Patients with atrial fibrillation are at increased risk of having a cardioembolic stroke. The use of oral anticoagulation is now well established to prevent strokes in patients with atrial fibrillation and a CHA2DS2-VASc (congestive heart failure, hypertension, age ≥75 years [2 points], diabetes mellitus, prior stroke/transient ischemic attack or thromboembolism [2 points], vascular disease, age 65 to 74 years, and sex category) score of greater than 1, beyond sex. However, the role of antiplatelet therapy, specifically aspirin in low-risk patients or as an alternative to oral anticoagulation, remains controversial. The most recent US guidelines conflict with the European guidelines, which do not recommend antiplatelet monotherapy for stroke prevention irrespective of stroke risk. The aim of this review is to summarize published studies that question the role of aspirin in preventing strokes associated with atrial fibrillation. Overall, aspirin is found to play a limited role in the prevention of stroke in patients with atrial fibrillation and is associated with a similar risk of hemorrhagic events compared with anticoagulants. The benefit of dual antiplatelet therapy as an alternative to oral anticoagulation requires further study.

Keywords: anticoagulation, antiplatelet therapy, cardioembolic stroke, thromboprophylaxis, vitamin K antagonist, warfarin

According to the Centers for Disease Control and Prevention, approximately 2.2 million people residing in the United States have atrial fibrillation. Atrial fibrillation is the most common cardiac arrhythmia. Its prevalence is underestimated, as it is undiagnosed in many patients because of the paroxysmal or asymptomatic nature of the disease. The American Stroke Association (ASA) and the American Heart Association (AHA) estimate that 15% of strokes result from untreated atrial fibrillation. Patients with atrial fibrillation have a 5-fold increased risk of ischemic stroke. In addition, atrial fibrillation is a source for 45% of all embolic strokes in the United States. Strokes associated with atrial fibrillation are disabling and associated with a high mortality rate. The rate of stroke varies between 2 to 10 per 100 patient-years without antithrombotic therapy.

Incidence of strokes in patients with atrial fibrillation increases with associated comorbidities. Risk stratification algorithms have evolved from CHADS2 (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke/transient ischemic attack or transient ischemic attack) to CHA2DS2-VASc. Patients with atrial fibrillation and a CHA2DS2-VASc score of greater than 1, beyond sex, have a higher risk of stroke.
ischemic attack [TIA] or thromboembolism [2 points]) to CHA2DS2-VASc (congestive heart failure, hypertension, age ⩾75 years [2 points], diabetes mellitus, prior stroke/TIA or thromboembolism [2 points], vascular disease, age 65 to 74 years, sex category) to identify risk factors that are associated with the development of strokes in patients with atrial fibrillation. As Gersh et al\textsuperscript{3} stated, “it is not just the arrhythmia but the company it keeps that is responsible for systemic thromboembolism.” The risk factors included in the CHA2DS2-VASc scoring system are more important in determining the thromboembolic risk than the presence of the atrial arrhythmia alone.\textsuperscript{5,6} Although the use of oral anticoagulation (OAC) is now well established to prevent strokes in patients with atrial fibrillation and CHA2DS2-VASc scores greater than 1, beyond sex, the role of antiplatelet therapy, specifically aspirin in low-risk patients or as an alternative to OAC therapy, is controversial.

According to a retrospective observational study\textsuperscript{7} that analyzed data on US patients with acute ischemic stroke and known history of atrial fibrillation admitted to hospitals participating in the “Get With the Guidelines-Stroke” program between 2012 and 2015, 84% of these patients were not taking OACs before their stroke. Thus, patients with atrial fibrillation who are receiving suboptimal medical therapy are at an increased risk of stroke that ultimately could be prevented.

