Atrial Fibrillation and Thromboembolism: Implications for stroke prevention

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Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice, affecting over 2 million adults.\textsuperscript{1} Prevalence rises sharply with age, from approximately 0.1% in individuals <50 years old to 9% in those \( \geq 80 \) years old.\textsuperscript{1} With an increasing elderly population, the number of individuals with AF is projected to exceed 5 million over the next few decades.\textsuperscript{1}

AF is a major cause of stroke in the elderly (Table 1).\textsuperscript{2} In addition to age, other major determinants of stroke risk in patients with AF include prior stroke/transient ischemic attack, hypertension, diabetes, congestive heart failure, and echocardiographic evidence of left ventricular dysfunction or an enlarged left atrium.\textsuperscript{3,4}

AF-related clots can arise from a number of anatomic locations, including the left atrium and its appendage, left ventricle, mitral valve, cerebral vasculature, and the ascending aorta.\textsuperscript{5} However, the majority of strokes in patients with AF are caused by clots originating in the left atrial appendage (LAA), a multi-lobed structure lined with endothelial cells (the endocardium).\textsuperscript{6} These clots are fibrin-rich, in contrast with the platelet-rich aggregations that form in coronary arteries.\textsuperscript{7} Fibrin-rich clots form when there is a greater contribution of the coagulation cascade over platelet activation, which explains the differing benefits of antiplatelet and anticoagulant therapies observed in clinical trials.

### Table 1. Risk of AF-Associated Stroke Increases With Age. Framingham Heart Study, 30-year Follow-up, \( N = 5184 \)

<table>
<thead>
<tr>
<th>Age group</th>
<th>Prevalence AF</th>
<th>Stroke rate (per 1000 patient-years)</th>
<th>Population attributable risk (%)*</th>
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</thead>
<tbody>
<tr>
<td>60–69</td>
<td>1.8%</td>
<td>4.5</td>
<td>21.2</td>
</tr>
<tr>
<td>70–79</td>
<td>4.7%</td>
<td>9.0</td>
<td>48.9</td>
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<tr>
<td>80–89</td>
<td>10.2%</td>
<td>14.3</td>
<td>71.4</td>
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*Adjusted for BP

Wolf et al.\textsuperscript{2}
“Fibrin-rich clots form when there is a greater contribution of the coagulation cascade over platelet activation, which explains the differing benefits of antiplatelet and anticoagulant therapies observed in clinical trials.”

**Critical factors in pathogenesis of LAA clots**

**Endocardial dysfunction:** Under healthy conditions, endothelial cells produce a number of bioactive molecules with anticoagulant and antiplatelet activities. Emerging data suggest that this function may be impaired in AF, with consequential development of a procoagulant surface.

Conway et al reported elevated levels of von Willebrand factor (vWF), a marker of endothelial cell dysfunction, in patients with AF. Cai et al conducted a study in pigs with pacing-induced AF and demonstrated that basal nitric oxide (NO) levels were significantly lower in the left atrium and LAA compared with controls without AF (P < 0.01 for both comparisons). This was accompanied by a 46% decrease in expression of NO synthase (NOS) in the left atrium of animals with AF compared with controls (P < 0.01). NO has important antithrombotic effects such as inhibiting expression of tissue factor (TF), which triggers the coagulation cascade, and inhibiting platelet adhesion to the endothelium.

**Reduced flow:** Loss of organized mechanical contraction and enlarged atria in AF lead to diminished flow velocity in the left atrium and LAA. A number of studies have linked left atrial stasis to clot formation and embolic events. In stasis-related clot formation (ie, low-shear conditions), activation of the coagulation cascade is the dominant mechanism, leading to fibrin-rich clots.

**Prothrombotic states:** AF is associated with increased levels of coagulation markers, including factor VIII, fibrinogen, D-dimer, prothrombin fragment 1,2 and thrombin-antithrombin complex. AF is also associated with platelet activation, as measured by increased levels of β-thromboglobulin, platelet factor 4, and P-selectin.

![Figure 1. Central role of thrombin in clot formation.](image-url)

**Thrombin:**

**Key target for stroke prevention**

Coagulation factors are proteases that circulate in their inactive forms. The coagulation cascade comprises a regulated series of linked reactions involving the sequential activation of these factors on the surface of activated cells such as endothelial cells or platelets. It is triggered by exposure or expression of tissue factor (TF) to form a complex with factor VIIa. This complex converts factor X to factor Xa. Factor Xa (in complex with factor Va) then converts prothrombin (factor II) to thrombin (factor IIa), the most important protein in the coagulation cascade.
Thrombin converts fibrinogen to fibrin, which polymerizes to form a three-dimensional matrix. Initially, only small amounts of thrombin are produced. However, a number of thrombin-related feedback loops amplify the process, resulting in production of a large bolus of thrombin and increased recruitment of platelets (Figure 1).

