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Oral Antithrombotic Agents for the Prevention of Stroke in Nonvalvular Atrial Fibrillation : A Science Advisory for Healthcare Professionals From the American Heart Association/American Stroke Association

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on behalf of the American Heart Association Stroke Council, Council on Quality of Care and Outcomes Research, Council on Cardiovascular Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease

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AHA/ASA Science Advisory

Oral Antithrombotic Agents for the Prevention of Stroke in Nonvalvular Atrial Fibrillation

A Science Advisory for Healthcare Professionals From the American Heart Association/American Stroke Association

The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists

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The rate of stroke among adults with atrial fibrillation (AF) varies widely, ranging between 1% and 20% annually (mean 4.5% per year) depending on comorbidities and a patient's history of prior cerebrovascular events.[1] Stratification of stroke risk is important, because the major risk of antithrombotic medications used to lower the incidence of AF-related stroke is bleeding. For warfarin, this involves balancing a bleeding risk of 1% to 12% per year against the risk of ischemic events, with its use generally reserved for individuals at greatest thromboembolic risk.[1–3] The advent of several new antithrombotic agents offers alternatives to warfarin and may lower the threshold for thromboembolic risk for initiating therapy in patients with AF.

In this update to the American Heart Association/American Stroke Association (AHA/ASA) "Guidelines for the Primary Prevention of Stroke"[4] and the prevention of stroke in patients with stroke or transient ischemic attack (TIA),[5] we review recent trials testing the safety and efficacy of a thrombin inhibitor (dabigatran) and 2 factor Xa inhibitors (rivaroxaban and apixaban) in preventing stroke in patients with AF, and we revise management recommendations.[4,5] Recommendations follow the AHA's and the American College of Cardiology's methods of classifying the level of certainty of the treatment effect and the class of evidence (Table 1).

Summary of Current AHA/ASA Guidelines for Vitamin K Antagonists/Antithrombotics in Patients With AF

Risk Stratification

The absolute risk of stroke varies 20-fold among AF patients according to age and associated vascular comorbidities. Several stroke risk stratification schemes have been developed and validated.[6–8] These, however, can yield differing results.[9] Current AHA guidelines use the $CHADS_2$ stratification scheme[7] ($CHADS_2$ is an acronym for Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, and prior Stroke or TIA). The $CHADS_2$ score was derived from independent predictors of stroke risk in patients with nonvalvular AF.[7] The score assigns 1 point each for congestive heart failure, hypertension, age ≥75 years, and diabetes mellitus and 2 points for prior stroke or TIA.[7] The score was validated in a large cohort study and in clinical trials.[6,10] For

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Table 1. Applying Classification of Recommendations and Level of Evidence

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	SIZE OF TREATMENT EFFECT: CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	CLASS IIa *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	CLASS IIb *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	CLASS III *No Benefit* or CLASS III *Harm* Procedure/Test / Treatment COR III: No benefit — Not Helpful / No Proven Benefit COR III: Harm — Excess Cost w/o Benefit or Harmful / Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit: is not recommended; is not indicated; should not be performed/ administered/ other; is not useful/ beneficial/ effective COR III: Harm: potentially harmful; causes harm; associated with excess morbidity/mortality; should not be performed/ administered/ other
Comparative effectiveness phrases†	treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B		

A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

†For comparative effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

example, in one cohort study,[10] those with a $CHADS_2$ score of 0 had a thromboembolic rate of 0.49 (95% confidence interval [CI], 0.30–0.78) per 100 person-years versus 1.52 (95% CI, 1.19–10.94) for $CHADS_2$ score=1, 2.50 (95% CI, 1.98–3.15) for $CHADS_2$ score=2, 5.27 (95% CI, 4.15–6.70) for $CHADS_2$ score=3, 6.02 (95% CI, 3.90–9.29) for $CHADS_2$ score=4, and 6.88 (95% CI, 3.42–13.84) $CHADS_2$ score=5 or 6. A limitation of the $CHADS_2$ scheme that applies to secondary prevention involves patients with prior stroke or TIA and no other risk factors.[2] These patients score 2 on the $CHADS_2$ scale (point estimate of thromboembolic risk 2.50 per 100 person-years), but in validation studies of the $CHADS_2$ score, patients with prior stroke or TIA averaged 7.40 strokes[10] to 10.8 strokes[6] per 100 patient-years. The CHA_2DS_2VASc index further refines the risk calculation of $CHADS_2$ by including additional variables.[11] Hemorrhage risk can also vary among individuals. Bleeding risk tools such as the HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/Alcohol concomitantly), RIETE (Registro Informatizado de la Enfermedad Tromboembólica), and ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) scores have been developed

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to estimate the likelihood of hemorrhage, but they have low predictive accuracy.[3,12–14]

Treatment Recommendations

Data from multiple clinical trials indicate the superiority of vitamin K antagonists over antiplatelet therapies for stroke prevention in AF patients. Pooled data from 5 primary prevention trials show a consistent benefit of warfarin across studies (overall relative risk [RR] reduction, 68%; 95% CI, 50%–79%), which reflects an absolute reduction in annual stroke rate from 4.5% for control patients to 1.4% in patients assigned to adjusted-dose warfarin.[1] This absolute risk reduction translates to 31 ischemic strokes prevented each year for every 1000 patients treated.

Anticoagulation is recommended for patients with AF with a $CHADS_2$ score ≥ 2, but there has been more variability in the choice of antithrombotic agent in patients at lower risk ($CHADS_2$ score $=1$).[4] Aspirin or no treatment is recommended for patients at very low risk ($CHADS_2$ score $=0$).

Overall, warfarin is relatively safe (annual rate of major bleeding of 1.3% compared with 1% for placebo or aspirin). Results from a large case-control study[15] and 2 randomized controlled trials[16,17] suggest that the efficacy of oral anticoagulation declines below an international normalized ratio (INR) of 2.0. The optimal intensity of oral anticoagulation for stroke prevention in patients with AF appears to be an INR of 2.0 to 3.0. Higher INRs are associated with increased risk of bleeding, as is the combination of an anticoagulant and an antiplatelet agent.[18] Similarly, decreased time in INR therapeutic range (TTR) reduces the safety and effectiveness of warfarin.[19] There are no data showing that increasing the intensity of anticoagulation or adding an antiplatelet agent provides additional protection against future ischemic cerebrovascular events for patients with AF who have an ischemic stroke or TIA while undergoing therapeutic anticoagulation.

Evidence supporting the efficacy of aspirin is substantially weaker than for warfarin. A pooled analysis of data from 3 trials reported an RR reduction (RRR) of 21% (95% CI, 0%–38%) compared with placebo.[20] A national effectiveness study found no benefit with aspirin and an overall risk reduction with warfarin.[21] At present, there are sparse data regarding the efficacy of alternative antiplatelet agents or combinations for stroke prevention in AF patients who are allergic to aspirin.[22]

The Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W) trial found that a vitamin K antagonist was superior to the combination of clopidogrel and aspirin in AF patients with at least 1 risk factor for stroke[23]; however, a TTR $<58\%$ showed no benefit of vitamin K antagonist over combination antiplatelet therapy.[19] An additional arm of this study (ACTIVE A) compared aspirin alone versus clopidogrel plus aspirin in AF patients who were considered "unsuitable for vitamin K antagonist therapy."[24] Although there was a small reduction in the rate of stroke with the combination of clopidogrel plus aspirin versus aspirin alone, major bleeding occurred in a higher percentage of the patients undergoing combination therapy, resulting in no net benefit.[23,24]

Current AHA/ASA Recommendations for Vitamin K Antagonists/Antithrombotics for the Prevention of a First Stroke

The following are the current AHA/ASA recommendations for vitamin K antagonists/antithrombotics for prevention of a first stroke[4]:

1. **Adjusted-dose warfarin (target INR, 2.0–3.0) is recommended for all patients with nonvalvular AF deemed to be at high risk and many deemed to be at moderate risk for stroke who can receive it safely *(Class I; Level of Evidence A).***
2. **Antiplatelet therapy with aspirin is recommended for low-risk and some moderate-risk patients with AF on the basis of patient preference, estimated bleeding risk if anticoagulated, and access to high-quality anticoagulation monitoring *(Class I; Level of Evidence A).***
3. **For high-risk patients with AF deemed unsuitable for anticoagulation, dual-antiplatelet therapy with clopidogrel and aspirin offers more protection against stroke than aspirin alone but with an increased risk of major bleeding and might be reasonable *(Class IIb; Level of Evidence B).***

Existing AHA/ASA Recommendations for Vitamin K Antagonists/Antithrombotics for the Prevention of Stroke in Patients With a History of Stroke or TIA

The following are existing AHA/ASA recommendations for vitamin K antagonists/antithrombotics for the prevention of stroke in patients with a history of stroke or TIA[5]:

1. **For patients with ischemic stroke or TIA with paroxysmal (intermittent) or permanent AF, anticoagulation with a vitamin K antagonist (target INR, 2.5; range, 2.0–3.0) is recommended *(Class I; Level of Evidence A).***
2. **For patients unable to take oral anticoagulants, aspirin alone *(Class I; Level of Evidence A)* is recommended. The combination of clopidogrel plus aspirin carries a risk of bleeding similar to that of warfarin and therefore is not recommended for patients with a hemorrhagic contraindication to warfarin *(Class III; Level of Evidence B).***

New Alternative Antithrombotic Agents for Stroke Prevention in Patients With AF

Dabigatran

Pharmacology

Dabigatran etexilate is an oral prodrug that is rapidly converted by a serum esterase to dabigatran, a direct, competitive inhibitor of factor IIa (thrombin). The absolute bioavailability is 6.5%, and the serum half-life is 12 to 17 hours.[25] Because of predictable pharmacokinetics, dabigatran can be administered at a fixed dose and does not require coagulation monitoring. Dabigatran pharmacokinetics are affected by renal function, because 80% is excreted renally. In contrast to warfarin, dabigatran is not metabolized by the cytochrome P450 (CYP3A4) system[25]; however, p-glycoprotein inhibitors such as dronedarone, ketoconazole, amiodarone, verapamil, and quinidine can increase dabigatran concentrations, whereas rifampin can decrease its effects.

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Clinical Trial Summary

The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) compared open-label warfarin with 2 fixed, blinded doses of dabigatran (110 or 150 mg twice daily) in patients with AF and at least 1 additional stroke risk factor (previous stroke or TIA, left ventricular ejection fraction <40%, New York Heart Association heart failure classification of II or higher, age ≥75 years, or age 65–74 years plus diabetes mellitus, hypertension, or coronary artery disease). Patients with stroke within 14 days or those with severe stroke within 6 months, increased bleeding risk, a creatinine clearance (CrCl) <30 mL/min, or active liver disease were excluded.[26] Low-dose aspirin or other antiplatelet therapy was permitted. Although dabigatran dose was concealed, patients randomized to dabigatran did not receive sham INR testing. Target INR for warfarin was 2.0 to 3.0.

The primary outcome was stroke or systemic embolism; secondary outcomes included stroke, systemic embolism, and death, although several additional outcomes were also prespecified, including myocardial infarction (MI). The primary safety outcome was major hemorrhage, and the trial was powered to demonstrate noninferiority versus warfarin with respect to the primary outcome. A net clinical benefit was defined as an unweighted composite of stroke, systemic embolism, pulmonary embolism, MI, death, or major hemorrhage.

A total of 18 113 patients were enrolled from 44 countries; the median follow-up was 2.0 years, and only 20 patients were lost to follow-up. Patients were elderly (71.6±8.7 years; 36% women) and had moderate to high risk of stroke ($CHADS_2$ 2.1±1.1; 20% with prior stroke, 32% with heart failure, and 23% with diabetes mellitus). Half of the patients were receiving warfarin before randomization.

For the primary outcome of stroke or systemic embolism, both dabigatran 110 mg twice daily (1.53% per year) and dabigatran 150 mg twice daily (1.11% per year) were noninferior to warfarin (1.69% per year); dabigatran 150 mg twice daily was also superior to warfarin (RR, 0.66; 95% CI, 0.53–0.82). Compared with warfarin, the risk of hemorrhagic stroke was lower with both dabigatran 110 mg twice daily (RR, 0.31; 95% CI, 0.17–0.56) and dabigatran 150 mg twice daily (RR, 0.26; 95% CI, 0.14–0.49).

For the outcome of net clinical benefit, dabigatran 150 mg twice daily (6.91% per year) was marginally superior to warfarin (7.09% per year; RR, 0.91; 95% CI, 0.82–1.00) but not dabigatran 110 mg twice daily (7.09% per year; RR, 0.98; 95% CI, 0.89–1.08). There was a trend toward lower all-cause mortality with dabigatran 150 mg twice daily (3.64% year) compared with warfarin (4.13% per year; RR, 0.88; 95% CI, 0.80–1.03) but not dabigatran 110 mg twice daily (3.75%; RR, 0.91; 95% CI, 0.80–1.03). No racial or ethnic subgroup analyses were included in the primary report on RE-LY.[26]

Major bleeding in RE-LY was lower with dabigatran 110 mg twice daily (2.71% per year; RR, 0.80; 95% CI, 0.69–0.93) but similar for dabigatran 150 mg twice daily (3.11% per year; RR, 0.93; 95% CI, 0.81–1.07) compared with warfarin (3.36% per year).[26] The rate of gastrointestinal bleeding was higher with dabigatran 150 mg twice daily (1.51% per year) than with warfarin (1.02% per year) or dabigatran 110 mg twice daily (1.12% per year; $P<0.05$). Rates of life-threatening and intracranial bleeding, respectively, were higher with warfarin (1.80% and 0.74%) than with either dabigatran 110 mg twice daily (1.22% and 0.23%) or dabigatran 150 mg twice daily (1.45% and 0.30%). In patients aged ≥75 years, intracranial bleeding risk was lower with dabigatran than with warfarin, but extracranial bleeding risk was increased with the 150-mg dose (5.10% versus 4.37%; $P=0.07$; P for interaction <0.001).[27]

The rate of MI was higher with dabigatran 150 mg twice daily (0.74% per year) than with warfarin (0.53% per year; RR, 1.38; 95% CI, 1.00–1.91).[26] After readjudication for silent MI during study site closure, 28 additional events were identified, and differences in rate of MI between treatment arms were no longer significant.[28] Post hoc analysis including these events found that MI occurred at annual rates of 0.82% per year with dabigatran 110 mg twice daily and 0.81% per year with dabigatran 150 mg twice daily compared with 0.64% with warfarin (hazard ratio [HR], 1.29; 95% CI, 0.96–1.75; $P=0.09$; and HR, 1.27; 95% CI, 0.94–1.71; $P=0.12$, respectively).[29] Net clinical benefit favored treatment with dabigatran. Patients with MI had higher baseline rates of aspirin and clopidogrel use. The interaction with on-treatment concomitant antiplatelet therapy and the risk of MI has not been evaluated. A meta-analysis of noninferiority trials that included 30 514 subjects found that dabigatran was associated with a higher risk of MI or acute coronary syndromes (odds ratio, 1.33; 95% CI, 1.03–1.71; $P=0.01$), with similar results when the revised RE-LY data were included.[30] In RE-LY, discontinuation rates for dabigatran were higher than for warfarin (16% dabigatran versus 10% warfarin at 1 year) and concordant with rates of dyspepsia (12% versus 6%).[26]

Higher baseline $CHADS_2$ scores were associated with an increased risk of stroke and systemic embolism in all 3 treatment arms.[31] The risk reduction with dabigatran 150 mg twice daily (compared with warfarin) was consistent across $CHADS_2$ categories. Similarly, bleeding risk increased across $CHADS_2$ categories, although both doses of dabigatran had lower rates of intracranial bleeding than with warfarin.

