Atrial Fibrillation Related Stroke

Robert W. Stein, M.D.
Disclosures

• No financial interest in any of the medications discussed.
• No conflicts of interest
• No off label use recommendations of unlabeled or unapproved drugs or devices
• I am a board certified vascular neurologist, medical director of a JC Primary Stroke Center, and medical director of the PBMC Anticoagulation Service.
Atrial Fibrillation: An Epidemic

• Over nine million people in the EU and the US (6) suffer from atrial fibrillation
• One in four people aged 40 years or older develop atrial fibrillation
• The number of people with atrial fibrillation is expected to double by 2050 to 18 - 20 million (15 – US)
• Prevalence increases by age from 1% between 60-65 years and 10% > 85 years
Who is Interested in AF and Stroke?

- American Heart Association / American Stroke Association – guidelines for treatment, data collection, education
- CMS – Hospital Quality Clinical Measure
- Joint Commission – one of 8 quality measures used to certify Primary Stroke Centers. The JC’s Sentinel Event Database showed that 7.2% of all adverse medications from January 1997 to December 2007 were related to anticoagulants, the type of medication used to prevent stroke in AF.
- Major pharmaceutical companies – hundreds of millions dollars in drug development, research, and marketing.
H. RES. 295

Promoting increased awareness, diagnosis, and treatment of atrial fibrillation to address the high morbidity and mortality rates and to prevent avoidable hospitalizations associated with this disease.

IN THE HOUSE OF REPRESENTATIVES

JUNE 2, 2011

Ms. Granger (for herself, Mr. Gonzalez, and Mr. Ruppersberger) submitted the following resolution; which was referred to the Committee on Energy and Commerce

RESOLUTION
House Resolution #295

- Bill to promote increased awareness, diagnosis, and treatment of atrial fibrillation to address the high morbidity and mortality rates and to prevent avoidable hospitalizations associated with this disease.
- Rep Kay Granger Texas and 42 cosponsors in House
- Senate passed this resolution unanimously
- Referred to House Subcommittee on Health where it stalled.
Atrial Fibrillation

• Irregular heart rate with ventricular contraction not preceded by atrial contraction.

• Atria contract at an excessively high rate and in an irregular way

• Normal rhythmic contractions of the cardiac atria are replaced by rapid irregular twitching of the muscular wall; the ventricles respond irregularly to the dysrhythmia bombardment from the atria
AF

• Loss of organized atrial electrical and mechanical activity
• Stasis of blood within the body of the atria and especially within the left atrial appendage. Left atrial appendage has a complex structure that includes small cul-de-sacs that allow blood stasis and thrombosis in the absence of mechanical contractions.
• Ejection velocity in the left atrial appendage is markedly depressed (<20 cm/sec) in patients with atrial fibrillation
• Risk of thrombus formation is inversely related to the left atrial appendage ejection velocity.
• Atrial fibrillation is associated with a hypercoagulable state.
Human atria, with ventricles removed.

Cardiac abnormalities associated with AF

- Hypertension
- Coronary artery disease
- Valvular heart disease
- Congestive heart failure
- Cardiomyopathy
- Pericarditis
- Congenital heart disease
- Cardiac surgery
Non cardiac abnormalities associated with AF

• Pulmonary embolism
• Chronic obstructive pulmonary disease (COPD)
• Obstructive sleep apnea
• Hyperthyroidism
• Obesity
Complications of AF

Embolic
  Stroke
  Systemic Embolism

Hemodynamic
  Fatigue
  Shortness of Breath
  Palpitations
  CHF
Stroke types

Ischemic Stroke

Clot

Hemorrhagic Stroke

Brain artery

Break in artery wall

Bleeding
Atherosclerosis of Artery
Atherosclerosis of Artery
Embolo in cerebral artery
Major types of cerebrovascular disease and their frequency

Harvard Stroke Series 756 patients
Atherosclerotic thrombosis (large vessel) - 32%
Lacunae- (small vessel) - 18%
Embolism (heart to artery) - 32%
Primary Intracerebral hemorrhage – 11%
Ruptured aneurysms/vascular malformation-7%
Hemorrhagic stroke
Right basal ganglia
Hypertensive ICH

Hypertensive Intracerebral Hemorrhage
Ischemic Stroke

Early Imaging studies: Normal CT Brain Scan/Abnormal MRI Brain Scan
Basic Pathophysiology of Ischemic Stroke

- Brain ischemia occurs when blood flow to part of the brain is disrupted.
- Survival of brain tissue depends on length of time brain is deprived of oxygen and glucose.
- Infarction occurs when areas of brain suffer irreversible changes because of prolonged interruption of blood flow.
Basic Pathophysiology of Ischemic Stroke

- Cells in center of infarcted tissue die.

