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Antithrombotic Therapy for Atrial Fibrillation : Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

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ANTITHROMBOTIC THERAPY AND PREVENTION OF THROMBOSIS, 9TH ED: ACCP GUIDELINES

Antithrombotic Therapy for Atrial Fibrillation

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

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Background: **The risk of stroke varies considerably across different groups of patients with atrial fibrillation (AF). Antithrombotic prophylaxis for stroke is associated with an increased risk of bleeding. We provide recommendations for antithrombotic treatment based on net clinical benefit for patients with AF at varying levels of stroke risk and in a number of common clinical scenarios.**

Methods: **We used the methods described in the Methodology for the Development of Antithrombotic Therapy and Prevention of Thrombosis Guidelines: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines article of this supplement.**

Results: **For patients with nonrheumatic AF, including those with paroxysmal AF, who are (1) at low risk of stroke (eg, $CHADS_2$ [congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack] score of 0), we suggest no therapy rather than antithrombotic therapy, and for patients choosing antithrombotic therapy, we suggest aspirin rather than oral anticoagulation or combination therapy with aspirin and clopidogrel; (2) at intermediate risk of stroke (eg, $CHADS_2$ score of 1), we recommend oral anticoagulation rather than no therapy, and we suggest oral anticoagulation rather than aspirin or combination therapy with aspirin and clopidogrel; and (3) at high risk of stroke (eg, $CHADS_2$ score of ≥ 2), we recommend oral anticoagulation rather than no therapy, aspirin, or combination therapy with aspirin and clopidogrel. Where we recommend or suggest in favor of oral anticoagulation, we suggest dabigatran 150 mg bid rather than adjusted-dose vitamin K antagonist therapy.**

Conclusions: **Oral anticoagulation is the optimal choice of antithrombotic therapy for patients with AF at high risk of stroke ($CHADS_2$ score of ≥ 2). At lower levels of stroke risk, antithrombotic treatment decisions will require a more individualized approach.**

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Abbreviations: AAD = antiarrythmic drug; ACS = acute coronary syndrome; ACTIVE = Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events; AF = atrial fibrillation; AFASAK = Atrial Fibrillation Aspirin and Anticoagulation; AFFIRM = Atrial Fibrillation Follow-up Investigation of Rhythm Management; $CHADS_2$ = congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack; CHA_2DS_2-VASc = congestive heart failure (or left ventricular systolic dysfunction), hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65 to 74 years, female sex; EAFT = European Atrial Fibrillation Trial; ESPS = European Stroke Prevention Study; INR = international normalized ratio; LAA = left atrial appendage; MI = myocardial infarction; PAF = paroxysmal atrial fibrillation; RCT = randomized controlled trial; RE-LY = Randomized Evaluation of Long-Term Anticoagulation Therapy; SPAF = Stroke Prevention in Atrial Fibrillation; TEE = transesophageal echocardiography; TIA = transient ischemic attack; VKA = vitamin K antagonist

Note on Shaded Text: Throughout this guideline, shading is used within the summary of recommendations sections to indicate recommendations that are newly added or have been changed since the publication of Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Recommendations that remain unchanged are not shaded.

2.1.8. For patients with AF, including those with paroxysmal AF, who are at low risk of stroke (eg, $CHADS_2$ [congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack] score = 0), we suggest no therapy rather than antithrombotic therapy (Grade 2B)**. For patients who do choose antithrombotic therapy, we suggest aspirin (75 mg to 325 mg once daily) rather than oral anticoagulation** (Grade 2B) **or combination therapy with aspirin and clopidogrel** (Grade 2B)**.**

Remarks: Patients who place an exceptionally high value on stroke reduction and a low value on avoiding bleeding and the burden associated with antithrombotic therapy are likely to choose antithrombotic therapy rather than no antithrombotic therapy. Other factors that may influence the choices above are a consideration of patient-specific bleeding risk and the presence of additional risk factors for stroke, including age 65 to 74 years and female gender, which have been more consistently validated, and vascular disease, which has been less well validated (see section 2.1.12). The presence of multiple non-$CHADS_2$ risk factors for stroke may favor oral anticoagulation therapy.

2.1.9. For patients with AF, including those with paroxysmal AF, who are at intermediate risk of stroke (eg, $CHADS_2$ score = 1), we recommend oral anticoagulation rather than no therapy (Grade 1B)**. We suggest oral anticoagulation rather than aspirin (75 mg to 325 mg once daily)** (Grade 2B) **or combination therapy with aspirin and clopidogrel** (Grade 2B)**. For patients who are unsuitable for or choose not to take an oral anticoagulant (for reasons other than concerns about major bleeding), we suggest combination therapy with aspirin and clopidogrel rather than aspirin (75 mg to 325 mg once daily)** (Grade 2B)**.**

Remarks: Patients who place an exceptionally high value on stroke reduction and a low value on avoiding bleeding and the burden associated with anticoagulant therapy are likely to choose oral anticoagulation rather than antiplatelet therapy. Other factors that may influence the choice among antithrombotic therapies are a consideration of bleeding risk and the presence of additional risk factors for stroke, including age 65 to 74 years and female gender, which have been more consistently validated, and vascular disease, which has been less well validated (see section 2.1.12). The presence of multiple additional non-$CHADS_2$ risk factors for stroke may favor oral anticoagulation therapy.

2.1.10. For patients with AF, including those with paroxysmal AF, who are at high risk of stroke (eg, $CHADS_2$ score = 2), we recommend oral anticoagulation rather than no therapy (Grade 1A)**, aspirin (75 mg to 325 mg once daily)** (Grade 1B)**, or combination therapy with aspirin and clopidogrel** (Grade 1B)**. For patients who are unsuitable for or choose not to take an oral anticoagulant (for reasons other than concerns**

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about major bleeding), we recommend combination therapy with aspirin and clopidogrel rather than aspirin (75 mg to 325 mg once daily) (Grade 1B)**.**

2.1.11. For patients with AF, including those with paroxysmal AF, for recommendations in favor of oral anticoagulation (including 2.1.9, 2.1.10, and excluding 2.2, 3.1, 3.2, 3.3), we suggest dabigatran 150 mg twice daily rather than adjusted-dose vitamin K antagonist (VKA) therapy (target INR range, 2.0-3.0) (Grade 2B)**.**

Remarks: Dabigatran is excreted primarily by the kidney. It has not been studied and is contraindicated in patients with severe renal impairment (estimated creatinine clearance of 30 mL/min or less). Clinicians should be aware that there is no antidote for dabigatran.

2.2. For patients with AF and mitral stenosis, we recommend adjusted-dose VKA therapy (target INR range, 2.0-3.0) rather than no therapy, aspirin (75 mg to 325 mg once daily), or combination therapy with aspirin and clopidogrel (all Grade 1B)**. For patients with AF and mitral stenosis who are unsuitable for or choose not to take adjusted-dose VKA therapy (for reasons other than concerns about major bleeding), we recommend combination therapy with aspirin and clopidogrel rather than aspirin (75 mg to 325 mg once daily) alone** (Grade 1B)**.**

3.1. For patients with AF and stable coronary artery disease (eg, no acute coronary syndrome within the previous year) and who choose oral anticoagulation, we suggest adjusted-dose VKA therapy alone (target international normalized ratio [INR] range, 2.0-3.0) rather than the combination of adjusted-dose VKA therapy and aspirin (Grade 2C)**.**

3.2. For patients with AF at high risk of stroke (eg, $CHADS_2$ score of 2 or greater) during the first month after placement of a bare-metal stent or the first 3 to 6 months after placement of a drug-eluting stent, we suggest triple therapy (eg, VKA therapy, aspirin, and clopidogrel) rather than dual antiplatelet therapy (eg, aspirin and clopidogrel) (Grade 2C)**. After this initial period of triple therapy, we suggest a VKA (INR 2.0-3.0) plus a single antiplatelet drug rather than VKA alone** (Grade 2C)**. At 12 months after intracoronary stent placement, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease (see section 3.1).**

For patients with AF at low to intermediate risk of stroke (eg, $CHADS_2$ score of 0 or 1) during the first 12 months after placement of an intracoronary stent (bare metal or drug eluting), we suggest dual antiplatelet therapy rather than triple therapy (Grade 2C)**. At 12 months after intracoronary stent placement, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease (see section 3.1).**

Remarks: Patients who place an exceptionally high value on stroke reduction and a low value on avoiding bleeding and the burden associated with anticoagulant therapy are likely to choose triple therapy rather than dual antiplatelet therapy. Other factors that may influence this choice are a consideration of bleeding risk and the presence of additional non-$CHADS_2$ risk factors for stroke (see section 2.1.12).

3.3. For patients with AF at intermediate to high risk of stroke (eg, $CHADS_2$ score of 1 or greater) who experience an acute coronary syndrome and do not undergo intracoronary stent placement, we suggest for the first 12 months, adjusted-dose VKA therapy (INR 2.0-3.0) plus single antiplatelet therapy rather than dual antiplatelet therapy (eg, aspirin and clopidogrel) or triple therapy (eg, warfarin, aspirin, and clopidogrel) (Grade 2C)**. After the first 12 months, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease (see section 3.1).**

For patients with AF at low risk of stroke (eg, $CHADS_2$ score of 0), we suggest dual antiplatelet therapy (eg, aspirin and clopidogrel) rather than adjusted-dose VKA therapy (INR 2.0-3.0) plus single antiplatelet therapy or triple therapy (eg, warfarin, aspirin, and clopidogrel) (Grade 2C)**. After the first 12 months, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease (see section 3.1).**

Remarks: Patients who place an exceptionally high value on stroke reduction and a low value on avoiding bleeding and the burden associated with anticoagulant therapy are likely to choose adjusted-dose VKA therapy plus single antiplatelet therapy rather than dual antiplatelet therapy. Other factors that may influence this choice are a consideration of bleeding risk and the presence of additional non-$CHADS_2$ risk factors for stroke (see section 2.1.12).

3.4. For patients with AF being managed with a rhythm control strategy (pharmacologic or

catheter ablation), we suggest that antithrombotic therapy decisions follow the general risk-based recommendations for patients with AF in section 2.1, regardless of the apparent persistence of normal sinus rhythm (Grade 2C)**.**

3.5. For patients with atrial flutter, we suggest that antithrombotic therapy decisions follow the same risk-based recommendations as for AF.

4.1.1. For patients with AF of greater than 48 h or unknown duration undergoing elective electrical or pharmacologic cardioversion, we recommend therapeutic anticoagulation (adjusted-dose VKA therapy, target INR range 2.0-3.0, low-molecular-weight heparin at full venous thromboembolism treatment doses, or dabigatran) for at least 3 weeks before cardioversion or a transesophageal echocardiography (TEE)-guided approach with abbreviated anticoagulation before cardioversion rather than no anticoagulation (Grade 1B)**. We recommend therapeutic anticoagulation for at least 4 weeks after successful cardioversion to sinus rhythm rather than no anticoagulation, regardless of the baseline risk of stroke** (Grade 1B)**. Decisions about anticoagulation beyond 4 weeks should be made in accordance with our risk-based recommendations for long-term antithrombotic therapy in section 2.1.**

4.1.2. For patients with AF of documented duration of 48 h or less undergoing elective cardioversion (electrical or pharmacologic), we suggest starting anticoagulation at presentation (low-molecular-weight heparin or unfractionated heparin at full venous thromboembolism treatment doses) and proceeding to cardioversion rather than delaying cardioversion for 3 weeks of therapeutic anticoagulation or a TEE-guided approach (Grade 2C)**. After successful cardioversion to sinus rhythm, we recommend therapeutic anticoagulation for at least 4 weeks rather than no anticoagulation, regardless of baseline stroke risk** (Grade 2C)**. Decisions about long-term anticoagulation after cardioversion should be made in accordance with our risk-based recommendations for long-term antithrombotic therapy in section 2.1.**

4.2. For patients with AF and hemodynamic instability undergoing urgent cardioversion (electrical or pharmacologic), we suggest that therapeutic-dose parenteral anticoagulation be started before cardioversion, if possible (Grade 2C)**, but that initiation of anticoagulation must not delay any emergency intervention** (Grade 2C)**. After successful cardioversion to sinus rhythm, we suggest therapeutic anticoagulation for at least 4 weeks after successful cardioversion to sinus rhythm rather than no anticoagulation, regardless of baseline stroke risk** (Grade 2C)**. Decisions about anticoagulation beyond 4 weeks should be made in accordance with our risk-based recommendations for long-term antithrombotic therapy in section 2.1.**

4.3. For patients with atrial flutter undergoing elective or urgent pharmacologic or electrical cardioversion, we suggest that the same approach to thromboprophylaxis be used as for patients with atrial fibrillation undergoing cardioversion.

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. One in four individuals aged 40 years will develop AF during his or her lifetime, and it has been estimated that by the year 2050, up to 16 million Americans will have AF.[1,2] Nonrheumatic AF is a strong, independent predictor of ischemic stroke associated with a fivefold increase in risk.[3] Without thromboprophylaxis, the risk of ischemic stroke in patients with nonrheumatic AF, as seen in the control arms of the original trials of antithrombotic therapy in AF, is ~5% per year.[4] Over the past 2 decades, considerable work has been done to evaluate antithrombotic therapies to prevent stroke in patients with AF, and the field continues to evolve with the emergence of a new generation of oral anticoagulants.

This article begins with a discussion of the methods used to develop our recommendations for antithrombotic therapy in patients with AF. Next, we provide our treatment recommendations, divided into the following sections:

1. Antithrombotic therapy in patients with AF in general (includes patients with permanent, persistent, or paroxysmal AF [PAF])
2. Antithrombotic therapy in patients with AF in special situations:
   - Stable coronary artery disease
   - Acute coronary syndrome (ACS)
   - Intracoronary artery stent
   - Acute ischemic stroke
   - Management with a rhythm control strategy
   - Chronic atrial flutter
3. Antithrombotic therapy for patients with AF undergoing cardioversion

The article ends with a discussion of practical issues in the use of adjusted-dose vitamin K antagonist (VKA) therapy in patients with AF and suggestions for future research.

Table 1 specifies the clinical question being addressed in this article (in PICO [population, intervention, comparator, outcomes] format) and the types of studies used. This article does not give recommendations for antithrombotic therapy in patients with AF around the time of surgical or invasive procedures (see Douketis et al[5]), at the time of presentation with acute stroke (see Lansberg et al[6]), or in patients with AF who have prosthetic heart valves (see Whitlock et al[7]). This article does not give recommendations for patients with AF who are pregnant. For general recommendations on antithrombotic therapy during pregnancy (ie, not specific to AF), see Bates et al.[8] Finally, the recommendations in this article apply to patients with persistent and permanent AF and to patients with PAF but do not apply to patients with a single, transient, self-limited episode of AF associated with acute illness.

1.0 Methods

To inform our guideline development, we searched for relevant articles published since the last literature search performed for the Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Specifically, for literature regarding the assessment of stroke risk in patients with AF, we searched Medline for articles published from January 1, 2005, to October 2009 using the search terms "atrial fibrillation," "atrial flutter," "risk assessment," "risk factors," "risk stratification," "stroke," and "thromboembolism." For literature regarding prevention of stroke and thromboembolism in patients with AF, we searched Medline for articles published from January 1, 2005, to October 2009 using the search terms "coumarins," "warfarin," "dicumarol," "phenprocoumon," "acenocoumarol," "fondaparinux," "idraparinux," "aspirin," "triflusal," "indobufen," "dabigatran," "ximelagatran," "rivaroxaban," "apixaban," "ticlopidine," "clopidogrel," "catheter ablation," "watchman," "PLAATO," "cardioversion," "atrial fibrillation," and "atrial flutter."

1.1 Outcomes of Interest

The outcomes most relevant to patients with AF include death, nonfatal stroke, systemic embolism, nonfatal major extracranial bleeding, and the burden and lifestyle limitations associated with outpatient antithrombotic therapy. To facilitate decision-making, the term stroke in this article includes ischemic stroke and intracranial hemorrhage (intracerebral, subdural, and subarachnoid hemorrhage). Although there may be some differences in the impact of these intracranial events (eg, subdural hemorrhage) on quality of life, we judged that on average, the impact would be similar. We also explicitly considered that outpatient antithrombotic therapy was associated with a burden to the patient, which in some cases, such as aspirin, is a requirement to take a daily medication, or in other cases, such as adjusted-dose VKA therapy, is not only a requirement to take a daily medication but also a requirement to limit one's lifestyle, restrict one's diet, and undergo frequent blood testing and clinic visits. For recommendations about patients with AF and stable coronary artery disease, intracoronary stent placement, or recent ACS (sections 3.1-3.3), we also considered the effect of different treatment options on the outcome of nonfatal myocardial infarction (MI).

1.2 Patient Values and Preferences

In developing our treatment recommendations, we attempted to account for patient values and preferences regarding these health states. In this guideline, a systematic review of studies assessing values and preferences related to antithrombotic therapy found that values for health states and preferences for treatments vary appreciably among individuals (MacLean et al[9]). The available literature has several limitations. The studies eliciting preferences were small and used different methods and tools, and most included a sizeable proportion of participants who had previously taken or were currently taking VKAs. Furthermore, there are inconsistencies across studies that often are difficult to explain, leaving considerable uncertainty about average patient values. Nevertheless, to make our recommendations, we required an estimate of average patient values for the relevant outcomes so that we could judge whether the trade-offs between benefit and harm would favor one course of treatment over another.

As described by Guyatt et al[10] in this guideline, to obtain our estimates of average patient values, we have used ratings of key health states from participating guideline panelists informed by our systematic review of the relevant literature. The results of the panelist value rating exercise suggest that on average, patients would find a typical nonfatal stroke (ischemic or hemorrhagic) approximately three times as aversive as a nonfatal major extracranial bleed (typically a GI bleed) and a typical nonfatal MI as aversive as a nonfatal major extracranial bleed.

With the exception of the choice between VKA therapy and no therapy, the choice of one antithrombotic treatment over another for long-term stroke prevention in AF will not lead to differences in all-cause mortality (section 2). Thus, for these choices that are not expected to result in a difference in mortality, for every 1,000 patients treated for 1 year, if the number of nonfatal strokes prevented is less than one-third of the number of nonfatal major extracranial bleeds caused by a given antithrombotic therapy, we have recommended against that intervention. If the number of nonfatal strokes prevented is appreciably more than one-third of the number of nonfatal major extracranial bleeding events that result from a given antithrombotic therapy, we have recommended in favor.

Making these trade-offs requires not only estimates regarding average patient values for the relevant outcomes but also best estimates of (1) the effect of a given treatment on these outcomes against a given comparator (ie, relative risk) and (2) the absolute event rates for these outcomes in untreated patients (or, for PICO questions of a treatment vs an active comparator, the absolute event rates in patients receiving the active comparator). In the following section, we present the methods used to obtain these estimates for our guidelines.

