

Prevention of Stroke in Patients with Atrial Fibrillation: The Role of New Antiarrhythmic and Antithrombotic Drugs

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Key Words

Atrial fibrillation · Ischemic stroke · Antiarrhythmic drug · Anticoagulation

Abstract

Background: Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. It is associated with increased cardiovascular mortality and morbidity, including stroke. **Results:** Rate or rhythm control and prevention of thromboembolism with oral anticoagulants are the main management objectives for patients with AF. Until recently, rhythm control studies did not show prevention of cardiovascular complications. However, dronedarone, a novel antiarrhythmic drug, has been shown to decrease stroke risk by 34% ($p = 0.027$). In addition, the Randomized Evaluation of Long-Term Anticoagulant Therapy trial showed significant stroke reductions with the anticoagulant dabigatran 150 mg b.i.d. compared with adjusted-dose warfarin (the results for dabigatran 110 mg b.i.d. were similar to warfarin). **Conclusions:** Novel anti-thrombotic agents and antiarrhythmic agents with cardiovascular prophylactic properties may enhance the management of stroke risk in patients with AF.

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Impact of Atrial Fibrillation

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, affecting approximately 1% of adults [1]. The prevalence of AF in the population increases dramatically with age, with AF occurring in 9% of those aged 80 years and older. In the USA alone, the prevalence of AF is projected to triple by 2050 [2].

Long-term studies have consistently associated AF with increased cardiovascular morbidity and mortality [3–5]. In the Framingham Heart Study, patients with AF had nearly a 5-fold increased risk of stroke compared with individuals without AF [6]. Data from that study demonstrated that the attributable risk of stroke for patients with AF increases progressively with age, ranging from 1.5% in individuals aged 50–59 years to 23.5% in those aged 80–89 years [6]. In the Modified Framingham Stroke Risk Profile, AF was shown to be an independent predictor of stroke for sex-specific, 10-year cumulative risk of stroke [7]. The Copenhagen City Heart Study found that AF increased the risk of stroke in women by 10-fold and doubled risk in men [8]. Moreover, that study showed an independent effect of AF on cardiovascular mortality, with a risk 2.5 times greater in women than in men [9]. Furthermore, in the Northern Manhat-

tan Stroke Study, AF was an independent risk factor for ischemic stroke along with hypertension, diabetes, coronary artery disease, physical inactivity and heavy alcohol use [10].

Guidelines jointly published by the American College of Cardiology, American Heart Association (AHA) and European Society of Cardiology classify recurrent AF as paroxysmal (self-terminating), persistent (non-self-terminating, usually lasting >7 days) and permanent (cardioversion has failed or is deemed inappropriate) [1]. The observational Euro Heart Survey on AF provided evidence that stroke risk with paroxysmal AF is 'at least comparable' to persistent or permanent AF [11]. Patients with permanent AF at baseline in the study had a higher stroke risk than patients with either persistent or paroxysmal AF, but actual ischemic stroke events at 1-year follow up were similar for all 3 patient groups (paroxysmal, 1.9%; persistent, 1.2%; permanent, 1.6%; $p = 0.592$). The survey showed a trend for higher prevalence of AF on electrocardiogram (ECG) at baseline in patients with paroxysmal AF who subsequently suffered stroke than in those who did not. However, at present there are no robust data demonstrating an association between AF burden (duration and frequency of AF) and stroke apart from an analysis by Capucci et al. [12] suggesting that AF lasting >24 h is associated with a higher stroke risk.

AF- and Stroke-Related Morbidity

Stroke in patients with AF is severer and is nearly twice as likely to be fatal compared with non-AF stroke [13]. This difference may be attributed to the development of larger thrombi in the left atrial appendage, which is relatively wide compared with other sites in the arterial circulation. Obviously, larger emboli may occlude proximal or territorial arteries of the brain [14]. The occlusion of larger arteries results in larger infarct volumes and consequently severer neurologic deficits and worse outcomes.

A population-based study in Italy showed that the annual mortality rate in patients with a first-ever ischemic stroke and AF was twice that of patients without AF [15]. AF has also been shown to be an independent historical predictor of myocardial infarction (MI) or vascular death after first ischemic stroke [16]. Moreover, patients with AF are at an increased risk of stroke recurrence after the first ischemic stroke [13, 17].

