an area of uncertainty, with differing recommendations for an ideal target rate. Despite no evidence showing superiority of strict control (<80 beats per minute resting), it is preferentially recommended by the AHA/ACC/HRS guideline.[17] Low-quality evidence showed a decrease in the incidence of stroke with lenient rate control compared to strict rate control (HR 0.35, 90% CI 0.13-0.92, NNT 43). Limited evidence showed no significant differences in mortality, cardiovascular hospitalizations, heart failure symptoms, quality of life, thromboembolic events, or bleeding between strict and lenient control, although this evidence was determined to be insufficient by the AHRQ report due to few studies and imprecision in the findings (AHRQ Evidence Table–Lenient versus Strict Rate Control).

There are also more potential harms with strict control because it may be harder to achieve and may require more medication with an increased likelihood of side effects. Because of the potential benefit of lenient control and the potential harms of strict control, lenient control is an appropriate strategy for most patients with AF. If symptoms due not improve, stricter control should be considered.

Recommendation 3: The AAFP recommends that clinicians discuss the risk of stroke and bleeding with all patients considering anticoagulation (good practice point). Clinicians should consider using the continuous $CHADS_2$ or continuous CHA_2DS_2-VASc for prediction for risk of stroke (weak recommendation, low-quality evidence) and HAS-BLED for prediction of risk for bleeding (weak recommendation, low-quality evidence) in patients with atrial fibrillation.

Although AF increases an individual's risk for stroke, this risk is further increased by the presence of other factors. Determining an individual patient's risk of stroke is important to identify appropriate management options. Commonly used risk assessment tools include the $CHADS_2$ and the CHA_2DS_2-VASc.

The $CHADS_2$ (Table 2) is calculated by giving one point for each of the risk factors except for prior stroke/TIA, which receives two points.[18,19] The CHA_2DS_2-VASc (Table 3) adds additional points for age, with two points for patients aged 75 and older, and one point for patients aged 65-74. This scoring system also adds one point for the presence of vascular disease (peripheral artery disease, myocardial infarction) and one point if the patient is female.[20]

Table 2. $CHADS_2$ Risk Assessment Score

	Risk Factor	Score (if present)
C	Congestive heart failure	1
H	Hypertension	1
A	Age 75+	1
D	Diabetes mellitus	1
S	Prior stroke or TIA	2
Total Score for a maximum of 6		

Low-quality evidence showed that both the $CHADS_2$ risk-stratification tool and the CHA_2DS_2-VASc tool provide modest stroke risk discrimination in patients with AF ($CHADS_2$ c-statistic = 0.71, 95% CI 0.66-0.75 and CHA_2DS_2-VASc c-statistic = 0.70, 95% CI 0.66-0.75). The CHA_2DS_2-VASc tool includes additional risk factors, which increases the number of patients eligible for anticoagulation but does not improve risk discrimination compared to the $CHADS_2$.

The ACC/AHA/HRS guideline makes a preferential recommendation for CHA_2DS_2-VASc, but because the tools perform similarly, both are reasonable to assist clinicians and patients in determining the risk of stroke (AHRQ Evidence Table–Thromboembolic Risk).

Because of the risk of bleeding associated with anticoagulation, an individual's risk factors for bleeding should be considered and discussed. Many of the risk factors for a major bleeding event overlap the risks of stroke, making it challenging to weigh the potential benefits and harms of anticoagulation. Aging is a significant risk factor for AF, with the prevalence increasing with advancing age. Anticoagulation is effective in reducing the morbidity and mortality of elderly patients, but these patients are also at an increased risk for bleeding. There are several tools available to evaluate risk of bleeding, with limited to modest risk discrimination. Low-quality evidence showed the HAS-BLED scale has slightly higher risk discrimination for major bleeding than HEMORRHAGES, BRI, or ATRIA for patients on warfarin. Evidence is lacking on how to use these scores and balance them with the risk of stroke (AHRQ Evidence Table–Bleeding Risk). Therefore, a discussion with the patient is essential to determine values and preferences before prescribing a particular anticoagulation strategy.

Table 3. CHA_2DS_2-VASc Risk Assessment Score

	Risk Factor	Score (if present)
C	Congestive heart failure	1
H	Hypertension	1
A	Age 75+	1
D	Diabetes mellitus	1
S	Prior stroke or TIA	2
V	Vascular disease	2
A	Age 65-74	1
Sc	Sex category (female)	1
Total Score for a maximum of 10		

Other risk-stratification tools evaluated in the AHRQ evidence report and updated literature search were found to be inferior to the $CHADS_2$, the CHA_2DS_2-VASc, and the HAS-BLED, or there was insufficient evidence to determine their ability to discriminate the risk of stroke.

Recommendation 4: The AAFP strongly recommends that patients with atrial fibrillation receive chronic anticoagulation unless they are at low risk of stroke (CHADS2 <2) or have specific contraindications (strong recommendation, high-quality evidence). Choice of anticoagulation therapy should be based on patient preferences and patient history. Options for anticoagulant therapy may include warfarin, apixaban, dabigatran, edoxaban, or rivaroxaban.