1.3 Estimating the Magnitude of Treatment Effect

For each clinical question, we extracted data regarding the previously discussed outcomes from the relevant clinical trials. When there were multiple randomized controlled trials (RCTs) addressing the same clinical question, we conducted meta-analyses using random-effects models and the Mantel-Haenszel method to obtain pooled estimates of treatment effect, expressed as relative risk. For studies that did not report the proportion of strokes that were fatal and nonfatal, we used all available data in the published report to obtain a best estimate of the effect of

Table 1—*[Introduction] Clinical Questions Addressed in This Article*

Section	Population	Intervention	Comparator	Outcomes of Interest	Available Methodology
		2. Patients with AF in general			
2.1.1	Patients with nonrheumatic AF	Adjusted-dose VKA	No therapy	Death	RCTs
2.1.2		Antiplatelet monotherapy (eg, aspirin)	No therapy	Nonfatal strokes Nonfatal major extracranial bleeds	
2.1.3		VKA	Antiplatelet monotherapy (eg, aspirin)	Systemic embolism Procedural complications (for percutaneous closure of left atrial appendage only)	
2.1.4		VKA	Aspirin + clopidogrel		
2.1.5		Aspirin + clopidogrel	Aspirin		
2.1.6		New oral anticoagulants	VKA		
2.1.11		Dabigatran	VKA		
2.1.13		Percutaneous closure of left atrial appendage	VKA		RCTs Cohort studies
2.2	Patients with AF and mitral stenosis	VKA	No therapy, antiplatelet monotherapy (eg, aspirin), or aspirin + clopidogrel		Cohort studies
		3. Management of antithrombotic therapy for patients with AF in special situations			
3.1	Patients with AF and stable coronary artery disease	VKA + aspirin	VKA	Death Nonfatal strokes	Cohort studies
3.2	Patients with AF and placement of an intracoronary stent (with or without recent ACS)	VKA + aspirin + clopidogrel	Aspirin + clopidogrel	Nonfatal MI Nonfatal major extracranial bleeds Systemic embolism	
3.3	Patients with AF and ACS who do not undergo intracoronary stent placement	VKA + aspirin	Aspirin + clopidogrel VKA + aspirin + clopidogrel		
3.4	Patients with AF being managed with a rhythm control strategy	VKA	No VKA	Death Nonfatal strokes	
3.5	Patients with chronic atrial flutter	Antithrombotic therapy options as per section 2.1		Nonfatal major extracranial bleeds Systemic embolism	
		4. Patients with AF undergoing cardioversion			
4.1.1	Patients with AF of > 48 h or unknown duration undergoing elective cardioversion	Minimum 3 wk anticoagulation before and 4 wk after cardioversion	No anticoagulation	Death Nonfatal strokes Nonfatal major extracranial bleeds	Cohort studies
		Abbreviated precardioversion anticoagulation + TEE-guided cardioversion	No anticoagulation	Systemic embolism	RCTs Cohort studies
4.1.2	Patients with AF of ≤ 48 h duration undergoing elective cardioversion	Anticoagulation before cardioversion	No anticoagulation before cardioversion		Cohort studies
4.2	Patients undergoing urgent cardioversion for hemodynamically unstable AF	Anticoagulation before cardioversion	No anticoagulation before cardioversion		Cohort studies
4.3	Patients undergoing elective or urgent cardioversion for atrial flutter	Anticoagulation before and after cardioversion	No anticoagulation		Cohort studies

ACS = acute coronary syndrome; AF = atrial fibrillation; MI = myocardial infarction; RCT = randomized controlled trial; TEE = transesophageal echocardiography; VKA = vitamin K antagonist.

treatment on nonfatal stroke by assuming a case fatality rate of 50% for hemorrhagic stroke and 25% for ischemic stroke based on population-based stroke registry data and the case fatality rates observed in the RCTs of patients with AF that reported such data.[11] For nonfatal major extracranial bleeding, we accepted the definition of major bleeding from the individual studies, and when the proportion of major extracranial bleeds that were fatal vs nonfatal was not reported, we applied the average case fatality rate for major extracranial bleeding reported across the relevant clinical trials (~15%). For the outcome of systemic embolism, we used the total number of events (fatal and nonfatal) because systemic embolism was an infrequent event and typically not reported as fatal vs nonfatal.

1.4 Deriving Baseline Risk of Stroke in Patients With AF

The risk of stroke varies considerably across different groups of patients with AF.[12] Simple validated tools for the assessment of stroke risk in patients with AF help in identifying those who are more likely to benefit than be harmed from antithrombotic therapy.

1.4.1 Pattern of AF: Guidelines have categorized the pattern of AF into (1) PAF, in which recurrent episodes terminate spontaneously within 7 days and usually in < 48 h; (2) persistent AF, in which the episode of AF does not self-terminate within 7 days or is terminated by cardioversion; and (3) permanent AF, in which AF is present for some time and cardioversion either has failed or has not been attempted.[13]

For patients with PAF, periods of sinus rhythm theoretically should lessen the risk of stroke, yet transitions from AF to sinus rhythm may acutely heighten risk in a manner similar to the increase in risk caused by cardioversion. Although some studies suggest that PAF is associated with a lower risk of stroke than persistent or permanent AF, patients with PAF generally are younger and have a lower prevalence of other stroke risk factors, and clinical trial data suggest that PAF confers a relative risk of stroke similar to persistent or permanent AF when controlling for associated stroke risk factors.[14-17] Pending further evidence, it seems reasonable to treat patients with PAF in a manner similar to those with persistent and permanent AF; thus, our risk-based treatment recommendations apply to patients with PAF and persistent and permanent AF.

1.4.2 Independent Risk Factors for Stroke in Patients With AF: Two recent systematic reviews have identified clinical and echocardiographic factors that are independently associated with an increased risk of stroke in patients with AF.[18,19] The individual studies from these systematic reviews, in addition to articles identified in an updated literature search performed for this guideline, are summarized in Tables S1 through S12 (tables that contain an "S" before the number denote supplementary tables not contained in the body of the article and available instead in an online data supplement; see the "Acknowledgments" for more information). In terms of clinical applicability, the most consistently identified risk factors for ischemic stroke among patients with AF are a history of ischemic stroke or transient ischemic attack (TIA)—the strongest dichotomous predictor of stroke risk—older age, hypertension, and diabetes. Although impaired left ventricular systolic function is a risk factor for stroke in AF, there are conflicting data about whether a history of congestive heart failure per se raises the risk of ischemic stroke in AF. Although age thresholds often are used in stroke risk schemes, stroke risk in AF increases continuously with age, appreciably rising from age 65 years onward.[20] There is moderate-quality evidence that women face a higher risk of stroke than men.[18] A history of coronary artery disease has not consistently been found to be an independent risk factor for stroke in patients with AF.[18] However, there is low-quality evidence that the presence of atherosclerotic vascular disease (eg, complex aortic plaque in the descending aorta seen on transesophageal echocardiography [TEE] or a history of peripheral arterial disease) independently predicts stroke risk among patients with AF.[21-23]

1.4.3 Stroke Risk Stratification Schema: Many risk stratification schema, which use various combinations of the risk factors discussed previously, have been developed to aid clinicians in the assessment of stroke risk in patients with nonrheumatic AF (Table S13).[12] Despite substantial efforts in this field over the past several decades, all available schema have only modest ability to predict stroke in patients with AF, with C statistics typically between 0.55 and 0.70.[4,24-43] (A C statistic of 0.50 indicates a model that does not discriminate better than chance alone, and a C statistic of 1.00 indicates perfect discrimination.)

The $CHADS_2$ score is the most validated risk scheme, having been independently tested in at least 10 separate cohorts after its original derivation.[24,32,35-46] The $CHADS_2$ score gives a single point for each of congestive heart failure (originally defined as a recent exacerbation of congestive heart failure), hypertension (defined as a history of hypertension, rather than a presence of elevated BP), age ≥ 75 years, and diabetes mellitus and two points for prior stroke or TIA (Table 2).[30]

Despite its widespread adoption and ease of use, the $CHADS_2$ score has limitations. First, congestive heart failure is not a consistently demonstrated independent predictor of stroke. Second, the risk associated with a history of hypertension may differ among patients with well-treated vs poorly treated hypertension.[46-48] Third, in most studies, the $CHADS_2$ score has only a modest ability to predict stroke in patients with AF (C statistic, 0.56-0.70).[24,32,35-46] Finally, the threshold of stroke risk at which treatment with oral anticoagulation will be preferred is likely to decrease with the emergence of new oral anticoagulants that do not require regular monitoring of the international normalized ratio (INR) and that may be associated with greater reductions in stroke and less risk of bleeding compared with adjusted-dose VKA therapy.[49] Thus, stroke risk stratification schema will need to evolve to more accurately identify patients who are at sufficiently low risk of stroke and can be treated with aspirin or no antithrombotic therapy, whereas all other patients with AF can be considered for oral anticoagulation.

The CHA_2DS_2-VASc (congestive heart failure [or left ventricular systolic dysfunction], hypertension, age < 75 years; diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65 to 74 years, female sex) score is a new risk scheme that combines the $CHADS_2$ score with additional moderate risk factors, which were also included in the 2006 American College of Cardiology/American Heart Association/European Society of Cardiology and National Institute for Health and Clinical Excellence AF practice guidelines.[29,50] Specifically, the CHA_2DS_2-VASc score assigns points as in the original $CHADS_2$ score (Table 2) with the exception of age ≥ 75 years, which is assigned two points. It also assigns a single point for each of the following additional

Table 2—*[Section 1.4.3] $CHADS_2$ Score[30] for Assessment of Stroke Risk in Patients With Nonrheumatic AF*

Risk Factor	Points
Recent **C**ongestive heart failure exacerbation	1
History of **H**ypertension	1
Age ≥ 75 y	1
Diabetes mellitus	1
Prior history of **S**troke or transient ischemic attack	2

$CHADS_2$ = congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack. See Table 1 legend for expansion of other abbreviation.

risk factors: female sex, age 65 to 74 years, and vascular disease (defined as a history of MI, peripheral arterial disease, or complex aortic plaque). The CHA_2DS_2-VASc score has been evaluated in at least five separate cohorts since its original description. With the exception of a recent study by Olesen et al,[24] all other studies have found that the predictive ability of CHA_2DS_2-VASc is similar to that of the $CHADS_2$ score (C statistics of each risk score is ~0.6 across the various studies) and not statistically significantly greater than that of $CHADS_2$.[36,40-43] Because the $CHADS_2$ score has been extensively validated and is easy for clinicians to remember and use, we use the $CHADS_2$ score as the principal approach for our risk-based treatment recommendations.

1.4.4 Estimating the Baseline Risk of Nonfatal Stroke by $CHADS_2$ Score: To develop our recommendations, we required estimates of the absolute rate of nonfatal stroke (ischemic or hemorrhagic) for patients according to their underlying risk of stroke, as characterized by their $CHADS_2$ score. Ideally, we would obtain these estimates of baseline risk from published annual rates of stroke, by $CHADS_2$ score, among untreated patients. However, such data are not available.

Therefore, to obtain estimates of annual stroke risk, we used pooled data from aspirin-treated patients enrolled in six clinical trials of antithrombotic therapy for stroke prevention in AF.[37] This published report presented data regarding ischemic stroke rates (fatal and nonfatal combined) on aspirin, stratified by $CHADS_2$ score. We used the following calculations to estimate the annual risk of nonfatal stroke (ie, ischemic and hemorrhagic) on aspirin: (1) multiplication of reported rates of ischemic stroke by 1.08 to account for additional hemorrhagic strokes on aspirin therapy (based on the observed ratio of ischemic:hemorrhagic strokes in aspirin arms of RCTs in patients with AF) and (2) an estimation that 50% and 25% of hemorrhagic and ischemic strokes, respectively, were fatal.

Depending on the clinical question being addressed by a particular recommendation, we adjusted these absolute rates of nonfatal stroke on aspirin to reflect the clinical scenario being addressed. For the recommendation addressing VKA therapy vs no treatment, for example, to estimate absolute rates of nonfatal stroke on no treatment, we increased our estimates of the rate of nonfatal stroke on aspirin by 21% to account for the estimated efficacy of aspirin in preventing stroke in AF). We therefore used the following absolute rates of nonfatal stroke in untreated patients to develop our recommendations: 0.8%, 2.2%, 4.5%, and 9.6% per year for patients with $CHADS_2$ scores of 0, 1, 2, and 3 to 6, respectively.

We have chosen to base our treatment recommendations on absolute rates of stroke derived from clinical trials, recognizing that these data have important limitations. Less than 10% of patients screened were enrolled in these historical trials, there was limited racial and ethnic diversity, and there is some evidence suggesting that stroke rates may now be lower than at the time these RCTs were conducted 2 decades ago possibly because of improved treatment of cardiovascular risk factors, such as hypertension.[51,52] However, despite these limitations, these clinical trial-based data regarding stroke events were systematically and prospectively collected, and they remain the best available source of stroke rates stratified by $CHADS_2$ score.

1.5 Deriving Baseline Risk of Death in Patients With AF

We used data from an observational health plan database study of 11,526 patients with nonvalvular AF (the Anticoagulation and Risk Factors in Atrial Fibrillation [ATRIA] Study) to obtain an estimate of the risk of all-cause mortality in patients with AF not treated with warfarin (53 deaths per 1,000 patient-years). Untreated patients in this cohort had a mean $CHADS_2$ score of 1.5, and a substantial majority (78%) of patients in the cohort had a $CHADS_2$ score of ≥ 1.[44] Although $CHADS_2$-specific rates of all-cause mortality are not available from this cohort, the risk of death is expected to be lower in low-risk patients with a $CHADS_2$ score of 0 because of their younger age, lower prevalence of vascular risk factors, and lower rates of fatal ischemic stroke.

1.6 Deriving Baseline Risk of Nonfatal Major Extracranial Bleeding

To develop our recommendations, we also required estimates of the baseline risk of nonfatal major extracranial bleeding in patients with AF. We obtained this estimate from observational studies of VKA therapy in cohorts that included exclusively or predominantly patients with AF (median rate of 1.3% per year across these studies).[44,53,54] To estimate the baseline risk of nonfatal major extracranial bleeding off VKA therapy, we used this median rate of bleeding on VKA therapy from the observational studies (1.3% per year) and divided by the pooled relative risk (2.58) of nonfatal major extracranial bleeding associated with VKA therapy, as obtained from RCTs of VKA therapy vs no therapy. Therefore, our estimate of the baseline risk of nonfatal major extracranial bleeding off therapy was 0.5% per year.

2.0 Antithrombotic Therapy for Patients With AF in General

Over the past 2 decades, numerous RCTs have investigated antithrombotic therapies to reduce the risk of thromboembolism, principally ischemic stroke, in patients with AF. In this section, we summarize the evidence and give treatment recommendations for VKA therapy, antiplatelet monotherapy (eg, aspirin), dual antiplatelet therapy with aspirin and clopidogrel, and new oral anticoagulants (eg, dabigatran) in patients with AF.

2.1 Patients With Nonrheumatic AF

2.1.1 VKAs vs No Therapy: Six RCTs that enrolled a total of 2,584 patients and address the primary prevention (Atrial Fibrillation Aspirin and Anticoagulation [AFASAK] 1, Boston Area Anticoagulation Trial for Atrial Fibrillation [BAATAF], Canadian Atrial Fibrillation Anticoagulation [CAFA], Stroke Prevention in Atrial Fibrillation [SPAF] I, Stroke Prevention in Nonrheumatic Atrial Fibrillation [SPINAF]) and secondary prevention (European Atrial Fibrillation Trial [EAFT]) of stroke in patients with AF provide high-quality evidence that VKA therapy reduces the risk of death by one-fourth and the risk of nonfatal stroke by two-thirds compared with no therapy (Table 3).[55-61] For patients with a $CHADS_2$ score of 0, the studies provide moderate-quality evidence that VKA therapy increases the risk of nonfatal major extracranial bleeding due to imprecision of the estimate (wide CIs). The studies provide high-quality evidence for patients with higher $CHADS_2$ scores.

Table 3—*[Sections 2.1.1, 2.1.8, 2.1.9, 2.1.10] Should VKAs Rather Than No Therapy Be Used in Patients With AF?*[a]

Quality Assessment								Summary of Findings			
						Study Event Rates (%)			Estimation of Absolute Effects 1 y Time Frame		
No. of Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	With No Therapy	With VKA	Relative Effect (95% CI)	With No Therapy	With VKA (95% CI)	Quality of Evidence
Death (critical outcome) mean follow-up 1.7 y											
6 RCTs	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	136/1,425 (9.5)	103/1,429 (7.2)	RR 0.72 (0.55-0.94)	53 per 1,000[b]	15 fewer deaths per 1,000[c] (from 3 fewer to 24 fewer)	High
Nonfatal stroke (critical outcome) mean follow-up 1.7 y; ischemic stroke and intracranial hemorrhage[d]											
6 RCTs	No serious limitations	No serious inconsistency	No serious Indirectness	No serious imprecision	Undetected	108/1,425[e] (7.6)	36/ 1,429[f] (2.5)	RR 0.34 (0.23-0.49)	$CHADS_2$ 0 points		High
									8 per 1,000[g]	5 fewer strokes per 1,000 (from 4 fewer to 6 fewer)	
									$CHADS_2$ 1 point		
									22 per 1,000	15 fewer strokes per 1,000 (from 11 fewer to 17 fewer)	
									$CHADS_2$ 2 points		
									45 per 1,000	30 fewer strokes per 1,000 (from 23 fewer to 35 fewer)	
									$CHADS_2$ 3-6 points		
									96 per 1,000	63 fewer strokes per 1,000 (from 49 fewer to 74 fewer)	
Nonfatal major extracranial bleeds (important outcome) mean follow-up 1.7 y											
6 RCTs	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	7/1,425 (0.5)	23/1,429 (1.6)	RR 2.58 (1.12-5.97)	5 per 1,000[h]	8 more bleeds per 1,000 (from 1 more to 25 more)	High[i]
Systemic embolism (important outcome) mean follow-up 1.7 y											
6 RCTs	No serious limitations	No serious inconsistency	No serious Indirectness	Imprecise[j]	Undetected	10/1,425 (0.7)	4/1,429 (0.3)	RR 0.42 (0.15-1.20)	4 per 1,000[k]	2 fewer systemic emboli per 1,000 (from 3 fewer to 1 more)	Moderate

(Continued)

Table 3—*Continued*

Quality Assessment								Summary of Findings			
						Study Event Rates (%)			Estimation of Absolute Effects 1 y Time Frame		
No. of Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	With No Therapy	With VKA	Relative Effect (95% CI)	With No Therapy	With VKA (95% CI)	Quality of Evidence
Burden of treatment (important outcome)											
N/A	No serious limitations	No serious limitations	No serious limitations	No serious limitations	N/A	N/A	N/A	VKA > no therapy	Warfarin: daily medication, lifestyle limitations, dietary restrictions, frequent blood testing and clinic visits		High

AFASAK = Atrial Fibrillation Aspirin and Anticoagulation; ATRIA = Anticoagulation and Risk Factors in Atrial Fibrillation; BAATAF = Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA = Canadian Atrial Fibrillation Anticoagulation; EAFT = European Atrial Fibrillation Trial; IPD = individual patient data; N/A = not applicable; RR = risk ratio; SPAF = Stroke Prevention in Atrial Fibrillation; SPINAF = Stroke Prevention in Nonrheumatic Atrial Fibrillation. See Table 1 and 2 legends for expansion of other abbreviations.

[a]Pooled estimates of treatment effect in this evidence profile are from a meta-analysis conducted for these guidelines, including data from 6 RCTs of adjusted-dose VKA therapy vs no antithrombotic therapy (AFASAK I, BAATAF, CAFA, EAFT, SPAF I, SPINAF).

[b]From Go et al,[44] which reported a mortality rate of 5.33 per 100 person-y in untreated (no warfarin) patients from an observational study (ATRIA cohort). The majority (78%) of the patients in ATRIA had a $CHADS_2$ score of ≥ 1.

[c]VKA therapy likely does not lead to any reductions in all-cause mortality compared with no therapy in low-risk patients with a $CHADS_2$ score of 0 because there is evidence suggesting that absolute reductions in ischemic stroke heavily depend on stroke risk (eg, small reductions at low $CHADS_2$ score), whereas the absolute increase in intracranial hemorrhage is relatively consistent across $CHADS_2$ categories (Singer et al[51]).

[d]Intracranial hemorrhage includes intracerebral, subdural, and subarachnoid bleeds. For studies that did not report the number of strokes that were fatal and nonfatal (CAFA, EAFT), we imputed values for the number of fatal and nonfatal strokes to estimate the pooled relative risk for nonfatal stroke across all eligible studies. Assumptions underlying these estimates are detailed in the section 1.3 of this article.

[e]Of the 108 nonfatal strokes on no therapy, an estimated 106 (98%) were ischemic, and two (2%) were hemorrhagic.

[f]Of the 36 nonfatal strokes on VKA therapy, an estimated 34 (94%) were ischemic, and two (6%) were hemorrhagic.

[g]We estimated the annual rates of nonfatal stroke (ischemic and hemorrhagic) on no therapy by extrapolating from observed annual rates of ischemic stroke (fatal + nonfatal), stratified by $CHADS_2$ score, in the aspirin arms of six historical RCTs in patients with AF (Gage et al[37]). Assumptions underlying these estimates are detailed in the section 1.4.4 of this article.

[h]Estimate of the rate of nonfatal major extracranial bleeding on no therapy is derived from rates in observational cohorts of predominantly patients with AF receiving adjusted-dose VKA therapy (median, 1.3%/y) and dividing by the relative risk of major bleeding on adjusted-dose VKA therapy observed in the RCTs (see section 1.6 of this article).

[i]Quality of evidence is moderate for patients with a $CHADS_2$ score of 0 because the recommendation would differ if the true increase in nonfatal major extracranial bleeding was one vs 25 bleeds per 1,000 patients in a given year.

[j]The 95% CI does not exclude the possibility of no effect.

[k]Based on rate of systemic embolism on aspirin of 0.3 per 100 patient-y reported in the IPD meta-analysis of warfarin vs aspirin by van Walraven et al[61] and a relative risk of 0.80 for aspirin vs no therapy for systemic embolism.

The studies also provide moderate-quality evidence that VKA therapy reduces the risk of systemic embolism (rated down for imprecision).