- There is a zone of hypoperfused tissue around the core of infarction which represents tissue that is potentially salvageable if reperfusion occurs within a short period of time.

- This zone of tissue is termed the ischemic penumbra.
Cerebral perfusion and ischemia

• The head is about 10% of body weight but it receives about 25% of the cardiac output.
• The brain is exquisitely vulnerable to interruptions of supply of oxygen and glucose.
• Cerebral blood flow determines the amount of oxygen and glucose delivered.
# Cerebral Blood Flow

<table>
<thead>
<tr>
<th>CBF ml/100g/min</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>55</td>
<td>normal</td>
</tr>
<tr>
<td>23-55</td>
<td>no effect</td>
</tr>
<tr>
<td>12-23</td>
<td>reversible deficit</td>
</tr>
<tr>
<td>&lt;12</td>
<td>infarction</td>
</tr>
</tbody>
</table>
Ischemic Penumbra: The Basis of acute stroke treatment

• Region of tissue where CBF is in 12-23ml/100g/min. “Stunned” but salvageable.

• Ischemic penumbra = marginally perfused tissue. Cells can survive if perfusion restored.

• All stroke will have some tissue which is irreversible damaged but there will be variable amounts of tissue marginally perfused which can contain viable neurons.

• Acute treatment of stroke attempts to restore blood flow.
Transient Ischemic Attack (TIA)

- “Mini-stroke” or warning stroke
- Same mechanism as ischemic stroke
- Same symptoms as stroke
- Different from stroke in that symptoms clear within minutes to hours.

Even if deficits resolve within hours, brain damage can occur. It is estimated that one third of TIAs would be considered as infarctions on the basis of DW-MRI findings.
Cardiac Abnormalities which can produce emboli and subsequently embolic stroke

- Atrial Fibrillation
- MI with mural thrombus
- Acute and subacute bacterial endocarditis
- Cardiomyopathy with akinetic segment or decreased ejection fraction
- Complication of cardiac surgery
- Valve prosthesis
- Nonbacterial thrombotic endocardial vegetations
- Prolapsed mitral valve
- Paradoxical embolus with patent foramen ovale
- Myxoma
Characteristics of embolic infarctions

• Embolus usually arrested at bifurcation or site of natural narrowing of the lumen.
• Any region of brain affected – superior division (upper trunk) of middle cerebral artery most common.
• Two hemispheres equally effected.
• Embolus usually breaks up within 48 hours after producing its damage.
• It is said that 75% of cardiogenic emboli end up in brain. It is not that the brain is a magnetic for emboli. Only 25% of cardiac output goes to brain.
• High frequency of clinically evident emboli is related to sensitivity of brain to ischemia and the difficulty identifying systemic none cerebral emboli.
Clinical Picture of Cerebral Embolism

• Donor source (heart) to recipient artery (a cerebral artery). In AF source is clot within left atrial appendage or atrium.
• Sudden maximal at onset deficit.
• Not preceded by stereotyped TIA. Deficits in other vascular territories.
• “Spectacular shrinking deficit.” Sudden complete or near complete resolution of severe neurologic deficit as embolus breaks up. tPA can help produce this effect.
• 4/5 embolic strokes anterior circulation = portion of cerebral blood flow in anterior circulation.
• 1/5 embolic stroke in posterior circulation = portion of cerebral blood flow in posterior circulation.
Clinical feature of embolic infarction

- Wedged shaped infarcts
- Multiple infarcts in different vascular territories.
- Can see hyperdense artery (often MCA) on CT scan
- Can have petechial hemorrhages, frank hemorrhage, or be just pale infarcts. Hemorrhage occurs because of lysis of the clot and reperfusion of dead ischemic tissue.
Hyperdense Middle Cerebral Artery Sign
Hyperdense MCA sign
Characteristics of AF related stroke

- More severe strokes
- Greater mortality
- Longer hospital stays
- Increased disability
- Significant risk of recurrent stroke if not treated.
- Presence of AF is an independent risk factor for stroke conferring a 5 fold increase in stroke risk.
- The increase in risk of stroke is similar for paroxysmal, persistent, permanent, asymptomatic AF.
Echocardiographic finding that predict increased risk of brain embolism in AF