Atrial fibrillation is a significant independent risk factor for stroke, causing 15%-20% of ischemic strokes.[2] Prophylactic treatment with anticoagulants has proven to be highly effective for the prevention of stroke in patients with AF. Vitamin K antagonists have been used successfully for more than 50 years and are considered to be the gold standard for anticoagulant therapy. Direct anticoagulants provide additional options for stroke prophylaxis in patients with AF. The risks, benefits, and burdens related to cost and quality of life are outlined in Table 5. Patients with multiple comorbidities—including diabetes mellitus, hypertension, heart failure, coronary artery disease, renal impairment, and cerebrovascular disease—were included in the studies. There is insufficient evidence to assess these subpopulations to determine their individual benefit from anticoagulation. Dose modifications may be required for patients with renal insufficiency, depending on the degree of renal impairment.

VKAs (Warfarin)

High-quality evidence has shown that VKAs reduce the risk of stroke (RR 0.36, 95% CI 0.26-0.51) and all-cause mortality over placebo (RR 0.74, 95% CI 0.57-0.97).[21] Although considered the gold standard for anticoagulation, VKAs have several disadvantages. They are associated with a significant increased risk of major bleeding.[22] VKAs have a narrow therapeutic window, which can result in the undertreatment of patients, thereby increasing their risk of stroke and embolism, as well as overtreatment of patients, which increases the risks of major bleeding. Patients on VKAs require frequent monitoring and dietary adjustments, which can be burdensome to patients and affect adherence.[23,24] Contraindications for warfarin include the following:[25]

- Pregnancy, except in women with mechanical heart valves
- Hemorrhagic tendencies or blood dyscrasias
- Recent or planned surgery of the central nervous system or eye, or traumatic surgery resulting in large open surfaces
- Potential high levels of noncompliance in unsupervised patients
- Hypersensitivity to warfarin
- Malignant hypertension

Direct Thrombin Inhibitor (Dabigatran)

One large, good-quality RCT evaluated two doses (110 mg and 150 mg twice daily) of the direct thrombin inhibitor dabigatran compared to warfarin. High-quality evidence showed that compared to warfarin, dabigatran at the 150 mg dose reduced the risk of stroke or embolism (RR 0.66, 95% CI 0.53-0.82, NNT 172) and intracranial hemorrhage (RR 0.40, 95% CI 0.27-0.60, NNT 227). However, high-quality evidence showed an increase in the risk of gastrointestinal bleeds (RR 1.50, 95% CI 1.19-1.89, NNH 204) without a significant difference in other major bleeding. Moderate-quality evidence showed that at this dose there was an increased risk of myocardial infarction (RR 1.38, 95% CI 1.00-1.91, NNH 476). High-quality evidence showed that the 110 mg dose of dabigatran was noninferior compared to warfarin for reducing the risk of stroke and intracranial hemorrhage (RR 0.91, 95% CI 0.74-1.11). This dose was also associated with a lower risk of major bleeding compared to warfarin (RR 0.80, 95% CI 0.69-0.93, NNT 153). Low-quality evidence showed a trend toward increased risk of myocardial infarction at the lower dose, but this did not reach statistical significance (RR 1.35, 95% CI 0.98-1.87) (Appendix C). The updated literature search included one fair quality observational study using registry data in China that was consistent with the conclusions that dabigatran was associated with a reduced incidence of stroke and intracranial hemorrhage compared to warfarin and aspirin.[26] Currently, dabigatran 110 mg is not approved by the U.S. Food and Drug Administration (FDA) for prevention of stroke in patients with AF.

Factor Xa Inhibitors (Apixaban, Rivaroxaban, and Edoxaban)

High-quality evidence showed that compared to warfarin, apixaban (5 mg twice daily) reduced the incidence of stroke (HR 0.79, 95% CI 0.66-0.95, NNT 303) and intracranial hemorrhage (HR 0.42, 95% CI 0.3-0.58, NNT 212) and caused less major bleeding (HR 0.69, 95% CI 0.60-0.80, NNT 104). Moderate-quality evidence showed a reduction in all-cause mortality (HR 0.89, 95% CI 0.80-0.99, NNT 238).[27] In patients unable to take warfarin, high-quality evidence showed apixaban to be superior to aspirin in reducing the risk of stroke (HR 0.45, 95% CI 0.32-0.62, NNT 48), with similar rates of major bleeding. Several subgroup analyses of the RCTs supported apixaban's superiority to aspirin for prevention of stroke and superiority to warfarin for risk of bleeding.[28-30] (Appendix D)

Moderate-quality evidence showed rivaroxaban (20 mg daily) to be noninferior to warfarin in prevention of stroke (HR 0.88, 95% CI 0.74-1.03). Moderate-quality evidence showed similar rates of major bleeding, and high-quality evidence showed no difference in all-cause mortality (HR 0.92, 95% CI 0.82-1.03) compared to warfarin (Appendix E).