Diagnosis of AF

Because of these compelling associations of AF with increased stroke risk, early diagnosis of all forms of arrhythmia using ECG seems crucial to stroke prevention. To enhance stroke prevention, ECG screening for asymptomatic AF in high-risk populations may be important, but the clinical value and feasibility needs to be evaluated in randomized trials [18]. Diagnosis of AF can be confirmed by bedside telemetry or an ambulatory Holter monitor [1]. However, AF is frequently undetected by short-term ECG monitoring, in instances such as their use in stroke units, and the sensitivity of a single 24-hour Holter ECG for AF detection is limited. Therefore, more effective diagnostic tools such as event recorders need to be established [19]. The likelihood of AF is especially high in patients with cryptogenic stroke, and extended ECG telemetry is likely to identify patients with heretofore undetected AF [20].

The management of this aspect of stroke risk is complicated by asymptomatic AF, which often goes undetected. In a study of patients with artificial pacemakers, Israel et al. [21] demonstrated a high incidence of AF recurrence >48 h duration in asymptomatic patients. The complications and risks of such silent episodes of AF are believed to be similar to those associated with symptoms [22].

Management and Treatment

In current guidelines, rate or rhythm control strategies and prevention of thromboembolism are the main management objectives for patients with AF [1]. Restoration of sinus rhythm aims to abolish symptoms of AF and reduce the cardiovascular and thromboembolic complications of this disorder. However, large trials have not shown a benefit of rhythm control over rate control strategies in this respect, which suggests that sinus rhythm is a marker of AF control rather than the instrumental cause of stroke-free survival.

Primary prevention of stroke in patients with AF is highly efficient and reduces the risk by 68% (relative risk reduction) compared with placebo [23]. Decisions regarding anticoagulation therapy are based on risk stratification [24]. For patients with AF, the CHADS₂ [Cardiac failure, Hypertension, Age, Diabetes, Stroke (doubled)] scoring system provides a clear framework for assessing stroke risk [25]. It incorporates elements of several stratification schemes and assigns 1 point each for congestive

Table 1. Mortality, thromboemboli and stroke in randomized AF trials

Trial	n	Follow-up years	Age years	Mortality %		Thromboembolic complication, %		Stroke or TIA, %	
				rhythm control	rate control	rhythm control	rate control	rhythm control	rate control
AF-CHF [37]	1,376	3.1	67	32	33	NR	NR	3	4
AFFIRM [38]	4,060	3.5	69.7	23.8	21.3	NR	NR	7.1	5.5
HOT-CAFE [39]	205	1.7	60.8	2.9	1.0	NR	NR	2.9	0
RACE [40]	522	2.3	68	6.8	7.0	7.9	5.5	NR	NR
STAF [41]	200	1.6	65	4	8	5	2	5	1

NR = Not reported; AF-CHF = Atrial Fibrillation and Congestive Heart Failure; AFFIRM = Atrial Fibrillation Follow-Up Investigation of Rhythm Management; HOT-CAFE = How to Treat Chronic Atrial Fibrillation; RACE = Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation; STAF = Strategies of Treatment of Atrial Fibrillation.

heart failure, hypertension, age ≥ 75 years and diabetes, and 2 points for a history of stroke or transient ischemic attack (TIA). The AHA/American Stroke Association (ASA) Council on Stroke evidence-based guidelines address the primary prevention of stroke in patients with AF [26].

For patients with ischemic stroke or TIA and AF, i.e. CHADS₂ ≥ 2 , adjusted-dose warfarin [target international normalized ratio (INR), 2.0–3.0] is recommended [24, 27]. Patients unable to take oral anticoagulants (OACs) should use aspirin 325 mg/day. The AHA/ASA guidelines recommend the initiation of OACs within 2 weeks of an ischemic stroke or TIA in patients with AF [27]. The UK National Institute for Health and Clinical Excellence (NICE) recommends that patients with disabling ischemic stroke who are in AF should be treated with aspirin 300 mg for the first 2 weeks before consideration of anticoagulation treatment [28]. The rationale for delaying OAC initiation is the potential for increased risk of early bleeding in patients with disabling strokes and large infarct volumes [29, 30].