The current US guidelines for stroke prevention are based on various classes and levels of evidence outlined jointly by the American College of Cardiology (ACC) and the AHA, which incorporate evidence from the ASA.\textsuperscript{8} Table 1 summarizes the main recommendations agreed upon by these associations.\textsuperscript{8,9} The antithrombotic agent is carefully selected based on the stroke and bleeding risks specific for each patient. The rate of major bleeding while taking anticoagulation therapy increases in patients with higher CHA2DS2-VASc scores. Tools such as the HAS-BLED (hypertension, abnormal renal and liver function, stroke, bleeding, labile international normalized ratio [INR], elderly, and drugs or alcohol use) and HEMORR\textsubscript{2}HAGES (hepatic or renal disease, ethanol abuse, malignancy, older age ⩾75 years), reduced platelet count or function, rebleeding risk [2 points], hypertension [uncontrolled], anemia, genetic factors, excessive fall risk, and stroke) schemes are used for appropriate selection of antithrombotic strategies in patients with atrial fibrillation with bleeding potential.\textsuperscript{11}

Oral anticoagulation therapy has proven superior to aspirin therapy in patients with atrial fibrillation. However, this overall clinical benefit excluded patients at low stroke risk with a CHA2DS2-VASc score of 0 or 1. There are conflicting opinions regarding whether antiplatelet therapy should be administered to these low-risk patients. The US guidelines\textsuperscript{8} support omitting antithrombotic therapy in patients with atrial fibrillation and a CHA2DS2-VASc score of 0, but they also support aspirin or OAC therapy in patients with a CHA2DS2-VASc score of 1. This recommendation is in contrast to the European Society of Cardiology (ESC) guidelines, which do not recommend antiplatelet monotherapy for stroke prevention irrespective of stroke risk.\textsuperscript{12}

In the present review, we summarize published studies that both support and question the role of antiplatelet therapy in preventing strokes associated with atrial fibrillation. The studies included in this review were the most-cited and well-known studies, to the best of our knowledge, regarding aspirin therapy for patients with atrial fibrillation.

Pathophysiology of Cardioembolic Strokes

In atrial fibrillation, the cardiac environment encompasses all 3 components of Virchow’s triad—blood stasis, endothelial damage, and hypercoagulability—thereby facilitating the development of thromboembolism. The electrical rhythm of atrial fibrillation impairs atrial systolic contraction, including the loss of “atrial kick,” resulting in stasis of blood in the left atrium and appendage.\textsuperscript{13} Additionally,
Comorbidities such as diabetes, hypertension, and atherosclerosis promote cardiac remodeling by causing left atrial dilation and endothelial dysfunction. A hypercoagulable state has been noted in atrial fibrillation with increased circulating platelet activators and plasma thrombotic complexes. Platelet activation occurs through surface receptors. When activated, platelets release storage granules, which promote platelet aggregation.

### Pharmacology of Antiplatelet and Anticoagulation Agents

There are 2 main pharmacologic options for stroke prevention in patients with atrial fibrillation: antiplatelet therapy and anticoagulation therapy. Two antiplatelet agents—aspirin and clopidogrel—have been studied.

### Table 1.

**Guideline Recommendations Regarding Antiplatelet and Anticoagulation Therapies for Patients With Atrial Fibrillation in Terms of Stroke Prophylaxis Based on Risk Stratification**

<table>
<thead>
<tr>
<th>CHA2DS2-VASc Score</th>
<th>Recommendation</th>
<th>Class of Evidence</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥0</td>
<td>Acceptable to omit antithrombotic therapy.⁸</td>
<td>IIA</td>
<td>B</td>
</tr>
<tr>
<td>≥0</td>
<td>OAC or aspirin (81-325 mg/d) may be administered.⁹</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>≥0</td>
<td>Aspirin (325 mg/d) can be used in patients with contraindication to OAC.⁹</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>1</td>
<td>Acceptable to omit antithrombotic therapy or initiate treatment with OAC or aspirin.⁶</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>≥1</td>
<td>Patients older than 75 y are at increased risk of bleeding and should have an INR goal between 1.6 to 2.5.⁹</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>≥2</td>
<td>OAC is recommended. Warfarin is preferred, especially in patients with end-stage chronic kidney disease (creatinine clearance &lt;15 mL/min) or undergoing hemodialysis. Target INR between 2 and 3. Dabigatran, rivaroxaban, and apixaban are acceptable alternatives in select patients.⁸</td>
<td>I</td>
<td>A (warfarin) B (NOACs)</td>
</tr>
<tr>
<td>≥2</td>
<td>For patients with ACS and AF, anticoagulation with warfarin is recommended unless contraindicated. Efforts should be directed to minimize duration of triple therapy.⁶</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>≥2</td>
<td>Dual antiplatelet therapy (aspirin and clopidogrel) can be used in patients in whom OAC (warfarin) is unsuitable (patient preference or physician assessment that OAC is not safe).⁹</td>
<td>IIb</td>
<td>B</td>
</tr>
</tbody>
</table>