- Thrombi seen in left atrium and atrial appendage
- Left atrial enlargement
- Mitral annulus calcification
- Left ventricular dysfunction
- Spontaneous echo contrast (smoke) in left atrium = interaction of plasma proteins and erythrocytes at low sheer rates. Marker of stasis in left ventricle.
Stroke Mortalities
3 year period

- 30 deaths related to acute stroke
- 11 hemorrhages
- 19 ischemic strokes
  - 15 had atrial fibrillation. Only 1 was on warfarin. 14 either did not want to be on an anticoagulant, felt to have a contraindication to warfarin, or found for the first time to have AF.
    - 4 had large vessel occlusion
    - AF stroke is deadly and patients are under treated with warfarin
Treatment options to prevent clot formation in AF

**Antithrombotics**
ASA 80-325 mg
ASA 80 mg plus Clopidogrel

**Anticoagulants**
Warfarin (INR 2-3)
Dabigatran (Pradaxa)
Rivaroxaban (Xarelto)
Apixaban (Eliquis)
Risk stratification of stroke in AF:
What is the chance that someone with AF will have a stroke? Bleed from RX?

• CHADS2 –CHF/Hypertension/age >75/ Diabetes / prior Stroke

• CHA2DS2VASc- CHF /hypertension /age >75-2/ Diabetes /Stroke / Vascular disease / age 65-74/ female sex

• HAS-BLED score – score for bleeding risk – Hypertension / abnormal renal function / abnormal liver function / stroke / bleeding tendency / labile INR / age >65 / antiplatelet drugs /alcohol use
Stroke Risk Stratification in AF

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Points</th>
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<tbody>
<tr>
<td>C</td>
<td>Recent Congestive heart failure exacerbation</td>
</tr>
<tr>
<td>H</td>
<td>Hypertension</td>
</tr>
<tr>
<td>A</td>
<td>Age ≥ 75 years</td>
</tr>
<tr>
<td>D</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>S</td>
<td>Prior history of Stroke or transient ischemic attack</td>
</tr>
</tbody>
</table>
CHADS 2 Risk Score:
Low 0-1
Moderate-High 2 or greater

<table>
<thead>
<tr>
<th>Score</th>
<th>Stroke (%/year)</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>1.9</td>
</tr>
<tr>
<td>1</td>
<td>2.8</td>
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<tr>
<td>2</td>
<td>4.0</td>
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<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>
# CHA$_2$DS$_2$-VASc

## 2009 Birmingham Schema Expressed as a Point-Based Scoring System

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure/LV dysfunction</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥ 75 y</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Stroke/TIA/TE</td>
<td>2</td>
</tr>
<tr>
<td><strong>Vascular disease</strong></td>
<td></td>
</tr>
<tr>
<td><em>(prior myocardial infarction, peripheral artery disease, or aortic plaque)</em></td>
<td>1</td>
</tr>
<tr>
<td>Age 65-74 y</td>
<td>1</td>
</tr>
<tr>
<td><strong>Sex category</strong></td>
<td></td>
</tr>
<tr>
<td><em>(i.e. female gender)</em></td>
<td>1</td>
</tr>
</tbody>
</table>

LV = left ventricular; TE = thromboembolism

## CHA2Ds-VASc Risk

<table>
<thead>
<tr>
<th>Score</th>
<th>Stroke (%/year)</th>
</tr>
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<tbody>
<tr>
<td>» 1</td>
<td>0</td>
</tr>
<tr>
<td>» 2</td>
<td>1.3</td>
</tr>
<tr>
<td>» 3</td>
<td>2.2</td>
</tr>
<tr>
<td>» 4</td>
<td>4.0</td>
</tr>
<tr>
<td>» 5</td>
<td>6.7</td>
</tr>
<tr>
<td>» 6</td>
<td>9.8</td>
</tr>
<tr>
<td>» 7</td>
<td>9.6</td>
</tr>
<tr>
<td>» 8</td>
<td>6.7</td>
</tr>
<tr>
<td>» 9</td>
<td>15.2</td>
</tr>
</tbody>
</table>
HAS-BLED Score for risk of hemorrhage while treated with warfarin for AF