In patients with AF, guideline-conformant use of OACs prior to stroke decreases the severity of recurrent or first-ever ischemic stroke. In a retrospective review of records for 13,559 patients with AF, Hylek et al. [31] found that therapeutic anticoagulation to INR > 2.0 reduced the frequency, severity and mortality of ischemic strokes. The benefits of preadmission warfarin were confirmed in an observational study of 948 patients admitted to hospitals in Ontario, Canada, with ischemic stroke and AF [32]. Data from the study showed that warfarin with a

therapeutic INR level (> 2) on admission reduced the initial stroke severity and reduced disability at discharge or death compared with nontherapeutic warfarin, aspirin or no antithrombotic treatment.

Whereas the WASPO (Warfarin vs. Aspirin for Stroke Prevention in Octogenarians) and BAFTA (Birmingham Atrial Fibrillation Treatment of the Aged) trials showed that warfarin was safe and effective in older individuals, the risk for bleeding does increase with age [33, 34]. Additionally, uncontrolled hypertension, history of MI or ischemic heart disease, cerebrovascular disease, anemia or a history of bleeding and the concomitant use of other drugs such as antiplatelet agents are associated with bleeding [35]. Bleeding risk stratification schemas have been proposed, such as the HEMORR₂HAGES score for AF patients [36], but additional validation of their value is needed.

AF Therapy and Stroke Reduction

A review of 5 randomized clinical trials in patients with AF (table 1) [37–41] showed that stroke and systemic emboli occurred more frequently in patients treated with a rhythm control strategy compared with a rate control strategy [42]. The author suggested that the difference may be related to discontinuation of warfarin treatment in patients thought to be converted to sinus rhythm. This finding highlights the need for the maintenance of long-term anticoagulation therapy in high-risk AF patients even if rhythm control is considered successful.

Stroke end points have not been regularly reported in clinical trials of antiarrhythmic drugs, and until recently

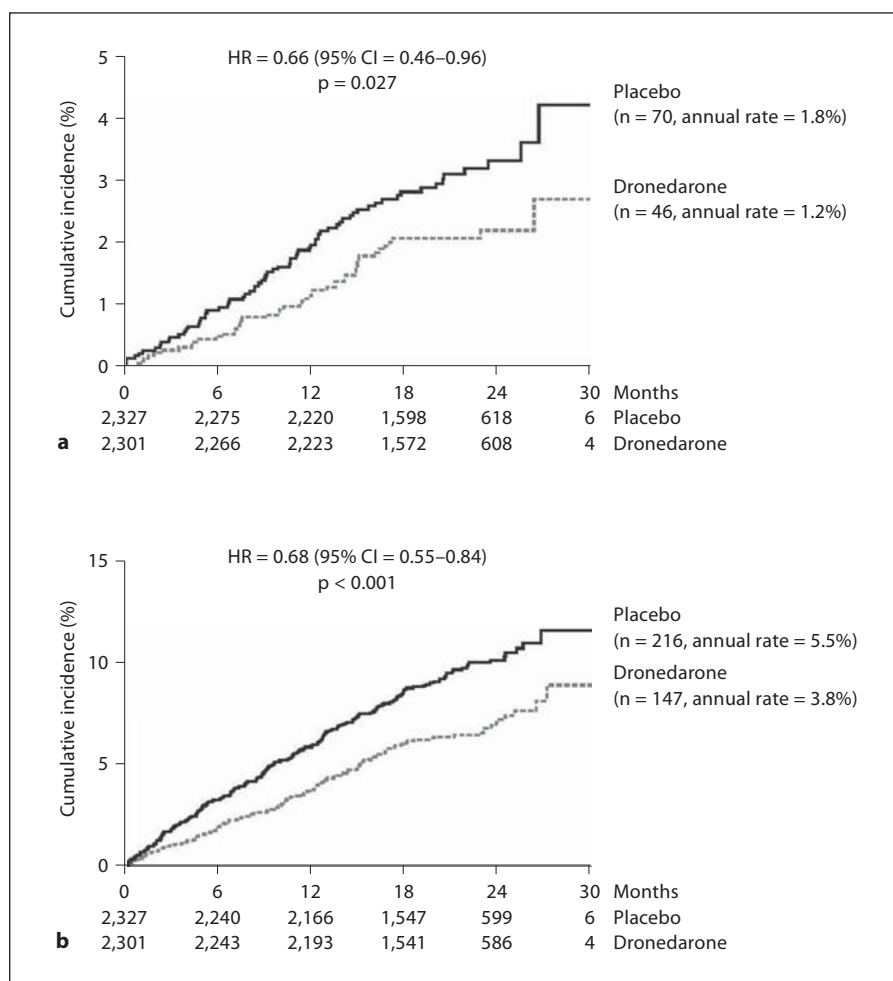


Fig. 1. Cumulative risk in the ATHENA study of **a** stroke and **b** the composite outcome of stroke, acute coronary syndrome or cardiovascular death [46]. Reprinted with the permission of *Circulation*.