A large RCT[31] that was published after the AHRQ report compared two doses of edoxaban (30 mg and 60 mg daily) to warfarin. Moderate-quality evidence showed the 60 mg dose of edoxaban to be noninferior to warfarin in reducing stroke and systemic embolism (HR 0.87, 95% CI 0.73-1.04). High-quality evidence showed that the 60 mg dose of edoxaban reduced risk of bleeding (HR 0.80, 95% CI 0.71-0.91, NNT 147) and cardiovascular mortality (HR 0.86, 95% CI 0.77 to 0.97, NNT 217). Moderate-quality evidence showed the 30 mg dose of edoxaban to be noninferior to warfarin for stroke (HR 1.07, 95% CI 0.87-1.31). High-quality evidence showed that the lower dose of edoxaban reduced major bleeding (HR 0.47, 95% CI 0.41-0.55, NNT 55) and cardiovascular mortality (HR 0.85, 95% CI 0.76-0.96, NNT 217) compared to warfarin. Evidence tables for these outcomes have been provided in Appendix F.

Antiplatelet Treatment

The updated AHRQ report did not address the efficacy of aspirin compared to no treatment for stroke prevention. It did compare aspirin to warfarin, aspirin plus clopidogrel, and the direct oral anticoagulants, all of which were superior to aspirin in preventing stroke but also showed increased risk for bleeding. The exception was apixaban, which was superior to aspirin in preventing stroke with a similar risk of bleeding (AHRQ Evidence Table–Apixaban versus Aspirin). Many experts have questioned the efficacy of aspirin for stroke prevention in AF. The evidence for benefit is based on a single 1991 RCT, with limited supporting evidence. The AHA/ACC/HRS guideline continues to present aspirin as an option for patients with a CHA_2DS_2-VASc = 1.

Other Considerations for Anticoagulation Therapies

Studies of the effectiveness of anticoagulation for the prevention of stroke generally include individuals with at least one to two additional risk factors for stroke ($CHADS_2$ ≥1 or 2). There is not sufficient evidence in the population of patients at low risk for stroke ($CHADS_2$ = 0) to recommend anticoagulation. As this population is less likely to benefit from anticoagulation, more consideration must be given to the potential harms of treatment. Therefore, it is recommended that clinicians avoid anticoagulation in patients at low risk of stroke (CHADS2 = 0). Individuals with only one additional risk factor ($CHADS_2$ = 1) may be appropriate candidates for anticoagulation. Aspirin can also be considered for these patients.

Table 4. Treatment Based on $CHADS_2$ Score

$CHADS_2$ Score	Recommended Treatment	Statement for Shared Decision Making
0	Do not anticoagulate	Benefit < Harm Patients without additional risk factors for stroke most likely will benefit less from treatment with a similar risk for bleeding.
1	Options include aspirin or anticoagulation	Benefit > Harm Patients with an additional risk factor for stroke will benefit from treatment. Aspirin can be considered for patients at an increased risk of bleeding. Choice of therapy should be based on patient preferences and bleed risk.
2-6	Recommend anticoagulation	Benefit > Harm Patients with additional risk factors for stroke will benefit from treatment. The evidence is currently insufficient to preferentially recommend one anticoagulant over others. Choice of anticoagulant should be based on patient preferences. Dual antiplatelet and anticoagulant therapy should not be used.

The $CHADS_2$ score is calculated by adding 1 point each for recent congestive heart failure (i.e., active within the past 100 days or documented by echocardiography), hypertension (systolic and/or diastolic), age at least 75 years, and diabetes mellitus, and adding 2 points for a history of stroke or transient ischemic attack. A score of 0 to 1 was designated as low risk; a score of 2 to 3 was designated as moderate risk; and a score of 4, 5, or 6 was designated as high risk.

The major concern with the direct anticoagulants has been the lack of a reversal agent if an individual has a major bleed. The anticoagulation effects of VKAs can be reversed with vitamin K or, for immediate reversal, with prothrombin complex concentrates. However, there is only one FDA-approved antidote for a direct oral agent, which is a reversal agent for dabigatran approved in 2015 for use in emergency situations.[32] Reversal agents for other oral anticoagulants are under investigation.

Currently, the evidence base does not allow for a preferential recommendation for one particular anticoagulant over another. Therefore, the choice of anticoagulant should be based on shared decision making between the patient and physician. Individuals on warfarin not consistently in the therapeutic range, and those who do not have cost constraints, should consider the direct oral anticoagulants. Evidence showed that these direct anticoagulants are as effective as warfarin in patients with renal insufficiency, but they have not been studied in patients with end-stage renal disease. Warfarin remains the preferred option for these patients.

Some of the benefits, risks, costs, and other considerations for the different anticoagulants can be found in Table 5.

Table 5. Oral Anticoagulants for Stroke Prevention in Patients with Atrial Fibrillation

Medication (30-day supply)	Dose*	Cost**	Benefits***	Risks***
Warfarin	Varies (Titrated to INR)	$10 (5 mg, #30)	• Inexpensive • Reversal agent available • Can use in end-stage renal disease (CrCl <15) • Well studied	• Bleeding • Contraindicated in pregnancy • Many potential food and drug interactions
Apixaban	5 mg twice daily	$375	↓ Stroke ↓ Major bleeding ↓ Intracranial hemorrhage ↓ All-cause mortality	• No reversal agent • Caution with use in end-stage renal disease
Dabigatran	150 mg twice daily	$365	↓ Stroke ↓ Intracranial hemorrhage • Reversal agent available	↑ MI ↑ GI bleeding • Not approved for use in end-stage renal disease
Edoxaban	60 mg daily	$300	↓ Major bleeding ↓ Cardiovascular mortality	• No reversal agent • Not approved for use in end-stage renal disease
Rivaroxaban	20 mg daily	$375	↓ Intracranial hemorrhage	• Bleeding (similar to warfarin) • No reversal agent • Not approved for use in end-stage renal disease

CrCl = creatinine clearance; GI = gastrointestinal; INR = international normalized ratio; MI = myocardial infarction.
*Dose of non-vitamin K antagonist oral anticoagulant (NOAC) should be adjusted for patients with renal insufficiency.
**Cost is approximate and varies by pharmacy.
***Benefits/risks of NOACs compared to warfarin

Recommendation 5: The AAFP strongly recommends against dual treatment with anticoagulant and antiplatelet therapy in most patients with atrial fibrillation (strong recommendation, moderate-quality evidence).

