Under-Treated Stroke Prevention in Atrial Fibrillation: The Risk of Bleeding versus the Risk of Stroke

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Baltimore, MD

Learning Objectives

• To recognize utilization of risk stratification to preventing stroke through the use of anticoagulants
• Describe the management of atrial fibrillation using anticoagulants for stroke prevention
• Review the efficacy and safety of current and emerging therapies for stroke prevention in AF
• Describe guideline recommendations for combining anticoagulants with antiplatelet therapy
Epidemiology of Atrial Fibrillation

- Most common sustained cardiac arrhythmia\(^1\)
- Currently affects > 2.3 million Americans, or 1% of population\(^1,2\)
- Preferentially affects men and the elderly\(^2\)
- Prevalence expected to increase by \(\geq 2.5\)-fold by 2050\(^2\)
- Lifetime risk of developing AF: 1 in 4 for men and women ≥ 40 years of age\(^1\)

Prevalence of Diagnosed AF


1.89 million adults in study population; N = 17,974 with AF

Causes of AF

- **Noncardiovascular causes**
  - Acute/chronic alcohol ingestion
  - Autonomic
  - DM
  - Genetic
  - Obesity
  - Pulmonary embolism
  - Severe lung diseases
  - Sleep apnea
  - Thyroid disorders
  - Others

- **Cardiovascular causes**
  - CAD
    - eg, post MI
  - HF
  - HTN
  - Primary electrical disorders
  - Valvular heart disease
  - Others

- **Iatrogenic causes**
  - Beta-agonists
  - Cardiac and noncardiac surgery
  - Intracardiac catheters
  - Local anesthetics, caffeinated beverages, other stimulants
  - OTC cold remedies

CAD = coronary artery disease; OTC = over-the-counter
The Spectrum of Atrial Fibrillation

Normal Heart
Normal Atrial Size

+/- Heart Disease
Mild/mod LAE

Diseased Heart
Significant LAE

PAF
Focal driver

Persistent AF
Focal initiation
Reentrant propagation

Beta blockers
Ic, III AADs
Focal RFA

Permanent AF
Reentry

Rate control/Anticoag
Ic, III AADs
IAD
Focal/linear RFA

Rate control/Anticoag. III AADs
AVJ RFA/pacer
Linear RFA

PAF: paroxysmal atrial fibrillation; AAD: antiarrhythmic drug; RFA: radiofrequency ablation; LAE: left atrial enlargement; IAD: implantable atrial defibrillator; AVJ: atrioventricular junction


Stroke Is the Most Common and Devastating Complication of AF

- All-cause stroke rate with AF is 5% per year
- AF - independent risk factor for stroke
  - ~5-fold increase in stroke risk
  - ~15% of all strokes caused by AF
  - Stroke risk increases with age
- Stroke risk persists asymptomatic AF

**Stroke Risk in AF: CHADS₂ Score**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>C Congestive HF</td>
<td>1</td>
</tr>
<tr>
<td>H Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>A Age &gt; 75</td>
<td>1</td>
</tr>
<tr>
<td>D Diabetes</td>
<td>1</td>
</tr>
<tr>
<td>S₂ Prior Stroke/TIA</td>
<td>2</td>
</tr>
</tbody>
</table>


**Risk of Stroke Without Warfarin in National Registry of Atrial Fibrillation (NRAF) by CHADS₂ Score**

Gage BF, et al. JAMA. 2001;285:2864-2870. *Crude stroke rate per 100 patient-years*
Atrial Fibrillation: Goals of Acute and Chronic Therapy

- Prevent stroke
- Slow ventricular response
- Restore and maintain normal sinus rhythm
- Improve symptoms
- Improve quality of life
- Reduce cost
- Prolong survival
Atrial Fibrillation Treatment Options

Rate Control
- Pharmacologic
  - Ca²⁺ blockers
  - β-blockers
  - Digitalis
- Nonpharmacologic
  - Ablate and pace

Maintenance of SR
- Pharmacologic
  - Class IC, Class III, β-blockers
- Nonpharmacologic
  - Catheter ablation
  - Pacing
  - Surgery (MAZE, pulmonary vein isolation)
  - Implantable atrial defibrillator

Stroke Prevention
- Pharmacologic
  - Warfarin
- Nonpharmacologic
  - Removal/isolation
  - LA appendage

Adapted from Prystowsky EN. Am J Cardiol. 2000;85(10A):3D-11D.