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⁸ Correlation of CHA2DS2-VASc (congestive heart failure, hypertension, age ≥75 years [2 points], diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism [2 points], vascular disease, age 65 to 74 years, sex category) score with annual percent risk of cardioembolic stroke. Score of 0 corresponds to 0.3% risk, score of 1 corresponds to 0.9% risk, score of 2 corresponds to 2.9% risk, score of 3 corresponds to 4.8% risk, score of 4 corresponds to 6.7% risk, score of 5 corresponds to 10% risk, score of 6 corresponds to 13.6% risk, score of 7 corresponds to 15.7% and score of 8 or 9 corresponds to 15.2%.¹⁰

⁹ It is recommended that international normalized ratio (INR) range be in the therapeutic range at least equal to or greater than 65% of the time while receiving vitamin K antagonist therapy.

¹⁰ Class of Evidence: I, strong recommendation for the studied treatment to be performed/administered; IIA, reasonable recommendation for studied treatment to be performed however additional studies with focused objectives are needed; IIb, recommendation for studied treatment may be considered however additional studies with broad objectives are needed and additional registry data would be useful; III, recommendation that treatment is not useful/effective and may be harmful given sufficient evidence from multiple randomized trials or meta-analyses.

¹ⁱ Level of Evidence: A, data derived from multiple randomized clinical trials and evaluated by multiple populations; B, data derived from a single randomized trial or nonrandomized studies with evaluation of limited populations; C, evidence taken from consensus of expert opinions, case studies and standard of care with evaluation from very limited populations.

Abbreviation: ACS, acute coronary syndrome; AF, atrial fibrillation; NOAC, novel oral anticoagulants; OAC, oral anticoagulation.
anticoagulants (NOACs; apixaban, dabigatran, edoxaban, and rivaroxaban) have been compared.\textsuperscript{18} Aspirin is effective in inhibiting hemostasis by impairing platelet aggregation. This is achieved by decreasing platelet thromboxane A2 synthesis and thus reducing thrombus formation.\textsuperscript{19} Aspirin also has additional antithrombotic effects by reducing thrombin generation, increasing fibrin clot permeability, and accelerating clot lysis by acetyling lysine residues in fibrinogen.\textsuperscript{19} Clopidogrel is a pro-drug with a 50% bioavailability, and only 15% of the prodrug is metabolized by cytochrome P450 system in the liver to generate an active metabolite.\textsuperscript{20} This metabolite works by selectively and irreversibly inhibiting the binding of adenosine diphosphate to platelet P2Y\textsubscript{12} receptors\textsuperscript{20} and results in interruption of the adenosine diphosphate-mediated activation of the glycoprotein IIb/IIIa complex, thereby inhibiting platelet activation, crosslinking, and aggregation.\textsuperscript{21} Warfarin inhibits vitamin K epoxide reductase, which is an enzyme involved in activating procoagulation protein factors (II, VII, IX, and XI).\textsuperscript{22} Vitamin K antagonists affect the INR, and the therapeutic INR range is between 2 and 3. In the 2000s, uncontrolled use of warfarin resulted in numerous hospitalizations and fatalities.\textsuperscript{23} As a result, anticoagulation therapy was underprescribed and patients received alternative therapies, such as antiplatelet therapy, for stroke prevention in the setting of atrial fibrillation.\textsuperscript{24} This trend resulted in inferior stroke protection compared with OAC. However, the introduction of NOACs in the past few years has offered an alternative to warfarin. These drugs offer attractive features over VKAs, including minimal food-drug interactions, fixed doses without routine coagulation monitoring, and targeted effect on anticoagulation cascade, thereby reducing bleeding profile significantly. The NOAC agents include direct thrombin inhibitors, such as dabigatran, and direct Factor Xa inhibitors, such as apixaban, edoxaban, and rivaroxaban.\textsuperscript{22} Dabigatran prevents thrombin from catalyzing the reaction of fibrinogen to fibrin.\textsuperscript{22} Apixaban, edoxaban, and rivaroxaban inhibit Factor Xa, thereby halting thrombin formation, which is a key step in the intersection of the intrinsic and extrinsic coagulation pathways.\textsuperscript{25} Four large multinational clinical trials (ARISTOTLE, RE-LY, Engage AF-TIMI 48, and ROCKET-AF) investigated the role of NOACs vs dose-adjusted warfarin in the prevention of strokes in patients with atrial fibrillation.\textsuperscript{26-30} These trials found that NOACs were not inferior to warfarin in preventing strokes and systemic embolism.