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (&gt;160 systolic)</td>
<td>1</td>
</tr>
<tr>
<td>Impaired renal function (creat&gt;2.3)</td>
<td>1</td>
</tr>
<tr>
<td>Impaired liver function</td>
<td>1</td>
</tr>
<tr>
<td>Hx of stroke</td>
<td>1</td>
</tr>
<tr>
<td>Hx of bleeding</td>
<td>1</td>
</tr>
<tr>
<td>Labile INRs</td>
<td>1</td>
</tr>
<tr>
<td>65 years</td>
<td>1</td>
</tr>
<tr>
<td>Drugs (antiplatelet, non steoidal)</td>
<td>1</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>1</td>
</tr>
</tbody>
</table>
HAS-BLED: Risk of major bleeding with anticoagulation

<table>
<thead>
<tr>
<th>Score</th>
<th>Major bleeding (%/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.13</td>
</tr>
<tr>
<td>1</td>
<td>1.02</td>
</tr>
<tr>
<td>2</td>
<td>1.88</td>
</tr>
<tr>
<td>3</td>
<td>3.74</td>
</tr>
<tr>
<td>4</td>
<td>8.7</td>
</tr>
<tr>
<td>5</td>
<td>12.5</td>
</tr>
<tr>
<td>6</td>
<td>Or greater no data available</td>
</tr>
</tbody>
</table>

Major bleeding: intracranial, hospitalization, hemoglobin decrease > 2 g/L, and/or transfusion
Treatment options to prevent clot formation in AF

Antithrombotics
ASA 80-325 mg
ASA 80 mg plus Clopidogrel

Anticoagulants
Warfarin (INR 2-3)
Dabigatran (Pradaxa)
Rivaroxaban (Xarelto)
Apixaban (Eliquis)
Risk Stratification

• Decision to prescribe an anticoagulant for a patient with AF is based upon assessing the risk (hemorrhage) and benefits (stroke prevention) of the anticoagulation and individualizing it to the patient and the patient’s preference.

• No one right answer.

• Multiple options and the patient needs to consider and decide what is right for them.
ASPRIN

- CHADS2=0 or 1
- 81 mg to 325mg PO daily
- Lower risk for bleeding than warfarin
- No need to check INRs etc
- Lower risk of major bleeds in patients who are a fall risk
- Higher risk of stroke than anticoagulants
ASA + Clopidogrel
CHAD2 = 1 or 2

• If not a candidate for warfarin or other anticoagulant then ASA plus clopidogrel can reduce stroke risk greater than ASA alone

• Risk for major bleeding increased
Warfarin

- Vit K antagonist
- Production of coagulation factors II, VII, IX, X impaired in the liver
- Rapidly absorbed. ½ life of 36 hours.
- Genetic variability (vit K epoxide reductase enzyme and CYP2C9) results in dose variability among individuals.
- Drugs can reduce GI absorption or interfere with metabolic clearance
- Drugs can inhibit synthesis or increase clearance of Vit k dependent factors
- Dietary intake of Vit K can impact anticoagulant effect of warfarin
Schematic representation of the coagulation cascade including our improved understanding of the role of the tissue factor (TF) pathway in initiating clotting; interactions between pathways; and the role of thrombin in sustaining the cascade by feedback activation of coagulation factors.

HK: high-molecular-weight kininogen; PK: prekallikrein; PL: phospholipid; PT: prothrombin; TH: thrombin.

Adapted from Ferguson et al, Eur Heart J 1998; Suppl 19:8.
Warfarin for AF

CHADS2 score 1 warfarin depending on patient and physician preference.

- For CHADS2 score 2 or greater.
- Goal INR= 2 to 3
- Must monitor INRs regularly
- Can be dangerous if fall risk or bleeding risk high
Warfarin for AF

• Therapeutic range INR 2-3
• Time in therapeutic range (TTR) is the computed percentage of time the patient spends within the prescribed range.
• Good anticoagulation control is associated with a reduction of stroke and hemorrhage risk.
• Time spent in TTR correlates with efficacy of prevent of stroke. In an UK General Practice Research Database study patients who spent 70% of time within TTR had a 79% reduced risk of stroke compared to patients with <30% of TTR. Mortality rates were also lower with TTR of at least 70%.
• If TTR can not be maintained > 65%, then most anticoagulation services feel that the risk benefit ratio for warfarin shifts to finding an alternative treatment strategy.
• Typical goal for an anticoagulation service TTR is 70-80% to optimize benefits and reduce harm for patients.
Time in therapeutic range

- Complications of warfarin are dependent upon TTR.
  - TTR < 60% mortality 4.2%, major bleed 3.86%
  - TTR 60-75% mortality 1.84%, major bleed 1.96%
  - TTR >75% mortality 1.69%, major bleed 1.69%
Predicting major bleeding in outpatients treated with warfarin

