Antithrombotic/Anticoagulation Therapies in Special Populations: New and Evolving Treatments

2012 NMQF Leadership Summit on Health Disparities/CBC Spring Health Braintrust

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Objectives

• Describe risk factors and stroke in atrial fibrillation (AF)
• Discuss morbidity and mortality associated with stroke in AF
• Recognize race/ethnicity and antithrombotic/anticoagulation therapy with older and newer agents
A Visual Representation of AF
Atrial Fibrillation

- A. AF impulses
- B. Chaotic signals through AV node
- C. Rapid ventricular impulses

Abbreviation: AV, atrioventricular

http://www.mayoclinic.com/health/medical/IM02486
Electrocardiogram (EKG) with AF

Irregular, irregular rhythm
Significance of AF

- AF a chronic, progressive cardiac disease
- AF most common arrhythmia
  - US prevalence estimated at 2-3 million
- AF interconnected with other common CV problems
- AF associated increased stroke, heart failure, and all-cause mortality
AF and Stroke

Stroke most common and devastating complication of AF

AF independent risk factor for stroke
–Risk increases with age;
–Over half all strokes patients >75 years
–Stroke risk persists even asymptomatic AF

AF: Common but Serious Arrhythmia

- Increase stroke risk similar for paroxysmal, persistent and permanent AF
- Strokes with AF usually more severe than from other causes, conferring increased risk of morbidity, mortality and poor functional outcome

AF-Associated Morbidity and Mortality

AF Risk Increases

Death: 1.5-1.9-fold ↑ in risk

Thromboembolism/ Stroke: 4.5-fold ↑ in risk

Hospitalization: 2-3-fold ↑ in risk
AF/AFL All-Cause Mortality

All-Cause Mortality

<table>
<thead>
<tr>
<th>AF/AFL</th>
<th>RR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes/No</td>
<td>2.42 (2.11-2.77)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Cumulative Event Rate

Years to Death

Number at risk

AF/AFL | 334 | 316 | 375 | 465 | 461 | 351 | 227 | 39
No AF/AFL | 27,247 | 26,768 | 25,997 | 25,037 | 22,164 | 13,183 | 6,664 | 833

Incidence of AF:
Framingham and Cardiovascular Health Study

Fuster, V. et al. J Am Coll Cardiol 2011;57:e101-e198:
2011 ACCF/AHA/HRS Focused Update Atrial Fibrillation Guideline
Prevalence of AF African Americans (mean age 67) and Whites (mean age 74) hospitalized heart failure

Race/Gender-Specific AF Incidence Rates in the ARIC Study

High Stroke Rate with Lower Prevalence AF in Blacks: the AF Paradox

- Epidemiological studies consistently demonstrate prevalence AF lower among blacks vs. whites.
- Large, cross-sectional study N=430,417 AF 8.0% whites vs. 3.8% blacks.
- The AF paradox - same studies prevalence of hypertension and other classical AF risk factors consistently higher in blacks

AF Paradox

• One suggestion: AF is not diagnosed as frequently or as sensitively in blacks; reflection of unequal access to healthcare?
• Another explanation: different disease subtypes, i.e. paroxysmal AF may occur more often in blacks, reducing Dx likelihood
AF Paradox

• Suggested survival bias: patients who die from AF selectively excluded from trials.

• Possibly explanation: AF a highly complex disease, result of several risk factors.

• Thus, although blacks have HTN, disproportionately also low level CAD among blacks.
Genetics appear major role in AF: analysis of the ARIC and CHS studies demonstrating that for every 10% increase in European ancestry among African Americans, the risk of incident AF increased by 13%.

Atrial Fibrillation

A. AF impulses

B. Chaotic signals through AV node

C. Rapid ventricular impulses

Abbreviation: AV, atrioventricular
Left Atrial Thrombus in Afib Patient

A. Left Atrium

B. Left Atrial Appendage Clot

Evidence-Based Clinical Practice Guidelines:
American College of Chest Physicians
Therapy and Prevention of Thrombosis,
9th Executive Summary

• Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel
• Guyatt, G. et al
• Chest 2012;141;7S-47S
Stroke Prevention

• Pharmacologic
  - Warfarin
  - Aspirin
  - Thrombin and Factor Xa Inhibitors

• Non-pharmacologic
  - Removal/isolation LA appendage
Risk of Stroke in Nonrheumatic AF