Role of Antiplatelet Therapy in Atrial Fibrillation

As mentioned, patients with atrial fibrillation have increased hypercoagulability and platelet activation. Based on this understanding, patients with atrial fibrillation may be only partially protected by inhibition of platelet aggregation by aspirin therapy. An analysis of trials comparing aspirin with placebo demonstrated that aspirin was associated with a 19% reduction of nondisabling stroke.\textsuperscript{31} However, the most recent randomized trial of aspirin vs placebo found a neutral effect.\textsuperscript{3} So, the benefit of aspirin is known but the effects are limited.

The protective effect of aspirin can be augmented with the addition of another antiplatelet agent. In the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE),\textsuperscript{17} combination therapy with aspirin and clopidogrel significantly reduced the rate of vascular events, especially strokes. The trial suggested that dual antiplatelet therapy (DAPT) could be an alternative treatment option for patients who cannot take anticoagulants for stroke prevention in the setting of atrial fibrillation.\textsuperscript{17} Furthermore, the Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Events (CHANCE) trial\textsuperscript{32} showed that DAPT was more effective than monotherapy for stroke prevention. A similar finding was seen in the Clopidogrel for High Atherothrombosis Risk and Ischemic Stabilization Management and Avoidance (CHARISMA) trial.\textsuperscript{33} The trial compared DAPT with aspirin monotherapy in
high-risk asymptomatic patients with 3 or more risk factors for cerebrovascular accidents and symptomatic patients with a history of cerebrovascular disease, coronary artery disease, or peripheral vascular disease. A 12.5% relative risk reduction in vascular events was observed in patients taking DAPT. However, DAPT was found to be associated with a high rate of hemorrhagic events, as seen in the Management of Atherothrombosis with Clopidogrel in High-risk (MATCH) trial, which investigated patients with recent ischemic stroke taking DAPT for prevention of future vascular events.

Antiplatelet therapy is the standard for prevention of recurrent vascular events in patients with prior ischemic strokes, with aspirin being the preferred choice. However, the CHANCE, CHARISMA, and MATCH studies investigated the use of aspirin in atherothrombotic strokes, not in cardioembolic strokes.

Antiplatelet Treatment and Ischemic Strokes

The Stroke Prevention in Atrial Fibrillation (SPAF) trial was an early multi-institutional, primary prevention study comparing the efficacy and safety of aspirin and warfarin with placebo. The superiority of both warfarin and aspirin relative to placebo resulted in early termination of the study. The rate of thromboembolic events was reduced by 42% in those who received aspirin and 67% in those who received warfarin. The risk of bleeding was 1.6% in the placebo group, 1.4% in the aspirin group, and 1.5% in the warfarin group. The use of antithrombotic therapy was favored in all patients except very low-risk patients. The efficacy of aspirin was unable to be fully observed because participants taking warfarin also composed a subset of all aspirin-eligible patients. The study concluded that aspirin or warfarin should be given to patients with atrial fibrillation for stroke prevention.

A subsequent trial, SPAF II, directly compared warfarin with aspirin therapy in 2 age groups. The patients were divided into warfarin and aspirin treatment groups. The rate of thromboembolic events per year was 3.6% in the warfarin group and 4.8% in the aspirin group, indicating that warfarin was more effective than aspirin therapy in the prevention of ischemic strokes that are atherothrombotic in origin. These strokes can also occur in patients with underlying atrial fibrillation.

Antiplatelet vs Anticoagulation Therapy for Stroke Prevention

Randomized trials have investigated the role of antiplatelet and anticoagulation therapies for primary and secondary prevention of thromboembolic events in patients with atrial fibrillation, as summarized in Table 2.

The Low Dose Aspirin, Stroke and Atrial Fibrillation (LASAF) study was an open multicenter trial that investigated the alternate-day dosing of aspirin in stroke prevention among patients with atrial fibrillation. The trial found that cardiovascular events and mortality rates were dramatically reduced between daily vs alternate-day dosing of aspirin therapy. However, the difference between daily aspirin vs control in event outcomes, including strokes, did not reach statistical significance.

