The Decision to Anticoagulate: Assessing whether Benefits Outweigh the Risks for Patients with Atrial Fibrillation

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Summary: In a review of relevant articles from the Medline database on stroke risk in atrial fibrillation (AF) and adverse events related to anticoagulation treatment, we found that research to date shows a major potential benefit of warfarin therapy (International Normalized Ratio [INR] 2.0–3.0) for patients with AF (68% risk reduction in primary stroke prevention with warfarin vs. placebo). Despite this highly significant reduction in stroke risk, fewer than 50% of eligible patients are treated, in many cases because of fears of intracranial hemorrhage (ICH). The decision to implement anticoagulant therapy to improve outcome requires balancing the decreased risk for stroke against the increased risk for ICH. Various methods have been developed to define patient-specific stroke risk. In contrast, risk for ICH strongly correlates with the intensity of anticoagulation, which is an unpredictable but controllable variable requiring frequent dose adjustments. Recent studies have also identified subgroups of patients with neurologic pathologies who are at increased risk for ICH. However, when the INR is properly controlled, the benefit from anticoagulation therapy for patients with AF and other risk factors for stroke exceeds the risk for ICH. Careful monitoring of anticoagulation and warfarin dose titration to maintain the INR between 2.0 and 3.0 is critical for reducing the risk for ICH, as is excluding patients with neurologic conditions that increase the likelihood of ICH. Future developments, such as the introduction of oral direct thrombin inhibitors with more predictable pharmacokinetics than warfarin, may further improve the benefit-to-risk ratio of anticoagulation therapy for patients with AF.

Key words: atrial fibrillation, stroke, intracranial hemorrhage, warfarin, anticoagulation

Introduction

Atrial fibrillation (AF) represents a growing public health problem in the United States.1–3 The overall prevalence of AF is estimated to exceed 0.9% in the general population, increasing with advancing age from 0.1% among adults aged < 55 years to 9.0% in those aged ≥ 80 years.4 The number of patients with AF is likely to increase 2.5-fold during the next 50 years, from approximately 2.3 million to > 5.6 million, reflecting a growing proportion of elderly individuals. Atrial fibrillation is associated with significant morbidity and mortality due to hemodynamic and cardioembolic complications.5–8 The Framingham Cohort Study detected an almost 5-fold excess of stroke in patients with AF compared with the age-adjusted incidence in patients without AF.9 Furthermore, stroke associated with AF has a poor prognosis, with an increased incidence of death or disability compared with stroke in patients without AF.10, 11

Randomized controlled trials have consistently demonstrated that long-term anticoagulant prophylaxis reduces stroke risk in patients with nonvalvular atrial fibrillation (NVAF).12–17 A formal meta-analysis of five primary prevention trials (Atrial Fibrillation, Aspirin, Anticoagulation Study [AFASAK], Boston Area Anticoagulation Trial in Atrial Fibrillation [BAATAF], Canadian Atrial Fibrillation Anticoagulation [CAFA], Veterans Affairs Stroke Prevention in Atrial Fibrillation [SPAF-I-III], and Stroke Prevention in Nonrheumatic Atrial Fibrillation [SPINAF]) detected a 68% (95% confidence interval [CI], 50–79%) reduction in risk for stroke with warfarin therapy versus placebo over an observational period of nearly 3,700 patient years.18 The efficacy of warfarin was consistent across all studies and patient subgroups.

Despite its potential benefits, anticoagulation use in AF is suboptimal in clinical practice. Only 15 to 44% of patients with

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AF and no contraindications actually receive warfarin. The reasons for the underuse of warfarin therapy are multifactorial, but patient-, physician-, and health care system-related factors have been implicated, particularly the perception that anticoagulant treatment carries a significant risk for major hemorrhage. This review will summarize the evidence related to the benefit-to-risk ratio of anticoagulation treatment for individual patients with AF and explore strategies for optimum management of this large and growing population.