Participants Stratified by CHADS$_2$ Score

- CHADS$_2$ Index
  - CHF  1 point
  - HTN  1 point
  - Age >75 y  1 point
  - DM  1 point
  - Stroke/TIA 2 points

<table>
<thead>
<tr>
<th>Score</th>
<th>Annual Risk*</th>
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<tr>
<td>0</td>
<td>1.9%</td>
</tr>
<tr>
<td>1</td>
<td>2.8%</td>
</tr>
<tr>
<td>2</td>
<td>4.0%</td>
</tr>
<tr>
<td>3</td>
<td>5.9%</td>
</tr>
<tr>
<td>4</td>
<td>8.5%</td>
</tr>
<tr>
<td>5</td>
<td>12.5%</td>
</tr>
<tr>
<td>6</td>
<td>18.2%</td>
</tr>
</tbody>
</table>

*N=1733

The coagulation cascade

- **Amplification of coagulation cascade**
  - FVIIa/TF Initiation
  - FXa/Va

- **Propagation**
  - FXIa

- **Limits thrombus growth**

- **Thrombus formation and stabilisation**

- **Platelets**

- **Thrombin Activatable Fibrinolysis Inhibitor**

- **Factor**

- **Fibrinolysis**

- **Thrombin**
Direct Factor Xa inhibition

- XIIa
- XIa
- IXa
- VIIa

Factors involved:
- Tissue factor
- Rivaroxaban
- Apixaban

Processes:
- Factor II (prothrombin)
- Fibrinogen
- Fibrin clot
The role of thrombin in coagulation

- Thrombin is a central player in thrombus formation.
- Thrombin converts fibrinogen to fibrin – an essential step in thrombus (clot) formation.
- Thrombin is the single most potent stimulus for platelet activation.
- Even small amounts of thrombin can activate factors V and VIII, thereby triggering additional thrombin generation.
Warfarin

Substantial risk of major bleedings (approximately 1.2% /year)

Warfarin

- Effective
- Reversible
- Inexpensive
- Slow onset of action
- Regular monitoring
- Food interaction
- Medication interaction
- Difficult titration—regular dose adjustments

Food sources of vitamin K include cabbage, cauliflower, spinach and other green, leafy vegetables, as well as cereals.
Clinician barriers to effective anticoagulation include:

- underestimation of warfarin benefit
- overutilization of aspirin as a warfarin alternative
- overestimation of patient fall risk.
Limitations of warfarin

- Narrow therapeutic window
- Wide variation in metabolism, with numerous food and drug interactions
- Need for regular coagulation monitoring and dose adjustment
- Slow onset/offset
Disadvantages of warfarin

- Clinical application limited to only 50% of indicated population.
- Despite frequent lab monitoring, up to 50% patients not maintained within narrow therapeutic window

Disadvantages of warfarin


Narrow therapeutic window
Genetic Variation between Individuals Affects Warfarin Dose

- Required to maintain stable INR - race/ethnicity data now available.
- Two main genetic factors influencing warfarin requirements:
  - mutations cytochrome P450 2C9 hepatic microsomal enzyme responsible for oxidative metabolism more potent warfarin S enantiomer
  - Vitamin K oxide reductase complex 1 (VKORC1) gene - main target for warfarin.
Ethnic Differences in Variant Allele Frequencies for Genes Important to Variable Warfarin Dose (CYP2C9 and VKORC1)

<table>
<thead>
<tr>
<th>Variant</th>
<th>Whites</th>
<th>Blacks</th>
<th>Asians</th>
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<tbody>
<tr>
<td>CYP2C9*2</td>
<td>8% to 18%</td>
<td>Rare</td>
<td>Rare</td>
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<tr>
<td>CYP2C9*3</td>
<td>5% to 13%</td>
<td>1% to 2%</td>
<td>2% to 5%</td>
</tr>
<tr>
<td>Others</td>
<td>Rare/absent</td>
<td>2% to 4%</td>
<td>Rare/absent</td>
</tr>
<tr>
<td>VKORC1 variant</td>
<td>35% to 45%</td>
<td>8% to 10%</td>
<td>90% to 95%</td>
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</table>

*Circulation. 2008;118:1383-1393*
Warfarin and Genetics

- Different effects in non-whites: blacks requiring higher doses for efficacy and Asians requiring lower doses.
- Differences response to warfarin may result in increased ICH among non-whites.
- Dosing algorithms based on genotypes prevalent in mostly whites cannot be routinely applied to blacks.
- Hispanics, although heterogeneous, similar warfarin genotypic profiles to whites.

