Anticoagulation Strategies in Atrial Fibrillation

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Atrial fibrillation (AF) is a major risk factor for stroke and systemic embolization, particularly in the elderly. Approximately 2.3 million adults in the United States have AF, and it is projected that this number will increase to approximately 5.6 million individuals by the year 2050, with over 50% aged 80 years or older. Vitamin K antagonists are currently the most widely accepted means of stroke prevention in patients with AF; unfortunately, this method of treatment is not a feasible option for many patients for numerous reasons. This article examines and compares the various newer therapeutic agents that have either been approved by the US Food and Drug Administration or are still in various stages of clinical testing, and provides an overview of established antithrombotic therapies. We also discuss the role of anticoagulation in the setting of cardioversion in patients with AF.

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KEY WORDS

Atrial fibrillation • Stroke • Antithrombotic therapy • Warfarin

Atrial fibrillation (AF), a common cardiac dysrhythmia, is a strong risk factor for stroke and systemic embolization.[1] These events are predominantly driven by the embolization of a thrombus from the left atrial appendage (LAA).[2]

AF is uncommon in individuals under age 50 years. However, at the onset of the sixth decade of life, the prevalence of this condition doubles approximately every 10 years, from 0.5% at age 50 to 59 years to almost 9% at age 80 to 89 years.[3,4] Approximately 70% of individuals with AF are

between ages 65 and 85.[5] The age-adjusted prevalence of AF is more common in men than in women[6,7] and also more common in white subjects than in African Americans.[8] Finally, it has been estimated that approximately 2.3 million adults in the United States have AF and it is projected that this number will increase to approximately 5.6 million individuals by the year 2050, with over 50% aged 80 years or older.[6]

In addition to the incremental risk of AF with advancing age, the risk of stroke with AF also increases with age. It has been shown that there is a steep increase in the risk of stroke in patients with AF ranging from 1.5% at age 50 to 59 years to 23.5% at age 80 to 89 years.[1] Other independent risk factors include hypertension, diabetes mellitus, moderate to severe left ventricular dysfunction, and obesity.[9] Epidemic obesity, with its hemodynamic effects and impact on left ventricular and left atrial structure and function, may also contribute to a higher prevalence of AF.[10]

The pathophysiology of thromboembolism in AF is not entirely clear. However, evidence suggests that the disorganized atrial contractions in AF lead to blood stasis, procoagulability, and thrombus formation in the atrium, with a large majority of the thrombi forming in the LAA.[2,11] Transesophageal echocardiogram (TEE) studies have shown that during AF there is a reduced LAA flow velocity due to disorganized mechanical contraction of the atria.[12,13] A reduced flow in the left atrium and LAA is associated with spontaneous echo contrast, thrombus formation, and embolic events.[14]

Vitamin K antagonists (VKAs) have consistently been shown to be superior to placebo and antiplatelet agents in both primary and secondary prevention trials in AF patients at intermediate to high risk for stroke (Congestive heart failure, Hypertension, Age, Diabetes mellitus, Stroke/transient ischemic attack [$CHADS_2$] ≥ 2). Based on evidence from multiple trials, VKAs are currently the preferred method of anticoagulation in patients with AF to prevent the occurrence of ischemic strokes.[15] Although VKAs have an excellent proven efficacy in preventing strokes and systemic embolism, it comes at the expense of increased bleeding complications and other disadvantages.

> ***Vitamin K antagonists have consistently been shown to be superior to placebo and antiplatelet agents in both primary and secondary prevention trials in AF patients at intermediate to high risk for stroke.***

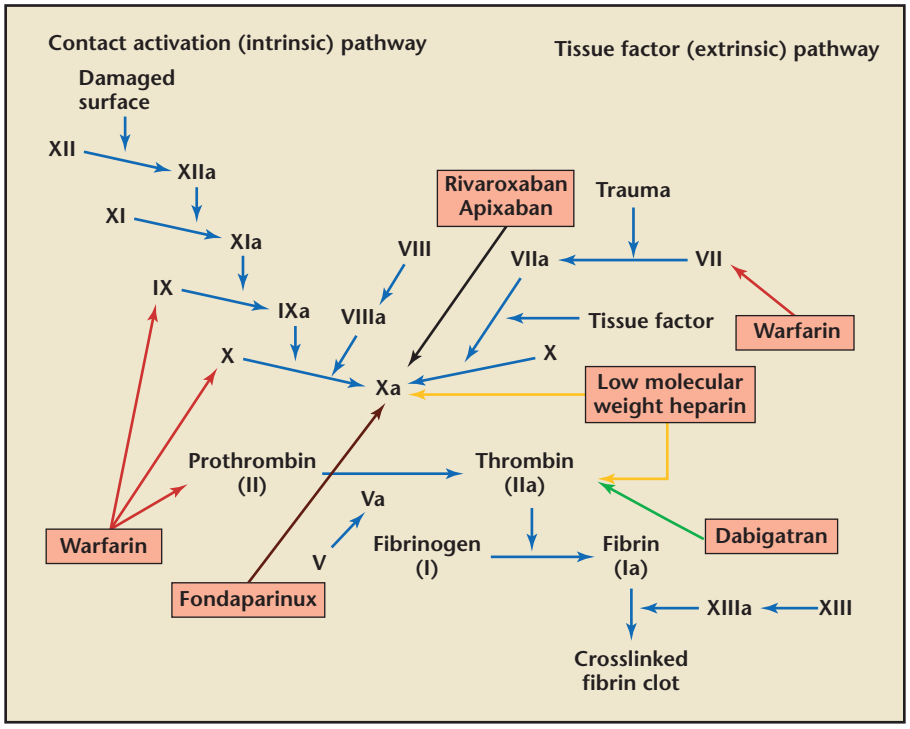
Over the past 5 decades oral anticoagulation in AF was limited to the use of VKAs. Numerous studies have attempted to discern alternate safe yet effective approaches to proper anticoagulation in patients with AF (Figure 1). These new oral anticoagulants fall into two categories: 1) orally effective direct thrombin inhibitors such as dabigatran, and 2) oral factor Xa (FXa) inhibitors such as apixaban and rivaroxaban.

