New Oral Anticoagulants

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Overview

- Why we need alternatives to warfarin
- Review of the 3 new oral anticoagulants
- Results from major trials:
  - Thromboprophylaxis in orthopedic surgery
  - Treatment of VTE
  - Stroke prevention in afib
- Cost effectiveness
- Monitoring/effects on anticoagulation tests
- Review advantages/disadvantages
What’s wrong with warfarin?

- Narrow therapeutic range
- Slow onset of action
- Slow offset of action (long duration of action, long elimination half life)
- Multiple drug and dietary interactions
- Monitoring required to maintain in therapeutic range

Thromb Haemost 2010;103:34-39
What’s wrong with warfarin?

- Difficult to manage for invasive procedures
- Impaired quality of life for the patient
- Labor intensive for health care provider
- Under-use of therapy due to fear of adverse events and complexity of management

Thromb Haemost 2010;103:34-39
What’s wrong with warfarin?

- Efficacy is dependent upon infrastructure
  - Time in therapeutic range (TTR) is associated with improved safety and efficacy
  - TTR is improved with AC management programs
  - TTR is greater in countries with more sophisticated health care infrastructure
What are the attributes of the ideal anticoagulant?

- Oral administration
- Rapid onset of action/rapid offset of action
- Wide therapeutic range
- Predictable therapeutic effect with fixed or weight-based dosing
- No food or drug-drug interactions

Thromb Haemost 2010;103:34-39
What are the attributes of the ideal anticoagulant?

- No monitoring required (but the ability to monitor if desired)
- Well defined pharmacokinetics in presence of renal or hepatic disease
- Easily reversible
- Cost effective

Thromb Haemost 2010;103:34-39
New oral anticoagulants

- Direct thrombin (IIa) inhibitor
  - Dabigatran (Pradaxa)

- Factor Xa inhibitors
  - Rivaroxaban (Xarelto)
  - Apixaban
Coagulation cascade and sites of action

- Coagulation cascade
  - Tissue Factor
  - Coagulation cascade
  - Prothrombin
  - Factor Xa
  - Thrombin

- Oral Factor Xa Inhibitor
  - LMWH
  - UFH
  - Fondaparinux
  - Warfarin

- Aspirin
  - ADP
  - Thromboxane A₂

- Thienopyridines
  - Platelet activation:
    - GP IIb/IIIa receptor expressed
  - Fibrinogen cross-linking at GP IIb/IIIa

- GP IIb/IIIa Inhibitors
  - Platelet aggregation
  - Thrombus

- DTI
  - Fibrinogen
  - Fibrin
Dabigatran--basics

- Direct thrombin (factor IIa) inhibitor
- Max anticoag activity 2-3 hours after ingestion
- Half life 7.1-17 hours
- Metabolism--conjugation
- Elimination--renal (80%), remainder excreted in bile
  - Contraindicated in patients with CrCl <30 ml/min
- Main side effect--dyspepsia (10%)
Dabigatran--basics

- Drug-drug interactions--least likely to have drug interactions
  - No P450 interactions
  - P glycoprotein substrate
    - Amiodarone (increases level by 60%), verapamil, rifampin, clarithromycin, quinidine (contraindicated)
  - Proton pump inhibitors
    - Reduce absorption by 20-30%

- No drug-food interactions
  - Food delays absorption, not clinically significant

- No antidote
- Dialyzable
Dabigatran--basics

- Unstable if not store in original bottle (desiccant in lid) or blister pack
- Must be used within 60 days (if maintained in original bottle or blister packs)
- No pill boxes
Dabigatran--approvals

- FDA indication:
  - Non-valvular atrial fibrillation
  - October 2010
  - 10/2010-1/2011 128,000 prescriptions to 86,000 patients

- Canada/EU
  - Approved for post-operative thromboprophylaxis
Rivaroxaban--the basics

- Direct factor Xa inhibitor
- Peak plasma concentration 2.5-4 hours after administration
- Half life--3.2-9.1 hours
- Metabolism: oxidation (via CYP3A4 and CYP2J2) and hydrolysis
- Elimination--2/3 renal, 1/3 fecal
Rivaroxaban--the basics

- Drug interactions--most likely to have interactions
  - CYP 3A4 and P glycoprotein substrate
  - Drugs that are substrates for both may cause more significant interaction
  - Ketoconazole, ritonavir, clarithromycin, erythromycin (increase levels 30-100%)
  - Rifampicin (decrease levels 50%)

- Drug-food interactions
  - Recommended to be taken with food
  - H2blockers, antacids no effect; no info on PPIs
Rivaroxaban--approvals

- Canada/EU--post operative thromboprophylaxis
- Not yet approved by the FDA
  - Delayed due to concerns in reporting of bleeding rates
    - Excluded surgical site bleeding from major bleeding category and reported it separately
Apixaban--the basics

- Direct factor Xa inhibitor
- Time to peak AC effect 3-3.5 hours
- Half life--8-15 hours
- Metabolism--oxidation (via CYP3A4) and conjugation
- Elimination--25% renal, 75% fecal
- Drug-drug interactions
  - Likely CYP3A4 interactions, but no data available
- Drug-food interactions
  - No information
Apixaban--approvals

- Not yet approved for clinical use or commercially available in the US or abroad
- Nearing EU approval for post operative thromboprophylaxis
# Oral Anticoagulants