Moderate-quality evidence showed that the concomitant use of aspirin or clopidogrel with warfarin significantly increased the risk of major bleeding compared to warfarin alone (warfarin plus ASA NNH 34, 95% CI 30-39; warfarin plus clopidogrel NNH 10, 95% CI 8-14). There was also moderate-quality evidence of an increased risk of ischemic stroke with warfarin plus aspirin and no significant difference in the risk of ischemic stroke with warfarin plus clopidogrel compared to warfarin alone (HR 1.27, 95% CI 1.14-1.40) (AHRQ Evidence Table–Warfarin + Antiplatelet Therapy). Conditions such as acute

myocardial infarction, ischemic heart disease, and ischemic stroke for which antiplatelet therapy is indicated are common comorbidities with atrial fibrillation. Balancing potential benefits against harms requires recognition of a significant increased risk of bleeding with dual therapy. There may be situations, such as immediately after stent placement, when dual therapy may be appropriate. The updated literature search identified a good-quality secondary analysis[33] of the data from a larger RCT that compared dabigatran to warfarin. This study found a significant increase in major bleeding with concomitant use of antiplatelet therapy with warfarin and with 110 mg and 150 mg doses of dabigatran (Table 6). The risk of major bleeding was even higher when dual therapy (ASA plus clopidogrel) was used along with warfarin or dabigatran. No studies were found that evaluated the risks of combination therapy with the other oral anticoagulants.

Table 6. Increased Risk of Major Bleeding with Dual Therapy

Treatment	Increased Risk (95% CI)	Number Needed to Harm
Warfarin + antiplatelet therapy	HR 1.5 (1.22-1.86)	55
Dabigatran 150 mg + antiplatelet therapy	HR 1.81 (1.46-2.24)	58
Dabigatran 110 mg + antiplatelet therapy	HR 1.53 (1.21-1.92)	62

CI = confidence interval; HR = hazard ratio.

CONCLUSIONS AND FUTURE RESEARCH

The purpose of this updated guideline is to provide clinical recommendations for primary care physicians to pharmacologically manage atrial fibrillation. Symptoms in the majority of patients with AF can be managed using a lenient rate-control strategy. The preferred treatment options for rate control include non-dihydropyridine calcium channel blockers and beta blockers. In patients with atrial fibrillation and additional risk factors for stroke, chronic anticoagulation is recommended. Prior to initiating treatment, clinicians should discuss the benefits and harms of the different anticoagulants, including potential medication cost and lifestyle modifications. Risk of bleeding should also be discussed. Careful risk assessment is essential, as patients with a low risk of stroke may not be appropriate for anticoagulation. Due to the increased risk of bleeding, dual therapy with aspirin and anticoagulants should be avoided.

This guideline was developed using available evidence; however, gaps were identified. New research into these areas may affect the recommendations, at which time the guideline will be updated accordingly. Research gaps that would provide important information include the following:

- Rate- and rhythm-control medications
  There were a limited number of studies comparing the different rate-control medications. The main outcome of these studies was control of ventricular rate, rather than long-term outcomes such as symptom control, quality of life, mortality, or other cardiovascular-related outcomes. There are numerous rhythm-control medications and a dearth of studies comparing their effectiveness. The current evidence used different combinations of drugs and reported maintenance of sinus rhythm as the only outcome. As with rate-control medications, further research is needed to compare effectiveness of the different drugs and to evaluate long-term outcomes More research examining the effectiveness of these drugs in more diverse patient populations is needed since the current evidence included only older adults with fewer symptoms.
- Lenient versus strict rate control
  More research is needed to evaluate long-term outcomes of lenient versus strict rate-control strategies.
- Direct oral anticoagulants
  There are currently no RCTs directly comparing the effectiveness and harms of the direct oral anticoagulants. Research is needed in special populations, such as those with multiple comorbidities and end-stage renal disease. Because risks for stroke and bleeding tend to overlap, a single score would be beneficial and aid in clinical decision making. There have been some attempts to combine the CHADS2 or CHA2DS2-VASc with HAS-BLED; however, the combined scores did not improve risk prediction. There is insufficient evidence for inclusion of imaging information in risk prediction.

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APPENDIX A: LITERATURE SEARCH STRATEGY

Search terms were similar to those presented in the AHRQ reports. Filters were used to specify study/article type, date range, humans only, and English. Specific search terms for each key question used in the guideline update are listed below.

AHRQ Treatment of Atrial Fibrillation

KQ1: What are the comparative safety and effectiveness of pharmacological agents used for ventricular rate control in patients with atrial fibrillation? Do the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest?