Estimating Probable Benefit from Anticoagulation Therapy

Inclusion Criteria for Clinical Trials

Patients with the characteristics of those studied in the clinical trials have been proven to benefit significantly from anticoagulation therapy with warfarin (Table I). This population was elderly, white, predominantly male, and presented with well-documented chronic or frequent paroxysmal AF. Risk reduction for stroke in this population ranged from 42 to 79% per year in five studies (Fig. 1).

The Importance of Risk Factors

The benefits of warfarin to patients at different levels of risk for stroke in the study population were determined in a meta-analysis. The fewest strokes were prevented in patients with AF and no other risk factors, whereas the largest number of strokes was prevented in the group of patients with AF and multiple risk factors (Fig. 2). This heterogeneity in stroke risk, and hence in the probable benefit from anticoagulation therapy, must be considered when planning treatment for a given patient.

TABLE I Characteristics of patients in clinical studies on the efficacy of antithrombotic therapy in prevention of stroke due to atrial fibrillation

<table>
<thead>
<tr>
<th>Mean age: 69 years (~20% &gt;75 years)</th>
<th>Male: 71%</th>
<th>White: 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comorbidities</td>
<td>Hypertension (%)</td>
<td>46</td>
</tr>
<tr>
<td>Mean INR</td>
<td>2.0–2.6</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Refs. No. 18 and 24.

Abbreviations: MI = myocardial infarction, TIA = transient ischemic attack, INR = International Normalized Ratio.

Stroke Risk Algorithms to Estimate Benefit

Several algorithms have been developed to predict stroke risk based on well-characterized risk factors. Strong independent predictors of stroke in patients with AF identified by multivariate analysis include a history of prior stroke/transient ischemic attack (TIA) (relative risk [RR] = 2.5), diabetes (RR = 1.7), hypertension (RR = 1.6), congestive heart failure (CHF) (RR = 1.4), age older (RR = 1.4 per decade), coronary artery disease (RR = 1.5), or echocardiographic evidence of moderate/severe left ventricular (LV) systolic dysfunction (RR = 2.5). A set of criteria developed by the American College of Chest Physicians (ACCP) classifies patients with AF into low-, intermediate-, and high-risk categories, in which low-risk patients are < 65 years and have no risk factors; patients in the intermediate risk are between 65 and 75 years with diabetes, coronary artery disease, or thyrotoxicosis; and high-risk patients are > 75 years or have LV dysfunction, more than one intermediate risk factor, or a history of hypertension.

![Fig. 1](image1.png)  
**Fig. 1** Incidence of stroke in major primary prevention trials of warfarin to prevent stroke in patients with atrial fibrillation. AFASAK = Aspirin vs. Warfarin in Atrial Fibrillation; BAAATAF = Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA = Canadian Atrial Fibrillation Anticoagulation; RRR = relative risk reduction; SPAF = Stroke Prevention in Atrial Fibrillation; SPINAF = Stroke Prevention in Nonrheumatic Atrial Fibrillation. □ = Control, ■ = warfarin. Adapted from Refs. 18 and 25.

![Fig. 2](image2.png)  
**Fig. 2** Event reduction with warfarin treatment in patients at different levels of risk. “Low risk,” “moderate risk,” and “high risk” are defined as 1, 3.5, and 6% annual risk of stroke without therapy, respectively. “Secondary prevention” patients have an intrinsic stroke risk of 12% per year.
A simple objective stroke-risk algorithm to assess the risk for stroke in patients with NVAF, the CHADS2 index, was derived from risk factors identified in two trials, Atrial Fibrillation Investigators (AFI) and SPAF, to facilitate risk stratification based on patient-specific risk factors for stroke.28 In this model, the CHADS2 score is calculated by assigning one point each for the presence of CHF (C), history of hypertension (H), age > 75 years (A), or diabetes (D), and adding two points for history of stroke or TIA (S).28 The CHADS2 index was validated in a chart review of 1,733 Medicare patients with AF and found to be highly predictive of stroke (c-statistic 0.82).28 There was a direct and accelerating relationship between the total CHADS2 score and adjusted stroke risk, with the stroke rate per 100 patient years without antithrombotic therapy increasing 1.5 times (95% CI, 1.3–1.7) for each one-point increase in the CHADS2 score (p < 0.001) (Table II).28 Thus, this simple score can be used to estimate the risk for stroke, and hence the likelihood of benefit from anticoagulation for a given patient.

