AHA/ASA Scientific Statement

Oral Antithrombotic Agents for the Prevention of Stroke in Atrial Fibrillation

A Statement 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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Stroke Council Professional Education Committee

• This slide presentation was developed by a member of the Stroke Council Professional Education Committee.

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• Key words included in the paper: atrial fibrillation, antithrombotic therapy, stroke prevention, treatment
### Applying classification of recommendations and levels of evidence

#### SIZE OF TREATMENT EFFECT

<table>
<thead>
<tr>
<th>CLASS I</th>
<th>Benefit &gt;&gt; Risk</th>
<th>Procedure/Treatment SHOULD be performed/administered</th>
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<tr>
<td>CLASS IIa</td>
<td>Benefit &gt;&gt; Risk</td>
<td>Recommendation in favor of treatment or procedure being useful/effective</td>
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<tr>
<td>CLASS IIb</td>
<td>Benefit ≥ Risk</td>
<td>Recommendation in favor of treatment or procedure being useful/effective</td>
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<tr>
<td>CLASS III</td>
<td>No Benefit or CLASS III Harm</td>
<td>Recommendation that procedure or treatment is not useful/effective and may be harmful</td>
</tr>
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#### 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

#### 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

#### 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

<table>
<thead>
<tr>
<th>Suggested phrases for writing recommendations</th>
<th>Level A</th>
<th>Level B</th>
<th>Level C</th>
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<tr>
<td>should be recommended</td>
<td>is recommended</td>
<td>is indicated</td>
<td>is useful/effective/beneficial</td>
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<tr>
<td>is useful/effective</td>
<td>is probably recommended/indicated</td>
<td>is reasonable</td>
<td>may/might be considered</td>
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<tr>
<th>Comparative effectiveness phrases</th>
<th>Level A</th>
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<tbody>
<tr>
<td>treatment/strategy A is recommended/indicated in preference to treatment B</td>
<td>treatment/strategy A is probably recommended/indicated in preference to treatment B</td>
<td>treatment/strategy A is probably recommended/indicated in preference to treatment B</td>
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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/effectiveness 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.

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Oral Antithrombotic Agents for the Prevention of Stroke in Atrial Fibrillation

• Introduction
  – Rate of stroke in atrial fibrillation (AF) ranges between 1% and 20% annually, depending on co-morbidities and history of prior cerebrovascular events
  – Major risk of antithrombotic use is bleeding
  – For warfarin, must balance bleeding risk of 1-12% per year against risk of ischemic events
  – New antithrombotic agents may lower threshold initiating therapy in patients with AF
    • dabigatran, rivaroxaban, apixaban
Summary of Current AHA/ASA Guidelines for Vitamin K Antagonists/Antithrombotics in AF

• Risk Stratification
  – Absolute risk of stroke varies 20-fold according to age and associated vascular co-morbidities
  – Current AHA guidelines use CHADS₂
    • 1 point each for congestive heart failure, hypertension, age ≥75 years, and diabetes mellitus
    • 2 points for prior stroke or transient ischemic attack (TIA)
    • Score of 0 had thromboembolic rate of 0.49; score of 1=1.52; 2=2.50; 3=5.27; 4=6.02; 5 or 6=6.88
  – Other risk calculations for stroke and hemorrhage
    • CHA₂DS₂VASc index, HAS-BLED, RIETE, and ATRIA
Summary of Current AHA/ASA Guidelines for Vitamin K Antagonists/Antithrombotics in AF

- Treatment Recommendations
  - Vitamin K antagonists are superior over antiplatelet therapies for stroke prevention in AF patients
    - Absolute reduction in annual stroke rate 4.5% to 1.4%
    - Anticoagulation recommended for CHADS$_2$ $\geq$ 2
  - Optimal International Normalized Ratio (INR) 2-3
  - National effectiveness found no benefit with aspirin
  - ACTIVE W-warfarin superior to clopidogrel and Aspirin
  - ACTIVE A-no net benefit of combination therapy
Summary of Current AHA/ASA Guidelines for Vitamin K Antagonists/Antithrombotics in AF

• Recommendations for prevention of first stroke
  
  – 1) adjusted-dose warfarin (target INR, 2.0-3.0)
    • All high-risk pts with AF and many moderate risk
    • Class I, Level of Evidence A
  