Anticoagulation and Antiplatelet Therapy
**Warfarin vs Placebo in Stroke Prevention in AF**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Favors Warfarin</th>
<th>Favors Placebo/Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFASAK-1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPAF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BAATAF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAFA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPINAF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EAFT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALL Trials</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

![Diagram showing Warfarin vs Placebo comparison](image)

*Warfarin reduces incidence of stroke by about 64%*


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**Aspirin vs Placebo in Stroke Prevention in AF**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Favors Antiplatelet</th>
<th>Favors Placebo/Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFASAK-1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPAF I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EAFT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESPS-II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LASAF, daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LASAF, alternate day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UK-TIA, 300 mg daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UK-TIA, 1200 mg daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>JAST</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin Trials</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAFT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESPS II, Dipyridamole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESPS II, Combination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Trials</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

![Diagram showing Aspirin vs Placebo comparison](image)

*Antiplatelet therapy reduces incidence of stroke by about 22%*

**Warfarin vs Antiplatelet Therapy in Stroke Prevention in AF**

- AFASAK I
- AFASAK II
- Chinese ATAFS
- EAFT
- PATAF
- SPAF II, ≤ 75 yrs
- SPAF II, >75 yrs
- Aspirin trials
- SIFA
- ACTIVE-W
- NASPEAF
- All Trials


**Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA)**

- 973 patients ≥ 75 yrs with AF assigned to warfarin (INR 2–3) vs aspirin (75 mg/day)
- Primary endpoint – fatal or disabling stroke, ICH or systemic embolism
  - Risk per year
    - Warfarin: 1.8%; Aspirin: 3.8%
    - Relative risk warfarin vs aspirin: 0.48; $P = 0.003$
- Major extracranial hemorrhage
  - Risk per year
    - Warfarin: 1.4%; Aspirin: 1.6%
    - Relative risk warfarin vs aspirin: 0.87

Importance of Time within Therapeutic Range
Patients Treated at Centers with TTR Below or Above 65%

![Graph](image1)

C+A: clopidogrel plus aspirin; OAC: oral anticoagulation therapy
RR: relative risk of stroke C+A vs OAC


Atrial Fibrillation Patients – 55% of Their Time in Therapeutic INR Range

![Graph](image2)

Major Hemorrhage in First Year of Warfarin Therapy


- 9 intracranial bleeds
- 3 fatal
- 8/9 age > 75

Warfarin Has a Narrow Therapeutic Window

Bleeding Risk Scores in AF

<table>
<thead>
<tr>
<th>ATRIA</th>
<th>HAS-BLED</th>
<th>HEMORR,G HAGES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia¹</td>
<td>Hypertension³</td>
<td>Hepatic⁸ or Renal disease²</td>
</tr>
<tr>
<td>Severe renal disease²</td>
<td>Abnormal Renal¹ or Liver function⁸</td>
<td>Ethanol abuse 1</td>
</tr>
<tr>
<td>Age ≥75 yrs</td>
<td>Stroke</td>
<td>Malignancy 1</td>
</tr>
<tr>
<td>Any prior hemorrhage</td>
<td>Bleeding</td>
<td>Older Age (&gt;75 yrs) 1</td>
</tr>
<tr>
<td>Hypertension³</td>
<td>Labile INR³</td>
<td>Reduced platelet number or function¹¹</td>
</tr>
<tr>
<td>E Elderly (&gt;65 yrs)</td>
<td>Drugs⁸ or Alcohol</td>
<td>Rebleeding¹² 2</td>
</tr>
</tbody>
</table>