no AF treatment apart from OAC has been conclusively shown to reduce stroke incidence [43]. The SAFE-T (Sotalol Amiodarone Atrial Fibrillation Efficacy Trial), which reported minor and major stroke rates, showed no significant differences in those end points for patients ($n = 655$) treated with amiodarone, sotalol or placebo [44].

Dronedarone, a novel antiarrhythmic drug, has been shown to reduce the risk for first cardiovascular hospitalization or death by 24% [95% confidence interval (CI) = 0.69–0.84; $p < 0.001$] in patients with AF and additional risk factors for death [45]. ATHENA (a Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 mg for the Prevention of Cardiovascular Hospitalization or Death from any Cause in Patients with Atrial Fibrillation/Atrial Flutter) randomized 4,628 patients to placebo or dronedarone 400 mg b.i.d. in addition to background OACs or antiplatelet

drugs [45]. Patients with either paroxysmal or persistent AF or atrial flutter were eligible for the study, and $>10\%$ of the patients had suffered either a TIA or a stroke before inclusion. The ATHENA trial did not include patients with permanent AF.

A post hoc analysis of the ATHENA data showed that dronedarone decreased the risk of stroke (ischemic or hemorrhagic) compared with placebo by 34% [46 (1.2% per year) vs. 70 (1.8% per year) stroke events, respectively; hazard ratio (HR) = 0.66 (95% CI = 0.46–0.96; $p = 0.027$)] in patients with paroxysmal or persistent AF or atrial flutter adequately treated by standard therapy, including antithrombotics (fig. 1) [46]. Patients with CHADS₂ scores ≥ 2 experienced a greater effect of dronedarone than patients with a CHADS₂ score ≤ 1 ($p = 0.03$ for interaction). The incidence of hemorrhagic stroke was the same for both dronedarone and placebo (0.2%, $p = 0.987$). The effect of dronedarone on stroke was similar regard-

less of whether patients were receiving OAC at baseline (HR = 0.74; 95% CI = 0.51–1.09; $p = 0.124$).

The incidences of major bleeding (1.0 vs. 0.9%, $p = 0.527$) and any bleeding (6.3 vs. 6.4%, $p = 0.972$) in ATHENA were similar in both treatment groups [46]. Moreover, the percentages of patients within the INR therapeutic range were similar for patients in both the dronedarone and placebo groups (~50% in either group) throughout the study. These findings suggest that dronedarone has minimal interaction with OACs and that together with novel predictable anticoagulants it may reduce the stroke rates to levels that are closer or comparable to patients without AF [47].

ATHENA is the first study of an antiarrhythmic drug to show a benefit in the reduction of stroke events. The authors of the post hoc analysis suggested several potential mechanisms behind this benefit [46]. In patients with AF, loss of contractility of the left atrial appendage is highly likely to be pathophysiologically linked to stroke. Improving contractility through restoration of the sinus rhythm may reduce the likelihood of emboli forming in the atrial appendage. However, the authors noted that this effect has not been found in previous trials of antiarrhythmic drugs. Dronedarone was associated with modest reductions in blood pressure and slowing of heart rate and reduced risk for acute coronary syndrome; reduction of blood pressure has been shown to decrease the risk of stroke. Moreover, the lack of interaction between dronedarone and OACs may have allowed for more stable INR in the ATHENA population. Other antiarrhythmic drugs, notably amiodarone, interact strongly with warfarin and thereby potentially affect INR stability [48]. While stroke was not a predefined end point of ATHENA, these findings are compelling and worthy of further study in randomized clinical trials. It is important to note that dronedarone is contraindicated in patients with New York Heart Association class IV heart failure or New York Heart Association class II–III heart failure with a recent decompensation requiring hospitalization or referral to a specialized heart failure clinic [49]. In draft guidance, the UK NICE recommends dronedarone as a second-line treatment of nonpermanent AF in patients with additional cardiovascular risk factors [50].