Guidelines for Management of Atrial Fibrillation

The concept of anticoagulant treatment based on stroke risk is the basis for several published guidelines on the management of AF. For example, a guideline from the American College of Cardiology (ACC), American Heart Association (AHA), and the European Society of Cardiology (ESC) recommends warfarin anticoagulant therapy (INR 2.0–3.0) for patients with AF > 60 years with such risk factors as diabetes, hypertension, coronary artery disease, heart failure, and LV dysfunction. Other identified risk factors include rheumatic heart disease, prosthetic heart valves, prior thromboembolism, and persistent atrial thrombus on transesophageal echocardiogram (TEE) (Table III).3 In addition, all patients with AF aged ≥ 75 years (especially women) should receive anticoagulant therapy. The ACCP stroke prevention guidelines are similar to those developed by the ACC/AHA/ESC and recommend an adjusted dose of warfarin (INR 2.0–3.0) for all patients with high-risk factors.29

Estimating Possible Risk from Anticoagulation Treatment

Although anticoagulants largely reverse the increased risk of stroke among patients with AF, the decision to implement anticoagulant therapy is based on the balance between the decreased risk for stroke and the increased risk for major bleeding (e.g., retroperitoneal or intracranial hemorrhage [ICH]),25 as it is imperative not to substitute one problem for another. The risk of warfarin-related ICH is a critical factor in this analysis because the mortality (~60%) and morbidity associated with this event most closely resemble the consequences of not providing anticoagulation to patients with AF.20, 31 Consequently, a patient’s risk for warfarin-related ICH must be considered in the clinical decision to initiate anticoagulation therapy.31, 32

<table>
<thead>
<tr>
<th>CHADS2 score</th>
<th>NRAF crude stroke rate per 100 patient years</th>
<th>NRAF adjusted stroke rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.2</td>
<td>1.9 (1.2–3.0)</td>
</tr>
<tr>
<td>1</td>
<td>2.8</td>
<td>2.8 (2.0–3.8)</td>
</tr>
<tr>
<td>2</td>
<td>3.6</td>
<td>4.0 (3.1–5.1)</td>
</tr>
<tr>
<td>3</td>
<td>6.4</td>
<td>5.9 (4.6–7.3)</td>
</tr>
<tr>
<td>4</td>
<td>8.0</td>
<td>8.5 (6.3–11.1)</td>
</tr>
<tr>
<td>5</td>
<td>7.7</td>
<td>12.5 (8.2–17.5)</td>
</tr>
<tr>
<td>6</td>
<td>44.0</td>
<td>18.2 (10.5–27.4)</td>
</tr>
</tbody>
</table>

Adjusted stroke rate = Expected stroke rate per 100 patient years from exponential survival model (assuming aspirin not taken).

Abbreviation: CI = confidence interval.

Adapted from Ref No. 28.

<table>
<thead>
<tr>
<th>Patient features</th>
<th>Antithrombotic therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 60 years</td>
<td>Aspirin (325 mg/day) or no therapy</td>
</tr>
<tr>
<td>No heart disease (lone AF)</td>
<td>Aspirin (325 mg/day)</td>
</tr>
<tr>
<td>Age &lt; 60 years Heart disease but no risk factors</td>
<td>Aspirin (325 mg/day)</td>
</tr>
<tr>
<td>Age ≥ 60 years No risk factors</td>
<td>Aspirin (325 mg/day)</td>
</tr>
<tr>
<td>Age ≥ 60 years</td>
<td>Oral anticoagulation (INR 2.0–3.0)</td>
</tr>
<tr>
<td>With diabetes mellitus or CAD</td>
<td>Addition of aspirin (81–162 mg/day) is optional</td>
</tr>
<tr>
<td>Age ≥ 75 years (especially women)</td>
<td>Oral anticoagulation (INR ≥ 2.0)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>Oral anticoagulation (INR 2.0–3.0)</td>
</tr>
<tr>
<td>LV ejection fraction ≤ 0.35</td>
<td>Oral anticoagulation (INR ≥ 2.5–3.5 may be appropriate)</td>
</tr>
<tr>
<td>Thyrotoxicosis</td>
<td>Oral anticoagulation (INR 2.0–3.0)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Oral anticoagulation (INR 2.0–3.0)</td>
</tr>
<tr>
<td>Rheumatic heart disease (mitral stenosis)</td>
<td>Oral anticoagulation (INR 2.0–3.0)</td>
</tr>
<tr>
<td>Prosthetic heart valves</td>
<td>Oral anticoagulation (INR 2.0–3.0)</td>
</tr>
<tr>
<td>Prior thromboembolism</td>
<td>Oral anticoagulation (INR 2.0–3.0)</td>
</tr>
<tr>
<td>Persistent atrial thrombus on TEE</td>
<td>Oral anticoagulation (INR 2.0–3.0)</td>
</tr>
</tbody>
</table>