The Japan Atrial Fibrillation Stroke Trial (JAST) was a multicenter prospective randomized trial that investigated the efficacy and safety profile of aspirin therapy vs control in patients with low-risk atrial fibrillation. The trial terminated early because a higher number of primary end points, including cardiovascular deaths and strokes, occurred in the aspirin treatment group. Aspirin was also associated with increased risk of bleeding. Interestingly, patients enrolled in the study were also at high risk for stroke. According to the AHA/ACC guidelines, these individuals should be taking anticoagulants; therefore, the preventive effects of aspirin could not be appreciated among them. The study concluded that aspirin as stroke prophylaxis was neither effective nor safe.
### Table 2
**Effects of Antiplatelet and Anticoagulation Therapies for Stroke Prevention in Patients With Atrial Fibrillation: Trial Summaries**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design and Patients</th>
<th>Interventions</th>
<th>Outcome Measure</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPAF I&lt;sup&gt;35&lt;/sup&gt;</td>
<td>Multicenter, prospective randomized trial; patients with AF</td>
<td>Aspirin (325 mg/d), warfarin (1.3 &lt; INR &lt; 1.8), and placebo</td>
<td>Prevention of primary events (ischemic stroke and systemic embolism)</td>
<td>Annual rate of primary events: 6.3% (placebo) and 3.6% (aspirin); reduced risk of primary events or deaths: 58% (warfarin) and 32% (aspirin)</td>
<td>Aspirin and warfarin are both effective; magnitude of reduction in events by warfarin vs aspirin could not be compared; aspirin or warfarin should be given to patients with AF to reduce stroke events.</td>
</tr>
<tr>
<td>SPAF II&lt;sup&gt;36&lt;/sup&gt;</td>
<td>Randomized trial; patients with AF aged &lt;75 and &gt;75 y</td>
<td>Warfarin (2 &lt; INR &lt; 4.5) and aspirin (325 mg/d)</td>
<td>Rate of thromboembolic events/y</td>
<td>Overall rate: 3.6% (warfarin) and 4.8% (aspirin); rate in patients aged &gt;75 y: 4.3% (aspirin) and 4.6% (warfarin)</td>
<td>Warfarin was more effective than aspirin for stroke prophylaxis.</td>
</tr>
<tr>
<td>LASAF&lt;sup&gt;37&lt;/sup&gt;</td>
<td>Multicenter trial; patients with AF</td>
<td>Daily aspirin (125 mg), aspirin on alternate days, and placebo</td>
<td>Cardiovascular events and stroke</td>
<td>Difference between daily aspirin and placebo for stroke was not statistically significant; reduction of cardiovascular event rates between aspirin groups: 7.7% (daily aspirin) and 2.2% (alternate day aspirin)</td>
<td>Low-dose aspirin on alternate days was efficient in preventing major cardiovascular events; for stroke prevention, aspirin was less effective.</td>
</tr>
<tr>
<td>JAST&lt;sup&gt;38&lt;/sup&gt;</td>
<td>Multicenter prospective randomized trial; patients with low risk AF but high stroke risk</td>
<td>Aspirin (150-200 mg/d) or control group (no antiplatelet or anticoagulation therapy)</td>
<td>Cardiovascular death or stroke events</td>
<td>End point annual rate: 3.1% (aspirin) vs 2.4% (control)</td>
<td>Trial was suspended early because of large cumulative end points in the aspirin group; low possibility of superiority of aspirin in prevention of primary end points; aspirin was not safe or effective in stroke prevention.</td>
</tr>
<tr>
<td>EAFT&lt;sup&gt;39&lt;/sup&gt;</td>
<td>Prospective multicenter cohort study; patients with AF after TIA or stroke</td>
<td>Standard oral anticoagulation (2.5 &lt; INR &lt; 4) vs aspirin (300 mg/d)</td>
<td>Secondary prevention of thromboembolic events</td>
<td>Annual rate of vascular events: 8% (anticoagulation), 15% (aspirin), and 17% (placebo)</td>
<td>Although aspirin was less effective, it was a safe alternative in patients with a contraindication to systemic anticoagulation therapy.</td>
</tr>
<tr>
<td>PATA&lt;sup&gt;40&lt;/sup&gt;</td>
<td>Primary care–based trial; patients with AF</td>
<td>Low-intensity anticoagulation (1.1 &lt; INR &lt;1.6), regular intensity anticoagulation (2.5 &lt; INR &lt;3.5), and aspirin (150 mg/d)</td>
<td>Thromboembolic events</td>
<td>Annual embolism incidence: 6% (aspirin) and 4% (anticoagulation); estimated reduction in incidence of embolism: 24% for aspirin vs 16% for anticoagulation</td>
<td>Anticoagulation therapy even at low intensity was superior to aspirin therapy alone.</td>
</tr>
</tbody>
</table>