**Amplification of coagulation cascade:** Thrombin activates several coagulation factors, including V, VIII, XI, and XIII. After conversion of fibrinogen, thrombin remains bound to fibrin, becoming part of the growing clot. Fibrin-bound thrombin remains active, continuing the activation process and rendering the clot a major reservoir of thrombin activity.

Thus, inhibition of thrombin activity not only suppresses fibrin formation, it suppresses thrombin generation.

**Platelet activation and recruitment:** Platelet responses to thrombin are mediated by a family of G protein-coupled receptors. Activation causes platelets to change shape, exposing the fibrinogen receptor, and to release a large number of biologically active molecules. Cross-linking of platelets with fibrinogen recruits circulating platelets to the clot.

**Accepted pharmacologic approaches to stroke prevention fail to meet clinical needs**

**Warfarin:** Current oral anticoagulant therapy for stroke prevention in AF is based on warfarin, an indirect thrombin inhibitor and a difficult drug to use (Table 2). Warfarin is a vitamin K antagonist. Coagulation factors II, VII, IX, and X require vitamin K for activation. Since these factors have turnover times of 24 to 60 hours, an anticoagulant effect is not achieved for 4 to 7 days.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Consequence</th>
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<tbody>
<tr>
<td>Slow onset of action</td>
<td>Initial concomitant therapy with a parenteral anticoagulant</td>
</tr>
<tr>
<td>Genetic variability in metabolism</td>
<td>Variable dose requirements</td>
</tr>
<tr>
<td>Multiple food and drug interactions</td>
<td></td>
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<tr>
<td>Narrow therapeutic index</td>
<td>Frequent coagulation monitoring</td>
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</table>

Warfarin also has a short-term procoagulant effect since the protein C pathway (a major endogenous antithrombotic mechanism) is vitamin K-dependent. Thrombomodulin, which is expressed on endothelial cell surfaces, binds thrombin, causing thrombin to undergo a conformational change and lose its procoagulant activity. The thrombin/thrombomodulin complex then activates protein C, a step that requires vitamin K as cofactor. In turn, activated protein C binds to protein S, and this complex deactivates factors Va and VIIIa. Since protein C has a much shorter half-life than the vitamin K-dependent coagulation factors, warfarin may cause a procoagulant state for the first 36 hours of therapy. These data are among the reasons why warfarin is commonly overlapped with parenteral heparin for 4 to 5 days, after which heparin is discontinued.
FUTURE ANTICOAGULANT OPTIONS: DIRECT THROMBIN INHIBITION (XIMELAGATRAN)

A number of anticoagulant therapies are currently under evaluation, including low–molecular-weight heparins (LMWHs), indirect thrombin inhibition (idraparinux), and direct thrombin inhibition (ximelagatran). Ximelagatran is the furthest along in clinical development.

Favorable pharmacologic profile: An oral direct thrombin inhibitor, ximelagatran is rapidly converted to its active form (melagatran) after absorption. The peak anticoagulant effect is reached as rapidly as that of subcutaneous LMWH. Since melagatran binds directly to thrombin, it inhibits both circulating and fibrin-bound thrombin. The anticoagulant response to fixed doses of ximelagatran is predictable, since the level of protein binding to melagatran is low. There is also no binding to platelet factor 4; consequently, there is no risk of thrombocytopenia. Finally, small peptides such as melagatran bind reversibly and transiently to the active site alone and do not interact with the fibrinogen and heparin binding sites on thrombin. This provides a rapid offset of action and a low risk of bleeding.

Clinical trials of warfarin: The relative risk reduction (59%) in five primary-prevention trials was similar to that observed in a secondary-prevention trial (68% reduction). The rate of intracranial hemorrhage was 0.3%/year in warfarin patients and 0.1% in placebo patients.

Antiplatelet agents: The use of aspirin or other oral antiplatelet agents for stroke prevention in AF is controversial. Meta-analysis of six trials comparing warfarin and aspirin demonstrated that adjusted-dose warfarin reduced the risk for all strokes by 36% (95% CI, 14% to 52%) compared with aspirin. The relative risk reduction for ischemic strokes was 46% (95% CI, 27% to 60%), although warfarin was associated with a 2.1-fold increase in risk for intracranial hemorrhage (95% CI, 1.0 to 4.6). Meta-analysis of six placebo-controlled trials of aspirin demonstrated that aspirin reduced the risk of all stroke by 22% (95% CI, 2% to 38%). However, in all but one trial (SPAF 1) the confidence intervals overlapped unity, and in that trial there was internal inconsistency. A trial is currently underway comparing adjusted-dose warfarin therapy with an aspirin-clopidogrel combination.