Risk factors for thromboembolism include heart failure, LV ejection fraction < 0.35, and history of hypertension.

Abbreviations: CAD = coronary artery disease, LV = left ventricular, TEE = transesophageal echocardiogram, AF = atrial fibrillation, INR = International Normalized Ratio.

Adapted from Ref. No. 3.
The annual rate of warfarin-related major bleeding averaged 1.3% (targeted INR generally 2.0–3.0) in five primary prevention trials in AF, compared with 1.0% in the placebo group. However, in the SPAF II trial (INR 2.0–4.5), the detected rates of warfarin-related major bleeding were 4.2% per year in patients aged ≥75 years and 1.7% in younger patients. The annual rate of ICH was 1.8% in patients > 75 years versus 0.5% in patients ≥75 years. The average INR for an older patient with ICH was 3.1 in the hospital. This suggests that older patients may require somewhat lower INR targets (Table III) as well as vigilant monitoring.

Risk Factors for Warfarin-Related Major Hemorrhage and Intracranial Hemorrhage

Case-control and prospective cohort studies have identified several risk factors for ICH among patients receiving warfarin. The intensity of anticoagulation is probably the most important, with the risk rising dramatically with an INR ≥ 4.0 (Fig. 3). In a study involving nearly 2,750 patients receiving oral anticoagulant therapy (primarily warfarin), multivariate analysis established that the risk of bleeding complications was significantly higher with INR ≥ 4.5 (RR = 5.96; 95% CI, 3.68–9.67; p < 0.0001). Prothrombin time ratio (PTR) emerged as an independent risk factor for ICH in a case-control study focused exclusively on ICH among patients taking warfarin.

Other risk factors that predict episodes of major hemorrhage include a history of bleeding (especially gastrointestinal [GI] bleeding); previous cerebrovascular accident; comorbid conditions, such as renal insufficiency; or the presence of prosthetic heart valves. The existence of uncontrolled hypertension may also increase the likelihood of bleeding. Some data suggest that increasing age is a risk factor; however, establishing a causal relationship between advanced age per se and increased risk for warfarin-related bleeding (and ICH) is problematic, since age may be associated with other risk factors for bleeding, such as comorbidities or poor compliance. Occult pathologic lesions (e.g., bladder tumors, GI ulcerations) may be unmasked by anticoagulation therapy. In particular, warfarin-related ICH may represent an unmasking of underlying cerebral vasculopathies associated with cerebral amyloid angiopathy (CAA) or leukoaraiosis. In CAA, most small arteries and arterioles show marked amyloid deposition, and vessel walls (except for endothelial cells) are often replaced totally by amyloid deposits. This results in fibrinoid necrosis and microaneurysmal dilatation, which is closely associated with CAA-related hemorrhage. A recent study demonstrated a strong association between CAA and warfarin-related lobar (but not deep hemispheric) hemorrhage. Similarly, abnormalities in the white matter of the brain associated with cerebral ischemia (leukoaraiosis) have been linked with increased bleeding risk. Findings from the Stroke Prevention in Reversible Ischemia Trial (SPIRIT) indicated that the finding of leukoaraiosis on a computed tomography (CT) scan was the strongest independent predictor of ICH in patients with cerebrovascular disease (hazard ratio [HR] = 2.7; 95% CI, 1.4–5.3). This relationship was not confounded by age or hypertension. Altogether, these findings suggest that patients with fragile, small, perforating arteries might be susceptible to microhemorrhage, which in the presence of excessive anticoagulation therapy could convert to clinically overt ICH.