New Oral Anticoagulants

- Do not require monitoring & at least as effective and safe as warfarin
- Although pharmacokinetics in these agents not require dose adjustment based on race/ethnicity, hints emerging efficacy and safety not same across all racial subgroups.
- For instance, a higher rate of ICH observed with rivaroxaban in black and Asian patients in ROCKET trial.

ACCF/AHA/HRS Focused Update

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

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Jonathan L. Halperin, MD, FACC, FAHA*; Juan Luis Tamargo, MD, FESC*; G. Neal Kay, MD, FACC*;
L. Samuel Wann, MD, MACC, FAHA, FESC*
2011 ACCF/AHA/HRS Focused Update on the Management of Patients With Atrial Fibrillation (Update on Dabigatran)

A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

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§Recused from voting on Section 8.1.4.2.5, Recommendation for Use of Oral Direct Thrombin Inhibitor Anticoagulant Agents.
||ACCF/AHA Task Force on Practice Guidelines Liaison.

March 2011
Dabigatran Etexilate Pharmacology

Inhibits coagulation by preventing thrombin-mediated effects, including cleavage of fibrinogen to fibrin monomers, activation of factors V, VIII, XI and XIII, and inhibition of thrombin-induced platelet aggregation.
Dabigatran Etexilate
Prescription Information

• Dosing
  – Oral: 150mg twice daily

Renal impairment:
  • Clcr 15-30 mL/min: 75mg twice daily
  • Clcr <15 mL/min: no recommendation

Hepatic impairment: No adjustment required
Dabigatran Exetilalte Pharmacokinetics

Bereznicki et al New antithrombotics for atrial fibrillation. Cardiovascular Therapeutics 2010 (28) 278–286

Dabigatran etexilate (BIBR 1408)

Absorption

Bioavailability ~7.2%

Microsomal carboxylesterases

Thrombin

Free thrombin

Inhibition

Inhibition

Inhibition

Renal excretion accounts for 80% of dabigatran clearance

Berezniicki et al New antithrombotics for atrial fibrillation. Cardiovascular Therapeutics 2010 (28) 278–286

Fig. 2. Pharmacology of dabigatran etexilate.
Dabigatran Etexilate Adverse Effects

- GI adverse reactions (35% vs. 24% on warfarin).
- These were commonly dyspepsia (including abdominal pain, discomfort, and epigastric discomfort) and gastritis-like Sx (including GERD, esophagitis, erosive gastritis and hemorrhage, ulcer).
Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Salim Yusuf, F.R.C.P.C., D.Phil., John Eikelboom, M.D., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeanne Varrone, M.D., Susan Wang, Ph.D., Marco Alings, M.D., Ph.D., Denis Xavier, M.D., Jun Zhu, M.D., Rafael Diaz, M.D., Basil S. Lewis, M.D., Harald Darius, M.D., Hans-Christoph Diener, M.D., Ph.D., Campbell D. Joyner, M.D., Lars Wallentin, M.D., Ph.D., and the RE-LY Steering Committee and Investigators*

ABSTRACT

BACKGROUND

Warfarin reduces the risk of stroke in patients with atrial fibrillation but increases the risk of hemorrhage and is difficult to use. Dabigatran is a new oral direct thrombin inhibitor.

METHODS

In this noninferiority trial, we randomly assigned 18,113 patients who had atrial fibrillation and a risk of stroke to receive, in a blinded fashion, fixed doses of dabigatran — 110 mg or 150 mg twice daily — or, in an unblinded fashion, adjusted-dose warfarin. The median duration of the follow-up period was 2.0 years. The primary outcome was stroke or systemic embolism.