(continued)
The European Atrial Fibrillation Trial (EAFT) was a prospective multicenter cohort study investigating secondary prevention of thromboembolic events in patients with atrial fibrillation after TIA or minor stroke. Study participants were randomly assigned to receive OAC, aspirin, or placebo. Results of the trial revealed that vascular disease, systemic embolism, stroke, and death were lower in patients treated with OAC, and stroke reduction was significant. Although aspirin was less effective, it was found to be a safe alternative in patients with a contraindication to OAC.

The Primary Prevention of Atrial Thromboembolism in Nonrheumatic Atrial Fibrillation (PATAF) study was a primary care–based trial designed to compare preventive efficacy of low-intensity anticoagulation vs regular intensity anticoagulation and aspirin for the occurrence of thromboembolic events in patients with atrial fibrillation. The study reported a lower annual incidence of embolism among patients receiving aspirin and a clinical reduction of incidence in patients receiving anticoagulation. This study proved that aspirin was inferior to even low-intensity anticoagulation in stroke prevention in patients with atrial fibrillation.

Table 2 (continued).
Effects of Antiplatelet and Anticoagulation Therapies for Stroke Prevention in Patients With Atrial Fibrillation: Trial Summaries

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design and Patients</th>
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<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFASAK</td>
<td>Single center, prospective randomized trial; patients with chronic AF</td>
<td>Warfarin (1.25 mg/d), aspirin (300 mg/d), combination (warfarin and aspirin), or adjusted dose warfarin (2 &lt; INR &lt; 3)</td>
<td>Thromboembolic events</td>
<td>Annual rate of major bleeding events: 0.8% (mini-dose warfarin), 0.3% (warfarin and aspirin), 1.4% (aspirin), and 1.1% (adjusted-dose warfarin)</td>
<td>Trial was prematurely terminated because other studies showed superiority of adjusted dose warfarin compared with less intensive antithrombotic treatment.</td>
</tr>
<tr>
<td>BAFTA43</td>
<td>Prospective randomized open label trial; patients with AF</td>
<td>Warfarin (2 &lt; INR &lt; 3) and aspirin (75 mg/d)</td>
<td>Stroke risk</td>
<td>Rate of cerebrovascular accidents decreased by 52% among anticoagulated patients; no significant difference in yearly risk of hemorrhage</td>
<td>Overall, anticoagulation was safe among elderly patients.</td>
</tr>
<tr>
<td>ACTIVE-A17</td>
<td>Double-blind, placebo-controlled study; patients with AF and ≥1 risk factor</td>
<td>DAPT or aspirin alone in patients who were not candidates for anticoagulants</td>
<td>Thromboembolic events</td>
<td>Annual stroke rate: 2.4% (DAPT) vs 3.3% (placebo) (relative risk 0.72, P&lt;.001); relative risk reduction in stroke: 28% for DAPT; major bleeding rate was 2%/y in the DAPT group and 1.3%/y in aspirin group (relative risk 1.57, P&lt;.001)</td>
<td>DAPT could be an alternative for patients who cannot take warfarin.</td>
</tr>
<tr>
<td>ACTIVE-W17</td>
<td>Open noninferiority trial; patients same as ACTIVE-A but able to take warfarin</td>
<td>Warfarin vs DAPT</td>
<td>Stroke rate</td>
<td>42% reduction in stroke rate among patients who received warfarin vs DAPT</td>
<td>DAPT reduced stroke rate more than aspirin but did not reduce stroke rate more than warfarin and had bleeding rates similar to warfarin.</td>
</tr>
</tbody>
</table>