The Risk for Intracranial Hemorrhage in Typical Populations with Atrial Fibrillation

Although excellent safety has been achieved with warfarin in clinical trials, some physicians have concerns that patient selection and/or the highly controlled conditions of a clinical trial do not reflect the likely results in normal practice. To address this concern, a chart review of a typical population of Medicare patients in Missouri was conducted between 1993 and 1996. The results indicated that the prescription of warfarin was associated with a 24% RR reduction in adverse outcomes after adjustment for potential confounding factors (p = 0.003), suggesting that the benefits of warfarin outweighed the risks in actual practice. Notably, the overall benefit of warfarin therapy extended to the frail elderly, a group that is traditionally undertreated.

Many physicians are concerned that patients prone to falling may be more likely to experience ICH, and choose not to prescribe anticoagulants for these patients. However, a systematic review of the literature showed that the risk for subdural hematoma is increased only 1.4-fold by falling, as most falls in the elderly (90%) do not result in major injury. If a patient is at high risk for stroke due to AF (i.e., 8% per year in those aged ≥75 years), he or she must fall about 295 times a year for anticoagulation to provide the greater danger. However, the risk from falling may be different for patients with neurologic pathologies, such as previous brain injuries, ischemic stroke, or CAA.

The most effective means of preventing warfarin-related ICH is tight control of therapy to minimize the risk of excessive anticoagulation. Consequently, several approaches have been
employed successfully to improve INR control, including the use of anticoagulation clinics and computerized clinical decision aids.\textsuperscript{41–43} If a high INR is found, it should be verified and investigated. Often, high INRs are due to a concomitant drug enhancing warfarin’s effects, incorrect dosing, or a dispensing error. A high INR can be managed by stopping warfarin therapy temporarily. As the effects of warfarin diminish slowly, it may be necessary to monitor these patients for several days. An elevated INR in the patient at risk for imminent or acute bleeding is treated more aggressively. Vitamin K in oral or parenteral preparation or infusion of fresh frozen plasma or prothrombin concentrate may be required (Table IV).

For the lowest risk of ICH, patients must be educated on the importance of taking their medication regularly, having frequent blood tests, restricting their alcohol intake, and avoiding activities that might result in head injuries.

**Recommendations for Managing Patients with Atrial Fibrillation**

Although the ACC/AHA/ESC guidelines stress the fact that a patient’s risk factors for stroke should determine whether anticoagulation therapy is given, the nature of a patient’s AF may influence the decision to prescribe anticoagulation therapy. Management of AF requires knowledge of presentation (paroxysmal, persistent, or permanent) and consideration of the need for, timing of, and appropriate method for the control of ventricular rate or restoration of sinus rhythm.\textsuperscript{3, 44} Some special cases are considered below.

**Newly Discovered Atrial Fibrillation**

Decisions regarding long- or short-term anticoagulation must be individualized based on each patient’s intrinsic risk of thromboembolism. In patients with self-limited episodes of paroxysmal AF, antiarrhythmic drugs are usually unnecessary (Fig. 4), and the need for anticoagulation depends on the presence of the risk factors described previously.\textsuperscript{3} If a patient is at high risk, thromboemboli may develop during relatively short periods of AF.

Patients with newly discovered persistent AF may be allowed to remain in AF, with attention to control of ventricular rate and anticoagulant therapy. If the decision is made to restore and maintain normal sinus rhythm (NSR), anticoagulation should precede cardioversion.\textsuperscript{3, 44} Possible approaches include outpatient oral anticoagulation (INR 2.0–3.0) for 3 weeks followed by cardioversion, or TEE-guided cardioversion with “short-term” oral or intravenous anticoagulation in the periprocedure period. Regardless of the approach, because mechanical atrial contraction may be delayed after restoration of sinus rhythm, anticoagulant therapy is mandatory for 3 to 4 weeks after cardioversion.