• Supra therapeutic range of INR.
• Low TTR
• Warfarin plus on steroidal anti inflammatory agents, ASA or clopidogrel
• Cohort of 70 patients in the Orbit AF study out of NIH and Duke with AF and warfarin therapy followed over 2.5 years. Of the 6 patients with major bleeding events 2 were on warfarin alone and 4 were on ASA and warfarin.
Preventable Strokes

• AF patients with stroke with no known contraindication to anticoagulation:
  • 1. 61% Not on warfarin
  • 2. 29% Sub therapeutic INR
  • 3. 10% INR in range
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
• Genetic variability in metabolism
Warfarin for AFib
Limitations Lead to Inadequate Treatment

Adequacy of Anticoagulation in Patients with AFib in Primary Care Practice

INR above target
6%

INR in target range
15%

Subtherapeutic INR
13%

No warfarin
65%

Warfarin anticoagulation through PBMC Anticoagulation Service

• 850 patients. 60% are treated for AF.
• Cohort of patients followed across the spectrum of healthcare. Ambulatory patients, in patients at PBMC, long term care, skilled nursing facility, home care, assisted living, and physician offices.
• Patient are seen by trained certified nurses following treatment protocols with consultation with medical director if patients fall outside the protocols.
• TTR for clinic 86%
• Below 60% TTR for AF regular triggers reevaluation of risk benefit ratio of anticoagulants
Bridging Therapies Provided

• Initiation of warfarin
• NPO in hospital
• Perioperative or peri procedural when CHADS2 score in 5 and 6 range.
• As requested by primary physician or cardiologist
Reversing of warfarin effect: Method depends upon urgency

• Hold warfarin
• Vit K. 10 mg oral first choice. As effective as IV (5 mg) and not associated with risk of anaphylaxis.
• Fresh frozen plasma
• 3 factor Prothrombin complex concentrate (II, IX, X). Need to give FFP also to get factor VII
• 4 factor Prothrombin complex concentrate (II, VII, IX, X). Small volume, rapid administration, Significant decline in INR in 10 minutes.
Low TTR Study

• Reviewed 29 patients with low TTR.
• Barriers to care: Polypharmacy, missed appointments, multiple anticoagulation service providers, frequent rescheduling of appointments, unintentional noncompliance related to cognitive difficulties, financial concerns, and transportation issues.
• 12/29 (41%) had cognitive impairments
• 10/29 (34%) transportation difficulties
• 11/29 (38%) financial difficulties
• 19/29 (66%) missed 49 appointments (average missed appointment = 2.6)
• 29 patients took a total of 395 medications (average 13.6)
Low TTR interventions

- Extended appointments with the same provider
- Include the patient’s caregiver in the appointment
- Use of care partners in the home
- Set up and reconciliation of pill box
- Review of medications with primary physician and consulting physicians in hopes of eliminating unnecessary medications
- More frequent appointments
- Provide additional educational opportunities
- Financial aid counseling
- Vouchers for transportation
- Financial assistance.
Properties of the Ideal Anticoagulant

Huge and growing market with need for long term treatment

- Oral once daily dosing for ease of administration
- Rapid onset of action. No need for bridging therapy
- Minimal food or drug interactions. Simple dosing
- Predictable anticoagulant effect. No need for monitoring degree of anticoagulation.
- Extra renal clearance. Safe in renal disease
- Rapid end of action. Simplifies management in cases of bleeding or intervention
- Antidote available. For emergencies.
- Well tolerated by all age groups
Optimal Candidates for New Drugs

Patients who:

• Find **INR testing burdensome**

• Despite adherence to provider recommendations, have low ‘time-in-range’. A warfarin patient who does not take medications will have the same compliance issues with a new anticoagulant.

• Can **afford** (or arrange to get) the new drugs

• Have **normal renal function**

• Have **normal hepatic function**
New anticoagulants

1. Dabigatran (Pradaxa)- direct thrombin inhibitor. Onset of action .5-4 hours. Steady state in 2.5 days. 80% renal excretion. Few drug and food interactions.

2. Rivaroxaban (Xarelto)-oral, reversible direct factor Xa inhibitor. Half life 9 hours except over 75 y.o., 12 hours. Onset of action 2-4 hours.1/3 renal clearance and rest hepatic metabolism.