  – 2) Antiplatelet therapy with aspirin
    • Low risk and some moderate risk (patient preference, bleeding risk, access to high-quality INR monitoring)
    • Class I, Level of Evidence A
  
  – 3) dual antiplatelet with clopidogrel and aspirin
    • High risk and unsuitable for anticoagulation
    • More protection than aspirin with increased bleeding
    • Class IIb, Level of Evidence B
Summary of Current AHA/ASA Guidelines for Vitamin K Antagonists/Antithrombotics in AF

• Recommendations for stroke prevention in patients with history of stroke or TIA
  – 1) anticoagulation with vitamin K antagonist
    • Target INR 2.5; range 2.0-3.0
    • Class I, Level of Evidence A
  – 2) patients unable to take oral anticoagulants, aspirin alone (Class I, Level of Evidence A)
    • Clopidogrel plus aspirin carries bleeding risk similar to warfarin and therefore is not recommended for patients with hemorrhagic contraindication to warfarin
    • Class III, Level of Evidence B
New Alternative Antithrombotics for Stroke Prevention in Patients with AF

- Dabigatran
  - Pharmacology
    - Prodrug converted by serum esterase to dabigatran
    - Direct, competitive inhibitor of factor IIa (thrombin)
    - Bioavailability 6.5%; Serum half-life 12-17 hours
    - Fixed dosing with no monitoring required
    - 80% renally excreted (pharmacokinetics affected by renal function)
    - Not metabolized by cytochrome P450 system
    - \( p \)-glycoprotein inhibitors can increase concentrations
      - Dronedarone, ketoconazole, amiodarone, verapamil, quinidine
      - Rifampin can decrease effects of dabigatran
Dabigatran Clinical Trial Summary

• RE-LY
  – Open-label warfarin compared to blinded doses of dabigatran (110 mg or 150 mg) twice daily
  – Participants with AF and at least one additional risk factor
  – Low-dose aspirin or other antiplatelet therapy permitted
  – Primary outcome: stroke or systemic embolism
    • Noninferiority versus warfarin
  – CHADS$_2$ 2.1±1.1
Dabigatran Clinical Trial Summary

• RE-LY (cont.)
  – Primary outcome for both doses non-inferior
    • 110 mg 1.53%/yr; 150 mg 1.11%/yr; warfarin 1.69%/yr
    – Dabigatran 150 mg twice daily was also superior to warfarin (RR 0.66, 95% CI 0.53-0.82)
  – Hemorrhagic stroke risk lower with both doses
  – Major bleeding
    • Lower with dabigatran (110 mg 2.71%/yr; 150 mg 3.11%/yr) compared to warfarin (3.36%/yr)
    • GI bleeding higher with dabigatran 150 mg twice daily (1.51%/yr) compared to warfarin (1.02%/yr)
Dabigatran Clinical Trial Summary

• RE-LY (cont.)
  – Limited data on patients with prior stroke or TIA
    • Similar rates of stroke or systemic embolism with warfarin (2.78%/yr), 150 mg (2.07%), and 110 mg (2.32%)
  – Time in INR therapeutic range (TTR)
    • Potent predictor of warfarin effectiveness and safety
  – Limited data on safety and efficacy in patients on aspirin or other antiplatelet therapy
Dabigatran Clinical Trial Summary

• RE-LY Limitations
  – Short median follow-up of 2.0 years
  – Factors affecting clearance and plasma concentrations could lead to variation of effect, safety, and efficacy
    • Kidney function, body mass index or volume of distribution
  – Proposed reversal
    • Activated recombinant factor VIIa or purified factor products
    • Emergency dialysis for rapid reversal
Dabigatran Cost-Effectiveness Analyses

• Several rigorous cost-effectiveness analyses in different health care systems have compared dabigatran to warfarin
  – Dabigatran 150 mg twice daily compared to warfarin
    • 10.84 vs 10.28 QALY
    • Incremental cost-effectiveness ratio (ICER) of $45,372 per QALY
      – Reduced to $12,386 per QALY when price/dose lower than expected

• Multiple studies also found increased QALYs with dabigatran and ICERs within thresholds for health care systems

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Dabigatran Cost-Effectiveness Analyses