2.1.2 Antiplatelet Monotherapy (Aspirin) vs No Therapy: Several RCTs of antiplatelet monotherapy vs no therapy in patients with AF have shown that antiplatelet therapy leads to, at best, a modest reduction in the risk of nonfatal stroke. Antiplatelet monotherapy in these trials was either with aspirin alone (AFASAK 1; SPAF I; EAFT; United Kingdom Transient Ischaemic Attack Aspirin trial [UK-TIA]; Low-Dose Aspirin, Stroke, Atrial Fibrillation [LASAF]; European Stroke Prevention Study [ESPS]-2; and Japan Atrial Fibrillation Stroke Trial [JAST]), aspirin in combination with fixed (ineffective) minidose warfarin (Swedish Atrial Fibrillation Trial [SAFT]), or dipyridamole (ESPS-2).[55,58,60,62-66] Aspirin dosing in these trials typically ranged from 50 to 325 mg/d. In the LASAF, JAST, and SAFT trials, aspirin was compared with a no-treatment control arm, whereas in the remaining trials, comparison was to placebo.[63,64,66] ESPS-2 and UK-TIA were stroke prevention trials conducted primarily in non-AF populations, and only the data from the subset of patients with AF are considered here.[62,65]

Pooled data from these trials provide moderate-quality evidence (rated down for imprecision) that antiplatelet monotherapy is associated with a 21% relative reduction in risk of nonfatal stroke compared with no treatment (Table 4). Although our confidence in the benefits of aspirin therapy is moderate, our confidence in its bleeding risk is high. Although the trials of antiplatelet monotherapy in patients with AF were underpowered to precisely estimate the risk of nonfatal major extracranial bleeding, trials of aspirin for the primary and secondary prevention of cardiovascular disease have conclusively demonstrated that aspirin is associated with an increased risk of major hemorrhage. An individual patient data meta-analysis combining data from six cardiovascular primary prevention trials (95,000 subjects) and a meta-analysis of 60 cardiovascular secondary prevention trials (94,000 subjects) found that aspirin is associated with a significant 50% to 60% relative increase, respectively, in the risk of major extracranial bleeding.[67,68] For the outcomes of death and systemic embolism, pooled estimates of treatment effect from trials of antiplatelet monotherapy in patients with AF were imprecise, leaving uncertainty about the impact of antiplatelet monotherapy on these outcomes when compared with no treatment (Table 4).

2.1.3 VKAs vs Antiplatelet Monotherapy (Aspirin): The evidence summarized in sections 2.1.1 and 2.1.2 implies that adjusted-dose warfarin is far superior to aspirin for the prevention of stroke in patients with AF but is likely to be associated with a greater risk of bleeding complications. Direct evidence regarding this clinical question comes from 11 RCTs (total of 6,526 patients) comparing adjusted-dose VKA therapy to antiplatelet monotherapy (AFASAK 1, AFASAK 2, Birmingham Atrial Fibrillation Treatment of the Aged [BAFTA], EAFT, National Study for Prevention of Embolism in Atrial Fibrillation [NASPEAF], Primary Prevention of Arterial Thromboembolism in Nonrheumatic AF in Primary Care Trial [PATAF], Studio Italiano Fibrillazione Atriale [SIFA], SPAF II, SPAF III, Vemmos et al,[69] and Warfarin vs Aspirin for Stroke Prevention in Octogenarians With AF [WASPO]) (Table 5).[55,60,70-77] Antiplatelet therapy was typically with aspirin 75 to 325 mg/d, but in the SIFA and NASPEAF studies, it was with indobufen and triflusal, respectively.[72,74] In SPAF III and one of the two antiplatelet arms of AFASAK II, aspirin was given in combination with fixed minidose (ineffective) warfarin.[70,76]

These trials provide high-quality evidence that adjusted-dose VKA therapy reduces by one-half the risk of nonfatal stroke compared with antiplatelet monotherapy. These trials suggest that VKA therapy increases the risk of nonfatal major extracranial bleeding by about 50% compared with aspirin (pooled risk ratio, 1.42; 95% CI, 0.89-2.29), but the quality of evidence was rated down to moderate because of imprecision. Indirect evidence from RCTs of adjusted-dose VKA therapy vs aspirin in other populations suggest that VKA therapy is likely associated with a true twofold to 2.5-fold increase in major bleeding risk.[78,79] For the outcomes of death and systemic embolism, pooled estimates of treatment effect from trials of VKA therapy in patients with AF were imprecise, leaving uncertainty about the impact of VKA therapy on these outcomes compared with antiplatelet monotherapy.

2.1.4 VKAs vs Dual Antiplatelet Therapy With Aspirin and Clopidogrel: The Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE) W trial assessed dual antiplatelet therapy with aspirin and clopidogrel as a potential alternative to VKA therapy (INR 2.0-3.0).[80] The trial was stopped early because of findings of superiority of VKA therapy (for their primary outcome of stroke, systemic embolism, MI, or vascular death) and did not find evidence of a difference in the risk of major bleeding (Table 6). Most patients (77%) were receiving VKA therapy before randomization, raising some concerns about generalizability of these findings to patients with AF who are being newly started on VKA therapy (ie, by enrolling mostly

Table 4—*[Section 2.1.2, 2.1.8] Should Antiplatelet (Aspirin) Monotherapy Rather Than No Therapy Be Used in Patients With AF?*[a,b]

Quality Assessment								Summary of Findings			
						Study Event Rates (%)			Estimation of Absolute Effects 1 y Time Frame		
No. of Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	With No Therapy	With Antiplatelet	Relative Effect (95% CI)	With No Therapy	With Antiplatelet (95% CI)	Quality of Evidence
Death (critical outcome) mean follow-up 2.1 y											
6 RCTs	No serious limitations	No serious inconsistency	No serious indirectness	Imprecise[c]	Undetected	231/2,152 (10.7)	215/2,246 (9.6)	RR 0.89 (0.75-1.05)	53 per 1,000[d]	6 fewer deaths per 1,000 (from 13 fewer to 3 more)	Moderate
Nonfatal stroke (critical outcome) mean follow-up 2.1 y; ischemic stroke and intracranial hemorrhage[e]											
8 RCTs	No serious limitations	No serious inconsistency	No serious indirectness	Imprecise[f]	Undetected	197/2,274[g] (8.7)	174/2,498[h] (7.0)	RR 0.79 (0.65-0.96)	$CHADS_2$ 0 points		Moderate
									8 per 1,000[i]	2 fewer strokes per 1,000 (from 0 fewer to 3 fewer)	
									$CHADS_2$ 1 point		
									22 per 1,000	5 fewer strokes per 1,000 (from 1 fewer to 8 fewer)	
									$CHADS_2$ 2 points		
									45 per 1,000	9 fewer strokes per 1,000 (from 2 fewer to 16 fewer)	
									$CHADS_2$ 3-6 points		
									96 per 1,000	20 fewer strokes per 1,000 (from 4 fewer to 34 fewer)	
Nonfatal major extracranial bleeds (important outcome)[j]											
60 RCTs	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	333/47,168 (0.7)	535/47,158 (1.1)	RR 1.60 (1.40-1.80)	5 per 1,000[k]	3 more bleeds per 1,000 (from 2 more to 4 more)	High

(Continued)

Table 4—*Continued*

Quality Assessment								Summary of Findings			
						Study Event Rates (%)			Estimation of Absolute Effects 1 y Time Frame		
No. of Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	With No Therapy	With Antiplatelet	Relative Effect (95% CI)	With No Therapy	With Antiplatelet (95% CI)	Quality of Evidence
Systemic embolism (important outcome) mean follow-up 2.1 y											
5 RCTs	No serious limitations	No serious inconsistency	No serious indirectness	Precise[l]	Undetected	21/2,061 (1.0)	17/2,052 (0.8)	RR 0.80 (0.43-1.52)	4 per 1,000[m]	1 fewer systemic embolism per 1,000 (from 2 fewer to 2 more)	Moderate

ESPS = European Stroke Prevention Study; JAST = Japan Atrial Fibrillation Stroke Trial; LASAF = Low-dose Aspirin, Stroke, Atrial Fibrillation; SAFT = Swedish Atrial Fibrillation Trial; UK-TIA = United Kingdom Transient Ischaemic Attack Aspirin Trial. See Table 1-3 legends for expansion of other abbreviations.

[a]Pooled estimates of treatment effect in this evidence profile, with the exception of nonfatal major extracranial bleeding[b], are from a meta-analysis conducted for these guidelines, including data from RCTs of antiplatelet monotherapy (typically aspirin) vs no therapy (AFASAK I, SPAF I, EAFT, ESPS-2, UK-TIA, LASAF, JAST, SAFT).

[b]To obtain a best estimate of the risk of nonfatal major extracranial bleeding on antiplatelet monotherapy, we used data from the Antithrombotic Trialists' Collaboration[68] meta-analysis of aspirin for the secondary prevention of cardiovascular disease.

[c]The 95% CI does not exclude the possibility of no effect.

[d]From Go et al,[44] which reported a mortality rate of 5.33 per 100 person-y in untreated (no warfarin) patients from an observational study (ATRIA cohort).

[e]Intracranial hemorrhage includes intracerebral, subdural, and subarachnoid bleeds. For studies that did not report the number of strokes that were fatal and nonfatal (EAFT, ESPS-2, UK-TIA, JAST), we imputed values for the number of fatal and nonfatal strokes to estimate the pooled relative risk for nonfatal stroke across all eligible studies. Assumptions underlying these estimates are detailed in section 1.3 of this article.

[f]Restricting meta-analysis exclusively to RCTs evaluating aspirin alone vs no antithrombotic therapy (ie, excluding SAFT, which used aspirin in combination with fixed minidose warfarin, and excluding the dipyridamole monotherapy arm of ESPS-2) results in an estimate of relative risk that includes no effect (relative risk, 0.81; 95% CI, 0.66-1.01).

[g]Of the 197 nonfatal strokes on no therapy, an estimated 193 (98%) were ischemic, and four (2%) were hemorrhagic.

[h]Of the 174 nonfatal strokes on antiplatelet therapy, an estimated 170 (98%) were ischemic, and four (2%) were hemorrhagic.

[i]We estimated the annual rates of nonfatal stroke (ischemic and hemorrhagic) on no therapy by extrapolating from observed annual rates of ischemic stroke (fatal + nonfatal), stratified by $CHADS_2$ score, in the aspirin arms of six historical RCTs in patients with AF (Gage et al[37]). Assumptions underlying these estimates are detailed in section 1.1.4 of this article.

[j]We used evidence from RCTs of aspirin for the secondary prevention of cardiovascular events to obtain a best estimate of the risk of major extracranial bleeding with antiplatelet monotherapy. Note that the study event rates and relative risk are for the outcome of all major extracranial bleeding (nonfatal and fatal events) because specific data regarding nonfatal events were not reported.

[k]Rates of nonfatal major extracranial bleeding on no therapy are extrapolated from rates observed in observational cohorts of patients receiving adjusted-dose VKA therapy (median, 1.3%/y) and dividing by the relative risk of major bleeding on adjusted-dose VKA therapy observed in the RCTs.

[l]The 95% CI does not exclude the possibility of appreciable harm or benefit with antiplatelet therapy.

[m]Based on rate of systemic embolism on aspirin of 0.3 per 100 patient-y reported in the IPD meta-analysis of warfarin vs aspirin by van Walraven et al[61] and a relative risk of 0.80 for aspirin vs no therapy for systemic embolism.

Table 5—*[Sections 2.1.3, 2.1.8, 2.1.9, 2.1.10] Should VKAs Rather Than Aspirin Be Used in Patients With AF?*[a]

Quality Assessment								Summary of Findings			
						Study Event Rates (%)			Estimation of Absolute Effects 1-y Time Frame		
No. of Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	With ASA	With VKA	Relative Effect (95% CI)	With ASA	With VKA (95% CI)	Quality of Evidence
Death (critical outcome) mean follow-up 1.8 y											
10 RCTs	No serious limitations	No serious inconsistency	No serious indirectness	Imprecise[b]	Undetected	351/3,020 (11.6)	327/2,835 (11.5)	RR 0.97 (0.85-1.12)	47 per 1,000[c]	1 fewer death per 1,000 (from 7 fewer to 6 more)	Moderate
Nonfatal stroke (critical outcome) mean follow-up 1.8 y; ischemic stroke and intracranial hemorrhage[d]											
11 RCTs	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	209/3,356[e] (6.2)	94/3,170[f] (3.0)	RR 0.48 (0.33-0.70)	$CHADS_2$ 0 points		High
									6 per 1,000[g]	3 fewer strokes per 1,000 (from 2 fewer to 4 fewer)	
									$CHADS_2$ 1 point		
									17 per 1,000	9 fewer strokes per 1,000 (from 5 fewer to 11 fewer)	
									$CHADS_2$ 2 points		
									36 per 1,000	19 fewer strokes per 1,000 (from 11 fewer to 24 fewer)	
									$CHADS_2$ 3-6 points		
									76 per 1,000	40 fewer strokes per 1,000 (from 23 fewer to 51 fewer)	
Nonfatal major extracranial bleeds (important outcome) mean follow-up 1.8 y											
11 RCTs	No serious limitations	No serious inconsistency	No serious indirectness	Imprecise[h]	Undetected	45/3,356 (1.3)	64/3,170 (2.0)	RR 1.42 (0.89-2.29)	8 per 1,000[i]	3 more bleeds per 1,000 (from 1 fewer to 10 more)	Moderate
Systemic embolism (important outcome) mean follow-up 1.8 y											
11 RCTs	No serious limitations	No serious inconsistency	No serious indirectness	Imprecise[j]	Undetected	20/3,356 (0.6)	13/3,170 (0.4)	RR 0.81 (0.40-1.64)	3 per 1,000[k]	1 fewer systemic embolism per 1,000 (from 2 fewer to 2 more)	Moderate

(Continued)

Table 5—*Continued*

Quality Assessment								Summary of Findings			
						Study Event Rates (%)			Estimation of Absolute Effects 1-y Time Frame		
No. of Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	With ASA	With VKA	Relative Effect (95% CI)	With ASA	With VKA (95% CI)	Quality of Evidence
Burden of treatment (important outcome)											
N/A	No serious limitations	No serious limitations	No serious limitations	No serious limitations	N/A	N/A	N/A	VKA > aspirin	Warfarin: daily medication, lifestyle limitations, dietary restrictions, frequent blood testing and clinic visits Aspirin: daily medication only		High

ASA = acetylsalicyclic acid; BAFTA = Birmingham Atrial Fibrillation of the Aged; NASPEAF = National Study for Prevention of Embolism in Atrial Fibrillation; PATAF = Primary Prevention of Arterial Thromboembolism in Nonrheumatic AF in Primary Care Trial; SIFA = Studio Italiano Fibrillazione Artiale; WASPO = Warfarin vs Aspirin for Stroke Prevention in Octogenarians With AF. See Table 1-3 legends for expansion of other abbreviations.

[a]Pooled estimates of treatment effect in this evidence profile are from a new meta-analysis of data from RCTs which included a comparison of warfarin and antiplatelet monotherapy (typically aspirin). In SPAF III and AFASAK II, aspirin was combined with fixed (ineffective) minidose warfarin (AFASAK I, AFASAK II, Vemmos et al[69], BAFTA, EAFT, NASPEAF, PATAF, SIFA, SPAF II, SPAF III, WASPO).

[b]The 95% CI does not exclude the possibility of appreciable harm or benefit with VKA therapy.

[c]Based on data from Go et al,[44] which reported a mortality rate of 5.33 per 100 person-y in untreated (no warfarin) patients from an observational study (ATRIA cohort) and an estimated relative risk of mortality of 0.89 for aspirin vs no therapy (Table 4).

[d]Intracranial hemorrhage includes intracerebral, subdural, and subarachnoid bleeds. For SPAF II, which did not report the number of strokes that were fatal and nonfatal, we imputed values for the number of fatal and nonfatal strokes to estimate the pooled relative risk for nonfatal stroke across all eligible studies. Assumptions underlying these estimates are detailed in section 1.3 of this article.

[e]Of the 209 nonfatal strokes on antiplatelet therapy, an estimated 202 (97%) were ischemic, and seven (3%) were hemorrhagic.

[f]Of the 94 nonfatal strokes on VKA therapy, an estimated 80 (85%) were ischemic, and 14 (15%) were hemorrhagic.

[g]We estimated the annual rates of nonfatal stroke (ischemic and hemorrhagic) on no therapy by extrapolating from observed annual rates of ischemic stroke (fatal + nonfatal), stratified by $CHADS_2$ score, in the aspirin arms of six historical RCTs in patients with AF (Gage et al[37]). Assumptions underlying these estimates are detailed in section 1.1.4 of this article.

[h]The 95% CI does not exclude appreciable harm with VKA therapy.

[i]Rates of nonfatal major extracranial bleeding on aspirin are extrapolated from rates observed in observational cohorts of patients receiving adjusted-dose VKA therapy (median, 1.3%/y), and relative risks of major extracranial bleeding associated with VKA therapy (RR, 2.56) and aspirin (RR, 1.60) compared with no therapy.

[j]The 95% CI does not exclude the possibility of appreciable benefit or harm with VKA therapy.

[k]Based on rate of systemic embolism on aspirin of 0.3 per 100 patient-y reported in the individual patient data meta-analysis of warfarin vs aspirin by van Walraven et al.[61]

Table 6—*[Sections 2.1.4, 2.1.9, 2.1.10] Should VKAs Rather Than Aspirin Plus Clopidogrel Be Used in Patients With AF?*

Quality Assessment								Summary of Findings			
						Study Event Rates (%)			Estimation of Absolute Effects 1-y Time Frame		
No. of Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	With ASA + Clopid	With VKA	Relative Effect (95% CI)	With ASA + Clopid	With VKA (95% CI)	Quality of Evidence
Death (critical outcome) median follow-up 1.3 y											
1 RCT	No serious limitations[a]	No serious inconsistency	No serious indirectness	Imprecise[b]	Undetected	159/3,335 (4.8)	158/3,371 (4.7)	RR 0.98 (0.79-1.22)	46 per 1,000[c]	1 fewer death per 1,000 (from 10 fewer to 10 more)	Moderate
Nonfatal stroke (critical outcome) median follow-up 1.3 y; ischemic stroke and intracranial hemorrhage[d]											
1 RCT	No serious limitations[a]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	72/3,335[e] (2.2)	41/3,371[f] (1.2)	RR 0.56 (0.39-0.82)	$CHADS_2$ 0 points		High
									5 per 1,000[g]	2 fewer strokes per 1,000 (from 1 fewer to 3 fewer)	
									$CHADS_2$ 1 point		
									13 per 1,000	6 fewer strokes per 1,000 (from 2 fewer to 8 fewer)	
									$CHADS_2$ 2 points		
									26 per 1,000	11 fewer strokes per 1,000 (from 5 fewer to 16 fewer)	
									$CHADS_2$ 3-6 points		
									55 per 1,000	24 fewer strokes per 1,000 (from 10 fewer to 34 fewer)	
Nonfatal major extracranial bleeds (important outcome) median follow-up 1.3 y[h]											
1 RCT	No serious limitations[a]	No serious inconsistency	No serious indirectness (77% of patients were receiving VKA at study entry)	Imprecise[i]	Undetected	85/3,335 (2.5)	78/3,371 (2.3)	RR 0.91 (0.67-1.23)	12 per 1,000[j]	1 fewer bleeds per 1,000 (from 4 fewer to 3 more)	Moderate

(Continued)

Table 6—*Continued*

Quality Assessment								Summary of Findings			
						Study Event Rates (%)			Estimation of Absolute Effects 1-y Time Frame		
No. of Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	With ASA + Clopid	With VKA	Relative Effect (95% CI)	With ASA + Clopid	With VKA (95% CI)	Quality of Evidence
Systemic embolism (important outcome) median follow-up 1.3 y											
1 RCT	No serious limitations[a]	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	18/3,335 (0.5)	4/3,371 (0.1)	RR 0.22 (0.07-0.65)	3 per 1,000[k]	2 fewer systemic emboli per 1,000 (from 1 fewer to 3 fewer)	High
Burden of treatment (important outcome)											
N/A	No serious limitations	No serious limitations	No serious limitations	No serious limitations	N/A	N/A	N/A	VKA > ASA + clopidogrel	Warfarin: daily medication, lifestyle limitations, dietary restrictions, frequent blood testing and clinic visits Aspirin + clopidogrel: daily medication only		High

ACTIVE = Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events. Clopid = clopidogrel. See Table 1-3 and 5 legends for expansion of other abbreviations.

[a]Results are based on a single RCT (ACTIVE W) that was stopped early for benefit.

[b]The 95% CI does not exclude appreciable harm or benefit with VKA therapy.