3. Apixaban (Eliquis)- oral, selective, reversible direct factor Xa inhibitor. Onset 3 hours. Half life 12 hours. Cleared 25 % renal, 75% feces. Few drug and food interactions
Coagulation cascade

Schematic representation of the coagulation cascade including our improved understanding of the role of the tissue factor (TF) pathway in initiating clotting; interactions between pathways; and the role of thrombin in sustaining the cascade by feedback activation of coagulation factors.

HK: high-molecular-weight kininogen; PK: prekallikrein; PL: phospholipid; PT: prothrombin; TH: thrombin.

Adapted from Ferguson et al, Eur Heart J 1998; Suppl 19:8.
# 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>
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</table>

Reversal of NOACs

Types of Studies Evaluating Reversal of New Oral Anticoagulants

<table>
<thead>
<tr>
<th>Method</th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral activated charcoal</td>
<td>No data</td>
<td>In vitro</td>
<td>No data</td>
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<tr>
<td>Hemodialysis</td>
<td>No data</td>
<td>Human volunteers</td>
<td>No data</td>
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<td>Fresh frozen plasma</td>
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<td>Mouse model</td>
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</tr>
<tr>
<td>Activated factor VIIa</td>
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<td>Rat model</td>
<td>Rat and baboon model</td>
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<tr>
<td>3-factor PCC</td>
<td>No data</td>
<td>No data</td>
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</tr>
<tr>
<td>4-factor PCC</td>
<td>No data</td>
<td>Human volunteers and rat model</td>
<td>Human volunteers</td>
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## Reversal of NOACs

Suggestions for Reversal of New Oral Anticoagulants

<table>
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<th>Rivaroxaban</th>
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<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 VIIa</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>

Dabigatran

- Direct Thrombin Inhibitor
- Alternative to warfarin for CHADS2=1 or greater in those non valvular atrial fibrillation
- RE-LY Trial showed superior to warfarin in preventing ischemic and hemorrhagic CVAs with reduced risk of life threatening bleeding but higher risk of GI bleeds
- Lab monitoring every 3-6 months.
- No reversal agent available for major bleeding events
TTR per Country in RELY

Stroke and Systemic Embolism

By Center TTR in RELY

- TTR=optimum therapeutic range
- cTTR=center’s mean TTR

Major Bleeding
By Center TTR in RELY


- TTR=optimum therapeutic range
- cTTR=center’s mean TTR
Rivaroxaban

- Oral factor Xa inhibitor
- Seems to be equivalent in efficacy to warfarin for CVA prevention and no difference in major bleeding events
- Demonstrates a reduction in intracranial hemorrhage
- Note: risk of thrombotic events increased for 28 days after stopping drug so may need to bridge with another anticoagulant during this time.
Apixaban

- Aristotle trial: warfarin versus apixaban 5 mg twice/day. Ischemic stroke rate similar. Hemorrhagic stroke rate reduced in the apixaban group. Apixaban found to be safer than warfarin in regards to major bleeding 2.13% per year versus 3.09% per year.
Problem with studies

- TTR of warfarin group
- Apixaban Trial: 62.2%
- Rivaroxaban Trial: 59%
- Dabigatran Trial: 64%

- If these patients were being treated by the PBMC Anticoagulation Service they would not be considered to be receiving adequate therapy and alternates to warfarin would be considered.
## ACCP Guidelines

For patients with Nonrheumatic AF, including those with Paroxysmal AF

<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$_2$ = 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</td>
<td>Oral anticoagulation</td>
<td>Aspirin with clopidogrel</td>
<td>Aspirin</td>
</tr>
<tr>
<td>(CHADS$_2$ = 1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High Risk (CHADS$_2$ = 2)</td>
<td>Oral anticoagulation (dabigatran 150 mg b.i.d. vs. VKA**)</td>
<td>Aspirin with clopidogrel</td>
<td>Aspirin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></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 Evidence Grade for Dabigatran recommendation

• 2B
  • Weak recommendation, moderate-quality evidence.
  • (2B) Benefits closely balanced with risks and burden. Evidence from randomized controlled trials with important limitation (inconsistent results, methodological flaws, indirect or imprecise) or very strong evidence from observational studies.
  • Best action may differ depending on circumstances or patient or societal values. Higher-quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate.
Atrial Fibrillation Related Stroke

- AF common and incidence is increasing
- AF related stroke nasty disease with significant morbidity and mortality
- Preventable
- Treatment options expanding
- Assess risks and benefits of potential therapies
- Patient preferences play major role in choices of therapy.
- Once reversing agents are available for the new anticoagulants and the price of the drugs decreases utilization will increase.
- New agents probably no better than well utilized warfarin.