**TABLE IV Reversing oral anticoagulation**

<table>
<thead>
<tr>
<th>Status</th>
<th>Treatment options</th>
</tr>
</thead>
<tbody>
<tr>
<td>INR above therapeutic range &gt; 3 but &lt; 5</td>
<td>Reduce warfarin dose or omit next dose and resume at a lower dose</td>
</tr>
<tr>
<td>INR &gt; 5 but &lt; 9, no clinically significant bleeding</td>
<td>Omit next 1–2 doses and resume at a lower dose; omit next dose and give vitamin K 2.5 mg, p.o. for 1 dose</td>
</tr>
<tr>
<td>INR 10–19, no clinically significant bleeding</td>
<td>Stop warfarin, administer vitamin K 5 mg, p.o. INR should decrease substantially in 24–48 h; may repeat dose if needed</td>
</tr>
<tr>
<td>INR &gt; 19, serious bleeding: patients requiring urgent surgery or major warfarin overdose</td>
<td>Stop warfarin, administer vitamin K 10 mg, in 50 ml PSS IVPB over at least 30 min; may supplement with 2–4 units of FFP depending on urgency. Vitamin K may be repeated every hour if needed\textsuperscript{a}</td>
</tr>
</tbody>
</table>

\textsuperscript{a} It may be difficult to achieve an anticoagulant effect of warfarin for up to 1 week. If continued anticoagulation required, use unfractionated heparin until the patient responds to warfarin.

**Abbreviations:** INR = International Normalized Ratio, p.o. = orally, PSS IVPB = physiologic saline solution-intravenous piggyback, FFP = fresh frozen plasma.

**Fig. 4** Pharmacologic management of patients with newly discovered atrial fibrillation (AF). HF = heart failure.\textsuperscript{3}
Atrial Fibrillation Following Cardiac Surgery

Atrial fibrillation occurs in 10 to 65% of patients after cardiac surgery and is associated with increased morbidity and mortality, as well as longer, more expensive hospital stays. Clinical information extracted from a recent literature review suggests that all patients with AF persisting for > 24 to 48 h after surgery and without contraindication should receive antiocoagulation therapy. If AF persists, a strategy of rhythm management or rate management should also be selected. For patients who are hemodynamically unstable or highly symptomatic, or who have a contraindication to anticoagulation, rhythm management with electrical cardioversion, amiodarone, or both is preferred. Treatment of the remaining patients should focus on rate control.

Atrial Fibrillation with Rate Control or in Predominantly Normal Sinus Rhythm

Insight into the role of anticoagulation therapy in patients with AF presenting with NSR was recently provided by the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial. Patients in the study had documented AF and ≥1 risk factors for stroke. Overall, the AFFIRM trial demonstrated that rate control plus anticoagulation in patients with AF is an acceptable primary therapy and produces a similar composite outcome (including death, disabling stroke, major bleeding, or cardiac arrest) as rhythm control plus anticoagulation. Although high rates of anticoagulation were used in both arms, most strokes occurred in patients who were not taking warfarin or had an INR < 2.0. Thus, the results from AFFIRM suggest that both restoration of sinus rhythm and AF rate control with simultaneous chronic warfarin anticoagulation have similar morbidity and mortality rates.

Atrial Flutter

An excess risk of stroke in patients with atrial flutter has only been reported recently. A longitudinal analysis of the Medicare database comparing inpatients (≥ 65 years) diagnosed with AF or atrial flutter with other hospitalized patients (control) found that stroke risk was significantly elevated in patients with atrial flutter (RR = 1.406; p < 0.0001), although the risk was below that observed with AF (RR = 1.642; p < 0.001). However, Kaplan-Meier analysis indicated that patients with atrial flutter subsequently develop an episode of AF in near-linear fashion over time, which translates into higher risk of stroke (Fig. 5). Based on these results, anticoagulation therapy is recommended in patients with atrial flutter.