[c]Based on data from Go et al,[44] which reported a mortality rate of 5.33 per 100 person-y in untreated (no warfarin) patients from an observational study (ATRIA cohort), an estimated relative risk of 0.89 for mortality with aspirin vs no therapy (Table 4), and an estimated relative risk of 0.98 for mortality with aspirin + clopidogrel vs aspirin (Table 7).

[d]Intracranial hemorrhage includes intracerebral, subdural, and subarachnoid bleeds. The published report did not provide the number of strokes that were fatal and nonfatal; therefore, we imputed values for the number of fatal and nonfatal strokes to estimate the relative risk for nonfatal stroke. Assumptions underlying these estimates are detailed in section 1.3 of this article.

[e]Of the 72 nonfatal strokes on aspirin + clopidogrel therapy, an estimated 67 (93%) were ischemic, and five (7%) were hemorrhagic.

[f]Of the 41 nonfatal strokes on VKA therapy, an estimated 31 (76%) were ischemic, and 10 (24%) were hemorrhagic.

[g]We estimated the annual rates of nonfatal stroke (ischemic and hemorrhagic) on aspirin + clopidogrel by extrapolating from observed annual rates of ischemic stroke (fatal + nonfatal), stratified by $CHADS_2$ score, in the aspirin arms of six historical RCTs in patients with AF (Gage et al[37]). Assumptions underlying these estimates are detailed in section 1.1.4 of this article.

[h]The published report did not provide the number of major extracranial bleeds that were fatal and nonfatal; therefore, we imputed values for the number of fatal and nonfatal major extracranial bleeds to estimate the relative risk for nonfatal major extracranial bleeds. Assumptions underlying these estimates are detailed in section 1.3 of this article.

[i]The 95% CI does not exclude appreciable harm or benefit with VKA therapy.

[j]Rate of nonfatal major extracranial bleeding on aspirin + clopidogrel is extrapolated from rates observed in observational cohorts of patients receiving VKA therapy (median, 1.3%/y) and estimated relative risks of nonfatal major extracranial bleeding associated with VKA therapy compared with no therapy (RR, 2.56), aspirin compared with no therapy (RR, 1.60), and aspirin + clopidogrel compared with aspirin (RR, 1.50).

[k]Estimate is derived from rate of systemic embolism on aspirin (0.3 per 100 patient-y) reported in the IPD meta-analysis by van Walraven et al[61] and estimated relative risk of 0.97 (95% CI, 0.67-1.40) for systemic embolism with combination aspirin + clopidogrel therapy vs aspirin observed in ACTIVE A (Table 7).

prior users of VKA therapy, the study sample may be more representative of patients in whom VKA therapy is well tolerated). In prespecified subgroup analyses, the investigators did not find evidence of a difference in the effect of VKA therapy on primary outcome in patients who were and were not receiving VKA therapy at study entry. However, there was a significant difference (interaction $P = .03$) in the effect on major bleeding, depending on whether patients were prior users of VKA therapy. For patients who were not receiving VKA therapy at study entry, VKA therapy was associated with a nonsignificant trend toward a 69% relative increase in major bleeding compared with dual antiplatelet therapy, whereas in patients already receiving VKA therapy at study entry, VKA therapy was associated with a nonsignificant trend toward a 24% relative decrease in major bleeding compared with dual antiplatelet therapy.

2.1.5 Dual Antiplatelet Therapy With Aspirin and Clopidogrel vs Aspirin Alone: The ACTIVE A study compared combination aspirin and clopidogrel therapy with aspirin alone.[81] The trial enrolled 7,554 patients considered unsuitable for VKA therapy (approximately one-half because of a physician's judgment that VKA was inappropriate, one-fourth because of a specific risk of bleeding, and one-fourth because of the patient's preference not to take a VKA as the sole reason) and found that combination therapy is more effective in reducing the risk of nonfatal stroke in patients with AF but also increases the risk of nonfatal major extracranial bleeds compared with treatment with aspirin alone (Table 7).

2.1.6 New Oral Anticoagulants vs VKAs: Antithrombotic therapy for AF is evolving rapidly because of the development of new oral anticoagulants that directly target different parts of the coagulation pathway, have a more predictable anticoagulant effect, and do not require INR monitoring. Included in this new group of drugs are direct thrombin inhibitors (eg, dabigatran) and direct factor Xa inhibitors (apixaban, rivaroxaban, edoxaban). Results of large phase 3 clinical trials of these agents in patients with AF have been recently published or will be reported soon (Table 8). Although ximelagatran is no longer approved for use by regulatory agencies because of concerns about severe liver toxicity, the Stroke Prevention Using an Oral Thrombin Inhibitor in Patients With AF (SPORTIF) III and V trials were a proof of principle that a direct thrombin inhibitor can achieve similar protection against stroke compared with warfarin (ie, findings met the investigators' prespecified noninferiority criterion) with no evidence of increased bleeding risk.[82,83]

The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial reported the results of a three-arm RCT of 18,113 patients with AF in which dabigatran 110 mg bid, and dabigatran 150 mg bid, were compared with open-label, adjusted-dose warfarin (target INR 2.0-3.0).[84] Based on best estimates of the proportion of strokes and major extracranial bleeds that were nonfatal (the published report did not present the number or proportion of fatal and nonfatal events), dabigatran at a dose of 150 mg bid is associated with a statistically significant one-third reduction in nonfatal stroke, with no evidence of a difference in the risk of nonfatal major extracranial bleeding compared with warfarin. Moreover, the data raised the possibility that dabigatran 150 mg bid may reduce all-cause mortality compared with warfarin (relative risk, 0.89; 95% CI, 0.79-1.01) (Table 9). In contrast, dabigatran at a dose of 110 mg bid was not associated with a significant difference in the risk of death, nonfatal stroke, nonfatal major extracranial bleeding, or systemic embolism (Table 10).

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) was a double-blind, double-dummy RCT comparing rivaroxaban 20 mg once daily to adjusted-dose warfarin (INR 2.0-3.0) in 14,264 patients with AF at increased risk of stroke (mean $CHADS_2$ score of 3.5).[85] In the intention-to-treat analysis, rivaroxaban was noninferior to warfarin for the primary end point of stroke (ischemic or hemorrhagic) or systemic embolism but was not superior to warfarin (hazard ratio, 0.88; 95% CI, 0.74-1.03). The trial did not find evidence of a difference in major bleeding between rivaroxaban and warfarin (hazard ratio, 1.04; 95% CI, 0.90-1.20). Major GI bleeding was more common with rivaroxaban than with warfarin (3.2% and 2.2%, respectively, $P < .001$). Mortality was not significantly different between rivaroxaban and warfarin.

The Apixaban vs Acetylsalicylic Acid to Prevent Strokes (AVERROES) RCT compared apixaban 5 mg bid to aspirin in 5,599 patients with AF who were demonstrated or expected to be unsuitable candidates for adjusted-dose VKA therapy.[86] The trial was stopped early for benefit and was consistent with the trials of VKA therapy vs aspirin (section 2.1.3), reporting that apixaban reduces by one-half the occurrence of the primary outcome of stroke and systemic embolism compared with aspirin (hazard ratio, 0.45; 95% CI, 0.32-0.62). The trial failed to demonstrate or exclude a difference in the risk of major extracranial bleeding with apixaban compared with aspirin (hazard ratio, 1.23; 95% CI, 0.74-2.05), and the results were consistent with those of earlier trials of VKA therapy vs aspirin (section 2.1.3), which suggest an increase in the risk of major extracranial

Table 7—*[Sections 2.1.5, 2.1.8, 2.1.9, 2.1.10] Should Aspirin Plus Clopidogrel Rather Than Aspirin Be Used in Patients With AF?*

Quality Assessment								Summary of Findings			
						Study Event Rates (%)			Estimation of Absolute Effects 1-y Time Frame		
No. of Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	With ASA	With ASA/Clopid	Relative Effect (95% CI)	With ASA	With ASA/Clopid (95% CI)	Quality of Evidence
Death (critical outcome) median follow-up 3.6 y											
1 RCT	No serious limitations	No serious inconsistency	No serious indirectness	Imprecise[a]	Undetected	841/3,782 (22.2)	825/3,772 (21.9)	RR 0.98 (0.90-1.07)	47 per 1,000[b]	1 fewer death per 1,000 (from 5 fewer to 3 more)	Moderate
Nonfatal stroke (critical outcome) median follow-up 3.6 y; ischemic stroke and intracranial hemorrhage[c]											
1 RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	315/3,782[d] (8.3)	226/3,772[e] (6.0)	RR 0.72 (0.61-0.85)	$CHADS_2$ 0 points		High
									6 per 1,000[f]	2 fewer strokes per 1,000 (from 1 fewer to 2 fewer)	
									$CHADS_2$ 1 point		
									17 per 1,000	5 fewer strokes per 1,000 (from 3 fewer to 7 fewer)	
									$CHADS_2$ 2 points		
									36 per 1,000	10 fewer strokes per 1,000 (from 5 fewer to 14 fewer)	
									$CHADS_2$ 3-6 points		
									76 per 1,000	21 fewer strokes per 1,000 (from 11 fewer to 30 fewer)	
Nonfatal major extracranial bleeds (important outcome) median follow-up 3.6 y[g]											
1 RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	112/3,782 (3.0)	167/3772 (4.4)	RR 1.50 (1.18-1.89)	8 per 1,000[h]	4 more bleeds per 1,000 (from 1 more to 7 more)	High

(Continued)

Table 7—*Continued*

Quality Assessment								Summary of Findings			
						Study Event Rates (%)			Estimation of Absolute Effects 1-y Time Frame		
No. of Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	With ASA	With ASA/Clopid	Relative Effect (95% CI)	With ASA	With ASA/Clopid (95% CI)	Quality of Evidence
Systemic embolism (important outcome) median follow-up 3.6 y											
1 RCT	No serious limitations	No serious inconsistency	No serious indirectness	Precise[i]	Undetected	56/3,782 (1.5)	54/3,772 (1.4)	RR 0.97 (0.67-1.40)	3 per 1,000[j]	0 fewer systemic emboli per 1,000 (from 1 fewer to 1 more)	Moderate

See Table 1-3, 5, and 6 legends for expansion of abbreviations.

[a]The 95% CI does not exclude the possibility of no effect.

[b]Based on data from Go et al,[44] which reported a mortality rate of 5.33 per 100 person-y in untreated (no warfarin) patients from an observational study (ATRIA cohort) and an estimated relative risk of mortality of 0.89 for aspirin vs no therapy (Table 4).

[c]Hemorrhagic stroke not clearly defined in published RCT report (ie, unclear whether subdural and subarachnoid bleeds were included in the definition of hemorrhagic stroke).

[d]The published RCT report did not present the proportion of nonfatal strokes in the aspirin arm that were ischemic vs hemorrhagic; however, of all strokes (fatal and nonfatal), 5% were hemorrhagic, and 95% were ischemic or of uncertain type.

[e]The published RCT report did not present the proportion of nonfatal strokes in the combination aspirin + clopidogrel arm that were ischemic vs hemorrhagic; however, of all strokes (fatal and nonfatal), 10% were hemorrhagic, and 90% were ischemic or of uncertain type.

[f]We estimated the annual rates of nonfatal stroke (ischemic and hemorrhagic) on aspirin by extrapolating from observed annual rates of ischemic stroke (fatal + nonfatal), stratified by $CHADS_2$ score, in the aspirin arms of six historical RCTs in patients with AF (Gage et al[37]). Assumptions underlying these estimates are detailed in section 1.1.4 of this article.

[g]The published report did not provide the number of major extracranial bleeds that were fatal and nonfatal; therefore, we imputed values for the number of fatal and nonfatal major extracranial bleeds to estimate the relative risk for nonfatal major extracranial bleeds. Assumptions underlying these estimates are detailed in section 1.3 of this article.

[h]Rates of nonfatal major extracranial bleeding on aspirin are extrapolated from rates in observational cohorts of patients receiving adjusted-dose VKA therapy (median, 1.3%/y) and relative risks of major extracranial bleeding associated with VKA therapy (RR, 2.56) and aspirin (RR, 1.60) compared with no therapy.

[i]The 95% CI does not exclude the possibility of no effect.

[j]Based on rate of systemic embolism on aspirin of 0.3 per 100 patient-y reported in the IPD meta-analysis of warfarin vs aspirin by van Walraven et al.[61]

Table 8—*[Section 2.1.6] Phase 3 RCTs of New Oral Anticoagulants in Patients With AF*

Trial	Intervention	Comparator	Status
SPORTIF III SPORTIF V	Ximelagatran	Warfarin (INR, 2.0-3.0)	Published[82,83]
RE-LY	Dabigatran (150 or 110 mg bid)	Warfarin (INR, 2.0-3.0)	Published[84]
AVERROES	Apixaban (5 mg bid)	Aspirin (81-324 mg daily)	Published[86]
ROCKET-AF	Rivaroxaban (20 mg once daily)	Warfarin (INR, 2.0-3.0)	Published[85]
ARISTOTLE	Apixaban (5 mg bid)	Warfarin (INR, 2.0-3.0)	Published[87]
ENGAGE-AF TIMI 48	Edoxaban (high- and low-dose regimens)	Warfarin (INR, 2.0-3.0)	Currently recruiting

ARISTOTLE = Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation; AVERROES = Apixaban versus Acetylsalicylic Acid to Prevent Strokes; ENGAGE-AF TIMI 48 = Effective Anticoagulation With Factor xA Next Generation in Atrial Fibrillation-Thrombolysis In Myocardial Infarction Study 48; INR = international normalized ratio; RE-LY = Randomized Evaluation of Long-Term Anticoagulation Therapy; 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; SPORTIF = Stroke Prevention Using an Oral Thrombin Inhibitor in Patients With AF.

bleeding with oral anticoagulation compared with aspirin.

ARISTOTLE (Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation) was a double-blind, double-dummy RCT comparing apixaban 5 mg bid to warfarin (INR 2.0-3.0) in 18,201 patients with AF (mean $CHADS_2$ score of 2.1).[87] Apixaban reduced by 21% the risk of the primary outcome of stroke (ischemic or hemorrhagic) or systemic embolism (hazard ratio, 0.79; 95% CI, 0.66-0.95) and reduced by 31% the risk of major bleeding (hazard ratio, 0.69; 95% CI, 0.60-0.80) compared with warfarin. There was no evidence of a difference in major GI bleeding between apixaban and warfarin (hazard ratio, 0.89; 95% CI, 0.70-1.15). All-cause mortality was lower with apixaban compared with warfarin (hazard ratio, 0.89; 95% CI, 0.80-0.998). In all three recently completed trials of novel anticoagulants vs warfarin (RE-LY, ROCKET-AF, and ARISTOTLE), the rate of intracranial hemorrhage (including both hemorrhagic stroke and other intracranial bleeds) was lower in patients assigned to the novel anticoagulant than in patients assigned to warfarin.[84,85,87,88]

2.1.7 General Approach to Recommendations About New Oral Anticoagulants in This Article: Our guideline panel elected to make recommendations only for those drugs that have received regulatory approval for use in AF (ie, dabigatran).[89] Although based on the results of a single trial, there is evidence from RE-LY that dabigatran is no worse than VKA therapy with respect to nonfatal major extracranial bleeding and that it is similar or superior to warfarin with respect to nonfatal stroke, systemic embolism, and all-cause mortality in patients with nonvalvular AF (section 2.1.6). Therefore, for patients with nonrheumatic AF, wherever we recommend (or suggest) VKA therapy, we also recommend (or suggest) the use of dabigatran, and in these situations, our recommendations simply refer to oral anticoagulation.[88] We address the specific question of whether to use dabigatran over adjusted-dose VKA therapy in section 2.1.11.

The data from RE-LY do not directly address the use of dabigatran in patients with AF and mitral stenosis (patients with hemodynamically relevant valvular disease were excluded from this study), or in patients with AF in other special situations (sections 2.2 and 3.0). Therefore, we have not extrapolated the data from RE-LY to these clinical situations and have instead restricted those recommendations for oral anticoagulation to adjusted-dose VKA therapy. There is direct evidence from RE-LY regarding the use of dabigatran in patients with AF undergoing cardioversion, and these data are summarized in section 4.1.1.

2.1.8 Recommendations for Patients With AF at Low Risk of Stroke (eg, $CHADS_2$ Score of 0): Patients at sufficiently low risk of ischemic stroke may opt for no treatment rather than antithrombotic therapy with either aspirin or an oral anticoagulant. For instance, for every 1,000 patients at low risk of stroke with a $CHADS_2$ score of 0, VKA therapy compared with no treatment is anticipated to result in five fewer nonfatal strokes at the expense of eight more nonfatal major extracranial bleeds and the additional burden of adjusted-dose VKA treatment (Table 3). Although VKA therapy is expected to reduce all-cause mortality in patients with AF in general, it is likely that this mortality benefit does not extend to low-risk patients. The absolute reduction in fatal ischemic stroke with VKA therapy will be far fewer such patients, whereas their absolute increase in fatal intracranial hemorrhage will be similar to those with higher $CHADS_2$ scores.[51]

For patients with a $CHADS_2$ score of 0, treatment with aspirin for 1 year may result in the prevention of two nonfatal strokes per 1,000 patients (moderate-quality evidence due to imprecision) at the expense of three additional nonfatal major extracranial bleeds per 1,000 patients compared with no treatment (Table 4). If stroke rates are truly declining over time,

Table 9—*[Section 2.1.6, 2.1.11] Should Dabigatran 150 mg bid Rather Than VKAs be Used in Patients With AF?*

Quality Assessment								Summary of Findings			
						Study Event Rates (%)			Estimation of Absolute Effects 1-y Time Frame		
No. of Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	With VKA	With Dabi 150 mg	Relative Effect (95% CI)	With VKA	With Dabigatran 150 (95% CI)	Quality of Evidence
Death (critical outcome) median follow-up 2.0 y											
1 RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision[a]	Undetected	487/6,022 (8.1)	438/6,076 (7.2)	RR 0.89 (0.79- 1.01)	38 per 1,000[b]	4 fewer deaths per 1,000 (from 8 fewer to 0 more)	Moderate
Nonfatal stroke (critical outcome) median follow-up 2.0 y; ischemic stroke and intracranial hemorrhage[c]											
1 RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	149/6,022[d] (2.5)	101/6,076[e] (1.7)	RR 0.67 (0.52-0.86)	$CHADS_2$ 0 points		High
									3 per 1,000[f]	1 fewer strokes per 1,000 (from 0 fewer to 1 fewer)	
									$CHADS_2$ 1 point		
									8 per 1,000	3 fewer strokes per 1,000 (from 1 fewer to 4 fewer)	
									$CHADS_2$ 2 points		
									17 per 1,000	6 fewer strokes per 1,000 (from 2 fewer to 8 fewer)	
									$CHADS_2$ 3-6 points		
									36 per 1,000	12 fewer strokes per 1,000 (from 5 fewer to 17 fewer)	
Nonfatal major extracranial bleeds (important outcome) median follow-up 2.0 y[g]											
1 RCT	No serious limitations	No serious inconsistency	No serious indirectness	Imprecise[a]	Undetected	264/6,022 (4.4)	286/6076 (4.7)	RR 1.07 (0.91-1.26)	13 per 1,000[h]	1 more bleed per 1,000 (from 1 fewer to 3 more)	Moderate
Systemic embolism (important outcome) median follow-up 2.0 y											
1 RCT	No serious limitations	No serious inconsistency	No serious indirectness	Imprecise[a]	Undetected	14/6,022 (0.2)	12/6076 (0.2)	RR 0.85 (0.39-1.84)	2 per 1,000[i]	0 fewer systemic emboli per 1,000 (from 1 fewer to 2 more)	Moderate

(Continued)

Table 9—*Continued*

Quality Assessment								Summary of Findings			
						Study Event Rates (%)			Estimation of Absolute Effects 1-y Time Frame		
No. of Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	With VKA	With Dabi 150 mg	Relative Effect (95% CI)	With VKA	With Dabigatran 150 (95% CI)	Quality of Evidence
Burden of treatment (important outcome)											
N/A	No serious limitations	No serious limitations	No serious limitations	No serious limitations	N/A	N/A	N/A	VKA >dabigatran	Warfarin: daily medication, lifestyle limitations, dietary restrictions, frequent blood testing and clinic visits Dabigatran: daily medication only		High

Dabi = dabigatran. See Table 1-3 legends for expansion of other abbreviations.

[a]The 95% CI does not exclude the possibility of no effect.

[b]Based on data from Go et al,[44] which reported a mortality rate of 5.33 per 100 person-y in untreated (no warfarin) patients from an observational study (ATRIA cohort) and an estimated relative risk of mortality of 0.72 for VKA vs no therapy (Table 3).