"Atrial Fibrillation"[majr] AND "heart rate"[majr] AND ("anti-arrhythmia agents"[Pharmacological Action] OR "anti-arrhythmia agents"[majr])

KQ2: What are the comparative safety and effectiveness of a strict rate-control strategy versus a more lenient rate-control strategy in patients with atrial fibrillation? Do the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest?

"Atrial Fibrillation"[majr] AND "heart rate"[majr] AND ("lenient"[tw] OR "strict"[tw]) OR "rate-control strategy"[All Fields]

KQ6: What are the comparative safety and effectiveness of rate-control therapies compared with rhythm-control therapies in patients with atrial fibrillation? Do the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest?

"Atrial Fibrillation"[majr] AND "heart rate"[majr] AND (nonpharmacological[tiab] OR "pacemaker, artificial"[majr] OR "catheter ablation"[majr] OR "anti-arrhythmia agents"[Pharmacological Action])

ARHQ Stroke Prevention in Atrial Fibrillation

KQ1: In patients with nonvalvular atrial fibrillation, what are the comparative diagnostic accuracy and impact on clinical decision making (diagnostic thinking, therapeutic, and patient outcome efficacy) of available clinical and imaging tools for predicting thromboembolic risk?

"Atrial Fibrillation"[majr] AND ("magnetic resonance imaging"[MeSH Major Topic] OR "cardiac imaging techniques"[majr]) AND ("stroke"[majr] OR "thromboembolism"[majr]) AND ("Sensitivity AND Specificity"[Mesh] OR "diagnosis"[Mesh] OR "decision making"[Mesh])

KQ2: In patients with nonvalvular atrial fibrillation, what are the comparative diagnostic accuracy and impact on clinical decision making (diagnostic thinking, therapeutic, and patient outcome efficacy) of clinical tools and associated risk factors for predicting bleeding events?

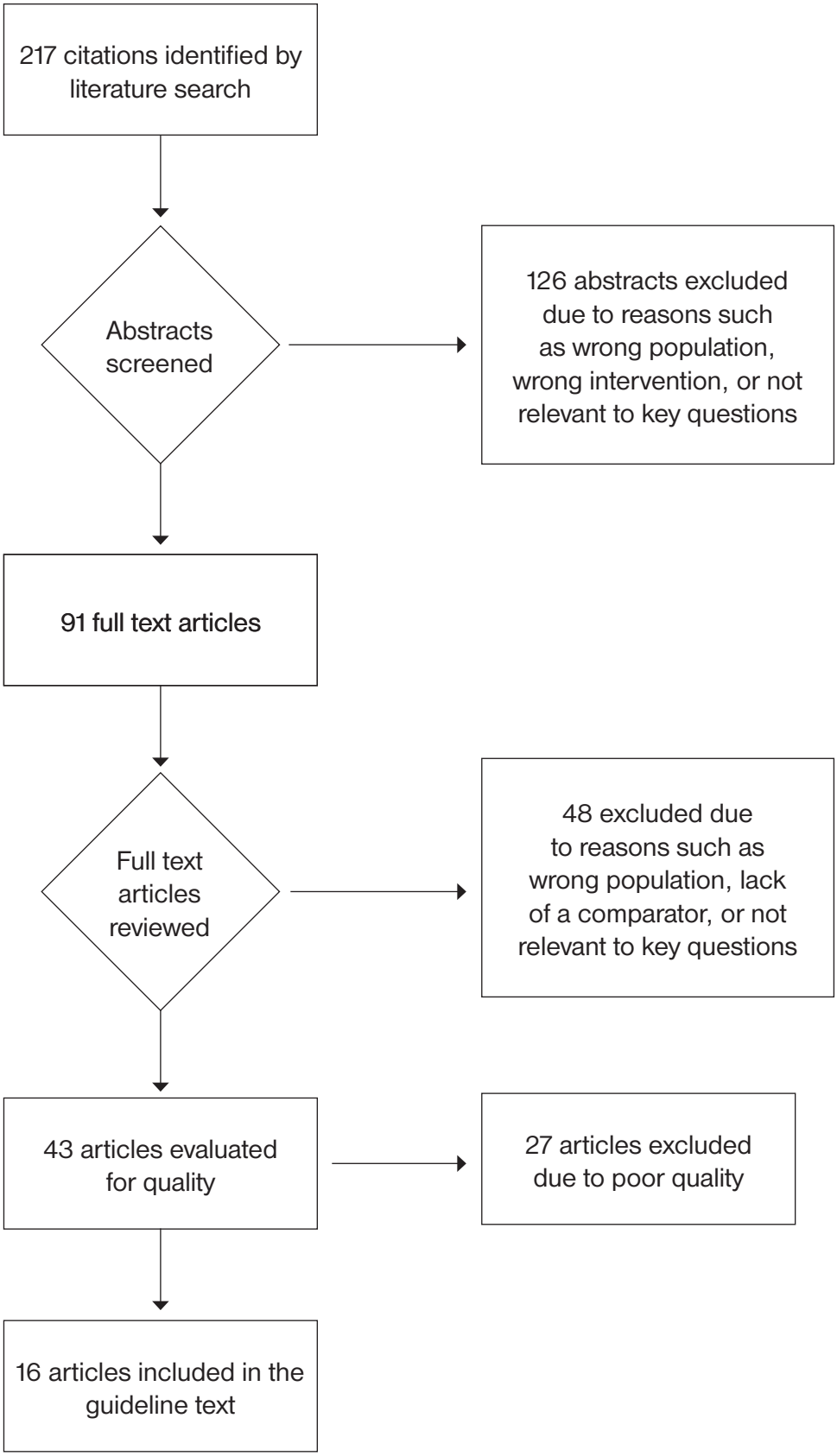
("Atrial Fibrillation"[majr] AND "hemorrhage"[majr]) AND ("Sensitivity AND Specificity"[Mesh] OR "diagnosis"[Mesh] OR "decision making"[Mesh] OR "Reproducibility of Results"[Mesh])