This article provides an overview of the established antithrombotic therapies for AF, and compares and contrasts the novel therapeutic agents available for stroke prevention in AF. Some of these novel agents are already approved by the US Food and Drug Administration (FDA) and are currently incorporated in the guidelines, whereas several others are being evaluated in various stages of clinical trials.

Risk Stratification for Stroke and Thromboembolism

The $CHADS_2$ score is a widely used risk index in AF, allocating 1 point

Figure 1. Location of action of various agents in the coagulation cascade.



for each individual risk factor, including congestive heart failure, hypertension, age > 75 years, and diabetes mellitus, and 2 points for prior stroke or transient ischemic attack (TIA). A $CHADS_2$ score of 0 is classified as low risk, 1 as intermediate risk, and > 2 as high risk. In patients with a score ≥ 2, chronic oral anticoagulation therapy with dose-adjusted VKAs is recommended to achieve a target international normalized ratio (INR) of 2.5 (range, 2-3).[16] The predictive value of this scoring system was evaluated in 1733 Medicare beneficiaries between ages 65 and 95 years with nonvalvular AF and determined that the stroke rate per 100 patient-years without antithrombotic therapy increased by a factor of 1.5 (95% confidence interval [CI], 1.3-1.7) for each 1-point increase in the $CHADS_2$ score; 1.9 (95% CI, 1.2-3.0) for a score of 0; 2.8 (95% CI, 2.0-3.8) for 1; 4.0 (95% CI, 3.1-5.1) for 2; 5.9 (95% CI, 4.6-7.3) for 3; 8.5 (95% CI, 6.3-11.1) for 4; 12.5 (95% CI, 8.2-17.5) for 5; and 18.2 (95% CI, 10.5-27.4) for 6.[17] However, there are various limitations to this scoring system, such as the large number of patients who fall into the intermediate-risk class, as well as the omission of various potential risk factors for thromboembolism,[18] including female sex, age between 65 and 74 years, and coronary artery disease.[19]

The CHA_2DS_2-VASc score includes congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, previous stroke/TIA, vascular disease, age 65 to 74 years, and a sex category. Here, age ≥ 75 years and previous stroke/TIA carry a double risk weight[20] (Table 1). Even though the CHA_2DS_2-VASc score had a similar C statistic to the $CHADS_2$ score, the former was found to be better at identifying patients at a truly low risk for thromboembolic events and it placed fewer patients in the intermediate-risk group.[21]

TABLE 1

CHA_2DS_2-VASc Scoring Criteria

Risk Factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥ 75 years	2
Diabetes mellitus	1
Stroke/TIA/thromboembolism	2
Vascular disease (prior MI, peripheral artery disease, or aortic plaque)	1
Age 65-74 years	1
Sex category (female sex)	1

LV, left ventricular; MI, myocardial infarction; TIA, transient ischemic attack.

A registry-based cohort study in Denmark conducted between 1997 and 2006 examined 73,538 patients with nonvalvular AF.[21] Of the 16,406 patients who were categorized to be low risk by $CHADS_2$, 6472 were classified as intermediate risk and 3565 were considered high risk according to CHA_2DS_2-VASc score. Of the 23,730 patients categorized as intermediate risk by $CHADS_2$, 21,999 were classified as high risk by CHA_2DS_2-VASc.

Furthermore, in patients at low risk, the rate of thromboembolism per 100 persons was 1.67 (95% CI, 1.47-1.89) with $CHADS_2$, and 0.78 (95% CI, 0.58-1.04) with CHA_2DS_2-VASc at 1-year follow-up. Similarly, patients at intermediate risk had a rate of 4.75 (95% CI, 4.45-5.07) with $CHAD_2$, and 2.01 (95% CI, 1.70-2.36) with CHA_2DS_2-VASc (Table 2). The authors concluded that CHA_2DS_2-VASc was superior at predicting high-risk patients when compared with $CHADS_2$, and was better at predicting low-risk patients who were truly low risk for thromboembolic events.

CHA_2DS_2-VASc was superior at predicting high-risk patients when compared with $CHADS_2$, and was better at predicting low-risk patients who were truly low risk for thromboembolic events.

Aspirin

Aspirin provides only minor protection against stroke in patients with AF. A meta-analysis of six trials demonstrated that aspirin reduced the incidence of stroke by 22%.[22] In these trials, antiplatelet therapy was compared with placebo.[23-28] It was concluded that the absolute risk reduction of stroke in patients taking aspirin versus placebo was 1.5% per year in primary prevention and 2.5% per year in secondary prevention. Furthermore, this meta-analysis associated aspirin with a relative risk (RR) reduction of 62% for nondisabling strokes versus 17% for disabling strokes.[22]

Warfarin

The Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF) was an unblinded, randomized, controlled trial that studied low-dose warfarin therapy (target prothrombin:time ratio = 1.2-1.5 times control) in patients with nonvalvular AF.[29] The control