[c]Intracranial hemorrhage includes intracerebral, subdural, and subarachnoid bleeds. The published report did not provide the number of strokes that were fatal and nonfatal; therefore, we imputed values for the number of fatal and nonfatal strokes to estimate the relative risk for nonfatal stroke. Assumptions underlying these estimates are detailed in section 1.3 of this article.

[d]Of the 149 nonfatal strokes on VKA therapy, an estimated 106 (71%) were ischemic, and 43 (29%) were hemorrhagic.

[e]Of the 101 nonfatal strokes on dabigatran therapy, an estimated 83 (82%) were ischemic, and 18 (18%) were hemorrhagic.

[f]We estimated the annual rates of nonfatal stroke (ischemic and hemorrhagic) on warfarin by extrapolating from observed annual rates of ischemic stroke (fatal + nonfatal), stratified by $CHADS_2$ score, in the aspirin arms of six historical RCTs in patients with AF (Gage et al[37]). Assumptions underlying these estimates are detailed in section 1.1.4 of this article.

[g]The published report did not provide the number of major extracranial bleeds that were fatal and nonfatal; therefore, we imputed values for the number of fatal and nonfatal major extracranial bleeds to estimate the relative risk for nonfatal major extracranial bleeds. Assumptions underlying these estimates are detailed in section 1.1.4 of this article.

[h]Rate of nonfatal major extracranial bleeding on warfarin is from observational cohorts of patients receiving adjusted-dose VKA therapy (median, 1.3%/y).

[i]Based on rate of systemic embolism on aspirin of 0.3 per 100 patient-y reported in the IPD meta-analysis of warfarin vs aspirin by van Walraven et al[61] and a relative risk for systemic embolism of 0.81 with VKA vs aspirin (Table 5).

Table 10—*[Section 2.1.6, 2.1.11] Should Dabigatran 110 mg bid Rather Than VKAs Be Used in Patients With AF?*

Quality Assessment								Summary of Findings			
						Study Event Rates (%)			Estimation of Absolute Effects 1-y Time Frame		
No. of Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	With VKA	With Dabi 110 mg	Relative Effect (95% CI)	With VKA	With Dabigatran 110 (95% CI)	Quality of Evidence
Death (critical outcome) median follow-up 2.0 y											
1 RCT	No serious limitations	No serious inconsistency	No serious indirectness	Imprecise[a]	Undetected	487/6,022 (8.1)	446/6,015 (7.4)	RR 0.92 (0.81-1.04)	38 per 1,000[b]	3 fewer deaths per 1,000 (from 7 fewer to 2 more)	Moderate
Nonfatal stroke (critical outcome) median follow-up 2.0 y; ischemic stroke and intracranial hemorrhage[c]											
1 RCT	No serious limitations	No serious inconsistency	No serious indirectness	Imprecise[a]	Undetected	149/6,022[d] (2.5)	132/6,015[e] (2.2)	RR 0.89 (0.70-1.12)	$CHADS_2$ 0 points		Moderate
									3 per 1,000[f]	0 fewer strokes per 1,000 (from 1 fewer to 0 more)	
									$CHADS_2$ 1 point		
									8 per 1,000	1 fewer strokes per 1,000 (from 2 fewer to 1 more)	
									$CHADS_2$ 2 points		
									17 per 1,000	2 fewer strokes per 1,000 (from 5 fewer to 2 more)	
									$CHADS_2$ 3-6 points		
									36 per 1,000	4 fewer strokes per 1,000 (from 11 fewer to 4 more)	
Nonfatal major extracranial bleeds (important outcome) median follow-up 2.0 y[g]											
1 RCT	No serious limitations	No serious inconsistency	No serious indirectness	Imprecise[a]	Undetected	264/6,022 (4.4)	250/6,015 (4.2)	RR 0.95 (0.80-1.12)	13 per 1,000[h]	1 fewer bleeds per 1,000 (from 3 fewer to 2 more)	Moderate

(Continued)

Table 10—*Continued*

Quality Assessment								Summary of Findings			
						Study Event Rates (%)			Estimation of Absolute Effects 1-y Time Frame		
No. of Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	With VKA	With Dabi 110 mg	Relative Effect (95% CI)	With VKA	With Dabigatran 110 (95% CI)	Quality of Evidence
Systemic embolism (important outcome) median follow-up 2.0 y											
1 RCT	No serious limitations	No serious inconsistency	No serious indirectness	Imprecise[a]	Undetected	14/6,022 (0.2)	11/6,015 (0.2)	RR 0.79 (0.36-1.73)	2 per 1,000[i]	0 fewer systemic emboli per 1,000 (from 1 fewer to 1 more)	Moderate
Burden of treatment (important outcome)											
N/A	No serious limitations	No serious limitations	No serious limitations	No serious limitations	N/A	N/A	N/A	VKA > dabigatran	Warfarin: daily medication, lifestyle limitations, dietary restrictions, frequent blood testing and clinic visits Dabigatran: daily medication only		High

See Table 1-3 and 9 legends for expansion of abbreviations.

[a]The 95% CI does not exclude the possibility of no effect.

[b]Based on data from Go et al,[44] which reported a mortality rate of 5.33 per 100 person-y in untreated (no warfarin) patients from an observational study (ATRIA cohort) and an estimated relative risk of mortality of 0.72 for VKA vs no therapy (Table 3).

[c]Intracranial hemorrhage includes intracerebral, subdural, and subarachnoid bleeds. The published report did not provide the number of strokes that were fatal and nonfatal; therefore, we imputed values for the number of fatal and nonfatal strokes to estimate the relative risk for nonfatal stroke. Assumptions underlying these estimates are detailed in section 1.3 of this article.

[d]Of the 149 nonfatal strokes on VKA therapy, an estimated 106 (71%) were ischemic, and 43 (29%) were hemorrhagic.

[e]Of the 132 nonfatal strokes on dabigatran therapy, an estimated 119 (90%) were ischemic, and 13 (10%) were hemorrhagic.

[f]We estimated the annual rates of nonfatal stroke (ischemic and hemorrhagic) on warfarin by extrapolating from observed annual rates of ischemic stroke (fatal + nonfatal), stratified by $CHADS_2$ score, in the aspirin arms of six historical RCTs in patients with AF (Gage et al[37]). Assumptions underlying these estimates are detailed in section 1.1.4 of this article.

[g]The published report did not provide the number of major extracranial bleeds that were fatal and nonfatal; therefore, we imputed values for the number of fatal and nonfatal major extracranial bleeds to estimate the relative risk for nonfatal major extracranial bleeds. Assumptions underlying these estimates are detailed in section 1.3 of this article.

[h]Rate of nonfatal major extracranial bleeding on warfarin is from observational cohorts of patients receiving adjusted-dose VKA therapy (median, 1.3%/y).

[i]Based on rate of systemic embolism on aspirin of 0.3 per 100 patient-y reported in the IPD meta-analysis of warfarin vs aspirin by van Walraven et al[61] and a relative risk for systemic embolism of 0.81 with VKA vs aspirin (Table 5).

then the already small benefits of antithrombotic therapy (number needed to treat for 1 year to prevent one nonfatal stroke of 500 for aspirin and 200 for VKA therapy) will be even smaller.

For patients who do choose antithrombotic therapy, the potential choices are aspirin, dual antiplatelet therapy with aspirin and clopidogrel, or oral anticoagulation. For every 1,000 patients with a $CHADS_2$ score of 0, treatment for 1 year with adjusted-dose VKA therapy or with combination aspirin and clopidogrel therapy compared with aspirin is anticipated to result in small reductions in nonfatal stroke and an increase in nonfatal major extracranial bleeding such that the net benefits of either VKA therapy or dual antiplatelet therapy with aspirin and clopidogrel would be small, particularly given the possibility of declining stroke rates over time (Tables 5, 7).

Recommendation

2.1.8. For patients with AF, including those with paroxysmal AF, who are at low risk of stroke (eg, $CHADS_2$ score = 0), we suggest no therapy rather than antithrombotic therapy (Grade 2B)**. For patients who do choose antithrombotic therapy, we suggest aspirin (75 mg to 325 mg once daily) rather than oral anticoagulation** (Grade 2B) **or combination therapy with aspirin and clopidogrel** (Grade 2B)**.**

Remarks: Patients who place an exceptionally high value on stroke reduction and a low value on avoiding bleeding and the burden associated with antithrombotic therapy are likely to choose antithrombotic therapy rather than no antithrombotic therapy. Other factors that may influence the choices above are a consideration of patient-specific bleeding risk and the presence of additional risk factors for stroke, including age 65 to 74 years and female sex, which have been more consistently validated, and vascular disease, which has been less well validated (see section 2.1.12). The presence of multiple non-$CHADS_2$ risk factors for stroke may favor oral anticoagulation therapy.

2.1.9 Recommendations for Patients With AF at Intermediate Risk of Stroke (eg, $CHADS_2$ Score of 1): For patients at intermediate risk of stroke with a $CHADS_2$ score of 1, compared with no therapy, 1 year of VKA therapy is expected to result in 15 fewer deaths and 15 fewer nonfatal strokes per 1,000 patients at the cost of eight more nonfatal major extracranial bleeds (Table 3). Regarding the choice between VKA therapy and aspirin, VKA therapy is anticipated to prevent nine nonfatal strokes for every 1,000 patients treated for 1 year compared with aspirin but will result in three additional bleeds and no reduction in all-cause mortality. However, because absolute rates of stroke may have fallen over the past 2 decades, we may be overestimating the absolute reduction in nonfatal stroke achieved with VKA therapy. Moreover, the true extent of bleeding risk with VKA therapy compared with aspirin therapy is unclear because the pooled estimate of the relative risk of bleeding from the relevant RCTs is imprecise (Table 5). The limited ability of $CHADS_2$ to accurately predict stroke risk (C statistic, 0.6-0.7), the considerable variability in patient values and preferences, and the burden and lifestyle limitations associated with adjusted-dose VKA therapy, introduce further uncertainty.

Compared with combination therapy with aspirin and clopidogrel, VKA therapy is expected to result in six fewer nonfatal strokes per 1,000 patients over a 1-year period, anywhere from four fewer to three more nonfatal major extracranial bleeds, and no reduction in all-cause mortality (Table 6). Uncertainty regarding the small net clinical benefit at a $CHADS_2$ score of 1 arises as a result of the limitations of the $CHADS_2$ score in estimating stroke risk and the possibility of declining absolute stroke rates over time. Uncertainty regarding the value of the small net benefit arises from the variability in patient values and preferences and the burden and lifestyle limitations associated with adjusted-dose VKA therapy.

For patients at intermediate risk of stroke with a $CHADS_2$ score of 1 who are unsuitable for or choose not to take an oral anticoagulant for reasons other than concerns about major bleeding (eg, difficulty maintaining a stable INR, lifestyle limitations of regular INR monitoring, dietary restrictions that are too burdensome, or costs of new anticoagulant drugs that are too high), combination therapy with aspirin and clopidogrel provides additional benefit of stroke reduction at the cost of additional bleeding (ACTIVE A trial) (Table 7). Patients opting for combination antiplatelet therapy rather than treatment with an oral anticoagulant should be informed that they are choosing an inferior treatment with regard to stroke prevention.

Recommendation

2.1.9. For patients with AF, including those with paroxysmal AF, who are at intermediate risk of stroke (eg, $CHADS_2$ score = 1), we recommend oral anticoagulation rather than no therapy (Grade 1B)**. We suggest oral anticoagulation rather than aspirin (75 mg to 325 mg once daily)** (Grade 2B) **or combination therapy with aspirin and clopidogrel** (Grade 2B)**. For patients who are unsuitable for or choose not to take an oral anticoagulant (for reasons other than concerns**

about major bleeding), we suggest combination therapy with aspirin and clopidogrel rather than aspirin (75 mg to 325 mg once daily) (Grade 2B)**.**

Remarks: Patients who place an exceptionally high value on stroke reduction and a low value on avoiding bleeding and the burden associated with anticoagulant therapy are likely to choose oral anticoagulation rather than antiplatelet therapy. Other factors that may influence the choice among antithrombotic therapies are a consideration of bleeding risk and the presence of additional risk factors for stroke, including age 65 to 74 years and female gender, which have been more consistently validated, and vascular disease, which has been less well validated (see section 2.1.12). The presence of multiple non-$CHADS_2$ risk factors for stroke may favor oral anticoagulation therapy.

2.1.10 Recommendations for Patients With AF at High Risk of Stroke (eg, $CHADS_2$ Score of ≥ 2, Which Includes Prior Ischemic Stroke or TIA): Patients at high risk of ischemic stroke, which includes patients with a history of ischemic stroke or TIA, can anticipate large benefits (ie, 15 fewer deaths and 30 fewer nonfatal strokes per 1,000 patients during 1 year of VKA therapy) with anticoagulation (Table 3).

For every 1,000 patients with a $CHADS_2$ score of 2 treated for 1 year with VKA therapy rather than aspirin, we anticipate 19 fewer nonfatal strokes at the expense of three more nonfatal major extracranial bleeds (Table 5). For every 1,000 such patients treated with VKA rather than combination therapy with aspirin and clopidogrel, we anticipate 11 fewer strokes and anywhere between four fewer to three more nonfatal major extracranial bleeds (Table 6). There is therefore a substantial net clinical benefit with oral anticoagulation.

For patients at high risk of ischemic stroke with a $CHADS_2$ score of ≥ 2 who are unsuitable for or who choose not to take an oral anticoagulant for reasons other than concerns about major bleeding (eg, difficulty maintaining a stable INR, lifestyle limitations of regular INR monitoring, dietary restrictions that are too burdensome, or costs of new anticoagulant drugs that are too high), aspirin and clopidogrel therapy will result in a substantial reduction in stroke compared with aspirin alone (ACTIVE A trial) (Table 7). Patients opting for combination antiplatelet therapy rather than treatment with an oral anticoagulant should be informed that they are choosing an inferior treatment with regard to stroke prevention.

Recommendation

2.1.10. For patients with AF, including those with paroxysmal AF, who are at high risk of stroke (eg, $CHADS_2$ score ≥ 2), we recommend oral anticoagulation rather than no therapy (Grade 1A)**, aspirin (75 mg to 325 mg once daily)** (Grade 1B)**, or combination therapy with aspirin and clopidogrel** (Grade 1B)**. For patients who are unsuitable for or choose not to take an oral anticoagulant (for reasons other than concerns about major bleeding), we recommend combination therapy with aspirin and clopidogrel rather than aspirin (75 mg to 325 mg once daily)** (Grade 1B)**.**

2.1.11 Recommendation Regarding Dabigatran vs Adjusted-Dose VKA Therapy: The RE-LY trial showed that dabigatran, at the higher dose of 150 mg bid, leads to reductions in nonfatal stroke, probable reductions in all-cause mortality, and no apparent increase in the risk of nonfatal major extracranial bleeding compared with VKA therapy (Table 9), whereas there was no evidence that dabigatran 110 mg bid leads to a significant reduction in relevant outcomes compared with VKA therapy (Table 10). In the United States, the Food and Drug Administration approved the use of dabigatran for the prevention of thromboembolism in patients with AF at a dose of 150 mg bid but not at a dose of 110 mg bid. However, the Food and Drug Administration did approve, based on pharmacokinetic considerations rather than direct evidence from RCTs in AF populations, a dose of 75 mg bid for patients with severe renal insufficiency (defined as a creatinine clearance 15-30 mL/min).[89]

For the question of whether to use dabigatran vs adjusted-dose VKA therapy, the evidence suggests net clinical benefit at the 150-mg dose. At the time of this writing, however, knowledge regarding the efficacy and safety of the new oral anticoagulants for patients with AF is still limited to one large randomized trial per agent. Uncommon but serious adverse effects may emerge with large-scale use of the drugs. Performance in usual clinical care may deteriorate because of less-restricted patient selection and suboptimal adherence to the unmonitored drug. For patients who do experience bleeding complications, clinicians need to be aware that there is no antidote to reverse the anticoagulant effects of dabigatran.[90] Given these concerns, it would be reasonable for VKA-experienced patients who are well controlled (ie, INR within therapeutic range a high proportion of the time) to continue on VKA therapy if they are satisfied with it and are tolerating it well rather than switching to dabigatran.

There is evidence from meta-analyses of RCTs[92] that home monitoring of VKA therapy reduces thromboembolic events by 42% compared with usual monitoring (see also Holbrook et al[91]), which is

similar to the 33% relative reduction in stroke achieved with dabigatran 150 mg bid compared with VKA therapy (Table 9).[84] Therefore, any advantages of dabigatran with respect to thromboembolism would likely not exist for motivated patients who are able to participate in home monitoring of their VKA therapy. Although home monitoring will reduce the burden of INR testing and VKA dose adjustment, the burdens of VKA therapy related to dietary restrictions and drug interactions will still exist, and there will be a cost for the home monitoring device and test strips. Therefore, depending on how patients value these burdens, some may choose dabigatran rather than home monitoring of VKA therapy.

Before prescribing dabigatran, clinicians need to judge whether the patient is similar enough to those enrolled in RE-LY that the clinical trial results are still likely to apply. In particular, the RE-LY study excluded patients with severe renal impairment (estimated creatinine clearance 30 mL/min or less).[84] The cost-effectiveness of the new anticoagulants compared with VKA therapy is another consideration. An economic analysis based on pricing of dabigatran in the United Kingdom (US $13 per day) estimated that dabigatran 150 mg bid would cost $45,372 more per quality-adjusted life year gained compared with warfarin for patients with AF aged 65 years with risk factors for stroke ($CHADS_2$ score of ≥ 1). The cost-effectiveness estimates in this model were sensitive to the pricing of dabigatran.[93]

Recommendation

2.1.11. For patients with AF, including those with paroxysmal AF, for recommendations in favor of oral anticoagulation (including 2.1.9, 2.1.10, and excluding 2.2, 3.1, 3.2, 3.3), we suggest dabigatran 150 mg twice daily rather than adjusted-dose VKA therapy (target INR range, 2.0-3.0) (Grade 2B)**.**

Remarks: Dabigatran is excreted primarily by the kidney. It has not been studied and is contraindicated in patients with severe renal impairment (estimated creatinine clearance of ≤ 30 mL/min). Clinicians should be aware that there is no antidote for dabigatran.

2.1.12 Tailoring These Recommendations to Individual Patients: As with all weak recommendations, treatment decisions should be individualized based on patient values and preferences, and in this case, an assessment of bleeding risk, and a consideration of additional risk factors for stroke.

Bleeding Risk Assessment—We have not made separate recommendations depending on patient bleeding risk because there are insufficient data to estimate reliably the absolute bleeding rates for patients in different categories of bleeding risk on different antithrombotic regimens. However, the following evidence regarding bleeding risk assessment may help to guide individualized treatment decisions for patients with AF.

One challenge in bleeding risk assessment for patients with AF is that many of the factors associated with an increased risk of major bleeding are also risk factors for ischemic stroke. For instance, older age, hypertension, congestive heart failure, and prior history of ischemic stroke—all of which are components of the $CHADS_2$ score—have been found in various studies of patients with AF to be independent predictors of bleeding while on VKA therapy.[94]

Several bleeding risk scores have been evaluated in cohorts of patients with AF (see Table 11).[53,95-98] However, these scores have not been extensively validated. Their ability to predict major bleeding is modest, with comparable C statistics across external validation studies (range, 0.61-0.66).[53,97-99] In scenarios where we make weak recommendations in favor of oral anticoagulation (eg, patients with a $CHADS_2$ score of 1), patients at high risk of major bleeding may decline oral anticoagulation.