There are limited data from RE-LY on patients with prior stroke or TIA. A subgroup analysis of 3623 subjects with stroke or TIA before randomization showed higher overall event rates than for those without stroke or TIA (2.38% versus 1.22% per year) but similar rates of stroke or systemic embolism with warfarin (2.78% per year), dabigatran 150 mg twice daily (2.07% per year), and dabigatran 110 mg twice daily (2.32% per year).[32] Dabigatran at either dose was superior to warfarin for the primary outcome (RR, 0.34 and 0.65, respectively; P for interactions=NS). The rate of major bleeding was lower in patients taking 110 mg dabigatran twice daily and similar in those taking 150 mg dabigatran twice daily compared with those taking warfarin. Results in patients with prior stroke or TIA were consistent with the overall RE-LY result, except that dabigatran 150 mg was noninferior to warfarin for the primary outcome rather than superior to it.

TTR is a potent predictor of warfarin effectiveness and safety.[33,34] A facility-level secondary analysis of the RE-LY trial compared the efficacy of dabigatran versus warfarin, stratified by quartiles of mean TTR of the enrolling center.[35] The median TTR in the warfarin arm was 64%, with

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significant patient- and site-level variation (44%–77%). In the warfarin arm, the rate of stroke or systemic embolism decreased with higher center TTR. Compared with warfarin, dabigatran 150 mg twice daily had a lower risk of stroke and dabigatran 110 mg twice daily had a lower risk of bleeding across all quartiles of TTR. Intracranial bleeding did not vary by center TTR but was lower for both doses of dabigatran. A major limitation of this facility-level analysis is that it did not evaluate patient-level differences in outcomes by TTR using a multilevel model that accounted for site-level effects, because correlation between individual patient TTR and facility TTR was modest (r^2=0.588). Moreover, TTR could not be estimated in 5% of centers, with these patients being excluded from the analysis.

Among 8989 RE-LY subjects who had been receiving long-term vitamin K antagonist therapy before randomization, efficacy was similar for the primary outcome with dabigatran 150 mg twice daily and 110 mg twice daily (RR, 0.81 and 0.72, respectively; *P* for interactions=NS).[26] There are no published data on bleeding events, tolerability, or stratification by prerandomization TTR in this subgroup.

There are very limited data on safety and efficacy in patients taking aspirin or other antiplatelet therapy, alone or in combination.[26] Aspirin was used continuously in only 20% of patients in all 3 treatment arms, and there are no published on-treatment data evaluating the safety or efficacy of combination therapy.

An important limitation of the RE-LY study is the short median follow-up (2.0 years) relative to the time horizon for anticoagulation in patients with AF. Measuring the anticoagulant effect of the drug is also challenging in clinical practice. The effects of dabigatran can be detected in the activated partial thromboplastin time, endogenous thrombin potential lag time, thrombin time, and ecarin clotting time.[36] Ecarin clotting time correlates best with plasma concentrations; however, activated partial thromboplastin time is an alternative and is generally prolonged in patients receiving dabigatran. Factors that affect clearance and plasma concentrations (kidney function, body mass index, or volume of distribution) could lead to variation of anticoagulation effect, safety, and efficacy. Use of activated recombinant factor VIIa or purified factor replacement products has been proposed for reversal of dabigatran[36]; however, both are costlier than vitamin K or fresh-frozen plasma.[37] The US package insert for dabigatran recommends emergency dialysis for rapid reversal of the antithrombotic effect, which may not be feasible in unstable patients.[38] None of the reversal strategies have been evaluated adequately for efficacy.

Cost-Effectiveness Analyses

Several rigorous cost-effectiveness analyses of dabigatran in different healthcare systems have compared dabigatran to warfarin using decision analysis with efficacy inputs from the RE-LY trial and quality of life and cost data from the medical literature or public reimbursement data.[39–43] There are minor differences in model structure across these studies, but significant differences in the base case patient risk profile and age, cost of complications, and time horizon. In the first published study, using a base case of a 65-year-old with $CHADS_2$ ≥1 and projected drug price of $13 per dose, dabigatran 150 mg twice daily compared with warfarin had increased quality-adjusted life-years (QALYs; 10.84 versus 10.28 QALYs) and an incremental cost-effectiveness ratio (ICER) of $45 372 per QALY gained with dabigatran.[39] The model was highly sensitive to dabigatran price and risk of stroke or intracranial hemorrhage while taking dabigatran or warfarin. When dabigatran pricing was announced to be significantly lower than this projected price, the ICER of dabigatran 150 mg twice daily decreased to $12 386 per QALY gained.[44] Sensitivity analyses demonstrated that for patients at higher risk for stroke (based on $CHADS_2$ score), the QALYs and ICER for dabigatran improved relative to warfarin. These results were robust over a wide range of model assumptions. A subsequent cost-effectiveness analysis performed a 4-way comparison of aspirin, warfarin, aspirin-clopidogrel, and dabigatran using networked analysis to derive efficacy estimates across treatments that have never been compared in clinical studies.[41] Dabigatran 150 mg and 110 mg twice daily were associated with higher QALYs than warfarin, aspirin, or aspirin-clopidogrel combination therapy. QALYs and ICERs varied by stroke risk and bleeding risk. A low risk of stroke favored aspirin, a moderate risk of stroke favored warfarin, and a high risk of stroke or hemorrhage favored dabigatran 150 mg twice daily. In this analysis, results were very sensitive to warfarin TTR, and dabigatran 150 mg twice daily was not cost-effective if warfarin anticoagulation quality was in the highest TTR quartile. Studies from Canada and the United Kingdom, using country-specific costs, have also found increased QALYs with dabigatran and ICERs well within the range of willingness-to-pay thresholds for their healthcare systems.[40,42,43]

Cost-effectiveness analyses can have several major limitations. The analyses cannot overcome limitations of the primary efficacy data, which in this case are drawn from a single trial with a short follow-up relative to the patient's lifetime horizon of anticoagulation use. Minor alterations in the durability of drug effect or changes in drug adherence could have large effects on real QALYs and costs. Additional costs or harms may become apparent with ongoing use outside of randomized trials. For example, none of these studies evaluated cost, utility, or harm related to periprocedural anticoagulation management. A patient may have several major procedures over the lifetime of anticoagulation use. Differences in hospital utilization or costs and harms of anticoagulation bridging for warfarin or short half-life (dabigatran) could dramatically impact ICERs. In addition, dabigatran was cost-effective but not cost-saving. Because of the high prevalence of AF and long time horizon of anticoagulation, widespread use of dabigatran instead of warfarin could lead to marked escalations in healthcare expenditures. Finally, these studies assessed cost-effectiveness from a healthcare system or societal perspective. Infrastructural costs, such as anticoagulation clinics, and indirect costs, such as lost wages and productivity, were not considered.

Postmarketing Surveillance

In the United States, dabigatran 150 mg twice daily but not 110 mg twice daily was approved by the US Food and Drug Administration (FDA). The FDA's justification for approving

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only the high-dose formulation was that superiority for stroke prevention with dabigatran 150 mg twice daily is a more desirable outcome than decreased nonfatal bleeding with dabigatran 110 mg twice daily.[45,46] A dose of 75 mg twice daily was approved for patients with low CrCl (15–30 mL/min), although these patients were excluded from enrollment in RE-LY.[47] There are no published comparative data on safety events for dabigatran in patients with chronic kidney disease.