KQ3: What are the comparative safety and effectiveness of specific anticoagulation therapies, antiplatelet therapies, and procedural interventions for preventing thromboembolic events:

a. In patients with nonvalvular atrial fibrillation?
b. In specific subpopulations of patients with nonvalvular atrial fibrillation?

("Atrial Fibrillation"[majr] AND ("stroke"[majr] OR "thromboembolism"[majr])) AND ("Anticoagulants"[Pharmacological Action] OR "Warfarin"[Mesh] OR coumadin[tw] OR "Vitamin K/antagonists and inhibitors"[Mesh] OR vitamin k[tw] OR "Heparin"[Mesh] OR "Enoxaparin"[Mesh] OR enoxaparin[tw] OR lovenox[tw] OR "rivaroxaban"[tw] OR rivaroxaban[tw] OR xarelto[tw] OR "dabigatran etexilate"[tw] OR dabigatran[tw] OR pradaxa[tw] OR heparin[tw] OR apixaban[tw] OR eliquis[tw] OR edoxaban[tw] OR lixiana[tw]) AND ("platelet aggregation inhibitors"[Pharmacological Action] OR "clopidogrel"[Supplementary Concept] OR clopidogrel[tw] OR plavix[tw] OR "Aspirin"[Mesh] OR aspirin[tw] OR "Dipyridamole"[Mesh] OR dipyridamole[tw] OR aggrenox[tw] OR persantine[tw] OR antiplatelet[tw] OR anti-platelet[tw] OR antiplatelets[tw] OR anti-platelets[tw])

APPENDIX B. UPDATED LITERATURE SEARCH PRISMA DIAGRAM



APPENDIX C. EVIDENCE TABLES FOR DABIGATRAN

Dabigatran (150 mg) compared to Warfarin for Patients with Atrial Fibrillation at an Increased Risk of Stroke

Quality assessment							Summary of findings				
№ of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates		Relative effect (95% CI)	Anticipated absolute effects	
							With warfarin	With dabigatran (150 mg)		Risk with warfarin	Risk difference with dabigatran (150 mg)
Stroke or Systemic Embolism											
12098 (1 RCT)	not serious	n/a	not serious	not serious	none	⊕⊕⊕⊕ HIGH	199/6,022 (3.3%)	134/6076 (2.2%)	**RR 0.66** (0.53 to 0.82)	33 per 1,000	**11 fewer per 1,000** (16 fewer to 6 fewer)
Major Bleeding											
12098 (1 RCT)	not serious	n/a	not serious	not serious	none	⊕⊕⊕⊕ HIGH	397/6,022 (6.6%)	375/6076 (6.2%)	**RR 0.93** (0.81 to 1.07)	66 per 1,000	**5 fewer per 1,000** (13 fewer to 5 more)
All-Cause Mortality											
12098 (1 RCT)	not serious	n/a	not serious	serious [1]	none	⊕⊕⊕◯ MODERATE	487/6,022 (8.1%)	234/6076 (3.9%)	**RR 0.88** (0.77 to 1.00)	81 per 1,000	**10 fewer per 1,000** (19 fewer to 0 fewer)
Cardiovascular Mortality											
12098 (1 RCT)	not serious	n/a	not serious	serious [1]	none	⊕⊕⊕◯ MODERATE	317/6022 (5.3%)	274/6076 (4.5%)	**RR 0.85** (0.72 to 0.99)	53 per 1,000	**8 fewer per 1,000** (15 fewer to 1 fewer)
Intracranial Hemorrhage											
12098 (1 RCT)	not serious	n/a	not serious	not serious	none	⊕⊕⊕⊕ HIGH	87/6022 (1.4%)	36/6076 (0.6%)	**RR 0.40** (0.27 to 0.60)	14 per 1,000	**9 fewer per 1,000** (11 fewer to 6 fewer)
Gastrointestinal Bleeding											
12098 (1 RCT)	not serious	n/a	not serious	not serious	none	⊕⊕⊕⊕ HIGH	120/6022 (2.0%)	182/6076 (3.0%)	**RR 1.50** (1.19 to 1.89)	20 per 1,000	**10 more per 1,000** (4 more to 18 more)
Myocardial Infarction											
12098 (1 RCT)	not serious	n/a	not serious	serious [1]	none	⊕⊕⊕◯ MODERATE	63/6022 (1.0%)	89/6076 (1.5%)	**RR 1.38** (1.00 to 1.91)	10 per 1,000	**4 more per 1,000** (0 fewer to 10 more)

CI = confidence interval; HR = hazard ratio; RCT = randomized controlled trial.