Additional Risk Factors for Stroke in Patients With AF—In addition to consideration of bleeding risk and patient values and preferences, for patients with a $CHADS_2$ score of 0 or 1, clinicians may wish to consider additional stroke risk factors when individualizing decisions about antithrombotic therapy. For instance, there is high-quality evidence that stroke risk increases continuously with age (rather than as a dichotomous function of age <75 or ≥ 75 years) and moderate-quality evidence that female sex is an independent predictor of stroke risk in patients with AF.[18,20] Thus, patients may be inclined to choose the more aggressive treatment option (eg, antithrombotic therapy rather than no therapy for patients with a $CHADS_2$ score of 0 and oral anticoagulation rather than aspirin for patients with a $CHADS_2$ score of 1) when these additional risk factors for stroke are present. The presence of multiple non-$CHADS_2$ risk factors for stroke may favor oral anticoagulation therapy. There is less-consistent evidence supporting an independent association between vascular disease (ie, prior MI, complex aortic plaque seen on TEE, and peripheral arterial disease) and the risk of stroke in patients with AF (section 1.4.2).[21-23]

2.1.13 Percutaneous Closure of the Left Atrial Appendage: Percutaneous closure of the left atrial appendage (LAA) has recently been evaluated as a nondrug alternative for stroke prevention in patients with AF. The PROTECT-AF (WATCHMAN Left

Table 11—*[Section 2.1.12] Bleeding Risk Scores*

	Low	Moderate	High	Calculation of Bleeding Risk Score
Outpatient Bleeding Risk Index[95,96]	0	1-2	≥3	1 point for each of: Age ≥65 y GI bleed in past 2 wk Previous stroke Comorbidities (recent MI, Hct <30%, diabetes, or creatinine >1.5 mg/dL)
$HEMORR_2HAGES$[98]	0-1	2-3	≥4	1 point for each of: **H**epatic or renal disease **E**thanol abuse **M**alignancy **O**lder age (>75 yr) **R**educed platelet count or function **H**ypertension (uncontrolled) **A**nemia **G**enetic factors (*CYP2C9* polymorphisms) **E**xcessive fall risk **S**troke 2 points for: Rebleeding risk (ie, prior bleed)
Shireman et al[97]	≤1.07	>1.07 to <2.19	≥2.19	(0.49 × age >70) + (0.32 × female) + (0.58 × remote bleed) + (0.62 × recent bleed) + (0.71 × alcohol/drug abuse) + (0.27 × diabetes) + (0.86 × anemia) + (0.32 × antiplatelet drug use), with 1 point for presence of each and 0 if absent
HAS-BLED[53,99]	0	1-2	≥3	**H**ypertension (ie, uncontrolled BP) **A**bnormal renal/liver function (1 point each) **S**troke **B**leeding history or predisposition **L**abile INR **E**lderly (eg, age >65 y) **D**rugs (eg, concomitant antiplatelet/NSAID) or alcohol (1 point each) Maximum 9 points

Hct = hematocrit; NSAID = nonsteroidal antiinflammatory drug. See Table 1 and 8 legends for expansion of other abbreviations.

Atrial Appendage System for Embolic PROTECTion in Patients With Atrial Fibrillation) study randomized 707 patients with AF to percutaneous closure of the LAA using the WATCHMAN device (Atritech, Inc) or adjusted-dose warfarin to achieve a target INR of 2.0 to 3.0.[100] Percutaneous LAA closure was associated with a statistically nonsignificant reduction in the risk of their primary efficacy outcome of stroke (ischemic or hemorrhagic), cardiovascular or unexplained death, or systemic embolism compared with warfarin (absolute risk reduction, 1.9% per year; 95% CI, 3.2% per year less to 1.2% per year more, with percutaneous LAA closure compared with adjusted-dose warfarin). However, there was a significantly higher rate of adverse events (excessive bleeding, procedure-related complications) in the percutaneous LAA closure arm (absolute risk increase, 3.0% per year). In particular, serious pericardial effusion (ie, requiring percutaneous or surgical drainage) occurred in 4.8% of patients in the percutaneous LAA closure arm. Another occlusion device, PLAATO [percutaneous LAA transcatheter occlusion], has not been tested in a randomized trial but has been evaluated in prospective, multicenter cohort studies in patients ineligible for warfarin.[101,102] At this time, we make no formal recommendations regarding LAA closure devices, pending more definitive research in this field.

2.2 Patients With AF and Mitral Stenosis

Patients with AF in the setting of rheumatic mitral valve disease, particularly mitral stenosis, are at high risk of stroke. Most RCTs of adjusted-dose VKA therapy in AF excluded such patients. We believe that the results of randomized clinical trials in patients with nonrheumatic AF can be generalized to patients with mitral stenosis.

Recommendation

2.2. For patients with AF and mitral stenosis, we recommend adjusted-dose VKA therapy (target INR range, 2.0-3.0) rather than no therapy, aspirin (75 mg to 325 mg once daily), or combination therapy with aspirin and clopidogrel (all Grade 1B)**. For patients with AF and mitral stenosis who are unsuitable for or choose not to take adjusted-dose VKA therapy (for reasons other than concerns about major bleeding), we recommend combination therapy with aspirin**

and clopidogrel rather than aspirin (75 mg to 325 mg once daily) alone (Grade 1B)**.**

3.0 Antithrombotic Therapy for Patients With AF in Special Situations

3.1 Patients With AF and Stable Coronary Artery Disease

Approximately one-third of patients with AF also have coronary artery disease.[51] A recurring question is whether patients with AF for whom oral anticoagulation is indicated because of a high risk of stroke (eg, $CHADS_2$ score of ≥ 2) and who have concomitant stable coronary artery disease should also use aspirin to prevent coronary heart disease events. In this article, we define stable coronary artery disease as the presence (or absence) of angina but no revascularization procedure (percutaneous coronary intervention or coronary artery bypass graft surgery) or hospitalization for ACS (ie, unstable angina, non-ST-segment elevation MI, or ST-segment elevation MI) in the past year. The studies discussed next provide low-quality evidence that combination therapy with adjusted-dose VKA therapy plus aspirin is not associated with reductions in stroke or MI but that it does increase by 1.5 to 2 times the risk of major bleeding compared with adjusted-dose VKA therapy alone.

The FFAACS (Fluindione, Fibrillation Auriculaire, Aspirin et Contraste Spontane) trial is the only RCT that directly compared adjusted-dose VKA therapy and aspirin to adjusted-dose VKA therapy alone. In this study, patients in both arms received fluindione (INR 2.0-2.6), and patients in the combination therapy arm also received aspirin 100 mg/d. The trial was stopped early after enrollment of only 157 patients because of excessive hemorrhage in the group receiving fluindione plus aspirin.[103] No conclusion can be drawn regarding efficacy for prevention of stroke or MI because there were so few events during a short duration of follow-up.

There is direct evidence from a nonrandomized comparison of patients enrolled in the SPORTIF trials that combination therapy (with warfarin [INR 2.0-3.0] plus aspirin) is associated with a nearly twofold greater risk of major bleeding compared with warfarin alone, with no significant reduction in stroke or MI.[104] Patients receiving aspirin were different from those not receiving aspirin (eg, those receiving aspirin more often had diabetes, coronary artery disease, and previous stroke or TIA). Although the analyses were adjusted for baseline differences in patient characteristics, there remains a high risk for bias.

A similar nonrandomized comparison of patients enrolled in the RE-LY trial reported that rates (likely unadjusted) of major bleeding were roughly 2 times higher for patients receiving aspirin in conjunction with either warfarin (INR 2.0-3.0) or dabigatran.[105] Analyses of observational data from a large population-based registry of hospitalized patients with AF also found a nearly twofold increase in the risk of bleeding requiring hospitalization or causing death when patients with AF received combination therapy with warfarin and aspirin vs warfarin alone.[106]

A systematic review of RCTs in diverse (mostly non-AF) patient populations that compared aspirin plus VKA therapy with VKA therapy alone, in which VKAs were administered to achieve the same target INR or given at the same fixed dose in both arms, found that combination VKA plus aspirin therapy was associated with a lower risk of cardiovascular events compared with VKA therapy alone but that this benefit was restricted to RCTs enrolling patients with mechanical heart valves. No benefit was seen with combination therapy in studies of patients with AF or coronary artery disease, although estimates of treatment effect were very imprecise. Combination therapy with VKA and aspirin was associated with a greater risk of major bleeding (pooled OR, 1.43; 95% CI, 1.00-2.02) compared with VKA therapy alone.[107]

Recommendation

3.1. For patients with AF and stable coronary artery disease (eg, no acute coronary syndrome within the previous year) and who choose oral anticoagulation, we suggest adjusted-dose VKA therapy alone (target INR range, 2.0-3.0) rather than the combination of adjusted-dose VKA therapy and aspirin (Grade 2C)**.**

3.2 Patients With AF and Placement of an Intracoronary Stent (With or Without Recent ACS)

Patients benefit from dual antiplatelet therapy (eg, aspirin and clopidogrel) for a finite duration following placement of an intracoronary stent (4 weeks after placement of a bare-metal stent; 3 to 6 months after placement of a drug-eluting stent [typically 3 months for -olimus stents and 6 months for -taxel stents]) (see Vandvik et al).[108] The principal objective of dual antiplatelet therapy after placement of an intracoronary stent is the prevention of stent thrombosis. Before the adoption of dual antiplatelet therapy in clinical practice, stent thrombosis occurred in 6% to 24% of patients after bare-metal stent placement and was associated with a high case fatality rate of nearly 50%.[109-113] Concomitantly, a number of studies compared a new strategy, aspirin plus ticlopidine (a thienopyridine precursor to clopidogrel), to the previously most successful strategy of aspirin plus warfarin in patients undergoing stent placement. A Cochrane systematic review of four randomized

trials including 2,436 patients found that a 30- to 42-day course of ticlopidine plus aspirin vs warfarin plus aspirin reduced the 30- to 42-day risk of nonfatal MI (relative risk, 0.50; 95% CI, 0.30-0.83; number needed to treat, 55) and revascularization (relative risk, 0.29; 95% CI, 0.16-0.56; number needed to treat, 33) with a possible reduction in major bleeding (relative risk, 0.36; 95% CI, 0.14-1.02) (see Table 11 in Vandvik et al,[108] sections 3.1-3.5).[114]

Based on these data, we recommend aspirin and clopidogrel over warfarin plus aspirin for a finite period following stent placement. For patients with AF receiving oral anticoagulation who undergo placement of an intracoronary stent, the dilemma arises about whether patients should be continued on oral anticoagulation during the time they are recommended to be on dual antiplatelet therapy, given the lack of direct evidence from RCTs addressing this question.

Treatment decisions in this scenario must balance the effect of each drug combination on (1) the risk of stroke, systemic embolism, and mortality due to AF; (2) the risk of recurrent MI (including stent thrombosis); and (3) the risk of bleeding related to antithrombotic therapy. Because of the very high risk for bias in the available observational studies that compare cardiovascular event rates in patients receiving triple therapy vs dual antiplatelet therapy after stent placement,[115-120] we have instead used indirect evidence from relevant RCTs to inform our recommendations. We assumed that the relative impact of triple therapy on death, nonfatal MI, and nonfatal major extracranial bleeds compared with dual antiplatelet therapy would be similar to that seen in 10 RCTs of warfarin plus aspirin compared with aspirin in patients with ACS.[121] For nonfatal stroke and systemic embolism, we assumed that the relative impact of triple therapy vs dual therapy would be similar to that seen in the ACTIVE W trial, which compared warfarin vs aspirin plus clopidogrel in patients with AF (Table 6).[80] This assumption may be underestimating the true effect of triple therapy on stroke and systemic embolism compared with dual therapy.

We used the same annual baseline event rates (ie, on dual antiplatelet therapy) for death, nonfatal stroke, and systemic embolism as were used in the evidence profile comparing VKA to aspirin plus clopidogrel in the general AF population (Table 6). For the annual risk of nonfatal MI and nonfatal major extracranial bleeding on aspirin plus clopidogrel, we used the rates reported in the clopidogrel arm of the PLATO (Study of Platelet Inhibition and Patient Outcomes) trial, which compared ticagrelor to clopidogrel in patients with ACS receiving aspirin.[122]

The indirect data summarized in Table 12 suggest that triple therapy may be associated with net clinical benefit compared with dual antiplatelet therapy for patients at high risk of stroke (eg, $CHADS_2$ score of ≥ 2), whereas the net benefit at lower levels of stroke risk is uncertain. The duration of triple therapy should be kept as brief as possible given the associated increase in bleeding risk. Because the risk of stent thrombosis falls significantly after 30 days with bare-metal stents and 3 to 6 months after drug-eluting stents, triple therapy should be continued only during this high-risk period and only among patients at higher risk of stroke. After the initial period of triple therapy, patients may be given VKA therapy plus a single antiplatelet drug until 12 months have elapsed from the time of stent placement (particularly if stent placement was performed in the setting of a recent ACS [see section 3.3] or if a drug-eluting stent was used).

It should be noted that patients with AF who have received a drug-eluting stent and who are at increased risk of late stent thrombosis (eg, ACS at presentation, diabetes, long lesions, narrow diameter of target vessel)[123] may choose to continue triple therapy for a full 12 months after stent placement if they place a low value on avoiding bleeding. At 12 months after stent placement, antithrombotic therapy can be given according to our recommendations for AF and stable coronary artery disease (section 3.1).

Recommendation

3.2. For patients with AF at high risk of stroke (eg, $CHADS_2$ score of 2 or greater) during the first month after placement of a bare-metal stent or the first 3 to 6 months after placement of a drug-eluting stent, we suggest triple therapy (eg, VKA therapy, aspirin, and clopidogrel) rather than dual antiplatelet therapy (eg, aspirin and clopidogrel) (Grade 2C)**. After this initial period of triple therapy, we suggest a VKA (INR 2.0-3.0) plus a single antiplatelet drug rather than VKA alone** (Grade 2C)**. At 12 months after intracoronary stent placement, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease (see section 3.1).**

For patients with AF at low to intermediate risk of stroke (eg, $CHADS_2$ score of 0 or 1) during the first 12 months after placement of an intracoronary stent (bare metal or drug eluting), we suggest dual antiplatelet therapy rather than triple therapy (Grade 2C)**. At 12 months after intracoronary stent placement, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease (see section 3.1).**

Remarks: Patients who place an exceptionally high value on stroke reduction and a low value on avoiding

Table 12—*[Sections 3.2, 3.3] Should Triple Therapy Rather Than Dual Antiplatelet Therapy Be Used in Patients With AF After Intracoronary Stent Placement?*

Quality Assessment								Summary of Findings			
						Study Event Rates (%)			Estimation of Absolute Effects 1-y Time Frame		
No. of Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	With Dual Therapy	With Triple Therapy	Relative Effect (95% CI)	With Dual Antiplatelet Therapy	With Triple Therapy (95% CI)	Quality of Evidence
Death (critical outcome)											
10 RCTs	No serious limitations	No serious inconsistency	Very serious indirectness[a]	Imprecise[b]	Undetected			RR 1.00 (0.82-1.22)	46 per 1,000[c]	0 more deaths per 1,000 (from 8 fewer to 10 more)	Low
Nonfatal stroke (critical outcome) median follow-up 1.3 y; ischemic stroke and intracranial hemorrhage											
1 RCT	No serious limitations	No serious inconsistency	Very serious indirectness[d]	No serious imprecision	Undetected	72/3,335 (2.2)	41/3,371 (1.2)	RR 0.56 (0.39-0.82)	$CHADS_2$ 0 points		Low
									5 per 1,000[e]	2 fewer strokes per 1,000 (from 1 fewer to 2 fewer)	
									$CHADS_2$ 1 point		
									13 per 1,000	6 fewer strokes per 1,000 (from 2 fewer to 8 fewer)	
									$CHADS_2$ 2 points		
									26 per 1,000	11 fewer strokes per 1,000 (from 5 fewer to 16 fewer)	
									$CHADS_2$ 3-6 points		
									55 per 1,000	24 fewer strokes per 1,000 (from 10 fewer to 34 fewer)	
Nonfatal MI (important outcome)											
10 RCTs	No serious limitations	No serious inconsistency	Very serious indirectness[a]	No serious imprecision	Undetected			RR 0.69 (0.54-0.88)	69 per 1,000[f]	21 fewer MI per 1,000 (from 8 fewer to 32 fewer)	Low
Nonfatal major extracranial bleeds (important outcome)											
10 RCTs	No serious limitations	No serious inconsistency	Very serious indirectness[a]	No serious imprecision	Undetected			RR 2.37 (1.62-3.47)	19 per 1,000[g]	26 more bleeds per 1,000 (from 12 more to 47 more)	Moderate
Systemic embolism (important outcome) median follow-up 1.3 y											
1 RCT	No serious limitations	No serious inconsistency	Very serious indirectness[d]	No serious imprecision	Undetected	18/3,335 (0.5)	4/3,371 (0.1)	RR 0.22 (0.07-0.65)	3 per 1,000[h]	2 fewer systemic emboli per 1,000 (from 1 fewer to 3 fewer)	Low

(Continued)

Table 12—*Continued*

Quality Assessment								Summary of Findings			
						Study Event Rates (%)			Estimation of Absolute Effects 1-y Time Frame		
No. of Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	With Dual Therapy	With Triple Therapy	Relative Effect (95% CI)	With Dual Antiplatelet Therapy	With Triple Therapy (95% CI)	Quality of Evidence
Burden of treatment (important outcome)											
N/A	No serious limitations	No serious limitations	No serious limitations	No serious limitations	N/A	N/A	N/A	Triple therapy > dual therapy	Triple therapy: daily medication, lifestyle limitations, dietary restrictions, frequent blood testing and clinic visits Dual antiplatelet therapy: daily medication only		High

PLATO = Study of Platelet Inhibition and Patient Outcomes; TIMI = Thrombolysis In Myocardial Infarction. See Table 1-3 legends for expansion of other abbreviations.

[a]We used the relative risk for all-cause mortality, nonfatal MI, and nonfatal major extracranial bleeding associated with warfarin + aspirin therapy vs aspirin alone in 10 RCTs of patients with acute coronary syndrome (Rothberg et al[121]) to estimate the effect of triple therapy vs dual antiplatelet therapy on all-cause mortality in patients with AF and acute coronary syndrome.

[b]The 95% CI does not exclude important harm or benefit with triple therapy.

[c]We used the same baseline estimates of mortality as for the general AF population receiving aspirin + clopidogrel. This was based on data from Go et al,[44] which reported a mortality rate of 5.33 per 100 person-y in untreated (no warfarin) patients from an observational study (ATRIA cohort), an estimated relative risk of 0.89 for mortality with aspirin vs no therapy (Table 4), and an estimated relative risk of 0.98 for mortality with aspirin + clopidogrel vs aspirin (Table 7).

[d]We used data from an RCT of warfarin vs aspirin + clopidogrel in patients with AF (ACTIVE W) to estimate the relative effect of triple therapy vs dual antiplatelet therapy on nonfatal stroke and systemic embolism in patients with AF and acute coronary syndrome. This assumption may be underestimating the potential benefit of triple therapy vs dual antiplatelet therapy in reducing nonfatal stroke.

[e]We estimated the annual rates of nonfatal stroke (ischemic and hemorrhagic) on aspirin + clopidogrel by extrapolating from observed annual rates of ischemic stroke (fatal + nonfatal), stratified by $CHADS_2$ score, in the aspirin arms of six historical RCTs in patients with AF (Gage et al[37]). Assumptions underlying these estimates are detailed in section 1.1.4 of this article.

[f]From clopidogrel (plus aspirin) arm of the PLATO trial of ticagrelor vs clopidogrel in patients with acute coronary syndrome.

[g]Based on the absolute rate of non-coronary artery bypass graft-related major bleeding (TIMI definition) reported in the clopidogrel (plus aspirin) arm of the PLATO trial minus the rate of fatal bleeding reported in this arm of the PLATO trial.

[h]Estimate is derived from rate of systemic embolism on aspirin (0.3 per 100 patient-y) reported in the individual patient data meta-analysis by van Walraven et al[61] and estimated relative risk of 0.97 (95% CI, 0.67-1.40) for systemic embolism with combination aspirin + clopidogrel therapy vs aspirin observed in ACTIVE A (Table 7).

bleeding and the burden associated with anticoagulant therapy are likely to choose triple therapy rather than dual antiplatelet therapy. Other factors that may influence this choice are a consideration of bleeding risk and the presence of additional non-$CHADS_2$ risk factors for stroke (see section 2.1.12).

3.3 Patients With AF and ACS Who Do Not Undergo Intracoronary Stent Placement

Dual antiplatelet therapy (eg, with aspirin and clopidogrel) rather than aspirin alone is recommended during the first 12 months after an ACS, regardless of whether patients also receive an intracoronary stent (Vandvik et al[108]). Many patients with AF (eg, $CHADS_2$ score of ≥ 1) will choose VKA therapy (eg, warfarin) to prevent future stroke (section 2.1). Therefore, treatment options in patients with AF and recent ACS may include warfarin plus dual antiplatelet therapy (ie, triple therapy), dual antiplatelet therapy, or warfarin plus single antiplatelet therapy. In this section, we specifically address patients with AF and ACS who do not undergo placement of an intracoronary stent.