TABLE 2

A Comparison Between $CHADS_2$ and CHA_2DS_2-VASc

Score/Risk Category	1-year Follow-up	5-year Follow-up	10-year Follow-up
$CHADS_2$			
0	1.7 (1.5-1.9)	1.3 (1.2-1.4)	1.2 (1.2-1.3)
1	4.8 (4.5-5.1)	3.7 (3.6-3.9)	3.6 (3.4-3.7)
2	7.3 (6.9-7.8)	5.6 (5.4-5.8)	5.4 (5.2-5.6)
3	15.5 (14.6-16.4)	10.3 (9.9-10.7)	9.9 (9.5-10.3)
4	21.6 (20.0-23.2)	14.00 (13.2-14.8)	13.7 (13.0-14.5)
5	19.7 (16.9-22.9)	13.0 (11.5-14.6)	12.6 (11.2-14.1)
6	22.4 (14.6-34.3)	16.8 (11.9-23.6)	17.2 (12.3-23.9)
$CHADS_2$			
Low risk (0)	1.7 (1.5-1.9)	1.3 (1.2-1.4)	1.2 (1.2-1.3)
Intermediate risk (1)	4.8 (4.5-5.1)	3.7 (3.6-3.9)	3.6 (3.4-3.7)
High risk (2-6)	12.3 (11.8-12.7)	8.3 (8.1-8.5)	8.0 (7.8-8.2)
CHA_2DS_2-VASc			
0	0.8 (0.6-1.0)	0.7 (0.6-0.8)	0.7 (0.6-0.8)
1	2.0 (1.7-2.4)	1.5 (1.4-1.7)	1.5 (1.3-1.6)
2	3.7 (3.4-4.1)	3.0 (2.8-3.2)	2.9 (2.8-3.1)
3	5.9 (5.5-6.3)	4.4 (4.2-4.6)	4.3 (4.1-4.5)
4	9.3 (8.7-9.9)	6.7 (6.4-7.0)	6.5 (6.2-6.7)
5	15.3 (14.4-16.2)	10.4 (10.0-10.9)	10.0 (9.5-10.4)
6	19.7 (18.2-21.4)	12.9 (12.1-13.7)	12.5 (11.8-13.3)
7	21.5 (18.8-24.6)	13.9 (12.5-15.5)	14.0 (12.6-15.5)
8	22.4 (16.3-30.8)	14.1 (10.8-18.3)	14.1 (10.9-18.2)
9	23.6 (10.6-52.6)	16.1 (8.0-32.2)	15.9 (8.0-31.8)
CHA_2DS_2-VASc			
Low risk (0)	0.8 (0.6-1.0)	0.7 (0.6-0.8)	0.7 (0.6-0.8)
Intermediate risk (1)	2.0 (1.7-2.4)	1.5 (1.4-1.7)	1.5 (1.3-1.6)
High risk (2-9)	8.8 (8.6-9.1)	6.0 (5.9-6.1)	5.7 (5.6-5.8)

Event rate (95% confidence interval) of hospital admission and death due to thromboembolism per 100 person-years.
Data from Olesen JB et al.[21]

group was not given warfarin but could choose to take aspirin; 420 patients were entered in the trial (212 in the warfarin group and 208 in the control group) and were followed for an average of 2.2 years. There were two strokes in the warfarin group (incidence, 0.41% per year) as compared with 13 strokes in the control group (incidence, 2.98% per year). This corresponded to a reduction of 86% in the risk of stroke (warfarin:control incidence ratio, 0.14; 95 % CI, 0.04-0.49; $P = .0022$) (Table 3). Also, there were a total of 37 deaths; the death rate was significantly lower in the warfarin group than in the control group (2.25% as compared with 5.97% per year, incidence ratio, 0.38 [95% CI, 0.17-0.82; $P = .005$]). There was one fatal hemorrhage in each group, but the warfarin group had a higher rate of minor hemorrhage than the control group (38 vs 21 patients). Finally, the frequency of bleeding leading to hospitalization or transfusion was essentially equal in both groups.

The Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation (SPINAF) Investigators evaluated low-intensity anticoagulation with warfarin (prothrombin:time ratio, 1.2-1.5) in 571 men with chronic nonvalvular AF.[30] The primary endpoint was cerebral infarction; secondary endpoints were cerebral hemorrhage

TABLE 3

Warfarin Effectively Reduces the Risk of Stroke in Patients With Nonvalvular Atrial Fibrillation

Study	Participants (N)	Target INR	Event Rate (%/y Warfarin, Placebo)	Relative Risk Reduction (%)
AFASAK	671	2.8-4.2	2.7, 6.2	56
SPAF I	1330	2.0-4.5	3.6, 6.3	67
BAATAF	420	1.2-1.5	0.41, 2.98	86
CAFA	378	2.0-3.0	3.5, 5.2	37
SPINAF	571	1.2-1.5	0.9, 4.3	79
EAFT	1007	2.5-4.0	8, 17	47

AFASAK, Atrial Fibrillation, Aspirin and Anticoagulant Therapy Study; BAATAF, Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA, Canadian Atrial Fibrillation Anticoagulation; EAFT, European Atrial Fibrillation Trial; INR, international normalized ratio; SPAF, Stroke Prevention in Atrial Fibrillation; SPINAF, Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation.

Data from Petersen P et al,[23] Stroke Prevention in Atrial Fibrillation Study,[24] the Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators,[29] the European Atrial Fibrillation Trial Study Group,[25] Connolly SJ et al,[31] and Ezekowitz MD et al.[30]

and death. Over the 1.7-year follow-up period, the primary endpoint occurred in 19 of the 265 patients in the placebo group and in four of the 260 patients in the warfarin group during an average follow-up of 1.8 years. The reduction in risk with warfarin therapy was 0.79 (95% CI, 0.52-0.90; $P = .001$).

The Canadian Atrial Fibrillation Anticoagulation (CAFA) study aimed to assess warfarin's impact on systemic thromboembolism and its underlying risk of hemorrhage.[31] The study randomized 187 patients to warfarin and 191 to placebo. The primary outcome event cluster included nonlacunar stroke, non–central nervous systemic embolism, and fatal or intracranial hemorrhage. The annual rates of the primary outcome event cluster were 3.5% in the warfarin group and 5.2% in the placebo group, with an RR reduction of 37% (95% CI, -63.5%, 75.5%; $P = .17$). Fatal or major bleeding occurred at annual rates of 2.5% in the warfarin group and 0.5% in the placebo group. Minor bleeding occurred in 16% of the warfarin group and 9% of the placebo group.

The European Atrial Fibrillation Trial (EAFT) examined 1007 nonvalvular AF patients with a recent TIA or minor ischemic stroke.[25] These patients were randomized to open anticoagulation or double-blind treatment with either aspirin, 300 mg/d, or placebo. Patients with a contraindication to anticoagulation were randomized to receive aspirin or placebo. The measure of outcome was death from vascular disease, stroke due to any cause, myocardial infarction, or systemic embolism. The mean follow-up was 2.3 years. The annual rate of outcome events was 8% in patients assigned to anticoagulants vs 17% in placebo-treated patients (hazard ratio [HR] 0.53; 95% CI, 0.36-0.79). The risk of stroke alone was reduced from 12% to 4% per year (HR 0.34; 95% CI, 0.20-0.57). Among all patients assigned to aspirin, the annual incidence of outcome events was 15%, against 19% in those on placebo (HR 0.83; 95% CI, 0.65-1.05). It was determined that anticoagulation was significantly more effective than aspirin (HR 0.60; 95% CI, 0.41-0.87). In addition, the incidence of major bleeding events was slightly higher in anticoagulation than aspirin but nonetheless low (2.8% per year on anticoagulation and 0.9% per year on aspirin).