Postmarketing surveillance reports of fatal bleeding events in patients treated with dabigatran have led to advisories from regulatory agencies. By November 2011, 256 case reports of bleeding events that resulted in death in association with dabigatran were recorded in a pharmacovigilance database of the European Economic Area.[48] The Therapeutic Goods Administration of Australia reported 209 adverse bleeding events associated with dabigatran, most commonly of gastrointestinal origin.[49] Some of the bleeding events occurred from the transition from warfarin to dabigatran. As a result, the Therapeutic Goods Administration,[50] European Medicines Agency,[48] and FDA[47] have issued advisories or revised product labeling advising physicians to assess renal function before prescribing and in clinical situations in which declines in kidney function could occur. In contrast to the FDA, the Therapeutic Goods Administration and European Medicines Agency recommend that dabigatran not be prescribed if CrCl is $<$30 mL/min.

Revised FDA labeling recommends reducing the dose of dabigatran to 75 mg twice daily when dronedarone or systemic ketoconazole is coadministered in patients with moderate renal impairment (CrCl 30–50 mL/min). The use of dabigatran and P-glycoprotein inhibitors in patients with severe renal impairment (CrCl 15–30 mL/min) should be avoided. As of the time of publication of the present statement, the FDA was analyzing postmarketing reports of adverse events for evidence of inappropriate dosing, use of interacting drugs, and other clinical factors that may be associated with bleeding events.[47] Postmarketing advisories have not indicated an increased risk of MI.

Existing AHA Recommendations

The existing AHA recommendation for use of dabigatran is reported below[51]:

1. **Dabigatran is useful as an alternative to warfarin for the prevention of stroke and systemic thromboembolism in patients with paroxysmal to permanent AF and risk factors for stroke or systemic embolization who do not have a prosthetic heart valve or hemodynamically significant valve disease, severe renal failure (CrCl <15 mL/min), or advanced liver disease (impaired baseline clotting function) *(Class I; Level of Evidence B)*.**

Rivaroxaban

Pharmacology

Rivaroxaban is a direct factor Xa inhibitor. It has ≈70% bioavailability, with a serum half-life of 5 to 9 hours. It has predictable pharmacokinetics and is administered as a fixed dose without coagulation monitoring. Rivaroxaban is metabolized by the CYP3A4 system, and there can be interactions with CYP3A4 inhibitors or inducers. Clearance is both renal (≈36% unchanged) and fecal (≈7% unchanged).

Clinical Trial Summary

The Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation (ROCKET AF) Trial[52] was a double-blind noninferiority trial that randomized 14 264 patients with nonvalvular AF who were at moderate to high risk of stroke (prior history of TIA, stroke, or systemic embolization or ≥2 additional risk factors) to rivaroxaban (20 mg/d) or dose-adjusted warfarin (target INR 2.0–3.0). The mean $CHADS_2$ score was 3.5, higher than the mean scores in the RE-LY and ARISTOTLE (Apixaban for Reduction In STroke and Other ThromboembolLic Events in atrial fibrillation) trials. Approximately 55% of subjects had a stroke, TIA, or systemic embolism before enrollment. Slightly more than one third of subjects also took aspirin at some time during the study. The median follow-up was 707 days.

The primary end point was the composite of ischemic and hemorrhagic stroke and systemic embolism, which occurred in 1.7% of subjects per year in the rivaroxaban group and 2.2% per year in the warfarin group (HR, 0.79; 95% CI, 0.66–0.96; $P<0.001$ for noninferiority). In the intention-to-treat analysis, the primary end point occurred in 2.1% of subjects per year in the rivaroxaban group and 2.4% per year in the warfarin group (HR, 0.88; 95% CI, 0.74–1.03; $P<0.001$ for noninferiority and $P=0.12$ for superiority). The primary safety end point was a composite of major and nonmajor clinically relevant bleeding, which occurred in 14.9% of patients per year in the rivaroxaban group and 14.5% in the warfarin group (HR, 1.03; 95% CI, 0.96–1.11; $P=0.44$). Lower rates of intracranial hemorrhage (0.5% versus 0.7%, $P=0.02$) and fatal bleeding (0.2% versus 0.5%, $P=0.003$) occurred in the rivaroxaban group than in the warfarin group.

There was a trend toward an interaction between presence or absence of a prior stroke, TIA, or systemic embolism for the primary end point and in the intention-to-treat analysis ($P=0.072$) and a significant interaction for safety ($P=0.039$). Among subjects without a history of stroke, TIA, or systemic embolism, the primary end point (efficacy) occurred in 2.57% of subjects in the rivaroxaban group and 3.61% of subjects in the warfarin group (HR, 0.71; 95% CI, 0.54–0.94), which suggests superiority of rivaroxaban for primary prevention of stroke or systemic embolism. The primary safety end point occurred in 1.67% of subjects with a prior history of stroke, TIA, or systemic embolism in the rivaroxaban group compared with 2.86% in the warfarin group (HR, 0.59; 95% CI, 0.42–0.83). Among subjects with a history of prior stroke, TIA, or systemic embolism, the primary end point (efficacy) occurred in 4.8% in the rivaroxaban group and 4.9% in the warfarin group (HR, 0.98; 95% CI, 0.8–1.2), with no difference for the secondary prevention of stroke or systemic embolism. The primary safety end point occurred in 3.5% of subjects with a history of prior stroke, TIA, or systemic embolism who were taking rivaroxaban versus 3.9% taking warfarin (HR, 0.91; 95% CI, 0.72–1.14).

Although there was no standardized definition of "warfarin naiveté" across the trials, 38% of subjects in ROCKET AF lacked exposure to vitamin K antagonists at enrollment. There

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was no interaction between prior history of vitamin K antagonist use and either efficacy or safety. Subjects naïve to vitamin K antagonists had a lower rate of the primary end point while taking rivaroxaban (3.79%) than those taking warfarin (4.94%) in the intention-to-treat analysis (HR, 0.76; 95% CI, 0.59–0.98).

J-ROCKET AF (Japanese Rivaroxaban Once daily oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation) was a prospective, randomized, double-blind phase 3 study in which 1280 Japanese subjects with AF were enrolled from 165 centers across Japan.[53] The primary objective of the study was to evaluate the safety of rivaroxaban 15 mg once daily (10 mg daily in patients with moderate renal impairment) versus dose-adjusted warfarin (target INR of 2.0–3.0 for patients <70 years of age and 1.6–2.6 for those patients ≥70 years of age). The study was designed to evaluate the noninferiority of rivaroxaban compared with warfarin for on-treatment bleeding.[53]

The primary safety end point in J-ROCKET was the time to first major or nonmajor clinically relevant bleeding event in both the rivaroxaban and warfarin arms. There were 11 versus 22 bleeding events in the rivaroxaban and warfarin arms, respectively (1.26 versus 2.61 events per 100 patients per year; HR, 0.48; 95% CI, 0.23–1.00).[54] Rivaroxaban was shown to be noninferior to warfarin for the primary efficacy end point (time to the first stroke or noncerebral systemic embolization).

The quality of warfarin anticoagulation management in the J-ROCKET trial is a concern. The TTR was lower than historical values in other warfarin trials.[54]

Several issues regarding interpretation of the results of the ROCKET-AF trial were raised during the FDA regulatory review.[55] These included uncertainty about the constancy assumption (ie, in noninferiority trials, "the control treatment, as administered in the new trial, must have the same magnitude of benefit relative to placebo as it had in the reference trials used to estimate its effect").[55] The mean TTR for warfarin-arm subjects was only 55% (versus 62%–73% in other recent trials). The on-treatment analysis was truncated 2 days after discontinuation of the randomized treatment, with higher rates of stroke or systemic embolization with rivaroxaban observed 2 to 7 days after discontinuation of the study medication. This highlights the importance of ensuring adequate anticoagulation after temporary or permanent rivaroxaban discontinuation for a reason other than bleeding. Finally, once-daily dosing was not supported by pharmacokinetic or pharmacodynamic data. Despite these concerns, rivaroxaban received FDA regulatory approval.