1. Hemoglobin <13 g/dl men; <12 g/dl women
2. Estimated glomerular filtration rate <30 ml/min or dialysis-dependent
3. Office or institutional blood pressure >160 mmHg
4. Presence of clinical, radiologic, or renal ultrasonography or serum creatinine ≥200 mmol/L without nephrotic syndrome
5. Presence of chronic liver disease or cirrhosis, or biochemical or histologic evidence of significant hepatic derangement, eg elevated alanine aminotransferase or aspartate aminotransferase or alkaline phosphatase >3 x upper limit normal, or coexistent with hepatic encephalopathy or ascites
6. Presence of chronic, diagnosed or renal transplantation or serum creatinine ≥200 mmol/L
7. Chronic renal failure or renal transplantation or serum creatinine ≥200 mmol/L
8. Unstable/high INRs or poor time in therapeutic range (eg <60%)
9. Concomitant use of drugs, such as antiplatelet agents, non-steroidal anti-inflammatory drugs, or alcohol abuse etc.
10. Cirrhosis, two-fold or greater elevation of AST or ALT, or albumin <3.6 g/dl
11. Platelets <75,000, use of antiplatelet therapy (eg daily aspirin) or NSAID therapy; or blood dyscrasia
12. Prior hospitalization for bleeding
13. Prior hospitalization for stroke or prior hemorrhage <30 g/dl
14. CYP2C9*2 and/or CYP2C9*3
15. Alzheimer’s dementia, Parkinson’s disease, schizophrenia, or any condition predisposing to repeated falls

Avoiding CNS Bleeding During Antithrombotic Therapy

- Blood pressure, blood pressure, blood pressure...
- Older patients with cerebrovascular disease are at special risk
- Use the lowest efficacious INR
- Don’t add antiplatelet agents to warfarin unless clearly indicated

The Dilemma of Current Oral Anticoagulant Therapy

- Warfarin—narrow therapeutic window
- Time in therapeutic range
  - Influenced by many factors
  - Important metric for assessing efficacy
- INR monitoring
  - Important for safety and efficacy
  - Labor intensive, complex and inefficient
- Warfarin—high rate of adverse events leads to underutilization

An Ideal Anticoagulant

<table>
<thead>
<tr>
<th>Desired Characteristic</th>
<th>Practical Advantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid onset of action</td>
<td>No need for overlap with heparin</td>
</tr>
<tr>
<td>Wide therapeutic index</td>
<td>Increased safety</td>
</tr>
<tr>
<td>Minimal side effects</td>
<td>Improved compliance; less monitoring</td>
</tr>
<tr>
<td>Oral formulation</td>
<td>Convenient administration</td>
</tr>
<tr>
<td>Predictable anticoagulant response</td>
<td>Fixed-dose unmonitored treatment</td>
</tr>
<tr>
<td>No food or drug interaction</td>
<td>No need for monitoring</td>
</tr>
<tr>
<td>Availability of antidote</td>
<td>Able to reverse in case of bleeding or urgent surgery</td>
</tr>
<tr>
<td>Cost effective</td>
<td>Accessibility</td>
</tr>
</tbody>
</table>

Emerging Therapies
Factor Xa Inhibitors and Direct Thrombin Inhibitors

Tissue Factor/VIIa

X

IX

IXa

VIIa

Va

Xa

II

IIa

Fibrinogen

Fibrin

Idrabiotaparinux

Rivaroxaban
Betrixaban
Apixaban
YM150
DU-176b

Dabigatran
AZD-0837

Recently Approved Agents to Prevent Stroke in Atrial Fibrillation

• Dabigatran (Pradaxa®)
  -Direct Thrombin (Factor II) Inhibitor
  -dosage 150 bid

• Rivaroxaban (Xarelto®)
  -Factor X inhibitor
  -dosage 20 mg evening meal

Apixaban (Eliquis®)
  -5 mg BID

Cost of either drug ~$6.75-$10/d
Meta-analysis of Efficacy and Safety of New Oral Anticoagulants

Dabigatran, Rivaroxaban, Apixaban vs. Warfarin in AF patients

**All cause stroke/SEE**

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
<th>NOA</th>
<th>Warfarin</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY</td>
<td>0.98 (0.93, 1.02)</td>
<td>1396/5162</td>
<td>2526/9222</td>
<td>20.07</td>
</tr>
<tr>
<td>ROCKET AF</td>
<td>0.96 (0.93, 1.00)</td>
<td>2097/862</td>
<td>2597/890</td>
<td>37.22</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>0.81 (0.78, 0.85)</td>
<td>2726/1326</td>
<td>2693/691</td>
<td>26.20</td>
</tr>
<tr>
<td>Subtotal</td>
<td>0.78 (0.75, 0.81)</td>
<td>6792/5162</td>
<td>7732/2122</td>
<td>101.86</td>
</tr>
</tbody>
</table>