The Stroke Prevention in Atrial Fibrillation (SPAF) study[24] compared aspirin, 325 mg/d, or warfarin with placebo for prevention of ischemic stroke and systemic embolism during a mean follow-up of 1.3 years, and the primary outcome was systemic emboli and ischemic stroke. The rate of primary events in the placebo group was 6.3% per year and was 3.6% per year in those patients assigned to aspirin (reduction of 42%; 95% CI, 9%-63%; $P = .02$). Warfarin was shown to reduce the risk of primary events by 67% (warfarin vs placebo, 2.3% vs 7.4% per year; 95% CI, 27%-85%; $P = .01$). Primary events or death were reduced 58% ($P = .01$) by warfarin and 32% ($P = .02$) by aspirin.

Similarly, in the Copenhagen Atrial Fibrillation, Aspirin and Anticoagulant Therapy Study (AFASAK) study,[23] the incidence of thromboembolic events and vascular mortality were significantly lower in the warfarin group than in the aspirin and placebo groups (which did not differ significantly). There was a 3% absolute

risk reduction in thromboembolic events (cerebral or systemic) in the warfarin group when compared with the control group. There was also a 2.1% absolute risk reduction in stroke (fatal and nonfatal).

Another meta-analysis by van Walraven and colleagues[32] compared the risk of vascular events and bleeding events in patients with nonvalvular AF treated with aspirin or VKA. The authors used pooled analysis from six randomized clinical trials that comprised 4052 patients with AF. These patients were randomly assigned to receive therapeutic doses of oral anticoagulant or aspirin with or without a low dose of oral anticoagulant. They concluded that patients on therapeutic doses of oral anticoagulants were significantly less likely to experience any stroke (2.4 vs 4.5 events per 100 patient-years; HR, 0.55; 95% CI, 0.43-0.71), ischemic stroke (HR, 0.48; 95% CI, 0.37-0.63), or cardiovascular events (HR, 0.71; 95% CI, 0.59-0.85). However, the patients on therapeutic doses of oral anticoagulants were at a higher risk for major bleeding (2.2 vs 1.3 events per 100 patient-years; HR, 1.71; 95% CI, 1.21-2.41). Treating 1000 patients with AF for 1 year with warfarin rather than aspirin would prevent 23 ischemic strokes at the expense of nine major bleeds. The superior efficacy and net benefit of VKA is more noticeable in high-risk AF patients.[32]

Yet another meta-analysis of 29 trials that included 28,044 participants (mean age, 71 years; mean follow-up, 1.5 years) demonstrated that when compared with placebo or no treatment, warfarin reduced stroke by 64% (95% CI, 49%-74%) whereas antiplatelet agents reduced stroke by 22% (95% CI, 6%-35%). This showed that adjusted-dose warfarin was more effective for stroke reduction than antiplatelet therapy (RR reduction, 39%; 95% CI, 22%-52%; 12 trials, 12,963 participants).[33]

Strokes in AF can be either cardioembolic or noncardioembolic in etiology. In a study of 217 ischemic strokes, 52% of which were classified as cardioembolic, 24% of which were noncardioembolic, and 24% of which were of uncertain etiology, the authors concluded that the proportion of cardioembolic stroke was lower in patients on warfarin therapy, whereas noncardioembolic strokes were lower in patients on aspirin therapy. Here, 56% of the ischemic strokes in AF patients taking warfarin were noncardioembolic when compared with the 16% in those taking aspirin. Similarly, adjusted dose warfarin reduced cardioembolic strokes in patients with AF by 83% when compared with aspirin.[34] This study also concluded that cardioembolic strokes were larger and, therefore, more disabling than noncardioembolic strokes.

Aspirin Versus Aspirin Plus Clopidogrel

There are many instances in which patients are unable or unwilling to take warfarin in the setting of AF. Many (if not most) of these patients are treated with aspirin. There is also clear benefit of combining clopidogrel and aspirin in acute coronary syndromes.[35] The Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE)-A trial examined the hypothesis that the addition of clopidogrel to aspirin would reduce the risk of vascular events in AF (Figure 2).[36] Participants were considered eligible for this trial if they were considered ineligible for VKA therapy while at the same time at an increased risk for an ischemic stroke. Of 7554 patients enrolled in the study, 3772 were assigned to receive clopidogrel in addition to aspirin, whereas the remaining 3782 received placebo along with aspirin. Over the 4 years of the study, $<$ 1% of patients were lost to follow-up. At 1 year, 16.3% of the clopidogrel group and 15.2% of the placebo group dropped out of the study due to discontinuation/nonadherence; at 4 years, this number increased to 39.4% and 37.1%, respectively. Stroke occurred in 296 patients receiving clopidogrel (2.4% per year) and 408 patients receiving placebo (3.3% per year). The rate of ischemic stroke was significantly lower in the clopidogrel group than in the placebo group (1.9% per year vs 2.8% per year; $P < .001$). The study concluded that clopidogrel added to aspirin reduced the risk of stroke by 28%, and increased the risk of an extracranial hemorrhage by 51%, while increasing the risk of intracranial hemorrhage by 87%.