The effect of rivaroxaban is reflected in the prothrombin time and endogenous thrombin potential. Prothrombin complex concentrate has been reported to reverse the effect of rivaroxaban[37]; however, no reversal strategies have been adequately evaluated for clinical efficacy.

Cost-Effectiveness Analyses, Postmarketing Surveillance, and Existing AHA Recommendations

Cost-effectiveness analyses have not been published. Rivaroxaban was recently approved for stroke prevention in patients with AF in the United States. Postmarketing surveillance data are not yet available. There are no existing AHA recommendations with regard to the use of rivaroxaban.

Apixaban

Pharmacology

Apixaban is a direct and competitive factor Xa inhibitor.[56] It has ≈50% bioavailability. Apixaban has a short half-life of 8 to 15 hours. It has predictable pharmacokinetics and is administered as a fixed dose without coagulation monitoring. Apixaban is metabolized by the CYP3A4 system, and there can be interactions with CYP3A4 inhibitors or inducers. Clearance is both renal (≈25% unchanged) and fecal (≈50% unchanged).

Clinical Trial Summary

The Apixaban Versus Acetylsalicylic Acid to Prevent Strokes in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) trial was a randomized, double-blind trial comparing the efficacy and safety of apixaban to aspirin in 5599 subjects with nonvalvular AF and ≥1 additional risk factor for stroke who were unsuitable for vitamin K antagonist therapy primarily on the basis of physician judgment or patient preference.[56] The dose of apixaban was 5 mg twice daily (94%) or 2.5 mg twice daily (6%), with the lower dose used for patients who met ≥2 of the following criteria: Age ≥80 years, weight ≤60 kg, or serum creatinine ≥1.5 mg/dL. The dose of aspirin was 81 mg (64%), 162 mg (27%), 243 mg (2%), or 324 mg (7%) at the discretion of the investigator. Subjects were a mean of 70 years old and had a mean $CHADS_2$ score of 2. Fourteen percent of patients had a prior stroke, and 9% reported concurrent aspirin use for more than half of the study duration. The study was terminated when an interim analysis found that apixaban was superior to aspirin for prevention of stroke or systemic embolism (1.6% per year versus 3.7% per year; HR, 0.45; 95% CI, 0.32–0.62; number needed to treat [NNT]=45; RRR=57%) with a similar rate of major bleeding (1.4% per year versus 1.2% per year; HR, 1.13; 95% CI, 0.74–1.75). Apixaban was superior to aspirin in preventing a disabling or fatal stroke (1% per year versus 2.3% per year; HR, 0.43; 95% CI 0.28–0.65; NNT=67; RRR=57%). The benefit of apixaban remained when aspirin doses were grouped (<162 mg or ≥162 mg). The net clinical benefit, a composite outcome of stroke, systemic embolism, MI, death of a vascular cause, or major bleeding, supported apixaban as being superior to aspirin (5.3% per year versus 7.2% per year; HR, 0.74; 95% CI, 0.6–0.9; NNT=48; RRR=26%).

AVERROES primarily enrolled subjects who had not had a prior stroke or TIA (86%). Apixaban was superior to aspirin for primary prevention of stroke or systemic embolism (1.5% per year versus 3% per year; NNT=62; RRR=50%) with a similar rate of major bleeding (1.1% per year versus 1% per year).[56] When analyzed by $CHADS_2$ score, apixaban was superior to aspirin in patients with a $CHADS_2$ score of 2 (2.1% per year versus 3.7% per year; NNT=56; RRR=43%) and a $CHADS_2$ score ≥3 (1.9% per year versus 6.3% per year; NNT=21; RRR=70%).

For those without prior stroke or TIA with a $CHADS_2$ score of 0 or 1, apixaban was equally safe and effective as aspirin for preventing stroke or systemic embolism (0.9% per year versus 1.6% per year; NNT=143; RRR=44%). Despite a greater number of patients, the CIs were wider for this subgroup than for those with higher $CHADS_2$ scores, so

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further delineation of risk with the CHA_2DS_2VASc score may enable future investigations to identify a subset of patients who may benefit from apixaban.[57]

Study drug was initiated a minimum of 10 days after the stroke in the small subgroup with prior stroke or TIA (14%). Apixaban was superior to aspirin for secondary prevention of stroke or systemic embolism (2.5% per year versus 8.3% per year; NNT=16; RRR=70%), with a similar rate of major bleeding (3.5% per year versus 2.7% per year).[56]

A vitamin K antagonist had been prescribed and discontinued in 40% of patients in the AVERROES study, with 14% discontinuing it within 30 days before screening. Apixaban was superior to aspirin for reduction in stroke or systemic embolism in patients who had previously taken a vitamin K antagonist (1.4% per year versus 4.2% per year; NNT=36; RRR=67%), as well as in patients who were naïve to a vitamin K antagonist (1.8% per year versus 3.3% per year; NNT=67; RRR=45%).[56]

The ARISTOTLE trial was a phase 3 randomized trial comparing apixaban to warfarin for the prevention of stroke (ischemic or hemorrhagic) or systemic embolization among patients with AF or atrial flutter and at least 1 additional risk factor for stroke.[58] To be eligible, AF had to be present at the time of enrollment or documented by ECG at 2 separate times at least 2 weeks apart within the prior 12 months. At least 1 of the following stroke risk factors was also required: Age ≥75 years; prior stroke, TIA, or systemic embolism; symptomatic heart failure within 3 months or left ventricular ejection fraction ≤40%; diabetes mellitus; or hypertension that required pharmacological treatment.

Study interventions were administered in a double-blind, double-dummy fashion. Subjects in the apixaban arm received 5 mg twice daily unless they met ≥2 of the following criteria for a lower 2.5-mg twice-daily dose: Age ≥80 years, body weight ≤60 kg, or serum creatinine >1.5 mg/dL (133 μmol/L). Subjects in the warfarin arm received 2-mg tablets initially, and dosing was adjusted to achieve a target INR of 2.0 to 3.0 in a blinded and algorithmic manner; therapeutic INRs were achieved a mean 62% of the time. Additionally, subjects in both arms were permitted to receive up to 162 mg of aspirin daily if clinically indicated.

Among 18 201 randomized patients followed up for a median of 1.8 years, 1.27% of apixaban-treated subjects experienced the primary outcome of stroke or systemic embolization compared with 1.60% of warfarin-treated subjects (HR, 0.79; 95% CI, 0.66–0.95). In prespecified hierarchical testing, both noninferiority ($P<0.001$) and superiority ($P=0.01$) of apixaban were demonstrated. A greater proportion of the benefit appeared to be related to the reduction in hemorrhagic stroke (49% reduction) compared with ischemic or uncertain types of stroke (8% reduction). Additional secondary end points of death (3.52% versus 3.94%; HR, 0.89; 95% CI, 0.80–0.99; $P=0.047$) and major bleeding (2.13% versus 3.09%; HR, 0.69; 95% CI, 0.60–0.80; $P<0.001$) favored apixaban.

Consistent treatment effects were seen across prespecified subgroups, including those based on concurrent aspirin use at randomization, warfarin use before study enrollment, type of AF (paroxysmal versus permanent), and prior stroke or TIA status. Subgroup analyses did suggest greater reduction in bleeding with apixaban among those without diabetes mellitus ($P=0.003$ for interaction) and among those with moderate or severe renal impairment ($P=0.03$ for interaction).