**Ischemic and unspecified stroke**

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
<th>NOA</th>
<th>Warfarin</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY</td>
<td>0.77 (0.73, 0.82)</td>
<td>1068/292</td>
<td>1426/222</td>
<td>27.29</td>
</tr>
<tr>
<td>ROCKET AF</td>
<td>0.91 (0.83, 1.01)</td>
<td>1067/882</td>
<td>1727/652</td>
<td>20.55</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>0.86 (0.80, 0.93)</td>
<td>1409/1576</td>
<td>1778/861</td>
<td>80.74</td>
</tr>
<tr>
<td>Subtotal</td>
<td>0.87 (0.83, 0.92)</td>
<td>4538/2722</td>
<td>5993/2119</td>
<td>101.86</td>
</tr>
</tbody>
</table>

**Hemorrhagic stroke**

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
<th>NOA</th>
<th>Warfarin</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY</td>
<td>0.90 (0.85, 0.95)</td>
<td>1245/756</td>
<td>4546/623</td>
<td>24.45</td>
</tr>
<tr>
<td>ROCKET AF</td>
<td>0.93 (0.87, 0.99)</td>
<td>2877/81</td>
<td>5979/82</td>
<td>34.84</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>0.81 (0.75, 0.87)</td>
<td>4081/20</td>
<td>7866/11</td>
<td>40.64</td>
</tr>
<tr>
<td>Subtotal</td>
<td>0.85 (0.80, 0.90)</td>
<td>2503/756</td>
<td>5122/82</td>
<td>101.86</td>
</tr>
</tbody>
</table>

**Major bleeding**

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
<th>NOA</th>
<th>Warfarin</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY</td>
<td>1.04 (0.98, 1.10)</td>
<td>3996/876</td>
<td>4241/632</td>
<td>35.85</td>
</tr>
<tr>
<td>ROCKET AF</td>
<td>1.02 (0.98, 1.06)</td>
<td>3857/111</td>
<td>3867/65</td>
<td>50.29</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>0.76 (0.71, 0.82)</td>
<td>2266/698</td>
<td>4043/62</td>
<td>32.11</td>
</tr>
<tr>
<td>Subtotal</td>
<td>0.85 (0.80, 0.90)</td>
<td>1212/876</td>
<td>1362/72</td>
<td>163.98</td>
</tr>
</tbody>
</table>

**Intracranial bleeding**

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
<th>NOA</th>
<th>Warfarin</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY</td>
<td>0.64 (0.58, 0.71)</td>
<td>5687/876</td>
<td>3862/632</td>
<td>26.13</td>
</tr>
<tr>
<td>ROCKET AF</td>
<td>0.60 (0.54, 0.66)</td>
<td>5727/111</td>
<td>3871/65</td>
<td>24.33</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>0.45 (0.40, 0.51)</td>
<td>1228/698</td>
<td>1426/62</td>
<td>29.24</td>
</tr>
<tr>
<td>Subtotal</td>
<td>0.65 (0.60, 0.70)</td>
<td>2212/876</td>
<td>2323/72</td>
<td>163.98</td>
</tr>
</tbody>
</table>

**GI Bleeding**

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
<th>NOA</th>
<th>Warfarin</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY</td>
<td>1.03 (0.99, 1.08)</td>
<td>1436/786</td>
<td>1345/632</td>
<td>30.09</td>
</tr>
<tr>
<td>ROCKET AF</td>
<td>1.01 (0.96, 1.07)</td>
<td>1547/111</td>
<td>1547/65</td>
<td>24.74</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>0.90 (0.85, 0.96)</td>
<td>1099/688</td>
<td>1193/65</td>
<td>21.17</td>
</tr>
<tr>
<td>Subtotal</td>
<td>0.96 (0.91, 1.01)</td>
<td>3662/786</td>
<td>3742/632</td>
<td>163.98</td>
</tr>
</tbody>
</table>

