

## AHA/ASA Publish Advisory on Oral Antithrombotics for Stroke Prevention in Nonvalvular Atrial Fibrillation

**Guideline source:** American Heart Association and American Stroke Association

**Evidence rating system used?** Yes

**Literature search described?** No

**Guideline developed by participants without relevant financial ties to industry?** No

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Among adults with atrial fibrillation, the annual rate of stroke ranges from 1 to 20 percent, depending on comorbidities and the patient's history of cerebrovascular events. Because of the risk of bleeding associated with antithrombotics such as warfarin (Coumadin) that are used to reduce the incidence of atrial fibrillation-related stroke, it is important to stratify and identify patients at increased risk of stroke. The CHADS<sub>2</sub> (congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, or previous stroke or transient ischemic event) scheme can help identify those patients. New antithrombotics provide alternatives to warfarin, and may lower the threshold for thromboembolic risk for initiating therapy in patients with atrial fibrillation.

This advisory summarizes existing American Heart Association/American Stroke Association (AHA/ASA) recommendations on antithrombotics for the prevention of first and additional strokes in patients with a history of stroke or transient ischemic attack (TIA). The report also reviews trials assessing the safety and effectiveness of dabigatran (Pradaxa), rivaroxaban (Xarelto), and apixaban (Eliquis) in preventing stroke in patients with atrial fibrillation, and presents revised management recommendations.

### Existing Recommendations

#### PREVENTION OF FIRST STROKE

Adjusted-dose warfarin is recommended for all patients with nonvalvular atrial fibrillation who are at high risk of stroke, and for some patients who are at moderate risk and can safely receive it.

Antiplatelet therapy with aspirin is recommended for patients with atrial fibrillation at low risk of stroke, and for some patients at moderate risk. Recommendations are based on patient preference, estimated bleeding risk (if the patient is receiving anticoagulant therapy), and access to high-quality anticoagulation monitoring.

In high-risk patients with atrial fibrillation and contraindications to anticoagulation therapy, dual-antiplatelet therapy with clopidogrel (Plavix) and aspirin provides more protection against stroke than aspirin alone. This therapy may be reasonable, but carries an increased risk of major bleeding.

#### PREVENTION OF STROKE IN PATIENTS WITH HISTORY OF STROKE OR TIA

Vitamin K antagonists are recommended for patients with a history of ischemic stroke or TIA who have intermittent or permanent atrial fibrillation.

Aspirin alone is recommended for patients who are unable to take oral anticoagulants. For patients who have a hemorrhagic contraindication to warfarin, the combination of aspirin and clopidogrel carries a risk similar to that of warfarin and is therefore not recommended for this group of patients.

#### ALTERNATIVE ANTITHROMBOTICS

Dabigatran may be used as an alternative to warfarin to prevent stroke and systemic thromboembolism in patients with intermittent to persistent atrial fibrillation and risk factors for stroke or systemic embolization,

but who do not have a prosthetic heart valve or hemodynamically significant valve disease, severe renal failure, or advanced liver disease.

Rivaroxaban has been approved for stroke prevention in patients with atrial fibrillation; however, there are no AHA recommendations concerning its use.

### New Recommendations

When considering these recommendations, physicians should be aware that several issues related to the clinical use of dabigatran, rivaroxaban, and apixaban are unresolved. For example, there are no published data that directly compare dabigatran, rivaroxaban, and apixaban with one another. Because these medications have short half-lives, patients who do not comply with treatment and miss doses may be at risk of thromboembolism. It is not known if patients who receive these medications but are otherwise eligible for thrombolysis can be safely treated with a thrombolytic agent for an acute ischemic stroke. In cases of hemorrhage, there are no antidotes to immediately reverse the actions of dabigatran, apixaban, or rivaroxaban.

Warfarin, apixaban, dabigatran, and rivaroxaban are all indicated for the prevention of first and recurrent stroke in patients with nonvalvular atrial fibrillation. Selection of a particular medication should be based on risk factors, cost, tolerability, patient preference, potential for drug interactions, and other clinical characteristics.

Dabigatran (150 mg twice daily) is an effective alternative to warfarin for preventing first and recurrent stroke in patients with nonvalvular atrial fibrillation and at least one additional risk factor who have a creatinine clearance (CrCl) greater than 30 mL per minute per 1.73 m<sup>2</sup> (0.50 mL per second per m<sup>2</sup>). Dabigatran (75 mg twice daily) in patients with atrial fibrillation and at least one additional risk factor who have severe renal impairment (CrCl of 15 to 30 mL per minute per 1.73 m<sup>2</sup> [0.25 to 0.50 mL per second per m<sup>2</sup>]) may be considered, but its safety and effectiveness have not been established. Dabigatran is not recommended in patients with more severe renal failure (CrCl less than 15 mL per minute per 1.73 m<sup>2</sup>).

Apixaban (5 mg twice daily) is an effective alternative to aspirin in patients with nonvalvular atrial fibrillation if vitamin K antagonist therapy is contraindicated and

if the patient has at least one additional risk factor and no more than one of the following characteristics: age 80 years or older, weight 133 lb (60 kg) or less, or serum creatinine level 1.5 mg per dL (114.38 μmol per L) or greater. This is also a relatively safe and effective alternative to warfarin for these patients.

Apixaban (2.5 mg twice daily) may be considered an alternative to aspirin or warfarin in patients with nonvalvular atrial fibrillation if vitamin K antagonist therapy is contraindicated and if the patient has at least one additional risk factor and two or more of the following characteristics: age 80 years or older, weight 133 lb or less, or serum creatinine level 1.5 mg per dL or greater. However, safety and effectiveness have not been established. Apixaban should not be used if a patient's CrCl is less than 25 mL per minute per 1.73 m<sup>2</sup> (0.42 mL per second per m<sup>2</sup>).

In patients with nonvalvular atrial fibrillation who are at moderate to high risk of stroke (e.g., history of TIA, stroke, or systemic embolization, or two or more additional risk factors), rivaroxaban (20 mg daily) is a reasonable alternative to warfarin. In patients with renal impairment and nonvalvular atrial fibrillation who are at moderate or high risk of stroke, with a CrCl of 15 to 50 mL per minute per 1.73 m<sup>2</sup> (0.25 to 0.83 mL per second per m<sup>2</sup>), rivaroxaban (15 mg daily) may be considered. However, safety and effectiveness have not been established. Rivaroxaban should not be used if a patient's CrCl is less than 15 mL per minute per 1.73 m<sup>2</sup>.

The safety and effectiveness of combining dabigatran, rivaroxaban, or apixaban with an antiplatelet agent have not been established.

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EDITOR'S NOTE: Because apixaban had not been approved for stroke prevention in patients with atrial fibrillation at the time this guideline was written, new data may be available that could affect the statements related to apixaban. ■

### Answers to This Issue's CME Quiz

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|-------------|-------------|--------------|
| Q1. A       | Q5. C       | Q9. A, B, C  |
| Q2. A, C, D | Q6. A, C, D | Q10. A, C    |
| Q3. A, B, D | Q7. C       | Q11. B       |
| Q4. D       | Q8. C       | Q12. A, B, D |