Cost-Effectiveness Analyses, Postmarketing Surveillance, and Existing AHA Recommendations

Cost-effectiveness analyses have not been published. Apixaban is not currently approved for stroke prevention in patients with AF in the United States; therefore, there are no postmarketing surveillance data. When apixaban is approved, there may be additional data made available that would affect the recommendations. No AHA recommendations regarding apixaban currently exist.

New Recommendations

It is important to acknowledge several unresolved issues related to the clinical use of dabigatran, rivaroxaban, and apixaban. There are no published data directly comparing dabigatran, rivaroxaban, and apixaban to one another, only comparisons to warfarin. The duration of follow-up in the clinical trials was limited. Factors relevant to long-term, real-world adherence are not known, especially if these new drugs are used outside of a care structure designed to assess adherence, such as an anticoagulation clinic. Because of their short half-lives, patients who are noncompliant and miss medication doses might be at risk for thromboembolism. Treatment decisions should account for differences in costs to patients, which could also affect compliance. Drug activity of the newer agents presently cannot be assessed in routine clinical practice, which poses a potential risk of undertreating or overtreating individuals. The transition from warfarin must be managed carefully and may constitute a period of increased risk. It is not known whether patients receiving these agents but otherwise eligible for thrombolysis can be treated safely with a thrombolytic agent (ie, intravenous recombinant tissue-type plasminogen activator) for an acute ischemic stroke. There are no antidotes to emergently reverse dabigatran, apixaban, or rivaroxaban in the setting of hemorrhage. Apixaban is not currently approved for stroke prevention in patients with AF in the United States (Table 2). Data reflecting clinical effectiveness (ie, the balance of benefits and risks of the newer agents as used in real-world settings) are only beginning to emerge for dabigatran and are unavailable for apixaban and rivaroxaban.

1. **Warfarin *(Class I; Level of Evidence A)*, dabigatran *(Class I; Level of Evidence B)*, apixaban *(Class I; Level of Evidence B)*, and rivaroxaban *(Class IIa; Level of Evidence B)* are all indicated for the prevention of first and recurrent stroke in patients with nonvalvular AF. The selection of an antithrombotic agent should be individualized on the basis of risk factors, cost, tolerability, patient preference, potential for drug interactions, and other clinical characteristics, including time in INR therapeutic range if the patient has been taking warfarin.**
2. **Dabigatran 150 mg twice daily is an efficacious alternative to warfarin for the prevention of first and recurrent stroke in patients with nonvalvular AF and at least 1 additional risk factor who have CrCl >30 mL/min *(Class I; Level of Evidence B)*.**
3. **On the basis of pharmacokinetic data, the use of dabigatran 75 mg twice daily in patients with AF**

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Table 2. Comparison of Key Studies of New Oral Antithrombotics

	RE-LY[26]	ROCKET-AF[52]	ARISTOTLE[58]	AVERROES[56]
Agent	Dabigatran 150 mg BID	Rivaroxaban 20 mg QD	Apixaban 5 mg or 2.5 mg BID*	Apixaban 5 mg BID*
Comparator	Warfarin	Warfarin	Warfarin	Aspirin 81–325 mg QD
Blinding	Open label	Double blind, double dummy	Double blind, double dummy	Double blind, double dummy
Sample size	18 113	14 264	18 201	5599
Mean age, y	72	73	70	70
Female, %	36	40	35	41
CHADS score	2.1	3.5	2.1	2.0
0–1, %	32	0	34	37
2, %	35	13	36	35
3–6, %	33	87	30	28
Previous stroke, %	20	34	19	14
Event rate vs comparator, %†	1.1 vs 1.7 ($P<0.001$)	2.1 vs 2.4 ($P=0.12$‡)	1.3 vs 1.6 ($P<0.001$)	1.6 vs 3.7 ($P<0.001$)
HR vs comparator†	0.66 (0.53–0.82)	0.88 (0.74–1.03)‡	0.79 (0.66–0.95)	0.45 (0.32–0.62)
No. needed to treat	167	Noninferior	303	48
Major bleeding vs comparator, %	3.6 vs 3.3	3.6 vs 3.4	2.1 vs 3.1	1.4 vs 1.2
ICH vs comparator, %	0.3 vs 0.7	0.5 vs 0.7	0.2 vs 0.5	0.4 vs 0.4

RE-LY indicates Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET-AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; ARISTOTLE, Apixaban for Reduction In STroke and Other ThromboembolLic Events in atrial fibrillation; AVERROES, Apixaban Versus Acetylsalicylic Acid to Prevent Strokes in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment; BID, twice per day; QD, every day; CHADS, Congestive heart failure, Hypertension, Age, Diabetes, prior Stroke or TIA; HR, hazard ratio; and ICH, intracerebral hemorrhage.

*Reduced dose used in select patients; refer to text.

†Stroke or systemic embolism.

‡P=NS for superiority in intention-to-treat analysis.

and at least 1 additional risk factor who have a low CrCl (15–30 mL/min) may be considered, but its safety and efficacy have not been established *(Class IIb; Level of Evidence C)*.

4. **Because there are no data to support the use of dabigatran in patients with more severe renal failure, dabigatran is not recommended in patients with a CrCl <15 mL/min *(Class III; Level of Evidence C)*.**
5. **Apixaban 5 mg twice daily is an efficacious alternative to aspirin in patients with nonvalvular AF deemed unsuitable for vitamin K antagonist therapy who have at least 1 additional risk factor and no more than 1 of the following characteristics: Age ≥80 years, weight ≤60 kg, or serum creatinine ≥1.5 mg/dL *(Class I; Level of Evidence B)*.**
6. **Although its safety and efficacy have not been established, apixaban 2.5 mg twice daily may be considered as an alternative to aspirin in patients with nonvalvular AF deemed unsuitable for vitamin K antagonist therapy who have at least 1 additional risk factor and ≥2 of the following criteria: Age ≥80 years, weight ≤60 kg, or serum creatinine ≥1.5 mg/dL *(Class IIb; Level of Evidence C)*.**
7. **Apixaban 5 mg twice daily is a relatively safe and efficacious alternative to warfarin in patients with nonvalvular AF deemed appropriate for vitamin K antagonist therapy who have at least 1 additional risk factor and no more than 1 of the following characteristics: Age ≥80 years, weight ≤60 kg, or serum creatinine ≥1.5 mg/dL, *(Class I; Level of Evidence B)*.**
8. **Although its safety and efficacy have not been established, apixaban 2.5 mg twice daily may be considered as an alternative to warfarin in patients with nonvalvular AF deemed appropriate for vitamin K antagonist therapy who have at least 1 additional risk factor and ≥2 of the following criteria: Age ≥80 years, weight ≤60 kg, or serum creatinine ≥1.5 mg/dL *(Class IIb; Level of Evidence C)*.**
9. **Apixaban should not be used if the CrCl is <25 mL/min *(Class III; Level of Evidence C)*.**
10. **In patients with nonvalvular AF who are at moderate to high risk of stroke (prior history of TIA, stroke, or systemic embolization or ≥2 additional risk factors), rivaroxaban 20 mg/d is reasonable as an alternative to warfarin *(Class IIa; Level of Evidence B)*.**
11. **In patients with renal impairment and nonvalvular AF who are at moderate to high risk of stroke (prior history of TIA, stroke, or systemic embolization or ≥2 additional risk factors), with a CrCl of 15 to 50 mL/min, 15 mg of rivaroxaban daily may be considered; however, its safety and efficacy have not been established *(Class IIb; Level of Evidence C)*.**
12. **Rivaroxaban should not be used if the CrCl is <15 mL/min *(Class III; Level of Evidence C)*.**
13. **The safety and efficacy of combining dabigatran, rivaroxaban, or apixaban with an antiplatelet agent have not been established *(Class IIb; Level of Evidence C)*.**

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Disclosures

Writing Group Disclosures

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/ Advisory Board	Other
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*Modest.