Pharmacokinetics of NOACs

<table>
<thead>
<tr>
<th></th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct factor inhibition</td>
<td>Xa</td>
<td>Ila</td>
<td>Xa</td>
</tr>
<tr>
<td>Bioavailability ($F_{rel}$)</td>
<td>80%</td>
<td>6%</td>
<td>80%</td>
</tr>
<tr>
<td>Peak action ($t_{max}$)</td>
<td>1–3 hr</td>
<td>1–3 hr</td>
<td>1–3 hr</td>
</tr>
<tr>
<td>Protein binding</td>
<td>84%</td>
<td>35%</td>
<td>92–95%</td>
</tr>
<tr>
<td>Renal clearance</td>
<td>25%</td>
<td>80%</td>
<td>33%</td>
</tr>
<tr>
<td>Elimination half life with creatinine clearance &gt; 80 ml/min</td>
<td>15.1 hr</td>
<td>13.8 hr</td>
<td>8.3 hr</td>
</tr>
<tr>
<td>Elimination half life with creatinine clearance 50–79 ml/min</td>
<td>14.6 hr</td>
<td>16.6 hr</td>
<td>8.7 hr</td>
</tr>
<tr>
<td>Elimination half life with creatinine clearance 30–49 ml/min</td>
<td>17.6 hr</td>
<td>18.7 hr</td>
<td>9.0 hr</td>
</tr>
<tr>
<td>Elimination half life with creatinine clearance &lt; 30 ml/min</td>
<td>17.3 hr</td>
<td>27.5 hr</td>
<td>9.5 hr</td>
</tr>
</tbody>
</table>

Coagulation Assays

<table>
<thead>
<tr>
<th>Coagulation Assays</th>
<th>Apixaban</th>
<th>Rivaroxaban</th>
<th>Dabigatran</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT</td>
<td>Not useful</td>
<td>Qualitative</td>
<td>Not useful</td>
</tr>
<tr>
<td>-dilute PT</td>
<td>Data n/a</td>
<td>Data n/a</td>
<td>Data n/a</td>
</tr>
<tr>
<td>-modified PT</td>
<td>Qualitative</td>
<td>Data n/a</td>
<td></td>
</tr>
<tr>
<td>aPTT</td>
<td>Not useful</td>
<td>Not useful</td>
<td>Qualitative</td>
</tr>
<tr>
<td>TT</td>
<td>No effect</td>
<td>No effect</td>
<td>Qualitative</td>
</tr>
<tr>
<td>-dTT/HEMOCLOT</td>
<td>No effect</td>
<td>No effect</td>
<td>Quantitative</td>
</tr>
<tr>
<td>Chromogenic Assays</td>
<td>Quantitative</td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td>-Anti-Xa</td>
<td>No effect</td>
<td>No Effect</td>
<td></td>
</tr>
<tr>
<td>-Anti-IIa</td>
<td>Quantitative</td>
<td>No Effect</td>
<td></td>
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</table>

n/a = not available

Reversal of NOACs
Suggestions for Reversal of New Oral Anticoagulants

<table>
<thead>
<tr>
<th></th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral activated charcoal</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Hemoperfusion with activated charcoal</td>
<td>Possible</td>
<td>Yes</td>
<td>Possible</td>
</tr>
<tr>
<td>Fresh frozen plasma</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Activated factor Vlla</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>3-factor PCC</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>4-factor PCC</td>
<td>Possible</td>
<td>Possible</td>
<td>Possible</td>
</tr>
</tbody>
</table>


Guidelines, Utilization, and Barriers
2011 ACCF/AHA/HRS Guidelines
Antithrombotic Therapy for Patients with Atrial Fibrillation