The indirect data summarized in Table 12 suggest that triple therapy may not be associated with net clinical benefit compared with dual antiplatelet therapy unless patients are at substantially high risk of stroke (eg, $CHADS_2$ score of ≥ 2), whereas the net benefit at lower levels of stroke risk is uncertain. Rather than triple therapy, a third therapeutic option in this clinical scenario (where stent thrombosis is not a concern) is to use a VKA plus single antiplatelet therapy. Unfortunately, there are no RCTs comparing warfarin plus single antiplatelet therapy to dual antiplatelet therapy. As described in Author et al (section 2.4) in this guideline, warfarin plus aspirin is associated with a significant reduction in risk of subsequent MI (relative risk, 0.69; 95% CI, 0.54-0.88) and stroke (relative risk, 0.56; 95% CI, 0.39-0.82) compared with aspirin alone in patients post-ACS.[121] The point estimates for these reductions in MI and stroke are greater than those seen with clopidogrel plus aspirin (relative risk, 0.77; 95% CI, 0.67-0.89) vs aspirin alone (relative risk, 0.86; 95% CI, 0.63-1.18) in the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial.[124] These data suggest that warfarin plus aspirin is at least as effective, and potentially more effective, than clopidogrel plus aspirin for the prevention of cardiovascular events after ACS. Warfarin plus aspirin was not given a recommendation in Author et al either as an alternative or in preference to dual antiplatelet therapy for patients post-ACS because of pragmatic issues (physician reluctance, burden of use, etc). However, these issues are not relevant for patients already receiving warfarin for AF.

Finally, there are no studies comparing warfarin plus aspirin to triple therapy (eg, warfarin, aspirin, and clopidogrel) in patients with AF and recent ACS. Use of triple therapy in this situation would be appropriate only if the risk reduction in MI and stroke achieved by adding the second antiplatelet agent is greater than the increase in bleeding risk. This seems unlikely in patients who are not undergoing stent placement and, thus, where there is no concern regarding stent thrombosis. Given the lack of direct evidence and mindful of the principle to first do no harm, we do not advocate the use of triple therapy in patients with AF who experience ACS but do not receive an intracoronary stent. However, patients placing a high value on MI and stroke reduction and a low value on avoiding bleeding may opt for an initial period of triple therapy (eg, 3-6 months) followed by warfarin plus aspirin.

Recommendation

3.3. For patients with AF at intermediate to high risk of stroke (eg, $CHADS_2$ score of 1 or greater) who experience an acute coronary syndrome and do not undergo intracoronary stent placement, we suggest, for the first 12 months, adjusted-dose VKA therapy (INR 2.0-3.0) plus single antiplatelet therapy rather than dual antiplatelet therapy (eg, aspirin and clopidogrel) or triple therapy (eg, warfarin, aspirin, and clopidogrel) (Grade 2C)**. After the first 12 months, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease (see section 3.1).**

For patients with AF at low risk of stroke (eg, $CHADS_2$ score of 0), we suggest dual antiplatelet therapy (eg, aspirin and clopidogrel) rather than adjusted-dose VKA therapy (INR 2.0-3.0) plus single antiplatelet therapy or triple therapy (eg, warfarin, aspirin, and clopidogrel) (Grade 2C)**. After the first 12 months, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease (see section 3.1).**

Remarks: Patients who place an exceptionally high value on stroke reduction and a low value on avoiding bleeding and the burden associated with anticoagulant therapy are likely to choose adjusted-dose VKA therapy plus single antiplatelet therapy rather than dual antiplatelet therapy. Other factors that may influence this choice are a consideration of bleeding risk and the presence of additional non-$CHADS_2$ risk factors for stroke (see section 2.1.12).

3.4 Patients With AF Managed by a Rhythm Control Strategy

Some patients with AF will be managed with antiarrhythmic drugs (AADs) to achieve and maintain normal sinus rhythm. Increasingly, patients with AF are also receiving catheter radiofrequency ablation procedures (pulmonary vein isolation) to maintain normal sinus rhythm. In the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial, in which many patients in the rhythm control arm did not receive anticoagulation, patients in a rhythm control strategy had a similar risk of stroke compared with patients in a rate control strategy (see also section 4.1.1).[125]

There are several RCTs of catheter ablation vs AAD therapy in patients with AF, typically those who have failed first-line therapy with AADs.[126-132] All trials found a significant reduction in AF recurrence at ~1 year of follow-up. However, AF recurrence in the catheter ablation arms ranged from 11% to 44% at ~1 year. The studies rarely reported on stroke outcomes, and all were underpowered to address this question. Given the results of the AFFIRM trial, the lack of longer-term follow-up data from catheter ablation RCTs regarding AF recurrence rates, and poor reporting of stroke outcomes, it would be prudent to base decisions about long-term antithrombotic therapy on a patient's underlying risk for stroke as recommended in section 2.1, and not on their underlying rhythm.

Recommendation

3.4. For patients with AF being managed with a rhythm control strategy (pharmacologic or catheter ablation), we suggest that antithrombotic therapy decisions follow the general risk-based recommendations for patients with AF in section 2.1, regardless of the apparent persistence of normal sinus rhythm (Grade 2C)**.**

3.5 Patients With Atrial Flutter

Many patients with persistent atrial flutter have periods of atrial flutter alternating with periods of AF.[133,134] The prevalence of thrombus in the body of the atria and atrial appendage on TEE in patients with atrial flutter ranges from 1% to 21%.[135-138] There are few data from longitudinal studies assessing the risk of thromboembolism with well-documented sustained atrial flutter. A study describing a series of 191 consecutive, unselected patients hospitalized for treatment of atrial flutter reported thromboembolism in 7% of patients during a mean follow-up of 26 months.[134] The role of anticoagulant therapy for patients with atrial flutter has not been evaluated in clinical trials, but because these patients often have concomitant AF or are at increased risk of developing AF, it is reasonable to base decisions regarding antithrombotic therapy on the risk stratification schemes used for AF (section 1.1).

Recommendation

3.5. For patients with atrial flutter, we suggest that antithrombotic therapy decisions follow the same risk-based recommendations as for AF.

4.0 Antithrombotic Therapy for Patients With AF Undergoing Cardioversion

To minimize the risk of stroke and systemic embolism associated with cardioversion, therapeutic anticoagulation (eg, with adjusted-dose oral VKAs; INR 2.0-3.0) conventionally is recommended for a minimum of 3 weeks before, during, and for a minimum of 4 weeks after the procedure. For some patients with AF of documented short duration (eg, ≤48 h), a common practice is to cardiovert without prolonged precardioversion anticoagulation. For patients with AF duration of >48 h or unknown duration, a TEE-guided approach is an alternative strategy that can simplify anticoagulation management before cardioversion. In this section, we summarize the evidence and give recommendations for the use of antithrombotic therapy in patients undergoing electrical or pharmacologic cardioversion for AF (or atrial flutter).

4.1 Patients Undergoing Elective Cardioversion of AF

4.1.1 Cardioversion of AF of More Than 48 h or Unknown Duration: Evidence favoring the efficacy of pericardioversion anticoagulation is based on observational studies in mostly patients undergoing electrical rather than pharmacologic cardioversion. There is moderate-quality evidence from a systematic review of 18 observational studies suggesting that the risk of stroke or thromboembolism is substantially lower in patients receiving pericardioversion anticoagulation than in those who receive no anticoagulation (0.3% vs 2.0%), translating to a relative risk of 0.16 (95% CI, 0.05-0.48) in favor of anticoagulation.[139] No data regarding major hemorrhagic events were reported in this systematic review.

The conventional duration of a minimum of 3 weeks therapeutic anticoagulation before cardioversion and a minimum 4 weeks afterward is based on indirect pathophysiologic data and evidence from observational studies and remains arbitrary. Observational data showing that thromboembolism was significantly more common at an INR of 1.5 to 2.4 before

cardioversion than an INR of ≥ 2.5 (0.93% vs 0%, $P = .012$) suggests the importance of maintaining a therapeutic INR in the pericardioversion period.[140] After cardioversion, results of observational studies suggest that the highest risk of stroke and thromboembolism is in the first 72 h after cardioversion and that the majority of thromboembolic complications will occur within 10 days of cardioversion.[141] However, TEE studies have demonstrated that despite restoration of sinus rhythm on the ECG, atrial mechanical dysfunction may persist for several weeks postcardioversion.[142]

A nonrandomized comparison of 1,270 patients enrolled in the RE-LY trial who underwent 1,983 cardioversions suggests that there may be no excess harm with dabigatran compared with warfarin when used for pericardioversion anticoagulation. Most cardioversions in this study (~80%) were performed after the protocol-assigned study anticoagulant was given for a minimum of 3 weeks before the procedure, and rates of stroke and systemic embolism at 30 days after cardioversion were low when oral anticoagulation with either warfarin or dabigatran was given before cardioversion (0.8%, 0.3%, and 0.6% with dabigatran 110 mg bid, dabigatran 150 mg bid, and warfarin, respectively).[143]

A TEE-guided approach with abbreviated anticoagulation before cardioversion is an alternative to the conventional approach of using a minimum of 3 weeks therapeutic precardioversion anticoagulation.[144] Under a TEE-guided strategy, patients receive anticoagulation and once therapeutic, undergo screening TEE. If thrombus is seen in either atrial appendage or atrium at the time of TEE, cardioversion is postponed, given the presumed high risk of thromboembolism. If no thrombus is seen, the patient proceeds immediately to cardioversion. A TEE-guided strategy requires an experienced echocardiographer because accurate visualization of thrombus may be operator dependent.

The Assessment of Cardioversion Using Transesophageal Echocardiography (ACUTE) RCT compared a TEE-guided strategy of abbreviated therapeutic anticoagulation with IV unfractionated heparin (started 24 h before cardioversion) or warfarin (INR 2.0-3.0) (started 5 days before cardioversion) to a strategy of therapeutic anticoagulation for at least 3 weeks before cardioversion.[145] The evidence is of low quality given the wide 95% CIs around the point estimates of effect on patient-important outcomes (Table 13). Thus, the results do not exclude with confidence the possibility of important benefit or harm with a TEE-guided approach compared with a conventional approach of 3 weeks anticoagulation precardioversion.

Acknowledging these uncertainties, a TEE-guided approach may be best suited for patients who are very symptomatic while in AF because cardioversion can be done sooner if the TEE is negative for thrombus. It may also suit patients who would prefer to avoid prolonged oral anticoagulation before cardioversion and those at increased risk for bleeding. However, the ability to avoid anticoagulation with a TEE-guided strategy is most relevant for patients without stroke risk factors and at low risk of recurrent AF in whom long-term anticoagulation beyond 4 weeks after cardioversion would not be required.

For patients undergoing a TEE-guided approach, low-molecular-weight heparin at full VTE treatment doses or IV unfractionated heparin (to maintain an activated partial thromboplastin time prolongation

Table 13—*[Section 4.1] Abbreviated Anticoagulation With TEE-Guided Cardioversion vs Conventional Anticoagulation for at Least 3 Weeks Before Cardioversion*

	Anticipated Absolute Effects (Time Frame Is 8 wk)				
Outcomes	Risk With Conventional Anticoagulation	Risk Difference With TEE + Abbreviated Anticoagulation[a] (95% CI)	Relative Effect (95% CI)	No. of Participants (Studies), Follow-up	Quality of The Evidence (GRADE)
Death	10 per 1,000[b]	14 more deaths per 1,000 (0 more to 52 more)	RR 2.44 (0.95-6.24)	1,222 (1 RCT), 8 wk	Low[c]
Nonfatal strokes	3 per 1,000[b]	5 more strokes per 1,000 (2 fewer to 38 more)	RR 2.44 (0.47-12.50)	1,222 (1 RCT), 8 wk	Low[c]
Nonfatal major extracranial bleeds[d]	15 per 1,000[b]	7 fewer bleeds per 1,000 (12 fewer to 9 more)	RR 0.54 (0.18-1.61)	1,222 (1 RCT), 8 wk	Low[c]

ACUTE = Assessment of Cardioversion Using Transesophageal Echocardiography; GRADE = Grades of Recommendations, Assessment, Development, and Evaluation; TEE = transesophageal echocardiography. See Tables 1 and 8 for expansion of other abbreviations.

[a]Abbreviated anticoagulation refers to either IV unfractionated heparin (started 24 h before cardioversion) or adjusted-dose warfarin (INR 2.0-3.0) (started 5 d before cardioversion).

[b]Assumed risk is the observed event rate from the control arm (ie, conventional anticoagulation) of the RCT by Klein et al[145] (ACUTE trial).

[c]No statistically significant effect, and CIs are very wide. Trial was not sufficiently large to demonstrate comparable safety between conventional and TEE-based strategies.

[d]Most of these were GI bleeds.

that corresponds to plasma heparin levels of 0.3-0.7 International Units/mL antifactor Xa activity) should be started at the time of TEE and cardioversion performed within 24 h of the TEE if no thrombus is seen. A few observational studies and one RCT have suggested that low-molecular-weight heparin has similar efficacy compared with heparin or warfarin for immediate anticoagulation before TEE.[146-150] Outpatients undergoing a TEE-guided approach may be started on a VKA (INR 2.5; range, 2.0-3.0) and the TEE and subsequent cardioversion scheduled for 5 days later (if the INR is in therapeutic range at that time). The new oral anticoagulants may also be suitable for outpatient treatment before TEE-guided cardioversion given their ease of use (eg, dabigatran achieves steady-state concentrations in 2-3 days after bid administration),[151] but they have not yet been studied for this purpose.

There is no direct evidence to guide decisions about the long-term management of anticoagulation in patients who appear to be in sinus rhythm 4 weeks after cardioversion. Several observational studies indicate that approximately one-half of patients will have recurrence of AF at 1 year after cardioversion.[152-156] The AFFIRM study, in which many patients stopped anticoagulation after initial (apparently) successful restoration of sinus rhythm, found similar rates of thromboembolism with a rhythm control strategy.[125] Finally, patients with PAF often are asymptomatic during episodes of AF recurrence, with one series suggesting that only one in every 12 paroxysms are symptomatic.[157] These observations suggest that decisions about long-term antithrombotic therapy should be primarily based on a patient's risk for stroke (see section 2.1) rather than on the prevailing rhythm at 4 weeks postcardioversion.

Recommendation

4.1.1. For patients with AF of greater than 48 h or unknown duration undergoing elective electrical or pharmacologic cardioversion, we recommend therapeutic anticoagulation (adjusted-dose VKA therapy, target INR range 2.0-3.0, low-molecular-weight heparin at full venous thromboembolism treatment doses, or dabigatran) for at least 3 weeks before cardioversion or a TEE-guided approach with abbreviated anticoagulation before cardioversion, rather than no anticoagulation (Grade 1B)**. We recommend therapeutic anticoagulation for at least 4 weeks after successful cardioversion to sinus rhythm, rather than no anticoagulation, regardless of the baseline risk of stroke** (Grade 1B)**. Decisions about anticoagulation beyond 4 weeks should be made in accordance with our risk-based recommendations for long-term antithrombotic therapy in section 2.1.**

4.1.2 Cardioversion of AF of 48 h Duration or Less: There is uncertainty over the precise duration of AF necessary for thrombus to develop and, hence, the threshold of AF duration below which precardioversion anticoagulation can be safely avoided. For AF of short duration (eg, ≤48 h), a common practice is to cardiovert without a TEE or prolonged precardioversion anticoagulation. However, observational studies have found left atrial thrombus on TEE in as many as 14% of patients with acute AF of short duration.[158,159] Moreover, because many individuals develop AF asymptomatically, it is often difficult to accurately determine a patient's duration of AF, making the 48-h rule difficult to apply.[160] No RCTs have compared different anticoagulation strategies in patients with AF of documented duration of ≤48 h. Observational data suggest that the risk of stroke or thromboembolism in these patients is similar to those who have received conventional anticoagulation for a minimum of 3 weeks before cardioversion.[140,161]

Recommendation

4.1.2. For patients with AF of documented duration of 48 h or less undergoing elective cardioversion (electrical or pharmacologic), we suggest starting anticoagulation at presentation (low-molecular-weight heparin or unfractionated heparin at full venous thromboembolism treatment doses) and proceeding to cardioversion rather than delaying cardioversion for 3 weeks of therapeutic anticoagulation or a TEE-guided approach (Grade 2C)**. After successful cardioversion to sinus rhythm, we recommend therapeutic anticoagulation for at least 4 weeks rather than no anticoagulation, regardless of baseline stroke risk** (Grade 2C)**. Decisions about long-term anticoagulation after cardioversion should be made in accordance with our risk-based recommendations for long-term antithrombotic therapy in section 2.1.**

4.2 Patients Undergoing Urgent Cardioversion for Hemodynamically Unstable AF

There are no published data regarding the optimal anticoagulation strategy to use before or during urgent cardioversion for patients with AF and hemodynamic instability. Initiation of anticoagulation immediately before urgent cardioversion (eg, with IV unfractionated heparin or low-molecular-weight heparin) would be expected to reduce the risk of stroke or thromboembolism based on studies

of elective cardioversion. It is important to note that the initiation of anticoagulation therapy should not delay any emergency interventions to stabilize the patient.

Recommendation

4.2. For patients with AF and hemodynamic instability undergoing urgent cardioversion (electrical or pharmacologic), we suggest that therapeutic-dose parenteral anticoagulation be started before cardioversion, if possible (Grade 2C)**, but that initiation of anticoagulation must not delay any emergency intervention** (Grade 2C)**. After successful cardioversion to sinus rhythm, we suggest therapeutic anticoagulation for at least 4 weeks after successful cardioversion to sinus rhythm rather than no anticoagulation, regardless of baseline stroke risk** (Grade 2C)**. Decisions about anticoagulation beyond 4 weeks should be made in accordance with our risk-based recommendations for long-term antithrombotic therapy in section 2.1.**

4.3 Patients Undergoing Elective or Urgent Cardioversion for Atrial Flutter

There are no published data regarding the optimal anticoagulation strategy to use for patients undergoing cardioversion for atrial flutter. Although some observational studies suggest that the risk of thromboembolism after cardioversion for atrial flutter is low, even without anticoagulation, other studies have documented a similar risk of thromboembolism in patients after cardioversion for atrial flutter and AF.[140,162,163] This may be because AF and atrial flutter often coexist.

Recommendation

4.3. For patients with atrial flutter undergoing elective or urgent pharmacologic or electrical cardioversion, we suggest that the same approach to thromboprophylaxis be used as for patients with atrial fibrillation undergoing cardioversion.

5.0 Practical Issues in the Management of VKA Therapy

5.1 Optimal Target INR Range

For a full discussion of optimal target INR range with VKA therapy across a variety of indications, see Holbrook et al[91] regarding evidence-based management of anticoagulation in this guideline. With respect to patients with AF specifically, several studies assessed oral anticoagulation at very-low INR targets or fixed low doses compared with adjusted-dose anticoagulation targeted at an INR of 2.0 to 3.0 and found that anticoagulation targeted at an INR of 2.0 to 3.0 was more effective in reducing the risk of stroke.[164] Observational studies have shown that the risk of ischemic stroke is much greater once INR levels are <2.0 and that there are no appreciable gains in efficacy with levels >2.0. However, there is a sharp increase in the risk of bleeding complications, particularly intracranial hemorrhage, as INR levels rise to >3.0 to 4.0.[165-169] A target INR value of 2.0 will result in patients spending a substantial proportion of time at subtherapeutic INR levels (ie, <2.0).[170] Given that bleeding risk does not rise substantially until INR levels are >3.0, and particularly >4.0, these data from AF populations support an optimal target INR range of 2.0 to 3.0, with a target value of 2.5 to maximize the time spent in the optimal INR range.[165-170]

5.2 Time in Therapeutic Range

For a full discussion of the importance of time in therapeutic range while on adjusted-dose VKA therapy, see Ageno et al[171] regarding oral anticoagulation in this guideline. With respect to patients with AF, there are several observational studies indicating that increasing time out of range is associated with poorer outcomes (eg, mortality, ischemic stroke, thromboembolism, major bleeding).[172-175]

6.0 Future Research

Approximately one in every three patients with AF also has coronary artery disease.[51] However, the optimal approach to antithrombotic therapy in these patients is unclear. Research is needed to determine the effect of treatment with oral anticoagulation and aspirin compared with oral anticoagulation alone on patient-important outcomes of vascular death, nonfatal stroke, nonfatal MI, nonfatal major extracranial bleeding, and nonfatal systemic embolism. Research is also needed to inform recommendations about different antithrombotic therapy regimens for patients with AF undergoing placement of an intracoronary artery stent or who experience an ACS (eg, triple therapy with oral anticoagulation, clopidogrel, and aspirin; dual antiplatelet therapy with clopidogrel and aspirin; or combination oral anticoagulation and aspirin or clopidogrel). Finally, all existing stroke risk stratification and bleeding risk stratification schema for patients with AF have modest predictive value, and development of more-accurate risk stratification systems is needed to facilitate a more-accurate estimation of net clinical benefit for individual patients.