†Significant.

Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
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*Modest.

†Significant.

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References

1. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation: analysis of pooled data from five randomized controlled trials [published correction appears in *Arch Intern Med*. 1994;154:2254]. *Arch Intern Med.* 1994;154:1449–1457.
2. Stroke Risk in Atrial Fibrillation Working Group. Independent predictors of stroke in patients with atrial fibrillation: a systematic review. *Neurology*. 2007;69:546–554.
3. Loewen P, Dahri K. Risk of bleeding with oral anticoagulants: an updated systematic review and performance analysis of clinical prediction rules. *Ann Hematol*. 2011;90:1191–1200.
4. Goldstein LB, Bushnell CD, Adams RJ, Appel LJ, Braun LT, Chaturvedi S, Creager MA, Culebras A, Eckel RH, Hart RG, Hinchey JA, Howard VJ, Jauch EC, Levine SR, Meschia JF, Moore WS, Nixon JV, Pearson TA. Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association [published correction appears in *Stroke*. 2011;42:e26]. *Stroke*. 2011;42:517–584.
5. Furie KL, Kasner SE, Adams RJ, Albers GW, Bush RL, Fagan SC, Halperin JL, Johnston SC, Katzan I, Kernan WN, Mitchell PH, Ovbiagele B, Palesch YY, Sacco RL, Schwamm LH, Wassertheil-Smoller S, Turan TN, Wentworth D. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2011;42:227–276.
6. Gage BF, van Walraven C, Pearce L, Hart RG, Koudstaal PJ, Boode BS, Petersen P. Selecting patients with atrial fibrillation for anticoagulation: stroke risk stratification in patients taking aspirin. *Circulation*. 2004;110:2287–2292.
7. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*. 2001;285:2864–2870.
8. Hart RG, Halperin JL, Pearce LA, Anderson DC, Kronmal RA, McBride R, Nasco E, Sherman DG, Talbert RL, Marler JR; Stroke Prevention in Atrial Fibrillation Investigators. Lessons from the Stroke Prevention in Atrial Fibrillation trials. *Ann Intern Med*. 2003;138:831–838.
9. Stroke Risk in Atrial Fibrillation Working Group. Comparison of 12 risk stratification schemes to predict stroke in patients with nonvalvular atrial fibrillation. *Stroke.* 2008;39:1901–1910.
10. Go AS, Hylek EM, Chang Y, Phillips KA, Henault LE, Capra AM, Jensvold NG, Selby JV, Singer DE. Anticoagulation therapy for stroke prevention in atrial fibrillation: how well do randomized trials translate into clinical practice? *JAMA*. 2003;290:2685–2692.
11. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on atrial fibrillation. *Chest*. 2010;137:263–272.
12. Lip GY, Frison L, Halperin JL, Lane DA. Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation: the HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) score. *J Am Coll Cardiol*. 2011;57:173–180.
13. Ruíz-Giménez N, Suárez C, González R, Nieto JA, Todolí JA, Samperiz AL, Monreal M; RIETE Investigators. Predictive variables for major bleeding events in patients presenting with documented acute venous thromboembolism: findings from the RIETE Registry. *Thromb Haemost*. 2008;100:26–31.
14. Fang MC, Go AS, Chang Y, Borowsky LH, Pomernacki NK, Udaltsova N, Singer DE. A new risk scheme to predict warfarin-associated hemorrhage: the ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) Study. *J Am Coll Cardiol*. 2011;58:395–401.
15. Hylek EM, Skates SJ, Sheehan MA, Singer DE. An analysis of the lowest effective intensity of prophylactic anticoagulation for patients with nonrheumatic atrial fibrillation. *N Engl J Med*. 1996;335:540–546.
16. EAFT (European Atrial Fibrillation Trial) Study Group. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. *Lancet.* 1993;342:1255–1262.
17. Stroke Prevention in Atrial Fibrillation Investigators. Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: Stroke Prevention in Atrial Fibrillation III randomised clinical trial. *Lancet.* 1996;348:633–638.
18. Akins PT, Feldman HA, Zoble RG, Newman D, Spitzer SG, Diener HC, Albers GW. Secondary stroke prevention with ximelagatran versus warfarin in patients with atrial fibrillation: pooled analysis of SPORTIF III and V clinical trials. *Stroke*. 2007;38:874–880.
19. Connolly SJ, Pogue J, Eikelboom J, Flaker G, Commerford P, Franzosi MG, Healey JS, Yusuf S; ACTIVE W Investigators. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by centers and countries as measured by time in therapeutic range. *Circulation*. 2008;118:2029–2037.
20. Singer DE, Albers GW, Dalen JE, Fang MC, Go AS, Halperin JL, Lip GY, Manning WJ; American College of Chest Physicians. Antithrombotic therapy in atrial fibrillation: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest.* 2008;133:546S–592S.
21. Olesen JB, Lip GY, Lindhardsen J, Lane DA, Ahlehoff O, Hansen ML, Raunsø J, Tolstrup JS, Hansen PR, Gislason GH, Torp-Pedersen C. Risks of thromboembolism and bleeding with thromboprophylaxis in patients with atrial fibrillation: a net clinical benefit analysis using a "real world" nationwide cohort study. *Thromb Haemost*. 2011;106:739–749.
22. Dale J, Myhre E, Storstein O, Stormorken H, Efskind L. Prevention of arterial thromboembolism with acetylsalicylic acid: a controlled clinical study in patients with aortic ball valves. *Am Heart J*. 1977;94:101–111.
23. Connolly S, Pogue J, Hart R, Pfeffer M, Hohnloser S, Chrolavicius S, Yusuf S; on behalf of the ACTIVE Investigators. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet*. 2006;367:1903–1912.
24. Connolly SJ, Pogue J, Hart RG, Hohnloser SH, Pfeffer M, Chrolavicius S, Yusuf S; ACTIVE Investigators. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. *N Engl J Med*. 2009;360:2066–2078.
25. Stangier J. Clinical pharmacokinetics and pharmacodynamics of the oral direct thrombin inhibitor dabigatran etexilate. *Clin Pharmacokinet*. 2008;47:285–295.
26. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener H-C, Joyner CD, Wallentin L; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation [published correction appears in *N Engl J Med*. 2010;363:1877]. *N Engl J Med.* 2009;361:1139–1151.
27. Eikelboom JW, Wallentin L, Connolly SJ, Ezekowitz M, Healey JS, Oldgren J, Yang S, Alings M, Kaatz S, Hohnloser SH, Diener H-C, Franzosi MG, Huber K, Reilly P, Varrone J, Yusuf S. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial. *Circulation*. 2011;123:2363–2372.
28. Connolly SJ, Ezekowitz MD, Yusuf S, Reilly PA, Wallentin L; Randomized Evaluation of Long-Term Anticoagulation Therapy Investigators. Newly identified events in the RE-LY trial. *N Engl J Med*. 2010;363:1875–1876.
29. Hohnloser SH, Oldgren J, Yang S, Wallentin L, Ezekowitz M, Reilly P, Eikelboom J, Brueckmann M, Yusuf S, Connolly SJ. Myocardial ischemic events in patients with atrial fibrillation treated with dabigatran or warfarin in the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial. *Circulation.* 2012;125:669–676.
30. Uchino K, Hernandez AV. Dabigatran association with higher risk of acute coronary events: meta-analysis of noninferiority randomized controlled trials. *Arch Intern Med.* 2012;172:397–402.
31. Oldgren J, Alings M, Darius H, Diener H-C, Eikelboom J, Ezekowitz MD, Kamensky G, Reilly PA, Yang S, Yusuf S, Wallentin L, Connolly SJ; RE-LY Investigators. Risks for stroke, bleeding, and death in patients with atrial fibrillation receiving dabigatran or warfarin in relation to the CHADS2 score: a subgroup analysis of the RE-LY trial. *Ann Intern Med.* 2011;155:660–667.
32. Diener HC, Connolly SJ, Ezekowitz MD, Wallentin L, Reilly PA, Yang S, Xavier D, Di Pasquale G, Yusuf S; RE-LY Study Group. Dabigatran compared with warfarin in patients with atrial fibrillation and previous transient ischaemic attack or stroke: a subgroup analysis of the RE-LY trial [published correction appears in *Lancet Neurol*. 2011;10:27]. *Lancet Neurol*. 2010;9:1157–1163.
33. Hylek EM, Go AS, Chang Y, Jensvold NG, Henault LE, Selby JV, Singer DE. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. *N Engl J Med*. 2003;349:1019–1026.
34. Jones M, McEwan P, Morgan CL, Peters JR, Goodfellow J, Currie CJ. Evaluation of the pattern of treatment, level of anticoagulation control,