1. Downgraded as CI approached or crossed threshold for not recommending dabigatran over warfarin.

Dabigatran (110 mg) Compared to Warfarin for Patients with Atrial Fibrillation at an Increased Risk of Stroke											
Quality assessment (from AHRQ report)							Summary of findings				
№ of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates		Relative effect (95% CI)	Anticipated absolute effects	
							With warfarin	With dabigatran (110 mg)		Risk with warfarin	Risk difference with dabigatran (110 mg)
Stroke or Systemic Embolism											
12037 (1 RCT)	not serious	n/a	not serious	not serious	none	⊕⊕⊕⊕ HIGH	199/6022 (3.3%)	182/6015 (3.0%)	**RR 0.91** (0.74 to 1.11)	33 per 1,000	**3 fewer per 1,000** (9 fewer to 4 more)
Major Bleeding											
12037 (1 RCT)	not serious	n/a	not serious	not serious	none	⊕⊕⊕⊕ HIGH	397/6022 (6.6%)	322/6015 (5.4%)	**RR 0.80** (0.69 to 0.93)	66 per 1,000	**13 fewer per 1,000** (20 fewer to 5 fewer)
All-Cause Mortality											
12037 (1 RCT)	not serious	n/a	not serious	serious [1]	none	⊕⊕⊕◯ MODERATE	487/6022 (8.1%)	446/6015 (7.4%)	**RR 0.91** (0.80 to 1.03)	81 per 1,000	**7 fewer per 1,000** (16 fewer to 2 more)
Cardiovascular Mortality											
12037 (1 RCT)	not serious	n/a	not serious	serious [1]	none	⊕⊕⊕◯ MODERATE	317/6022 (5.3%)	289/6015 (4.8%)	**RR 0.90** (0.77 to 1.06)	53 per 1,000	**5 fewer per 1,000** (12 fewer to 3 more)
Intracranial Hemorrhage											
12037 (1 RCT)	not serious	n/a	not serious	not serious	none	⊕⊕⊕⊕ HIGH	87/6022 (1.4%)	27/6015 (0.4%)	**RR 0.31** (0.20 to 0.47)	14 per 1,000	**10 fewer per 1,000** (12 fewer to 8 fewer)
Myocardial Infarction											
12037 (1 RCT)	not serious	n/a	not serious	very serious [1,2]	none	⊕⊕◯◯ LOW	63/6022 (1.0%)	86/6015 (1.4%)	**RR 1.35** (0.98 to 1.87)	10 per 1,000	**4 more per 1,000** (0 fewer to 9 more)
Gastrointestinal Bleeding											
12037 (1 RCT)	not serious	n/a	not serious	serious [1]	none	⊕⊕⊕◯ MODERATE	120/6022 (2.0%)	133/6015 (2.2%)	**RR 1.10** (0.86 to 1.41)	20 per 1,000	**2 more per 1,000** (3 fewer to 8 more)

CI = confidence interval; HR = hazard ratio; RCT = randomized controlled trial.

1. Downgraded as CI approached or crossed threshold for not recommending dabigatran over warfarin.
2. Downgraded by AHRQ due to imprecision for this outcome.

APPENDIX D. EVIDENCE TABLE FOR APIXABAN

Apixaban Compared to Warfarin for Patients with Atrial Fibrillation at an Increased Risk of Stroke											
Quality assessment (from ARHQ report)							Summary of findings				
№ of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates		Relative effect (95% CI)	Anticipated absolute effects	
							With warfarin	With apixaban		Risk with warfarin	Risk difference with apixaban
Stroke or Systemic Embolism											
18423 (2 RCTs)	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ HIGH	268/9155 (2.9%)	212/9268 (2.3%)	**HR 0.79** (0.66 to 0.95)	29 per 1,000	**6 fewer per 1,000** (10 fewer to 1 fewer)
Major Bleeding											
18423 (2 RCTs)	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ HIGH	463/9155 (5.1%)	329/9268 (3.5%)	**HR 0.69** (0.60 to 0.80)	51 per 1,000	**15 fewer per 1,000** (20 fewer to 10 fewer)
Intracranial Hemorrhage											
18140 (1 RCT)	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ HIGH	122/9052 (1.3%)	52/9088 (0.6%)	**HR 0.42** (0.30 to 0.58)	13 per 1,000	**8 fewer per 1,000** (9 fewer to 6 fewer)
All-Cause Mortality											
18423 (2 RCTs)	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ HIGH	669/9155 (7.3%)	603/9268 (6.5%)	**HR 0.890** (0.800 to 0.998)	73 per 1,000	**8 fewer per 1,000** (14 fewer to 0 fewer)

CI = confidence interval; HR = hazard ratio; RCT = randomized controlled trial.