Abbreviations: AF, atrial fibrillation; DAPT, dual antiplatelet therapy; INR, international normalized ratio; TIA, transient ischemic attack.
The Second Copenhagen Atrial Fibrillation, Aspirin and Anticoagulation (AFASAK 2) study was a randomized prospective trial conducted from a single center that recruited patients with chronic atrial fibrillation. The trial studied the rate of bleeding events associated with the incidence of thromboembolic events in patients receiving warfarin, aspirin, combination therapy, or adjusted dose warfarin. The study was prematurely terminated because other studies showed superiority of adjusted dose warfarin therapy for stroke prophylaxis in atrial fibrillation compared with less intensive antithrombotic treatment. Aspirin was associated with risk of major bleed very close to that of adjusted-dose warfarin therapy.

The ACTIVE study was a randomized, double-blinded, international multicenter trial. Participants were those with atrial fibrillation and at least 1 risk factor from CHA2DS2-VASc. They were randomly assigned to receive clopidogrel or placebo in addition to aspirin. Patients who were considered to be candidates for VKA therapy were enrolled in ACTIVE W, and those remaining were enrolled in ACTIVE A. The rate for major vascular events and death was lower among the clopidogrel and aspirin treatment group compared with placebo. The results in the ACTIVE A group provided strong evidence for DAPT in stroke prevention among patients with atrial fibrillation. In the ACTIVE W group, VKA reduced the rate of stroke significantly when compared with clopidogrel and aspirin therapy. For patients eligible for warfarin therapy, warfarin was superior to aspirin as long as the time in therapeutic range (TTR) was greater than or equal to 65%. However, VKA and DAPT were equivalent if TTR was less than 65%.

Role of NOACs in Atrial Fibrillation

Novel oral anticoagulants are superior to aspirin therapy for stroke prevention, especially in the case of VKA intolerance, for patients with atrial fibrillation. This finding became evident after the results of the Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) trial was published. The study randomly assigned patients with atrial fibrillation who were deemed not appropriate candidates for VKA therapy to either apixaban or aspirin therapy. The annual rate of a thromboembolic event was 1.6% in the apixaban group compared with 3.7% in the aspirin group. No difference was found in major bleeding events between the 2 treatment groups. The trial ended early because there was a clear treatment benefit with apixaban in stroke reduction and systemic embolic events.

The ESC stated, “the bleeding risk on aspirin is not different to the bleeding risk on VKA or NOAC therapy, while VKA and NOACs, but not aspirin, effectively prevent strokes in [atrial fibrillation] patients.” As stated earlier, the ESC eliminated antiplatelet monotherapy, specifically aspirin, in their recommendations for stroke prophylaxis in patients with atrial fibrillation regardless of stroke risk. Patients with a CHA2DS2-VASc score of 0 for males and 1 for females are truly at low risk for stroke, while patients with CHA2DS2-VASc risk factors beyond sex need OAC. The ESC advocates for NOACs over VKA for stroke prevention in these patients.

Bleeding Risk With Aspirin vs Anticoagulation Therapies

The bleeding risk in patients taking aspirin compared with that in patients taking NOACs has been studied in stroke prevention therapies for patients with atrial fibrillation. The AVERROES and Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) studies have shown aspirin and OAC agents to have comparable bleeding risk profiles. In the AVERROES trial, there was no difference in major bleeding events between apixaban and low-dose aspirin. The BAFTA study investigated the effects of warfarin vs aspirin for stroke prevention among elderly patients with atrial fibrillation. The randomization of participants to treatment groups was ethical because inclusion was...
restricted to patients for whom there was clinical uncertainty as to which of the 2 treatments should be used. The study proved warfarin could be safely used in the elderly group. Moreover, aspirin was less effective than OAC in preventing thromboembolisms and had a comparable bleeding risk profile.\textsuperscript{43} The ACC/AHA\textsuperscript{8} and the ESC\textsuperscript{12} recommend the use of anticoagulation even in elderly patients with 2 or more risk factors for stroke; however, these guidelines place them at a higher risk of bleeding, which can be managed with a lower targeted INR.