RESULTS

From the Population Health Research Institute, McMaster University and Hamilton Health Sciences, Hamilton, ON, Canada (S.J.C., S.Y., J.E., J.P., E.T.); Lankenau Institute for Medical Research and the Heart Center, Wynnewood, PA (M.D.E., A.P.); Uppsala Clinical Research Center, Uppsala, Sweden (J.O., L.W.); Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT (P.A.R., J.V., S.W.); Working Group on Cardiovascular Research the Netherlands, Utrecht, the Netherlands (M.A.); St. John’s National Academy of Health Sciences, Bangalore, India (D.X.); FuWai Hospital, Beijing (J.Z.); Estudios Clínicos Latinoamérica, Rosario, Argentina (R.D.); Lady

*For all authors, see list on page 1010.
RELY Trial Information

• Results
  – Rate of MI higher with both dabigatran groups than warfarin group
  – Rate of major bleeding or life-threatening bleeding higher with warfarin than with either 110mg or 150mg dabigatran.
  – Significantly higher rate major GI bleeding with dabigatran at 150mg dose than with warfarin

### Table 2  Recommendation for emerging antithrombotic agents

<table>
<thead>
<tr>
<th>2011 Focused update recommendation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class I</strong></td>
<td></td>
</tr>
<tr>
<td>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 (creatinine clearance $&lt;15$ mL/min) or advanced liver disease (impaired baseline clotting function). $^3$ (Level of Evidence: B)</td>
<td>New recommendation</td>
</tr>
</tbody>
</table>
Should dabigatran be used?

• Advantage of wide therapeutic window, but compliance may influence safety and efficacy
• Need of twice daily dosing may increase nonadherence
• No specific antidote yet to reverse antithrombotic activity
• Safety and efficacy with renal & hepatic impairment?
• Safety and efficacy patients at high risk of bleeding?

Terry K W et al. Dabigatran etexilate versus warfarin as the oral anticoagulant of choice? A review of clinical data
Rivaroxaban
Human Factor Xa/rivaroxaban complex

Oral, direct Factor Xa inhibitor, high selectivity for Factor Xa

Roehrig et al., J Med Chem 2005; Perzborn et al., J Thromb Haemost 2005
Primary Efficacy Outcome

Stroke and non-CNS Embolism

No. at risk:
Rivaroxaban  6958  6211  5786  5468  4406  3407  2472  1496  634
Warfarin     7004  6327  5911  5542  4461  3478  2539  1538  655

Event Rates are per 100 patient-years
Based on Protocol Compliant on Treatment Population

HR (95% CI): 0.79 (0.66, 0.96)
P-value Non-Inferiority: <0.001
ROCKET AF Summary

Efficacy:
- Rivaroxaban non-inferior to warfarin for prevention stroke and non-CNS embolism
- Superior to warfarin while patients taking study drug
- By intention-to-treat, rivaroxaban non-inferior to warfarin but not superior

Safety:
- Similar rates bleeding and adverse events
- Less ICH and fatal bleeding with rivaroxaban

Conclusion: rivaroxaban proven alternative to warfarin for moderate or high risk AF patients
Rivaroxaban Black Box Warning

- DISCONTINUING IN PATIENTS RIVAROXABAN WITH NONVALVULAR ATRIAL FIBRILLATION
- Places patients at an increased risk of thrombotic events.
- If rivaroxaban discontinued for a reason other than pathological bleeding, consider administering another anticoagulant
Who should remain on warfarin?

- Patient already receiving warfarin and stable whose INR is easy to control
- If dabigatran, rivaroxaban, apixaban (not approved) not available
- Cost
- If patient not likely to comply with twice daily dosing (dabigatran)
- Chronic kidney disease (GFR < 15 ml/min)
Summary

• AF is a complex, costly, progressive and often debilitating disease

• AF can be present with, be affected by, and serve as a contributing factor in a wide range of CV conditions

• Associated with increased long-term risk of stroke, heart failure and all-cause mortality
Newer anticoagulants are challenging warfarin for prevention of stroke in AF

Dabigatran, direct thrombin inhibitor, and rivaroxaban, oral direct factor Xa inhibitor, approved for prevention of stroke in NVAF
Summary

- Newer anticoagulants do not require regular testing INR, as with warfarin
- Patients difficult to maintain in therapeutic INR range may be good candidates for a newer agent
- Educational efforts surrounding warfarin in past decades will need to be repeated for the newer agents
Thank You!