Table 3. Ximelagatran—Emerging New Oral Anticoagulant

<table>
<thead>
<tr>
<th>Feature</th>
<th>Consequence</th>
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<tr>
<td>Direct inhibition of thrombin</td>
<td>Potent anticoagulant activity</td>
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<tr>
<td>Active against free- and clot-bound thrombin</td>
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<tr>
<td>Transient, reversible binding</td>
<td>Rapid offset of action</td>
</tr>
<tr>
<td>Rapid onset of action</td>
<td>No need for concomitant therapy with a parenteral anticoagulant</td>
</tr>
<tr>
<td>Predictable anticoagulant response</td>
<td>Fixed dose (no dosage adjustment)</td>
</tr>
<tr>
<td>Virtually no known food or drug interactions</td>
<td>No need for coagulation monitoring</td>
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<tr>
<td>Wide therapeutic index</td>
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Maintaining an adequate level of anticoagulation is critical to reducing stroke-related morbidity and mortality. However, warfarin has a narrow therapeutic window and maintaining warfarin therapy within the therapeutic range is a major problem. Effective anticoagulation is achieved at international normalized ratios (INRs) of ≥2. Therapeutic efficacy does not increase as INR increases, but risk of hemorrhage does, particularly at INRs >3. Warfarin interacts with numerous drugs and foods and there is substantial genetic variability in its metabolism. Few patients maintain completely stable levels of anticoagulation over time. In clinical practice, target INR values are attained in only 50% to 60% of patients.
of bleeding. Thus, ximelagatran is viewed as a potential clinical advance over warfarin (Table 3).

**Clinical trial experience (SPORTIF Program):** The Stroke Prevention using an ORal Thrombin Inhibitor in patients with atrial Fibrillation (SPORTIF) trials evaluated ximelagatran for stroke prevention in AF. SPORTIF III and SPORTIF V were large-scale evaluations of ximelagatran (36 mg twice daily) versus adjusted-dose warfarin in patients with AF and ≥1 risk factors for stroke. The design of SPORTIF III and V permitted a pooled analysis of the results. SPORTIF III (N = 3407) was an open-label, parallel-group study, with blinded outcome assessment; SPORTIF V (N = 3922) had a double-blind parallel-group design. In both trials, the primary outcome was stroke or systemic embolism, and the objective was to establish the non-inferiority of ximelagatran relative to warfarin for prevention of the primary outcome (Figure 2).

The quality of warfarin control achieved in both trials was superior to that in clinical practice: INR values within 1.8 to 3.2 were achieved 81% of the time in SPORTIF III and 83% of the time in SPORTIF V.

**SPORTIF III results:** After a mean follow-up of 17 months, the primary outcome (intention-to-treat analysis) occurred in 1.6%/yr of ximelagatran patients and 2.3%/yr of warfarin patients. The absolute difference in the primary outcome rate was -0.7% per year (95% CI, -1.5 to 0.1; P = 0.1000). These CIs fell within the prespecified margins for establishing non-inferiority of ximelagatran. Major bleeding was defined as (1) an associated decrease in hemoglobin ≥2 g/dL; (2) the need for transfusion of ≥2 units; or (3) involving a critical site, such as intracranial. This outcome occurred in 1.3% and 1.8% of ximelagatran and warfarin patients, respectively, a nonsignificant difference. Combined major or minor bleeding occurred significantly less often in ximelagatran patients: 25.5% and 29.5%, respectively (P = 0.007).

**SPORTIF V results:** After a mean follow-up of 20 months, the primary outcome (intention-to-treat analysis) occurred in 51 (1.6%/yr) of the ximelagatran group and 37 (1.2%/yr) of the warfarin group. The absolute difference in the primary outcome rate was 0.45% (95% CI, -0.13 to 1.03; P = 0.13). These CIs met the criteria for ximelagatran non-inferiority. Combined major or minor bleeding occurred significantly less often in ximelagatran patients: 37% and 47%, respectively (P < 0.0001).

**SPORTIF III and V combined data:** In the prespecified pooled analysis, the primary outcome occurred in 91 patients in the ximelagatran group.
and 93 in the warfarin group (Figure 3). The absolute difference in the primary outcome rate was –0.03%/yr, confirming ximelagatran non-inferiority. This analysis also showed a trend in favor of less major bleeding in ximelagatran patients: 1.9% (ximelagatran) versus 2.5% (warfarin, \( P = 0.054 \)). Net clinical benefit (as assessed by combined primary outcome, major bleeding, and death) also favored ximelagatran: 5.2% versus 6.2% (\( P = 0.038 \)).