Due to the uncertainty that exists with regard to the risk of bleeding in patients receiving dual antiplatelet therapy (DAPT) over extended periods of time, the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial attempted to determine the frequency and time course of bleeding in patients receiving DAPT with either established vascular disease or those with cardiovascular risk factors. In this study, the primary safety endpoint was severe bleeding, according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) definition,[37] which includes fatal bleeding, intracranial hemorrhage, or bleeding leading to hemodynamic compromise requiring blood or fluid replacement, inotropic support, or surgical intervention. The trial concluded that there was an increased risk of bleeding with long-term use of clopidogrel.[38,39] The rate of the primary safety endpoint was 1.7% in

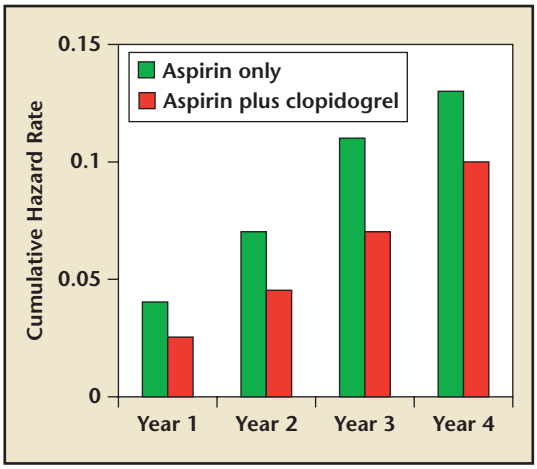


Figure 2. Cumulative incidence for stroke, based on treatment groups. Data from Connolly SJ et al.[36]

the clopidogrel group and 1.3% in the placebo group (RR, 1.25; 95% CI, 0.97-1.61; $P = .09$). Furthermore, the rate of moderate bleeding was 2.1% in the clopidogrel group, as compared with 1.3% in the placebo group (RR, 1.62; 95% CI, 1.27-2.08; $P < .001$). Finally, the rate of intracranial hemorrhage was similar in the two treatment groups.[40] Subsequent analysis of the data from the CHARISMA trial revealed that, compared with aspirin alone, there was a significant increase in cardiovascular death ($P = .01$) observed in asymptomatic, primary prevention patients receiving DAPT.[41] However, it should be noted that the use of antiplatelet therapy in patients with a history of stroke is a class III indication.

Aspirin Plus Clopidogrel Versus VKA

The objective of the ACTIVE-W trial was to determine whether aspirin (75-100 mg) + clopidogrel (75 mg) was statistically noninferior to warfarin (target INR, 2-3) in the prevention of vascular events in patients at high risk for stroke in the setting of AF.[42]

In patients on oral anticoagulation therapy/warfarin, there were 165 primary vascular events (annual risk, 3.93%) as compared with 234 in those on aspirin + clopidogrel (annual risk 5.60%; RR, 1.44; 95% CI, 1.18-1.76; $P = .0003$). Furthermore, patients on anticoagulation therapy who were already on this treatment at study entry tended to trend toward a greater reduction in vascular events (RR, 1.50; 95% CI, 1.19-1.89) as well as a significantly ($P = .03$ for interaction) lower risk of major bleeding with oral anticoagulation therapy (RR, 1.30; 95% CI, 0.94-1.79) when compared with patients not on this treatment at the onset of this study (RR, 1.27; 95% CI, 0.85-1.89 and RR, 0.59; 95% CI, 0.32-1.08, respectively).[42] The study was terminated early due to the superiority of oral anticoagulation when compared with aspirin + clopidogrel for the prevention of vascular events in patients with AF at high risk for stroke.[42]

Thrombin Inhibitors

Direct thrombin inhibitors (DTIs) bind directly to thrombin and prevent its interaction with substrates, thus preventing the conversion of fibrinogen to fibrin by thrombin. DTIs inactivate the fibrin-bound thrombin as well as the fluid-phase thrombin.[43]

Ximelagatran is a DTI and the first drug in this class to be taken orally. In the Stroke Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) III and V trials, ximelagatran was shown to be as effective as warfarin in reducing the risk of stroke in patients with nonvalvular AF.[44] However, this medication was withdrawn from the market due to rare and potentially fatal hepatotoxicity.[45,46]

Dabigatran is a potent, direct competitive inhibitor of thrombin. The Randomized Evaluation of Long Term Anticoagulation Therapy (RE-LY) study was a randomized phase III clinical trial designed to compare two different doses of dabigatran, 110 mg twice daily (D110), and 150 mg twice daily (D150), with open-label use of adjusted-dose warfarin (INR, 2-3) in 18,113 patients with an increased risk of stroke from nonvalvular AF.[47] A total of 32% of patients had a $CHADS_2$ score of 0 or 1, 35% had a score of 2, and 33% had a score between 3 and 6, respectively. Patients with recent stroke (< 14 d) and glomerular filtration rate (GFR) < 30 mL/min were excluded from the trial. The primary outcome of the study was stroke or systemic embolism, whereas the primary safety outcome was major hemorrhage. In the warfarin group the rate of primary outcome was 1.7% per year when compared with the 1.53% per year rate associated with the D110 group (RR with dabigatran, 0.91; 95% CI, 0.74-1.11; $P < .001$ for noninferiority) and 1.11% per year in the D150 group (RR, 0.66; 95% CI, 0.53-0.82; $P < .001$ for superiority). Furthermore, in the warfarin group, the rate of a major bleed was 3.36% per year when compared with the 2.71% per year in the D110 group ($P = .003$) and 3.11% per year in the D150 group ($P = .31$). Similarly, in the warfarin group, the rate of a hemorrhagic stroke was 0.38% per year

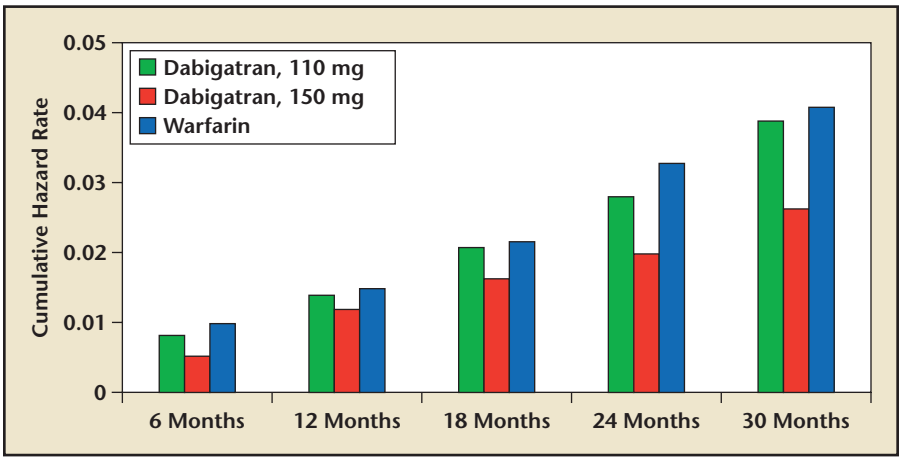


Figure 3. Cumulative hazard rates for stroke or systemic embolism, based on treatment groups. Data from Connolly SJ et al.[47]