<table>
<thead>
<tr>
<th>Level of Risk</th>
<th>ACCP Recommendation</th>
<th>Alternative*</th>
<th>Not Recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk (CHADS&lt;sub&gt;2&lt;/sub&gt; = 0)</td>
<td>No Therapy</td>
<td>Aspirin</td>
<td>Oral anticoagulation or combination therapy with aspirin and clopidogrel</td>
</tr>
<tr>
<td>Intermediate Risk (CHADS&lt;sub&gt;2&lt;/sub&gt; = 1)</td>
<td>Oral anticoagulation</td>
<td>Aspirin with clopidogrel</td>
<td>Aspirin</td>
</tr>
<tr>
<td>High Risk (CHADS&lt;sub&gt;2&lt;/sub&gt; = 2)</td>
<td>Oral anticoagulation (dabigatran 150 mg b.i.d. vs. VKA**)</td>
<td>Aspirin with clopidogrel</td>
<td>Aspirin</td>
</tr>
</tbody>
</table>

*For patients with AF unsuitable for, or who refuse, oral anticoagulant (for reasons other than concerns about major bleeding)  
**VKA = adjusted-dose vitamin K antagonist

ACCP Guidelines
For patients with Nonrheumatic AF, including those with Paroxysmal AF

Clinical Challenges
With New Anticoagulants

• No validated tests to measure anticoagulation effect
• No established therapeutic range
• No antidote for most agents
• Assessment of compliance more difficult than with vitamin K antagonists
• Potential for unknown long-term adverse events
• Balancing cost against efficacy
• Lack of head-to-head studies comparing new agents


Stroke prophylaxis with warfarin or dabigatran for patients with non-valvular atrial fibrillation-cost analysis

n=402 followed in AC clinic for 19 months

Key points
• Cost of AC largely driven by drug price for dabigatran and quality of INR control for warfarin.
• Cost of dabigatran to prevent one stroke per year is about four to five times that of warfarin.
• Majority of patients on warfarin therapy are not troubled by frequent blood testing.

Age and Ageing Advance Access published February 28, 2012
Optimal Candidates for New Drugs

Patients who:

- Find **INR testing burdensome**
- Despite adherence to provider recommendations, have **low ‘time-in-range’**
- Can **afford** (or arrange to get) the new drugs
- Have **normal renal function**

Optimal Candidates for Warfarin

Patients who:

- Have (borderline) **renal insufficiency**
- Are **taking stable dose of warfarin** and do not find INR testing burdensome
- Have **access to self-testing** machine
- Are concerned about the **lack of** an evidence-based **reversal** strategy
**Why Do Patients with AF Not Receive Warfarin?**

*A review of physician surveys showed:*
- Perceived risk > benefit
- Patients unreliable
- Difficulty of maintaining therapeutic INR

**Barriers: Physician Perceptions**
- Physicians underestimate risk of stroke and overestimate risk of bleed
- Physicians believe patients will refuse therapy, but when surveyed, patients overwhelmingly choose therapy to avoid stroke

**Barriers: Health System**
- Monitoring therapy was inconvenient
- Physicians wanted someone else to manage therapy

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**Strategies to Reduce Practice Gaps in Anticoagulation Management for Patients with AF**

**System-level strategies**

- Increasing the number of anticoagulant clinics
- Increasing physician reimbursement for anticoagulant monitoring
- Reminders about stroke risk with AF
- Pharmacist flagging of non-anticoagulated patients with AF

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Strategies to Reduce Practice Gaps in Anticoagulation Management for Patients with AF

Patient and physician strategies

• Online warfarin dosing calculators to assist with warfarin initiation
• Patient information about warfarin
• Decision aids
• Ongoing patient education to reinforce long-term adherence with therapy
• Patient self-monitoring or self-management of anticoagulation with Internet-based warfarin dosing programs for patients


Summary

• AF-projected to affect > 5 million Americans by 2050
• AF increases the risk of stroke by ~5 fold
• Risk factors for stroke include age > 75 years, prior stroke/TIA, CHF, hypertension, and DM
• Anticoagulation therapy reduces the risk of stroke by ~64% and death by ~25%; antiplatelet therapy reduces the risk of stroke by ~22%
• Warfarin—narrow therapeutic window of effectiveness and safety
• Strategies improving warfarin utilization should be associated with improved patient outcomes
• New therapies for stroke prevention in AF-direct thrombin inhibitors, factor Xa inhibitors, are effective, reduce ICH, more costly