7.0 Conclusions

Stroke is a serious complication of AF, but its risk varies considerably across different groups of patients with AF. Antithrombotic prophylaxis for stroke is associated with an increased risk of bleeding. We provide recommendations for antithrombotic treatment based on net clinical benefit for patients with AF at varying levels of stroke risk. Oral anticoagulation is the optimal choice of antithrombotic therapy for patients with AF at high risk of stroke (eg, $CHADS_2$ score ≥ 2). At lower levels of stroke risk, antithrombotic treatment decisions will require a more individualized approach that takes into consideration patient values and preferences, bleeding risk, and the presence of non-$CHADS_2$ stroke risk factors. The role of oral anticoagulation for the prevention of stroke in patients with AF will evolve as the results of large, ongoing, phase 3 RCTs of new oral anticoagulants are published and as experience with these new agents in clinical practice continues to grow.

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Dr Fang: contributed as a panelist.
Dr Hylek: contributed as a panelist.
Dr Schulman: contributed as a panelist.
Dr Go: contributed as a panelist.
Dr Hughes: contributed as a panelist.
Dr Spencer: contributed as a panelist.
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He has served as a consultant on stroke prevention in atrial fibrillation to Bayer Healthcare Pharmaceuticals; Boehringer Ingelheim GmbH; Bristol-Myers Squibb; Daiichi-Sankyo, Inc; Johnson & Johnson; Merck and Co, Inc; Pfizer Inc; and Sanofi-Aventis LLC. Dr. Singer has published numerous articles on stroke prevention in atrial fibrillation and has given numerous lectures and research presentations on this topic. Dr Lane is in receipt of an investigator-initiated educational grant from Bayer Healthcare Pharmaceuticals and has participated in speaker activities for Bayer Healthcare Pharmaceuticals, Boehringer Ingelheim GmbH, Bristol-Myers Squibb/Pfizer Inc, and the Thrombosis Research Institute. She has also received support (travel and accommodation) to attend conferences from AstraZeneca and Boehringer Ingelheim GmbH. 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Dr Hylek has participated in a symposium sponsored by Boehringer Ingelheim, served on advisory boards (Bayer Healthcare Pharmaceuticals; Boehringer Ingelheim GmbH; Bristol-Myers Squibb; Daiichi-Sankyo, Inc; Johnson & Johnson; Merck and Co, Inc; Ortho-McNeil Pharmaceutical, Inc; and Pfizer Inc) for amounts totaling < $10,000 and participated at the steering committee level for several pharmaceutical-sponsored studies (ARISTOTLE trial sponsored by Bristol-Myers Squibb and Pfizer Inc [< $10,000] and ORBIT-AF Registry sponsored by Ortho-McNeil Pharmaceutical, Inc [< $10,000]). Dr Go has received research funding from the National Heart, Lung, and Blood Institute related to antithrombotic therapy in atrial fibrillation and was a site principal investigator for a clinical trial sponsored by Johnson & Johnson and Bayer Healthcare Pharmaceuticals. Dr Halperin has received consulting fees from the following pharmaceutical manufacturers for advisory activities involving the development of anticoagulant drugs, none of which are currently approved for clinical use in any indication in the United States: Astellas Pharma, US; Bayer AG HealthCare; Boehringer Ingelheim; Daiichi Sankyo; Johnson & Johnson; and Sanofi-Aventis. He has received honoraria from Portola Pharmaceuticals, Inc as a member of the Data Safety Monitoring Board of its Phase II EXPLORE-AF trial involving an investigational anticoagulant for prevention of thromboembolism in patients with atrial fibrillation. He has received consulting fees from Biotronik, Inc as co-chair of the Steering Committee for the IMPACT clinical trial evaluating the use ambulatory monitoring technology in approved implanted cardiac arrhythmia devices to guide anticoagulation therapy for stroke prevention. 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Role of sponsors: The sponsors played no role in the development of these guidelines. Sponsoring organizations cannot recommend panelists or topics, nor are they allowed prepublication access to the manuscripts and recommendations. Guideline panel members, including the chair, and members of the Health & Science Policy Committee are blinded to the funding sources. Further details on the Conflict of Interest Policy are available online at http://chestnet.org.

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Additional information: The supplement Tables can be found in the Online Data Supplement at http://chestjournal.chestpubs.org/content/141/2_suppl/e531S/suppl/DC1.

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CHEST Online Data Supplement

Antithrombotic Therapy for Atrial Fibrillation

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

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Table S1—*Studies Assessing Prior Stroke/TIA as an Independent Predictor of Stroke in Patients With AF*

Study/Year	Multivariate OR/RR (95% CI)	*P* Value
Pooled estimate[1]	2.5 (1.8-3.5)	.59 (for heterogeneity)
Studies included in pooled estimate:		
AFI[2]/1994	2.5 (NR)	< .05
SPAF I-III Aspirin[3]/1999	2.9 (NR)	< .001
Stöllberger et al[4]/1998	3.7 (1.5-7.5)	.002
Wang et al[5]/2003	1.9 (1.1-3.3)	NR
Studies not included in pooled estimate:		
AFI Echo[6]/1998[a]	3.5 (1.8-6.7)	< .001
Aronow et al[7]/1998	1.6 (1.1-2.2)	< .009
Hart et al[8]/2000 (intermittent AF)	4.1 (NR)	.01
Hart et al[8]/2000 (sustained AF)	2.7 (NR)	< .001
SPAF I[9]/1992	2.1 (NR)	.04
Stöllberger et al[10]/2004	2.14 (NR)	.045
van Latum et al[11]/1995	1.6 (1.0-2.6)	< .05
Van Staa et al[12]/2011	2.86 (2.53-3.22)	< .05

AF = atrial fibrillation; AFI = Atrial Fibrillation Investigators; NR = not reported; RR = risk ratio; SPAF = Stroke Prevention in Atrial Fibrillation; TIA = transient ischemic attack.

[a]Subset of patients from AFI[6] with echocardiographic data available.

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Table S2—*Studies Assessing Hypertension as an Independent Predictor of Stroke in Patients With AF*

Study/Year	Multivariate OR/RR (95% CI)	*P* Value
Pooled estimate[1]	2.0 (1.6-2.5)	.29 (for heterogeneity)
Studies included in pooled estimate:		
AFI[2]/1994	1.6 (NR)	< .05
Moulton[13]/1991	1.9 (1.2-3.1)	< .05
SPAF I-III Aspirin[3]/1999	2.0 (NR)	< .001
Stöllberger et al[4]/1998	3.6 (1.8-8.4)	.001
Studies not included in pooled estimate:		
AFI Echo[6]/1998[a]	1.5 (0.9-2.5)	.13
Aronow et al[14]/1989	12.5 (NR)	< .01
Aronow et al[7]/1998	NR	NS
Cabin et al[15]/1990	NR	NS
Hart et al[8]/2000 (intermittent AF)	3.4 (NR)	.003
Hart et al[8]/2000 (sustained AF)	1.8 (NR)	.008
Petersen et al[16]/1990	NR	NS
Seidl et al[17]/1998	6.5 (1.5-4.5)	< .05
SPAF I[9]/1992	2.2 (1.1-4.3)	.02
SPAF III[18]/1998[b]	3.3 (1.7-6.9)	.001
Stöllberger et al[10]/2004	NR	NS
Wang et al[5]/2003[c]	NR	NS
Studies assessing uncontrolled hypertension only[d]:		
Hart et al[8]/2000 (intermittent AF)	NR	NS
Hart et al[8]/2000 (sustained AF)	2.8 (NR)	< .001
SPAF I-III Aspirin[3]/1999	2.3 (NR)	< .001
van Latum et al[11]/1995	1.7 (1.0-2.9)	NS
Van Staa et al[12]/2011 (≥ 180 vs < 120 mm Hg)	2.74 (1.21-6.19)	< .05
Van Staa et al[12]/2011 (140-159 vs < 120 mm Hg)	2.74 (1.21-6.19)	< .05
Van Staa et al[12]/2011 (160-179 vs < 120 mm Hg)	1.49 (0.55-4.00)	NS
Wang et al[5]/2003	1.1/10 mm	< .05

NS = not significant. See Table S1 legend for expansion of other abbreviations.

[a]Subset of patients from AFI (1994)[2] with echocardiographic data available.

[b]Defines hypertension as diagnosed hypertension.

[c]Defines hypertension as use of BP-lowering medication.

[d]Defined as systolic BP > 160 mm Hg, unless otherwise stated.

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Table S3—*Studies Assessing Increasing Age as an Independent Predictor of Stroke in Patients With AF*

Study/Year	Multivariate OR/RR (95% CI)	*P* Value
Pooled estimate[1]	1.5 (1.3-1.7)/decade	.59 (for heterogeneity)
Studies included in pooled estimate:		
AFI[2]/1994	1.4 (NR)/decade	< .05
Moulton et al[13]/1991 (for age > 75)	1.7 (1.0-2.8)	< .05
SPAF I-III Aspirin[3]/1999	1.8 (NR)/decade	< .001
Stöllberger et al[4]/1998	1.1 (1.0-1.1)[a]	< .001
Wang et al[5]/2003	1.3 (NR)/decade	< .05
Studies not included in pooled estimate:		
AFI Echo[6]/1998[b]	1.5 (NR)/decade	.006
Cabin et al[15]/1990 (for age > 70)	NR	NS
Hart et al[8]/2000 (intermittent AF)	2.1 (NR)/decade	< .001
Hart et al[8]/2000 (sustained AF)	1.7 (NR)/decade	< .001
Inoue and Atarashi[19]/2000 (paroxysmal AF; for age > 65 y)	3.3 (1.92-5.81)	.0001
Nakagami et al[20]/1998	1.3 (1.0-1.7)/decade	NS
SPAF I[9]/1992	1.2 (0.9-1.6)/decade	NS
SPAF III[18]/1998	1.7 (1.1-2.6)/decade	.01
van Latum et al[11]/1995	NR	NS
Van Staa et al[12]/2011 (age, < 50 vs 60-69 y)	0.14 (0.06-0.34)	< .05
Van Staa et al[12]/2011 (age, ≥ 80 vs 60-69 y)	2.22 (1.78-2.76)	< .05
Van Staa et al[12]/2011 (age, 50-59 vs 60-69 y)	0.44 (0.28-0.69)	< .05
Van Staa et al[12]/2011 (age, 70-79 vs 60-69 y)	1.42 (1.12-1.78)	< .05

See Table S1 and S2 legends for expansion of abbreviations.
[a]Age entered as a continuous variable.
[b]Subset of patients from AFI (1994)[2] with echocardiographic data available.

Table S4—*Studies Assessing Diabetes as an Independent Predictor of Stroke in Patients With AF*

Study/Year	Multivariate OR/RR (95% CI)	*P* Value
Pooled estimate[1]	1.7 (1.4-2.0)	.69 (for heterogeneity)
Studies included in pooled estimate:		
AFI[2]/1994	1.7 (NR)	< .05
SPAF I-III Aspirin[3]/1999	1.9 (NR)	.02
Stöllberger et al[4]/1998	NR	NS
Wang et al[5]/2003	1.8 (1.4-3.1)	NR
Studies not included in pooled estimate:		
AFI Echo[6]/1998[a]	1.7 (1.0-2.9)	.05
Aronow et al[7]/1998	NR	NS
Petersen et al[16]/1990	NR	NS
Seidl et al[17]/1998	NR	NS
SPAF III[18]/1998	NR	NS
Van Staa et al[12]/2011	1.33 (1.14-1.55)	< .05

See Table S1 and S2 legends for expansion of abbreviations.
[a]Subset of patients from AFI[2] with echocardiographic data available.

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Table S5—*Studies Assessing Heart Failure as an Independent Predictor of Stroke in Patients With AF*

Study/Year	Multivariate OR/RR (95% CI)	*P* Value
AFI[2]/1994	1.4 (NR)	NS
AFI Echo[6]/1998[a] (with echocardiographic data)	1.4 (0.8-2.3)	.16
AFI Echo[6]/1998[a] (without echocardiographic data)	1.7 (1.1-2.7)	.03
SPAF[18]/1998	NR	NS
SPAF I[9]/1992	2.6 (1.0-4.2)	.01
SPAF I-III Aspirin[3]/1999	NR	NS
Stöllberger et al[8]/1998[b]	NR	NS
Stöllberger et al[10]/2004[b]	NR	NS
Van Staa et al[12]/2011	1.26 (1.11-1.42)	< .05

See Table S1 and S2 legends for expansion of abbreviations.
[a]Subset of patients from AFI[2] with echocardiographic data available.
[b]Defined as New York Heart Association functional class > II.

Table S6—*Studies Assessing LV Dysfunction/Hypertrophy (Using Echocardiography) as an Independent Predictor of Stroke in Patients With AF*

Study/Year	Multivariate OR/RR (95% CI)	*P* Value
AFI Echo[6]/1998	1.4 (0.8-2.3)	.16
Aronow et al[7]/1998	1.8 (1.2-2.7)	.003
Aronow et al[7]/1998 (LV hypertrophy)	2.8 (1.8-4.4)	.0001
Aronow et al[14]/1989 (LV hypertrophy)	6.56 (NR)	< .01
SPAF[21]/1992	2.6 (1.4-4.9)	.003
SPAF I-III Aspirin[3]/1999 (using 2D echocardiography)	NR	NS
SPAF I-III Aspirin[3]/1999 (using M-mode echocardiography)	NR	NS
Stöllberger et al[4]/1998	NR	NS

2D = two dimensional; LV = left ventricular. See Table S1 and S2 legends for expansion of other abbreviations.

Table S7—*Studies Assessing Valvular Heart Disease[a] as an Independent Predictor of Stroke in Patients With AF*

Study/Year	Multivariate OR/RR (95% CI)	*P* Value
AFI Echo[6]/1998 (mitral valve prolapse)	0.29 (NR)	NS
AFI Echo[6]/1998 (mitral valve regurgitation)	1.07 (NR)	NS
Aronow et al[7]/1998 (aortic stenosis)	NR	NS
Aronow et al[7]/1998 (mitral annular calcifications)	NR	NS
Nakagami et al[20]/1998 (mitral valve regurgitation)	0.45 (0.20-0.97)	< .05
van Staa et al[12]/2011	1.65 (1.01-2.71)	< .05

See Table S1 and S2 legends for expansion of abbreviations.
[a]Specific type of valvular heart disease in parentheses.

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Table S8—*Studies Assessing Female Sex as an Independent Predictor of Stroke in Patients With AF*

Study/Year	Multivariate OR/RR (95% CI)	*P* Value
AFI[2]/1994	NR	NS
AFI Echo[6]/1998[a]	NR	NS
Aronow et al[7]/1998	NR	NS
Aronow et al[14]/1989	0.85 (NR)	NS
Cabin et al[15]/1990	NR	.014
Fang et al[22]/2005 (all women)	1.6 (1.3-1.9)	< .05
Fang et al[22]/2005 (women aged > 75 vs men aged > 75 y)	1.8 (1.4-2.3)	< .05
Fang et al[22]/2005 (women aged ≤ 75 vs men aged ≤ 75 y)	1.6 (1.0-2.3)	NS
Hart et al[8]/2000 (intermittent AF)	NR	NS
Hart et al[8]/2000 (sustained AF)	1.8	.004
Inoue and Atarashi[19]/2000[b] (paroxysmal AF)	0.50 (0.27-0.93)	.0291
Moulton[13]/1991	NR	NS
Nakagami et al[20]/1998	0.98 (0.55-1.72)	NS
Petersen et al[23]/1990	NR	NS
SPAF III[18]/1998	NR	NS
SPAF I-III Aspirin[3]/1999 (all women)	1.6 (NR)	.01
SPAF I-III Aspirin[3]/1999 (women aged > 75 y)	3.0 (NR)	.002
Stöllberger et al[4]/1998	NR	NS
van Latum et al[11]/1995	1.5 (1.0-2.4)	.05
Van Staa et al[12]/2011[b]	1.05 (0.94-1.19)	NS
Wang et al[5]/2003	1.9 (1.2-3.1)	< .05

See Table S1 and S2 legends for expansion of abbreviations.
[a]Subset of patients from AFI[2] with echocardiographic data available.
[b]Reference sex in original study was female; reported values of RR have been inverted to be directly comparable with other studies.

Table S9—*Studies Assessing Estrogen-Based HRT as an Independent Predictor of Stroke in Patients With AF*

Study/Year	Multivariate OR/RR (95% CI)	*P* Value
Fang et al[22]/2005 (22% HRT use)	1.0 (0.7-1.4)	NS
SPAF I-III Aspirin[3]/1999 (33% HRT use at entry)	3.1 (NR)	.007

HRT = hormone replacement therapy. See Table S1 and S2 legends for expansion of other abbreviations.

Table S10—*Studies Assessing Coronary Artery Disease as an Independent Predictor of Stroke in Patients With AF*

Study/Year	Multivariate OR/RR (95% CI)	*P* Value
AFI[2]/1994 (history angina)	NR	NS
AFI[2]/1994 (history myocardial infarction)	1.7 (NR)	NS
Aronow et al[14]/1989 (history myocardial infarction)	4.84 (NR)	< .01
Petersen et al[23]/1990 (history myocardial infarction)	1.7 (NR)	.0375
SPAF III[18]/1998	NR	NS
SPAF I-III Aspirin[3]/1999	NR	NS
Stöllberger et al[4]/1998	NR	NS

Other studies have examined peripheral artery disease as an independent predictor of stroke in patients with AF.[24,25] See Table S1 and S2 legends for expansion of abbreviations.

Table S11—*Studies Assessing Carotid Artery Stenosis as an Independent Predictor of Stroke in Patients With AF*

Study/Year	Multivariate OR/RR (95% CI)	*P* Value
SPAF II[26]/1994	1.8 (0.5-3.6)	.55

See Table S1 legend for expansion of abbreviations.

Table S12—*Studies Assessing Left Atrial Thrombus as an Independent Predictor of Stroke in Patients With AF*

Study/Year	Multivariate OR/RR (95% CI)	*P* Value
Stöllberger[4]/1998	2.4 (0.9-6.9)	.09

See Table S1 for expansion of abbreviations.
[a]One-half of the 10 patients with left atrial thrombus received anticoagulant therapy, likely blunting the predictive value.

Table S13—*Stroke Risk Stratification Schema*

Study/Year	Low Risk	Intermediate Risk	High Risk
AFI[3]/1994	Age < 65 y and no risk factors	Age > 65 y and no other risk factors	Prior stroke/TIA, hypertension, diabetes
SPAF[18]/1998	No risk factors	Hypertension, diabetes	Prior stroke/TIA, women > 75 y, men > 75 y with hypertension
$CHADS_2$[27]/2001	Score 0	Score 1-2	Score 3-6
AFI[28]/2003	No risk factors	No intermediate risk category	Previous stroke/TIA, hypertension, diabetes, angina, previous MI
Framingham[5]/2003	Score 0-7	Score 8-15	Score 16-31
NICE guidelines[29]/2006	Age < 65 y with no moderate/high risk factors	Age ≥ 65 y with no high risk factors Age < 75 y with hypertension, diabetes or vascular disease[a]	Previous stroke/TIA or thromboembolic event Age ≥ 75 y with hypertension, diabetes or vascular disease Clinical evidence of valve disease or heart failure, or impaired left ventricular function
ACC/AHA/ESC guidelines[30]/2006	No risk factors	Age ≥ 75 y, or hypertension, or heart failure, or LVEF < 35%, or diabetes	Previous stroke, TIA or embolism, or ≥ 2 moderate risk factors of (age ≥ 75y, hypertension, heart failure, LVEF ≤ 35%, diabetes)
8th ACCP guidelines[31]/2008	No risk factors	Age > 75 y, or hypertension, or moderately or severely impaired LVEF and/or heart failure, or diabetes	Previous stroke, TIA or embolism, or ≥ 2 moderate risk factors of (age ≥ 75y, hypertension, moderately or severely impaired LVEF and/or heart failure, diabetes)
$CHADS_2$-VASc[32]/2009	No risk factors	One combination risk factor: (heart failure/LVEF ≤ 40, hypertension, diabetes, vascular disease,[a] female gender, age 65-74)	Previous stroke, TIA or embolism, or age ≥ 75 y, or ≥ 2 combination risk factors (heart failure/LVEF ≤ 40, hypertension, diabetes, vascular disease,[a] female gender, age 65-74)

ACC/AHA/ESC = American College of Cardiology/American Heart Association/European Society of Cardiology; $CHADS_2$ = congestive heart failure, hypertension, age > 75 years, diabetes, prior stroke or transient ischemic attack [doubled]; LVEF = left ventricular ejection fraction; NICE = National Institute for Health and Clinical Excellence; TIA = transient ischemic attack.
[a]Myocardial infarction, peripheral artery disease, or aortic placque.

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