**Cryptogenic Stroke and Underlying Atrial Fibrillation**

Approximately 40\% of ischemic strokes have an unidentifiable source and as a result are classified as cryptogenic strokes.\textsuperscript{45} These strokes may be due to undetected paroxysmal atrial fibrillation.\textsuperscript{46} In these patients, failure to start OAC could facilitate recurrent ischemic strokes and other thromboembolic events. According to the AHA and the ASA, patients with cryptogenic stroke should be treated with dual antiplatelet therapy along with aggressive management of stroke risk factors. A global survey found that more than 90\% of physicians are prescribing antiplatelet therapy for secondary prevention of cryptogenic stroke; however, there is emerging evidence that OAC is more beneficial.\textsuperscript{46}

The Warfarin-Aspirin Recurrent Stroke Study compared the efficacy of anticoagulation with antiplatelet therapy in cryptogenic stroke. The study found that no significant benefit of warfarin existed when compared with aspirin in secondary prevention of noncardioembolic strokes. Warfarin, however, was found to be associated with one-third fewer recurrent strokes than aspirin in patients with cryptogenic stroke of suspected embolic origin.\textsuperscript{46,47} The study suggested that warfarin should be used when antiplatelet therapies have failed or when the patient has warfarin intolerance.

The 30-Day Cardiac Event Monitor Belt for Recording Atrial Fibrillation After a Cerebral Ischemic Event (EMBRACE) trial\textsuperscript{48} randomized patients with cryptogenic stroke into 2 groups of either 30-day event recorder or the conventional 24-hour cardiac monitor. The results revealed a higher detection rate of occult atrial fibrillation in the intervention group than in the control group, which led to increased conversion from antiplatelet to OAC among patients in the intervention group. Additional studies have shown this finding as well, such as the Cryptogenic Stroke and Underlying Atrial Fibrillation (CRYSTAL AF) trial,\textsuperscript{49} which identified more patients with atrial fibrillation in the implantable cardiac monitoring group than those undergoing periodic ambulatory electrocardiograms.

**Discussion**

According to our review, aspirin was not found to significantly reduce the rate of cardioembolic stroke. It was found to be associated with a strong increased risk in all-cause mortality.\textsuperscript{50,51} There are several reasons accounting for the limitations of aspirin therapy. Several of the studies comparing aspirin with other therapies were terminated prematurely because of overwhelming evidence of the inferiority of aspirin compared with OAC therapy. This finding resulted in a reduced power to detect meaningful differences between therapies. Moreover, the 2 largest studies that were conducted before the development of the CHADS\textsubscript{2} score made it difficult to extrapolate a unified estimate of stroke risk across the general atrial fibrillation population. Also, some of these studies might have enrolled a relatively ill cohort population as a result of selection bias. For example, the cause of death was unknown in 43\% of patients who died in the PATAF trial and 21\% of the patients who died in the AFASAK trial.\textsuperscript{41,42,44} The treating clinicians may have precluded the benefit of anticoagulation in these patients. Moreover, it has been more than 20 years since most of these studies have been conducted; since then, NOACs have emerged and have been found to be more effective than VKAs and aspirin in patients with atrial fibrillation.
At present, there is significant evidence against the use of aspirin for stroke prevention in patients with atrial fibrillation. This practice is not supported. Antiplatelet therapy reduces the risk for stroke by 22% while VKA does by 64%.\textsuperscript{17} Of the several trials comparing aspirin with placebo for primary stroke prevention in patients with atrial fibrillation, the SPAF trial\textsuperscript{35} was only able to demonstrate superior efficacy of aspirin over placebo. Dual antiplatelet therapy has not been shown to be superior to antiplatelet monotherapy for ischemic noncardioembolic strokes. Moreover, for management of cryptogenic strokes, DAPT is the criterion standard of therapy. Oral anticoagulants are another potential therapy, as there is a known association between cryptogenic strokes and occult atrial fibrillation. However, when OAC is contraindicated, DAPT is the preferred alternative with the caveat that it may not be as effective as OACs.

Conclusion
Aspirin therapy has a limited role in the prevention of stroke in patients with atrial fibrillation. Specifically, aspirin as antiplatelet monotherapy remains uncertain because of paucity in data. However, aspirin is related to an increased risk of atheroembolic events when compared with OAC. Aspirin is associated with a similar risk of hemorrhagic events compared with NOACs and warfarin. Overall, antithrombotic therapy should be individualized, based on shared decision making, regarding the risk of stroke and bleeding as well as the patient’s values and preferences. The benefit of DAPT as an alternative to OAC requires further study.

References