compared with 0.12% per year in the D110 group ($P < .001$) and 0.10% per year in the D150 group ($P < .001$). Finally, with respect to the warfarin group, the mortality rate was 4.13% per year when compared with 3.75% per year in the D110 group ($P = .13$) and 3.64% per year in the D150 group ($P = .051$) (Figure 3). The authors of the RE-LY trial concluded that patients in the D110 group had rates of strokes and systemic embolization similar to patients on warfarin but had lower rates of major hemorrhage. Patients in the D150 group had lower rates of stroke and systemic embolization when compared with warfarin, but similar rates of major hemorrhage. Intracranial and subarachnoid hemorrhage were substantially (> 60%) lower with D150 than with warfarin, although major gastrointestinal bleeding was almost 60% higher with D150**.** In addition, previous VKA use/exposure did not influence the benefits of dabigatran at either dose when compared with warfarin,[48] indicating it would be safe to switch from warfarin to dabigatran. From a risk–benefit perspective, the reduced rate of stroke as well as lower intracranial bleeding justifies the utilization of D150 over warfarin in the majority of patients with nonvalvular AF.

A post-hoc analysis of the RE-LY trial examined all the patients who underwent cardioversion during this trial.[49] A total of 1983 cardioversions were performed on 1270 patients, with 647, 672, and 664 in the D110, D150, and warfarin groups, respectively. For the D110, D150, and warfarin groups, TEE was performed before 25.5%, 24.1%, and 13.3% of cardioversions. Of these, 1.8%, 1.2%, and 1.1% showed a left atrial thrombus, respectively. The majority of the cardioversions performed were on the RE-LY protocol-assigned study drug taken for at least 3 weeks before this procedure (76.4%, 79.2%, and 85.5% in D110, D150, and warfarin, respectively). The majority of patients continued on the protocol-assigned study drug after cardioversion (85.8%, 88.7%, and 94.3% in D110, D150, and warfarin; D110 versus warfarin, $P < .0001$; D150 vs warfarin; $P = .0003$). This post-hoc analysis demonstrated that stroke and systemic embolic event rates within 30 days of cardioversion were low (0.77%, 0.30%, and 0.60% in D110, D150, and warfarin, respectively; D110 vs warfarin; $P = .71$; D150 vs warfarin; $P = .45$). Furthermore, the rates of stroke and systemic embolism were similar in patients with TEE before cardioversion (0.61%, 0.00%, and 1.14% for D110, D150, and warfarin, respectively; D110 vs warfarin; $P = .65$; D150 vs warfarin; $P = .17$) and without TEE (0.83%, 0.39%, and 0.52% for D110, D150, and warfarin, respectively; D110 vs warfarin; $P = .54$; D150 vs warfarin; $P = .75$).

Dabigatran has been shown to be a cost-effective alternative to warfarin in patients aged 65 years or older with nonvalvular AF and an increased risk for stroke.[50,51] Based on RE-LY trial evidence, the FDA recently approved dabigatran for stroke prevention in AF and this new medication is incorporated in the AF guidelines from the American College of Cardiology, the American Heart Association, and the Heart Rhythm Society.[52]

Factor Xa Inhibitors

The activation of prothrombin to thrombin in the coagulation cascade is mediated by the action of FXa and factor Va (the active forms of factor X and V, respectively).[53] Medications in this class include agents that block FXa either directly or indirectly. The indirect inhibitors act through an antithrombin-dependent mechanism.[54,55] On the other hand, direct FXa inhibitors bind directly to FXa and block interaction with its substrates.[56] These direct FXa inhibitors are able to bind and inhibit free FXa as well as FXa bound to platelets.[57]

Indirect FXa (idraparinux, fondaparinux, and low molecular weight heparin [LMWH]) are similar to unfractionated heparin in their ability to inactivate FXa. However, unlike unfractionated heparin, LMWH has only partial ability to inactivate thrombin whereas idraparinux and fondaparinux have no effect on thrombin inhibition. In other words, idraparinux and fondaparinux increase the rate of inactivation of FXa by antithrombin,

which in turn leads to the inhibition of thrombin generation, but not thrombin inactivation.

Idraparinux is a synthetic pentasaccharide that has a high affinity for antithrombin and has a long half-life, allowing for once-weekly administration.[58,59] The Atrial Fibrillation trial of Monitored, Adjusted Dose VKA, comparing Efficacy and safety with Unadjusted SanOrg 34006/idraparinux (AMADEUS) trial in 4576 patients was undertaken to compare idraparinux with VKA for prevention of thromboembolism in patients with AF.[60] A total of 2283 patients were to receive idraparinux, and 2293 patients were to receive VKA/warfarin. The trial was stopped after a mean follow-up period of 10.7 months because of an excess of clinically relevant bleeding with idraparinux (346 cases vs 226 cases; 19.7 vs 11.3 per 100 patient-years; $P < .0001$). There were 21 cases of intracranial bleeding with idraparinux versus 9 with VKA (1.1 vs 0.4 per 100 patient-years; $P = .014$). However, idraparinux was shown to be noninferior to VKA in prevention of thromboembolism in patients with AF. There were 18 cases of thromboembolism in the idraparinux group as compared with 27 cases in the VKA group (0.9 vs 1.3 per 100 patient-years; HR 0.71; 95% CI 0.39-1.30; $P = .007$). Finally, there were 62 deaths with idraparinux as compared with 61 with VKA (3.2 vs 2.9 per 100 patient-years; $P = .49$).

Like idraparinux, fondaparinux is a synthetic pentasaccharide that has an affinity for antithrombin.[61] Unlike the weekly dosing of idraparinux, fondaparinux has to be administered subcutaneously daily.[62] The Fifth Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS-5) trial compared the efficacy and safety of fondaparinux and enoxaparin in patients with unstable angina or myocardial without ST-segment elevation.[63] The study concluded that fondaparinux was similar to enoxaparin in reducing the risk of ischemic events, but it substantially reduced major bleeding and improved long-term morbidity and mortality. Thus, fondaparinux has become incorporated into the acute coronary syndrome guidelines; however, to date, no significant trials exist evaluating this drug in patients with AF.