• Major Limitations
  – Primary efficacy data drawn from single trial with short follow-up relative to patient’s lifetime horizon of anticoagulation use
    • Additional costs or harms may become apparent with use
  – Dabigatran was cost-effective, not cost-saving
    • May lead to marked escalations in health care expenditures
  – Infrastructural costs (anticoagulation clinics) or indirect costs (lost wages and productivity) were not considered
Dabigatran Post-marketing Surveillance

• Fatal bleeding events have led to advisories from regulatory agencies
  – Assess renal function prior to prescribing
  – TGA (Australia) and EMA (Europe) recommend that dabigatran not be prescribed if creatinine clearance is <30 mL/min
  – FDA continues to analyze post-marketing reports of adverse events for factors that may be associated with bleeding events
  – No indication of increased risk of myocardial infarction
Current AHA Recommendations for Dabigatran

- 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 (creatinine clearance <15 mL/min), or advanced liver disease (impaired baseline clotting function) (Class I, Level of Evidence B).
New Alternative Antithrombotics for Stroke Prevention in Patients with AF

• Apixaban
  – Pharmacology
    • Direct and competitive factor Xa inhibitor
    • Bioavailability 50%; Serum half-life 8-15 hours
    • Fixed dosing with no monitoring required
    • Metabolized by cytochrome P450 (CYP3A4) system
    • Clearance
      – renal (25% unchanged)
      – fecal (50% unchanged)
Apixaban Clinical Trial Summary

• AVERROES
  – Randomized, double-blind trial comparing efficacy and safety of apixaban to aspirin
  – Subjects with AF and one risk factor for stroke
  – Unsuitable for vitamin K antagonist therapy
    • Physician judgment or patient preference
  – Apixaban doses 5 mg twice daily (94%) or 2.5 mg twice daily (6%); Aspirin 81 mg - 324 mg
  – Mean CHADS$_2$ score of 2
Apixaban Clinical Trial Summary

• AVERROES (cont.)
  – Terminated when interim analysis found apixaban superior to aspirin for prevention of stroke or systemic embolism
    • 1.6%/yr versus 3.7%/yr (HR 0.45 [0.32-0.62]; RRR=57%)
    • Similar rates of major bleeding: 1.4%/yr versus 1.2%/yr (HR 1.13 [0.74-1.75])
  – Apixaban superior to aspirin for secondary prevention of stroke or systemic embolism
    • 2.5%/yr versus 8.3%/yr (RRR=70%; NNT=16)
    • Similar rate of major bleed: 3.5%/yr versus 2.7%/yr
Apixaban Clinical Trial Summary

• ARISTOTLE
  – Phase III, randomized trial comparing apixaban to warfarin for prevention of stroke or systemic embolization
  – Subjects with AF and one risk factor for stroke
  – Apixaban doses 5 mg twice daily or 2.5 mg twice daily if certain criteria met
  – Warfarin therapeutic INR achieved 62% of the time
  – Both arms permitted up to 162 mg of aspirin
Apixaban Clinical Trial Summary

• ARISTOTLE (cont.)
  – Primary outcome of stroke or systemic embolization, non-inferiority and superiority demonstrated
    • Apixaban 1.27% compared to warfarin 1.60%
    • HR 0.79 [0.66-0.95]
  – Major bleeding
    • Apixaban 2.13% vs. warfarin 3.09%
    • HR 0.69[0.60-0.80]
  – Greater proportion of benefit related to reducing hemorrhagic stroke rather than ischemic stroke
Apixaban

• Cost-effectiveness analyses have not been published
• Post-marketing Surveillance
  – Not currently approved for stroke prevention in patients with AF in the United States
• Current AHA recommendations
  – none
New Alternative Antithrombotics for Stroke Prevention in Patients with AF

• Rivaroxaban
  – Pharmacology
    • Direct and competitive factor Xa inhibitor
    • Bioavailability 70%; Serum half-life 5-9 hours
    • Fixed dosing with no monitoring required
    • Metabolized by cytochrome P450 (CYP3A4) system
    • Clearance
      – renal (36% unchanged)
      – fecal (7% unchanged)
Rivaroxaban Clinical Trial Summary

- ROCKET AF Trial
  - Randomized, double-blind non-inferiority trial comparing efficacy and safety of rivaroxaban to dose-adjusted warfarin (target INR 2.0-3.0)
  - Moderate- to high-risk subjects with AF
  - Rivaroxaban dose 20 mg daily
  - 55% of subjects had a stroke, TIA, or systemic embolism prior to enrollment
  - Median follow-up of 707 days
Rivaroxaban Clinical Trial Summary