In both trials, elevated liver enzymes typically occurred between 2 and 6 months after initiation of treatment and returned to baseline either spontaneously or after cessation of treatment.\(^3^5,3^6\) In SPORTIF III, serum alanine aminotransferase (ALT) levels rose above 3× the upper limit of normal (ULN) in 0.8% of patients in the warfarin group and 6.3% of the ximelagatran group (\( P < 0.001 \)).\(^3^5\) In SPORTIF V, ALT levels >3× ULN occurred 0.8% of the warfarin group and 6% of ximelagatran group (\( P < 0.001 \)).\(^3^6\)

SPORTIF III and V demonstrated that oral ximelagatran was at least as effective as dose-adjusted warfarin in prevention of stroke in AF patients. Further, ximelagatran caused less bleeding than warfarin and offered fixed oral dosing without the need for coagulation monitoring.

**Conclusions**

Stroke is the major cause of morbidity and mortality in patients with AF. The model of stroke pathogenesis in AF that has emerged in recent years emphasizes thrombin as a critical mediator via (1) activation of other coagulation factors, thereby amplifying its own production, and (2) platelet activation. Clinical trials validate this model, demonstrating that effective anticoagulant activity even with indirect thrombin inhibitors can achieve substantial reductions in stroke risk—significantly greater than those achieved with antiplatelet therapy. However, warfarin, the only currently available oral anticoagulant, has several limitations that render it a difficult drug to use in clinical practice.

Direct thrombin inhibition (ximelagatran) appears to be a clinical advance over warfarin. Used in fixed doses without coagulation monitoring, ximelagatran provided effective anticoagulation therapy with a low risk of bleeding in clinical trials. Its efficacy combined with the virtual absence of drug and food interactions, the absence of a need for anticoagulation monitoring, its rapid onset of action, and its fixed dose administration make ximelagatran a very attractive first-line drug to treat patients with AF at risk for stroke.

“Net clinical benefit (as assessed by combined primary outcome, major bleeding, and death) also favored ximelagatran: 5.2% versus 6.2% (\( P = 0.038 \)).”
REFERENCES


SELF-ASSESSMENT QUESTIONS

Please check the appropriate answer for each question on the Answer Key. Instructions for obtaining CME credit are provided on the back of the Answer Key.

1. The number of individuals currently with AF is estimated to be how much?
   a. 2 million
   b. 5 million
   c. 10 million

2. The majority of AF-related clots arise in which anatomic location?
   a. Left atrial appendage
   b. Left ventricle
   c. Mitral valve
   d. Ascending aorta
   e. Cerebral vasculature

3. Unlike the endothelium, the endocardium is not a source of nitric oxide.
   a. True
   b. False

4. The majority of AF-related clots are formed under which hemodynamic conditions?
   a. High shear
   b. Low shear

5. Vitamin K antagonism may have procoagulant as well as anticoagulant effects.
   a. True
   b. False

6. Anticoagulant therapy is more effective in reducing AF-related stroke than antiplatelet therapy.
   a. True
   b. False

7. Potential advantages of the oral direct thrombin inhibitor ximelagatran over warfarin include:
   a. No coagulation monitoring
   b. Fixed dosing
   c. Virtually no food and drug interactions
   d. Rapid onset of anticoagulation
   e. All of the above

8. In the SPORTIF III and V trials, INR values of 1.8 to 3.2 were achieved in warfarin patients what proportion of the time?
   a. 50%
   b. 60%
   c. 70%
   d. 80%

9. With regard to primary outcome (stroke or systemic embolism) SPORTIF III and V consistently demonstrated that ximelagatran was...
   a. Clinically equivalent to warfarin
   b. More effective than warfarin
   c. Less effective than warfarin

10. With regard to combined major and minor bleeding, SPORTIF III and V consistently demonstrated that ximelagatran caused...
    a. Significantly more bleeding
    b. Significantly less bleeding

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Answer Key

Please check the correct box for each question. There is only 1 correct response for each question.

1. A  B  C
2. A  B  C  D  E
3. A  B
4. A  B
5. A  B
6. A  B
7. A  B  C  D  E
8. A  B  C  D
9. A  B  C
10. A  B

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<td>Importance to physicians</td>
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<tr>
<td>Increased my knowledge</td>
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<td>1</td>
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<tr>
<td>Did not promote particular product or company</td>
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