Rivaroxaban is a direct competitive inhibitor of FXa and can bind both free and clot-bound Xa.[64,65] The Rivaroxaban Once daily oral direct FXa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) trial was a randomized, double-blind, double-dummy, event-driven trial in 14,264 patients conducted to assess the noninferiority of rivaroxaban when compared with warfarin in patients with AF (documented AF within 6 months) with a history of stroke or at least two independent risk factors for future strokes (intermediate to high risk). Patients were equally randomized to dose-adjusted warfarin (target INR, 2-3) or rivaroxaban, 20 mg/d (15 mg/d if GFR = 30-49 mL/min). Patients with a $CHADS_2$ score of 1 were not enrolled in the study. Only 13% of all patients had a $CHADS_2$ score of 2, and the remaining 87% had a $CHADS_2$ score of ≥ 3.

The primary efficacy endpoint of all-cause stroke and non–central nervous system embolism occurred in 2.12% per year in patients treated with rivaroxaban and in 2.42% of patients treated with warfarin ($P = .117$). Major bleeding occurred in 3.6% of patients in the rivaroxaban group versus 3.45% in the warfarin group ($P = .576$), and the rate of intracranial hemorrhage was significantly lower with rivaroxaban compared with warfarin (0.49% vs 0.74%, $P = .019$).[66]

Apixaban is another direct FXa inhibitor that has been studied in the setting of AF. The premise of the Apixaban versus Acetylsalicylic Acid to Prevent Strokes (AVERROES) trial was to study apixaban as an alternative to aspirin for stroke prevention in patients unwilling or unable to take VKA in the setting of AF. This trial was a double blind, double-dummy superiority trial of apixaban, 5 mg twice daily and 2.5 mg twice daily compared with aspirin, 81 to 324 mg/d in patients with AF, at least one risk factor for stroke, and who are unsuitable or have failed VKA therapy. In this study, the primary outcome was stroke or a systemic embolism, and the primary safety outcome was major bleeding.[67] The trial was stopped early due to clear evidence of a reduction in stroke and systemic embolism with apixaban compared with aspirin.[68]

Apixaban for reduction in stroke and other Thromboembolic events in atrial fibrillation (ARISTOTLE) trial evaluated the noninferiority and superiority of apixaban compared with warfarin (target INR, 2-3) at reducing stroke (ischemic and hemorrhagic) and systemic embolism among 18,206 patients with AF and at least one additional risk factor for stroke.[69] The primary outcome of the study was either ischemic or hemorrhagic stroke, or systemic embolism. The follow-up period was approximately 1.8 years. The study found that the rate of the primary outcome was 1.27% per year in the apixaban group compared with 1.60% per year in the warfarin group (HR with apixaban, 0.79; 95% CI, 0.66-0.95; $P < .001$ for noninferiority; $P = .01$ for superiority). Furthermore, the rate of major bleeding was 2.13% per year in the apixaban group

compared with 3.09% per year in the warfarin group (HR, 0.69; 95% CI, 0.60-0.80; $P < .001$). The rate of hemorrhagic stroke was also lower in the apixaban group at 0.24% per year compared with 0.47% per year in the warfarin group (HR, 0.51; 95% CI, 0.35-0.75; $P < .001$); and the rate of ischemic or uncertain type of stroke was 0.97% per year in the apixaban group and 1.05% per year in the warfarin group (HR, 0.92; 95% CI, 0.74-1.13; $P = .42$). The study results concluded that apixaban was superior to VKA in prevention of systemic embolism and stroke, and had a lower bleeding risk.[70]

Anticoagulation During Cardioversion

Direct current cardioversion is now considered standard, effective, and beneficial therapy in the treatment of AF and atrial flutter. Nevertheless, there is an established risk of thromboembolic events in patients who have undergone electrical cardioversion for AF.[71,72] Although most embolic events occur during the first 72 hours after cardioversion, these can occur up to and even after the 10 days following cardioversion.[73] In fact, the conversion of AF to sinus rhythm by pharmacologic or electric cardioversion may acutely increase the risk of an embolism by 10-fold.[74]

Direct current cardioversion is now considered standard, effective, and beneficial therapy in the treatment of AF and atrial flutter. Nevertheless, there is an established risk of thromboembolic events in patients who have undergone electrical cardioversion for AF.

A prospective cohort study published in 1969 examined 437 patients in whom electrical cardioversion was attempted: 228 patients were on long-term anticoagulation therapy versus 209 patients who were not placed on anticoagulation. Among those in whom the arrhythmia was successfully converted, there were embolic events in two of the 186 patients in the anticoagulated group and in 11 of the 162 patients in the group without anticoagulation. The study concluded that cardioversion without anticoagulation resulted in a 5.3% incidence of clinical thromboembolism, when compared with an incidence of only 0.8% ($P = .012$) in patients receiving oral anticoagulants.[75]

A large retrospective study has shown that at the time of cardioversion, the INR should be 2.5 if the duration of AF was uncertain or > 2 days.[76] In this study, the records of 1950 patients who underwent 2639 attempts of direct current cardioversion were reviewed. In 1932 instances, cardioversion was preceded by warfarin therapy for 3 weeks. There were no embolic complications in 779 attempts in which the INR was ≥ 2.5 (95% CI, 0%-0.48%). Of the 756 cases in whom the INR was < 2.5 or not measured, nine suffered thromboembolic events. The authors concluded that embolism was significantly less at an INR of 2.5, when compared with an INR between 1.5 and 2.4.