OAC Therapies

The efficacy of warfarin in reducing the risk of stroke in patients with AF has been confirmed by randomized, placebo-controlled clinical trials [51]. A meta-analysis of 6 major studies (Copenhagen Atrial Fibrillation, Aspirin and Anticoagulation; Stroke Prevention in Atrial Fibril-

lation; Boston Area Anticoagulation Trial for Atrial Fibrillation; Stroke Prevention in Nonrheumatic Atrial Fibrillation; Canadian Atrial Fibrillation Anticoagulant study; and European Atrial Fibrillation Trial) revealed a 64% reduction in the risk of stroke in patients with nonrheumatic AF treated with warfarin compared with placebo [52].

A secondary analysis of the Atrial Fibrillation Investigators database of 12 published clinical trials showed that patient age has no impact on the relative benefits of OACs compared with placebo or antiplatelet therapy [53]. However, since older patients are at higher risk of ischemic stroke, the 'absolute benefit' of OAC is likely to increase with patient age.

Andersen and Olsen [54] demonstrated that anticoagulant therapy reduces poststroke mortality in patients with AF and ischemic stroke. In their study ($n = 3,670$), survival was almost doubled in the patients who received anticoagulation treatment compared with those who received no treatment (HR = 1.91; 95% CI = 1.44–2.52). In a meta-analysis of 29 randomized trials of antithrombotic agents in patients ($n = 28,044$) with nonvalvular AF, Hart et al. [55] found that warfarin reduced the risk of ischemic stroke by 64% (95% CI = 49–74%).

The REACH (Reduction of Atherothrombosis for Continued Health) registry confirmed the relationship between CHADS₂ score and stroke risk in a worldwide population of patients with AF [56]. However, anticoagulant use ranged from 44.7% of the patients with CHADS₂ score 0 to 60.0% of the patients with CHADS₂ score 4. In clinical practice it appears that OAC treatment is not tailored to stroke risk [57, 58], although adherence to the guidelines reduces the risk of stroke [59]. The risk of hemorrhage and need for frequent monitoring of prothrombin time or INR with conventional adjusted-dose warfarin has led to the investigation of alternative treatment options.

Other Antithrombotic Therapies

The therapeutic alternatives to warfarin include antiplatelet agents such as aspirin and clopidogrel. However, aspirin is far less effective than adjusted-dose warfarin in reducing the risk of stroke in patients with AF (approximately 22 vs. 60% reduction) [55].

In the Stroke Prevention in Atrial Fibrillation III trial, the efficacy of a combination of low-intensity, fixed-dose warfarin with aspirin was compared with adjusted-dose warfarin [60]. After a mean follow-up of 1.1 years, the rate of ischemic stroke and systemic embolism with the combination therapy was significantly higher compared with adjusted-dose warfarin ($p < 0.0001$), and the trial was dis-

continued. The secondary analysis of the Atrial Fibrillation Investigators database of 12 clinical trials found that, compared with placebo, both OACs and antiplatelet agents significantly reduced the risk of ischemic stroke in patients with nonvalvular AF (OACs: HR = 0.36; 95% CI = 0.29–0.45; antiplatelets: HR = 0.81; 95% CI = 0.72–0.90) [53]. However, the researchers also found that the benefit of antiplatelet therapy decreased significantly with age ($p < 0.01$) while the benefit of OACs did not vary.

The combined use of antiplatelet agents for the prevention of vascular events, including stroke, has been investigated in the ACTIVE W (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events) trial [61]. In ACTIVE W, warfarin was superior to clopidogrel plus aspirin for the prevention of vascular events in AF patients at high risk of stroke [relative risk (RR) = 1.44; 95% CI = 1.18–1.76; $p = 0.0003$]. The recently reported ACTIVE A trial evaluated clopidogrel added to aspirin in comparison with placebo plus aspirin in patients with AF who had an increased stroke risk but for whom warfarin was unsuitable [62]. The results of the study demonstrated that clopidogrel in addition to aspirin reduced the risk for stroke from 3.3 to 2.4% per year (RR = 0.72; 95% CI = 0.62–0.83; $p < 0.001$), with an increase in risk for major bleeding not related to stroke from 1.3 to 2.0% (RR = 1.57; 95% CI = 1.29–1.92; $p < 0.001$).