APPENDIX E. EVIDENCE TABLE FOR RIVAROXABAN

Rivaroxaban Compared to Warfarin for Patients with Atrial Fibrillation at an Increased Risk of Stroke											
Quality assessment (from AHRQ report)							Summary of findings				
№ of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates		Relative effect (95% CI)	Anticipated absolute effects	
							With warfarin	With rivaroxaban		Risk with warfarin	Risk difference with rivaroxaban
Stroke or Systemic Embolism											
15542 (2 RCTs)	not serious	serious[1]	not serious	not serious	none	⊕⊕⊕◯ MODERATE	263/7772 (3.4%)	199/7770 (2.6%)	**HR 0.88** (0.74 to 1.03)	34 per 1,000	**4 fewer per 1,000** (9 fewer to 1 more)
Major Bleeding											
15542 (2 RCTs)	not serious	not serious	not serious	not serious	none	⊕⊕⊕◯ MODERATE[1]	510/7772 (6.6%)	533/7770 (6.9%)	**HR 1.04** (0.90 to 1.20)	66 per 1,000	**3 more per 1,000** (6 fewer to 13 more)
All-Cause Mortality											
14264 (1 RCT)	not serious	n/a	not serious	not serious	none	⊕⊕⊕⊕ HIGH	250/7133 (3.5%)	208/7131 (2.9%)	**HR 0.92** (0.81 to 1.03)	35 per 1,000	**3 fewer per 1,000** (7 fewer to 1 more)
Cardiovascular Mortality											
14264 (1 RCT)	not serious	n/a	not serious	not serious	none	⊕⊕⊕◯ MODERATE[1]	193/7133 (2.7%)	170/7131 (2.4%)	**HR 0.89** (0.73 to 1.10)	27 per 1,000	**3 fewer per 1,000** (7 fewer to 3 more)

CI = confidence interval; HR = hazard ratio; RCT = randomized controlled trial.

1. Downgraded due to on-treatment analysis of certain outcomes

APPENDIX F. EVIDENCE TABLES FOR EDOXABAN

Edoxaban (60 mg dose) Compared to Warfarin for Patients with Atrial Fibrillation at an Increased Risk of Stroke

Quality assessment							Summary of findings				
№ of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates		Relative effect (95% CI)	Anticipated absolute effects	
							With warfarin	With edoxaban (60 mg dose)		Risk with warfarin	Risk difference with edoxaban (60 mg dose)
Stroke or Systemic Embolism											
14071 (1 RCT)	not serious	n/a	not serious	serious [1]	none	⨁⨁⨁◯ MODERATE	337/7,036 (4.8%)	296/7,035 (4.2%)	**HR 0.87** (0.73 to 1.04)	48 per 1,000	**6 fewer per 1,000** (13 fewer to 2 more)
Major Bleeding											
14024 (1 RCT)	not serious		not serious	not serious	none	⨁⨁⨁⨁ HIGH	524/7,012 (7.5%)	418/7,012 (6.0%)	**HR 0.80** (0.71 to 0.91)	75 per 1,000	**14 fewer per 1,000** (21 fewer to 6 fewer)
All-Cause Mortality											
14071 (1 RCT)	not serious	n/a	not serious	serious [1]	none	⨁⨁⨁◯ MODERATE	839/7,036 (11.9%)	773/7,035 (11.0%)	**HR 0.92** (0.83 to 1.01)	119 per 1,000	**9 fewer per 1,000** (19 fewer to 1 more)
Cardiovascular Mortality											
14071 (1 RCT)	not serious	n/a	not serious	not serious	none	⨁⨁⨁⨁ HIGH	611/7,036 (8.7%)	530/7,035 (7.5%)	**HR 0.86** (0.77 to 0.97)	87 per 1,000	**12 fewer per 1,000** (19 fewer to 2 fewer)

CI = confidence interval; HR = hazard ratio; RCT = randomized controlled trial.

1. Downgraded as CI approached or crossed threshold for not recommending edoxaban over warfarin

Edoxaban (30 mg dose) Compared to Warfarin for Patients with Atrial Fibrillation at an Increased Risk of Stroke

Quality assessment							Summary of findings				
№ of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates		Relative effect (95% CI)	Anticipated absolute effects	
							With warfarin	With edoxaban (30 mg dose)		Risk with warfarin	Risk difference with edoxaban (30 mg dose)
Stroke or Systemic Embolism											
14070 (1 RCT)	not serious	not serious	not serious	serious [1]	none	⨁⨁⨁◯ MODERATE	232/7,036 (3.3%)	253/7,034 (3.6%)	**HR 1.07** (0.87 to 1.31)	33 per 1,000	**2 more per 1,000** (4 fewer to 10 more)
Major Bleeding											
14014 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	524/7,012 (7.5%)	254/7,002 (3.6%)	**HR 0.47** (0.41 to 0.55)	75 per 1,000	**39 fewer per 1,000** (43 fewer to 33 fewer)
All-Cause Mortality											
14070 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	839/7,036 (11.9%)	737/7,034 (10.5%)	**HR 0.87** (0.79 to 0.96)	119 per 1,000	**15 fewer per 1,000** (24 fewer to 4 fewer)
Cardiovascular Mortality											
14070 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	611/7,036 (8.7%)	527/7,034 (7.5%)	**HR 0.85** (0.76 to 0.96)	87 per 1,000	**13 fewer per 1,000** (20 fewer to 3 fewer)

CI = confidence interval; HR = hazard ratio; RCT = randomized controlled trial.

1. Downgraded as CI approached or crossed threshold for not recommending edoxaban over warfarin