Over 90% of thrombi are located within or involving the LAA in patients with AF.[77] The use of conventional transthoracic echocardiography has been found to be unreliable in the detection of LAA thrombi, whereas TEE has demonstrated a very high accuracy in detection of these thrombi.[78,79] This allows for early cardioversion among patients without TEE evidence of LAA thrombus. It is important to mention, however, that the sensitivity of TEE is not 100%. The occurrence of thromboembolism has been demonstrated among patients who did not receive anticoagulation, despite the absence of a thrombus in the LAA on the TEE prior to cardioversion.[80,81]

In the past, it was common practice to cardiovert patients with AF for a short duration (< 48 h) without the use of a TEE or precardioversion anticoagulation. A study published in 1997 consisting of patients who had symptomatic AF for < 48 hours and underwent either pharmacologic or electrical cardioversion demonstrated a < 1% rate of thromboembolism.[82] A report on retrospective data on patients with AF < 48 hours showed 0.5% incidence of embolism in patients who did not receive precardioversion and postcardioversion anticoagulation, and 0% incidence in patients who received anticoagulation.[74] In the setting of AF for a short duration (< 48 h), although the risk of embolism appears to be low, initiating heparin, use of TEE, or delaying cardioversion (for 1 month until proper anticoagulation is achieved) may be appropriate, especially in high-risk patients.[83] As reviewed, dabigatran therapy appears to be as effective as warfarin for reducing strokes and TIAs following cardioversion.[49]

Conclusions

AF is a highly prevalent condition in the United States. The risk of thromboembolism and stroke can be measured by various quantifiable risk factors. In the past, warfarin has been the standard treatment for anticoagulation in patients with an increased risk for stroke. Recently, there have been various clinical trials to evaluate the efficacy and safety of novel medications that could potentially replace VKAs (Table 4). The results of these trials vary from inferior to beneficial. At present, aspirin may be

TABLE 4

Anticoagulation Agents and Their Various Properties

Drug	Dose	Mechanism of Action	Half-Life	Route of Administration	Adjusted Dose for Renal Dysfunction	Reversal Agents
Aspirin	81 mg, 325 mg	Nonselective inhibition of COX-1, COX-2	Dose-dependent	Orally	N/A	None
Warfarin	Titrate to INR 2-3	Inhibitor of epoxide reductase; decreased synthesis of clotting factors II, VII, IX, X	20-60 h	Orally	N/A	Vitamin K
Dabigatran	150 mg BID	Direct thrombin inhibitor	14-17 h	Orally	CrCl 15-30 mL/min, > 75 mg (BID)	N/A
Rivaroxaban	20 mg/d	Direct factor Xa inhibitor	5-9 h in patients aged 20-45 y; 11-13 h in those ≥ 65 years	Orally	CrCl 15-50 mL/min, 15 mg/d	N/A
Apixaban	To be announced (possible dosage, 5 mg BID)	Direct factor Xa inhibitor	10-14 h	Orally	N/A	N/A

BID, twice daily; COX, cyclooxygenase isoenzyme; CrCl, creatine clearance; INR, international normalized ratio.

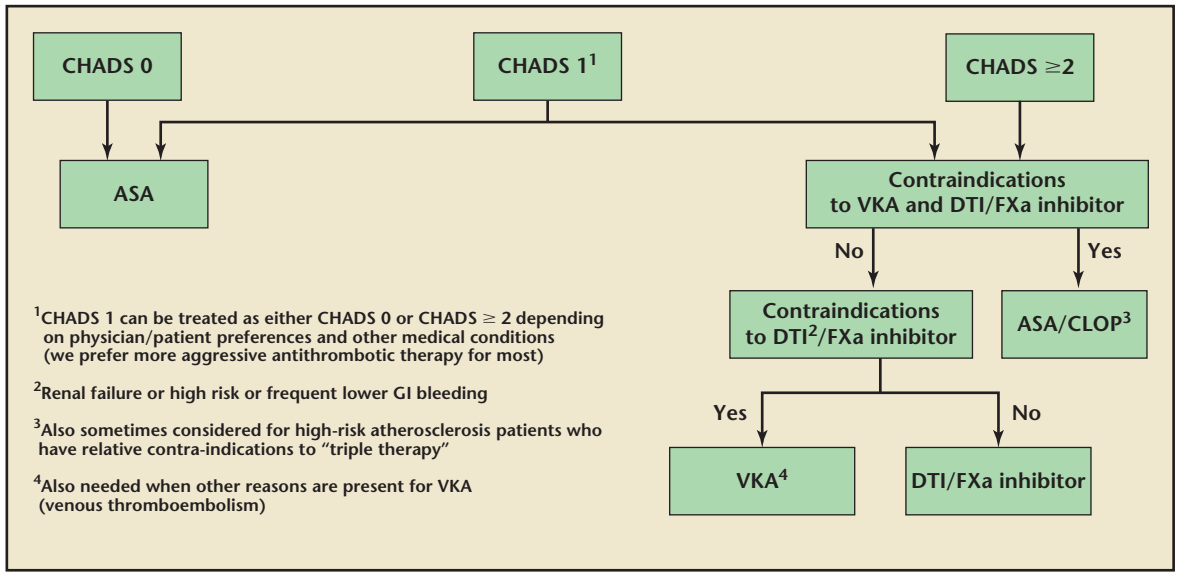


Figure 4. Algorithm for antithrombotic management of nonvalvular atrial fibrillation. ASA, aspirin; CHADS, congestive heart failure, hypertension, age, diabetes mellitus, stroke/transient ischemic attack; CLOP, clopidogrel; DTI, direct thrombin inhibitor; FXa, factor Xa; GI, gastrointestinal; VKA, vitamin K antagonist.

indicated for very low-risk patients, and aspirin plus clopidogrel in combination appear to be superior to aspirin alone. However, VKAs are superior to aspirin and clopidogrel. Most recently, novel agents, particularly dabigatran and apixaban, have proven to be superior to warfarin. It is likely that in the near future these newer medications will overshadow VKAs as the standard of care therapy in the prevention of thromboembolism and stroke in patients with AF (Figure 4). ■

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MAIN POINTS

- The prevalence of atrial fibrillation (AF) is increasing, probably due to increasing age, obesity, and other factors, including advanced heart disease, in the general population.
- There is considerable risk of devastating stroke with AF, especially when other risk factors are present.
- Warfarin markedly reduces the risk of stroke in AF, and does so considerably better than aspirin and aspirin combined with other platelet drugs (eg, clopidogrel).
- Other oral drugs are now available, including factor Xa inhibitors and direct thrombin inhibitors, which are preferred by many patients with AF and are equal to or superior to warfarin for reducing the risk of stroke.
- Clinicians need to consider the risks and benefits of various antithrombotic therapies to determine the best treatment for an individual patient with AF.