In 2 randomized clinical trials ($n = 7,329$) the oral direct thrombin inhibitor ximelagatran was compared with warfarin and found to be as effective in preventing stroke and systemic embolism in patients with AF [63]. In the SPORTIF III (Stroke Prevention using an ORal Thrombin Inhibitor in atrial Fibrillation) study, acute MI occurred at a statistically nonsignificantly higher rate among patients receiving ximelagatran than in those receiving warfarin (1.1 vs. 0.6%, respectively) [64]. However, in SPORTIF V, the opposite result was found (1.0 vs. 1.4%) [65]. An analysis of both study databases combined revealed that a total of 50 patients in either treatment group experienced an acute MI. Of those, 8 ximelagatran patients and 13 warfarin patients died [63]. There was no difference in major bleeding rates between the 2 treatments. However, ximelagatran was subsequently withdrawn because of abnormal liver function tests.

RE-LY (Randomized Evaluation of Long-Term Anticoagulant Therapy), the largest AF stroke prevention trial undertaken to date, evaluated 2 doses of the active direct thrombin inhibitor dabigatran (110 and 150 mg b.i.d.) in 18,113 patients with nonvalvular AF [66]. At a low dose (110 mg b.i.d.) dabigatran was as effective as adjusted-dose warfarin in reducing the primary outcome of stroke

or systemic embolism, and at a high dose (150 mg b.i.d.) it was superior to warfarin. The primary outcome occurred at rates of 1.69% per year in patients receiving warfarin and 1.53 and 1.11% per year in patients receiving dabigatran 110 and 150 mg, respectively. The RRs compared with warfarin were 0.91 for 110 mg (95% CI = 0.74–1.11; $p < 0.001$ for noninferiority) and 0.66 for 150 mg (95% CI = 0.53–0.82; $p < 0.001$ for superiority). The rates of major bleeding were significantly lower for dabigatran 110 mg than warfarin (2.71 vs. 3.36% per year, $p = 0.003$) but similar to warfarin for the higher dose of dabigatran (3.11%, $p = 0.31$). Intracranial bleeding was significantly lower for both doses of dabigatran than for warfarin ($p < 0.001$ for each dose vs. warfarin). Gastrointestinal bleeding was significantly higher for dabigatran 150 mg than for warfarin ($p < 0.001$) but comparable between dabigatran 110 mg and warfarin. The rates of MI were higher for either dose of dabigatran than for warfarin (RR = 1.35; 95% CI = 0.98–1.87, $p = 0.07$, and RR = 1.38; 95% CI = 1.00–1.91, $p = 0.048$, for dabigatran 110 and 150 mg, respectively). The difference in risk for MI led the researchers to speculate that warfarin may provide better protection against coronary ischemia than dabigatran.

The option to have 2 different doses with either higher efficacy or a lower bleeding rate is appealing and raises the question of which patient might qualify for the one or the other. One might discuss that patients with lower CHADS₂ scores (1, 2 and possibly 3) qualify for the low dose and patients with CHADS₂ ≥ 3 for the high dosage. While this concept may be intriguing, it is important to consider that a high cardioembolic risk means that the bleeding risk is higher as well. These questions therefore need to be answered by future trials.

Cost of Managing Stroke

The stroke-related costs vary greatly depending on region and stroke severity. In a meta-analysis of 120 cost surveys from 15 countries (predominantly USA, UK and Sweden), Luengo-Fernandez et al. [67] found a range of USD 468 to 146,149, with a mean cost of USD 19,018 (median = USD 14,571) per event. In the USA, the annual costs of AF-associated stroke are estimated at USD 12 billion (2006) [68].

Nevertheless, the costs of caring for patients with stroke associated with AF have been demonstrated to be significantly higher than for those whose stroke was not associated with AF. In the Berlin Acute Stroke study, the mean direct costs per patient were approximately 33% greater for AF-related stroke (EUR 11,799) than for non-AF stroke (EUR 8,817) [69].

Conclusions

Patients with AF have a high risk of stroke and are also at an increased risk of stroke recurrence. Warfarin is currently the standard of care for high-risk AF patients and in patients with AF who have had a stroke or TIA. However, warfarin therapy requires regular monitoring and poses an increased risk for hemorrhagic complications. Also, despite clear recommendations in treatment guidelines, warfarin is underutilized by at-risk patients. Novel antithrombotic agents and antiarrhythmic agents offer new opportunities for the management of stroke risk in patients with AF.

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