Drugs for Oral Anticoagulation Therapy

Currently, stroke prevention for patients with AF consists of rapid anticoagulation using intravenous heparin or subcutaneous low-molecular-weight heparin (LMWH), followed by transition to oral anticoagulation (warfarin) for long-term therapy. Intravenous heparin may be preferred for inpatients, whereas LMWH may be preferred for outpatients as it can be provided without monitoring.

Although warfarin is the current mainstay of oral anticoagulation treatment in AF, it has some disadvantages, including its slow onset of action (2 to 7 days). Warfarin also has a narrow therapeutic window and its anticoagulant effects are unpredictable. Furthermore, its indirect mode of action, variable dose–response relationship, and sensitivity to drug- and diet-induced changes in absorption or metabolism complicate patient monitoring and dose adjustment. Fixed-dose warfarin regimens do not achieve the desired therapeutic range. The SPAF III study, using fixed doses of warfarin (average dose of 2.0 mg/day, INR of 1.3), failed to show benefit because average INRs were below therapeutic levels. Inadequate INR regulation can also result in serious complications, as evidenced by high rates of bleeding reported in older case reports and observational studies conducted before the introduction of the INR system.

Emerging Oral Anticoagulants

The limitations of warfarin therapy have prompted research into new anticoagulants that have a wider therapeutic window between thrombosis and prevention of hemostasis (enhanced safety) as well as more predictable dosing (less monitoring). The first oral direct thrombin inhibitor (DTI) to reach phase 3...
clinical trials is ximelagatran, a prodrug of melagatran, with rapid onset of action, reversible activity, and good bioavailability (20%).53–57 Unlike warfarin, this novel oral DTI is characterized by predictable dose-linear pharmacokinetics and no clinically significant food–or drug–drug interactions. Other oral DTIs (e.g., L-375378, UK-156406, BIBR 1048, and 3DP-4815) and oral factor Xa inhibitors (e.g., SQ-313, HMR-2906) are in earlier stages of development.58

Recently, interim results were presented from the Stroke Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation IV (SPORTIF IV) trial, which compared ximelagatran with warfarin as long-term anticoagulation for the prevention of stroke in patients with chronic NVAF.59 In this ongoing, open-label extension study, patients with NVAF and at least one additional stroke risk factor received either fixed-dose ximelagatran 36 mg b.i.d. (n = 187) or adjusted-dose warfarin INR 2.0–3.0 (n = 67). No routine coagulation monitoring was performed for ximelagatran. At interim analysis (21–24 months of treatment), the number of strokes/TIs per 100 treatment years was either equivalent or less in the ximelagatran-treated group (1.3 vs. 5.2 for ximelagatran and adjusted-dose warfarin, respectively).59 There was a trend toward a decrease in major bleeding with ximelagatran (0.9 vs. 2.6, respectively). Ximelagatran was well tolerated in the study. Asymptomatic S-alanine amino transferase elevation was observed in a few ximelagatran-treated patients, but these levels decreased spontaneously during continued treatment or discontinuation of therapy.

Once ximelagatran or another novel oral anticoagulant is available for routine clinical use, the risk of ICH associated with excessive anticoagulation may be reduced because the dosing will be more predictable and is likely to stay within the safe range. Furthermore, a reduced need for monitoring would make anticoagulation therapy more convenient for both patients and physicians.

**Conclusion**

Research to date clearly shows a major potential benefit of anticoagulant therapy for high-risk patients with AF.12–17,26 When warfarin is properly managed in a high-risk patient, anticoagulation treatment is likely to be safer than lack of treatment. It is important to maintain the INR consistently between 2.0 and 3.0. Patients with such risk factors as CHF, hypertension, or age > 75 years, and any detectable degree of AF should be given anticoagulation therapy unless they have comorbidities that may cause bleeding.

However, the variability of responses to warfarin increases the risk of ICH, which is more likely to occur if the INR is high. In addition, the complexity of warfarin management makes this therapy unsuitable for patients who are not compliant or have poor access to medical care. Developments in alternative oral anticoagulants, such as ximelagatran, may improve the benefit-to-risk ratio of anticoagulation therapy for patients with AF, and thereby simplify the risk-assessment process.

**References**