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and outcome of treatment with warfarin in patients with non-valvar atrial fibrillation: a record linkage study in a large British population. *Heart*. 2005;91:472–477.
35. Wallentin L, Yusuf S, Ezekowitz MD, Alings M, Flather M, Franzosi MG, Pais P, Dans A, Eikelboom J, Oldgren J, Pogue J, Reilly PA, Yang S, Connolly SJ; RE-LY Investigators. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. *Lancet*. 2010;376:975–983.
36. van Ryn J, Stangier J, Haertter S, Liesenfeld K-H, Wienen W, Feuring M, Clemens A. Dabigatran etexilate: a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. *Thromb Haemost*. 2010;103:1116–1127.
37. Eerenberg ES, Kamphuisen PW, Sijpkens MK, Meijers JC, Büller HR, Levi M. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. *Circulation*. 2011;124:1573–1579.
38. Cotton BA, McCarthy JJ, Holcomb JB. Acutely injured patients on dabigatran. *N Engl J Med*. 2011;365:2039–2040.
39. Freeman JV, Zhu RP, Owens DK, Garber AM, Hutton DW, Go AS, Wang PJ, Turakhia MP. Cost-effectiveness of dabigatran compared with warfarin for stroke prevention in atrial fibrillation. *Ann Intern Med*. 2011;154:1–11.
40. Pink J, Lane S, Pirmohamed M, Hughes DA. Dabigatran etexilate versus warfarin in management of non-valvular atrial fibrillation in UK context: quantitative benefit-harm and economic analyses. *BMJ*. 2011;343:d6333.
41. Shah SV, Gage BF. Cost-effectiveness of dabigatran for stroke prophylaxis in atrial fibrillation. *Circulation*. 2011;123:2562–2570.
42. Sorensen S, Kansal A, Connolly S, Peng S, Linnehan J, Bradley-Kennedy C, Plumb J. Cost-effectiveness of dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation: a Canadian payer perspective. *Thromb Haemost*. 2011;105:908–919.
43. Spackman E, Burch J, Faria R, Corbacho B, Fox D, Woolacott N. *Dabigatran Etexilate for the Prevention of Stroke and Systemic Embolism in Atrial Fibrillation: Evidence Review Group Report.* York, United Kingdom: National Institute for Health and Clinical Excellence, Centre for Health Economics; 2011.
44. Freeman JV, Turakhia MP. Dabigatran compared with warfarin for stroke prevention in atrial fibrillation. *Ann Intern Med*. 2011;154:570–571.
45. Beasley BN, Unger EF, Temple R. Anticoagulant options: why the FDA approved a higher but not a lower dose of dabigatran. *N Engl J Med*. 2011;364:1788–1790.
46. Summary Minutes of the Cardiovascular and Renal Drugs Advisory Committee (September 20, 2010). http://www.fda.gov/downloads/Advisory%20Committees/CommitteesMeetingMaterials/%20Drugs/CardiovascularandRenalDrugs%20AdvisoryCommittee/UCM236322.pdf. Accessed November 15, 2011.
47. US Department of Health & Human Services, US Food and Drug Administration. FDA Drug Safety Communication: safety review of post-market reports of serious bleeding events with the anticoagulant Pradaxa (dabigatran etexilate mesylate). http://www.fda.gov/Drugs/DrugSafety/ucm282724.htm#data. Accessed December 7, 2011.
48. European Medicines Agency updates on safety of Pradaxa [news release]. London, United Kingdom: European Medicines Agency; November 18, 2011. http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2011/11/WC500117818.pdf. Accessed December 6, 2011.
49. Australian Government Department of Health and Ageing Therapeutic Goods Administration. Dabigatran (Pradaxa): risk of bleeding relating to use. http://www.tga.gov.au/safety/alerts-medicine-dabigatran-111005.htm. Accessed December 7, 2011.
50. Australian Government Department of Health and Ageing Therapeutic Goods Administration. Dabigatran (Pradaxa) & the risk of bleeding: new recommendations for monitoring kidney function. http://www.tga.gov.au/safety/alerts-medicine-dabigatran-111103.htm. Accessed December, 7 2011.
51. Wann LS, Curtis AB, January CT, Ellenbogen KA, Lowe JE, Estes NAM 3rd, Page RL, Ezekowitz MD, Slotwiner DJ, Jackman WM, Stevenson WG, Tracy CM; on behalf of the 2006 ACC/AHA/ESC Guidelines for the Management of Patients With Atrial Fibrillation Writing Committee. 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (updating the 2006 guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines [published correction appears in *Circulation*. 2011;124:e173]. *Circulation*. 2011;123:104–123.
52. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365:883–891.
53. Trial Results Center. Trials Register No. NCT00494871. http://www.trialresultscenter.org/study12240-ROCKET-J.htm. Accessed December 5, 2011.
54. Beasley N, Dunnmon P, Rose M. FDA Draft Briefing Document for the Cardiovascular and Renal Drugs Advisory Committee (CRDAC). Clinical Review: NDA 202439: Xarelto (rivaroxaban). http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/drugs/CardiovascularandRenalDrugsAdvisoryCommittee/ucm270796.pdf. Accessed December 5, 2011.
55. Fleming TR, Emerson SS. Evaluating rivaroxaban for nonvalvular atrial fibrillation: regulatory considerations. *N Engl J Med*. 2011;365:1557–1559.
56. Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S, Flaker G, Avezum A, Hohnloser SH, Diaz R, Talajic M, Zhu J, Pais P, Budaj A, Parkhomenko A, Jansky P, Commerford P, Tan RS, Sim KH, Lewis BS, Van Mieghem W, Lip GY, Kim JH, Lanas-Zanetti F, Gonzalez-Hermosillo A, Dans AL, Munawar M, O'Donnell M, Lawrence J, Lewis G, Afzal R, Yusuf S; AVERROES Steering Committee and Investigators. Apixaban in patients with atrial fibrillation. *N Engl J Med*. 2011;364:806–817.
57. Olesen JB, Lip GY, Hansen ML, Hansen PR, Tolstrup JS, Lindhardsen J, Selmer C, Ahlehoff O, Olsen AM, Gislason GH, Torp-Pedersen C. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. *BMJ*. 2011;342:d124.
58. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365:981–992.

KEY WORDS: AHA Scientific Statements ■ atrial fibrillation ■ antithrombotic therapy ■ stroke prevention ■ treatment

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