• ROCKET AF Trial (cont.)
  – Primary outcome of stroke or systemic embolization, non-inferiority demonstrated
    • Rivaroxaban 1.7%/yr compared to warfarin 2.2%/yr
    • HR 0.79 [0.66-0.96]; p<0.001 for non-inferiority
  – Major and non-major clinically relevant bleeding
    • Rivaroxaban 14.9% vs. warfarin 14.5%
    • HR 1.03 [0.96-1.11]
  – Intracranial hemorrhage (0.5% vs. 0.7%, p=0.02)
  – Fatal bleeding (0.2% vs. 0.5%, p=0.003)
Rivaroxaban Clinical Trial Summary

• J-ROCKET AF Trial
  – Randomized, double-blind non-inferiority trial comparing the safety of rivaroxaban (15 mg) to dose-adjusted warfarin (target INR 2.0-3.0 if <70 years of age and 1.6-2.6 if ≥70 years of age)
  – Designed to evaluate the non-inferiority of rivaroxaban compared to warfarin for bleeding
  – Not powered to demonstrate efficacy
  – Baseline CHADS₂ score ≥3
    • 85% of Rivaroxaban group
    • 82% of Warfarin group
Rivaroxaban Clinical Trial Summary

• J-ROCKET AF Trial (cont.)
  – Primary safety outcome of major or non-major clinically relevant bleeding event
    • Rivaroxaban 1.26%/yr versus warfarin 2.61%/yr
    • HR 0.48 [0.23-1.00]
  – Limitations
    • Low target INR than U.S. standards
    • higher rates of prior stroke
    • only Japanese subjects
Rivaroxaban Clinical Trial Summary

• J-ROCKET AF Trial (cont.)
  – Concern towards quality of warfarin management
  • Post-treatment rates were 22.8 (rivaroxaban) versus 6.2 (warfarin) events per 100 patient/years
    – Concern that warfarin management during trial was suboptimal
    – TTR lower than historical values in other warfarin trials
Rivaroxaban Clinical Trial Interpretation

• TTR for warfarin-arm only 55%
  – Compared to 62%-73% in other recent trials
• “on-treatment” analysis truncated 2 days after discontinuation of treatment
  – Higher rates of stroke or systemic embolization with rivaroxaban 2-7 days after discontinuation
• Once daily dosing not supported by pharmacodynamic data
• Despite these concerns, rivaroxaban received FDA approval
Rivaroxaban

- Cost-effectiveness analyses have not been published
- Post-marketing Surveillance
  - Recently approved for stroke prevention in patients with AF in the United States
  - Post-marketing surveillance data are not yet available
- Current AHA recommendations
  - none
New AHA/ASA Recommendations

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 atrial fibrillation. 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 on warfarin.
New AHA/ASA Recommendations

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 one additional risk factor who have normal creatinine clearance (CrCl) (>30 mL/min) (Class I, Level of Evidence B).

3. Based on pharmacokinetic data, the use of dabigatran 75 mg twice daily in patients with AF and at least one 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).
New AHA/ASA Recommendations

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, ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL, apixaban 5 mg twice daily is an efficacious alternative to aspirin (Class I, Level of Evidence B).
New AHA/ASA Recommendations

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 ≤60kg, or serum creatinine ≥15 mg/dL (Class IIb, Level of Evidence C).
New AHA/ASA Recommendations

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 ≤60kg, or serum creatinine ≥15mg/dL (Class I, Level of Evidence B).
New AHA/ASA Recommendations

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 $\geq$ 80 years, weight $\leq$ 60kg, or serum creatinine $\geq$ 15mg/dL (Class IIb, Level of Evidence C).

9. Apixaban should not be used if the CrCl is less than 25 mL/min (Class III, Level of Evidence C).
New AHA/ASA Recommendations

10. In patients with nonvalvular AF who are at moderate to high risk of stroke (prior history of TIA, stroke, or systemic embolization or at least two additional risk factors), rivaroxaban 20 mg daily 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 at least two additional risk factors), with a CrCl of 15-50 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).
New AHA/ASA Recommendations

12. Rivaroxaban should not be used if the CrCl is less than 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).