<table>
<thead>
<tr>
<th>Drug</th>
<th>Warfarin</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Dabigatran</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>Vitamin K epoxide reductase</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
<td>Thrombin</td>
</tr>
<tr>
<td>Half-life (hours)</td>
<td>40</td>
<td>3.2-9.1</td>
<td>8-15</td>
<td>7.1-17</td>
</tr>
<tr>
<td>Monitoring</td>
<td>INR-adjusted</td>
<td>Not needed</td>
<td>Not needed</td>
<td>Not needed</td>
</tr>
<tr>
<td>Administration</td>
<td>Once daily</td>
<td>Once daily</td>
<td>Once-twice daily</td>
<td>Once-twice daily</td>
</tr>
<tr>
<td>Metabolism</td>
<td>CYP450</td>
<td>66% fecal; 33% renal</td>
<td>75% fecal; 25% renal</td>
<td>20% fecal; 80% renal</td>
</tr>
<tr>
<td>Antidote or treatment of bleeding</td>
<td>Vit K + FFP, APCC, or recombinant FVIIa</td>
<td>Recombinant Factor Xa derivative, APCC, recombinant FVIIa</td>
<td>Recombinant Factor Xa derivative</td>
<td>No antidote</td>
</tr>
<tr>
<td>Assay</td>
<td>PT/INR</td>
<td>Antifactor Xa, PiCT, HepTest</td>
<td>Antifactor Xa</td>
<td>Ecarin Clotting time</td>
</tr>
<tr>
<td>Drug Interactions</td>
<td>CYP 2C9, 1A2, 3A4</td>
<td>CYP 3A4 Inhibitor</td>
<td>CYP 3A4 Inhibitor</td>
<td>PPI decrease absorption</td>
</tr>
</tbody>
</table>

VTE prevention--dabigatran

○ RE-MODEL and RE-NOVATE
  ● Non-inferiority trials
  ● TKA (RE-MODEL) THA (RE-NOVATE)
  ● Dabigatran 150 mg or 220 mg daily vs. enoxaparin 40 mg SQ pre op (EU dosing regimen)
  ● Dabigatran non-inferior; no difference in bleeding

○ RE-MOBILIZE
  ● TKA
  ● Dabigatran 150 mg or 220 mg daily vs. enoxaparin 30 mg BID post op (NA dosing regimen)
  ● Dabigatran failed to show non-inferiority; no difference in bleeding

VTE prevention--rivaroxaban

- RECORD-1, 2, 3
  - Rivaroxaban 10 mg daily vs. enoxaparin 40 mg daily
  - Rivaroxaban superior to warfarin*
  - No difference in bleeding complications

- RECORD-4
  - Rivaroxaban 10 mg vs. enoxaparin 30 mg BID
  - Rivaroxaban superior to warfarin*
  - No difference in bleeding complications

*Composite outcome: VTE and all-cause mortality

VTE prevention--apixaban

- ADVANCE-1
  - Total knee arthroplasty
  - Apixaban 2.5 mg BID vs. enoxaparin 30 mg BID
  - Treatment for 12 days
  - Failed to show non-inferiority*

- ADVANCE-2
  - Total knee arthroplasty
  - Apixaban 2.5 mg BID vs. enoxaparin 40 mg daily
  - Treatment for 12 days
  - Apixaban superior to enoxaparin*

- No difference in bleeding in either study

*Primary outcome composite VTE and all cause mortality

VTE prevention--apixaban

- ADVANCE-3
  - Total hip arthroplasty
  - Apixaban 2.5 mg BID vs. enoxaparin 40 mg daily (apixaban post op, enoxaparin pre op)
  - Treatment for 35 days
  - Primary outcome asymptomatic or symptomatic DVT, PE or death
    - 27 apixaban, 74 enoxaparin; RR 0.36 (0.22-0.54) for non-inferiority and superiority
  - No difference in bleeding

NEJM 2010;363:2487-98
VTE treatment--dabigatran

- RE-COVER
  - Dabigatran 150 mg BID vs. adjusted dose warfarin x 6 months (after initial IV anticoagulation)
  - Acute VTE (proximal DVT or PE)
  - Primary outcome: recurrent, symptomatic objectively confirmed VTE and related deaths
    - 2.4% dabigatran, 2.1% warfarin (HR 1.10 (0.65-1.84)
    - Dabigatran non-inferior to warfarin; failed to meet superiority
  - Safety:
    - Major bleeding: 1.6% dabigatran, 1.9% warfarin
    - Any bleeding: 16.1% dabigatran, 21.9% warfarin

NEJM 2009;361:2342
VTE treatment--rivaroxaban

- EINSTEIN
  - Symptomatic DVT
  - Rivaroxaban 15 mg BID x 3 weeks, followed by 20 mg daily vs. enoxaparin followed by VKA
  - Continued treatment arm: rivaroxaban vs. placebo for an add’l 6-12 months
  - Non-inferior compared to VKA for recurrent VTE; superior to placebo for continuation arm
  - No difference in bleeding

NEJM 363;26:2499-2510
Stroke prevention in aﬁb—
dabigatran

- **RE-LY**
  - Non-valvular aﬁb
  - 18,113 patients, 951 sites, 44 countries
  - Mean CHADS$_2$ score 2.1
  - Mean TTR 64%
  - 110 or 150 mg BID dabigatran vs. adjusted dose warfarin

  **Results:**
  - 110 mg BID non-inferior to warfarin (182 vs. 199 events 1.53%/yr vs. 1.69% p<0.001) with significantly less major bleeding
  - 150 mg BID superior to warfarin (134 vs. 199 events; 1.11%/yr vs. 1.69% p<0.001) with no difference in major bleeding, however significantly less ICH
  - Rates MI higher on dabigatran (0.53%/yr warfarin, 0.72%/yr 110 mg, 0.74%/yr 150 mg p=0.048)

  - Long term follow up ongoing

NEJM 2009;361:1139-51
RE-LY: Dabigatran

Modified from NEJM 2009;361:1139-51.
TTR in RE-LY by country

Lancet 2010;376:975-83
TTR in RE-LY by country

Threshold above warfarin superior to dual antiplatelet Rx

US: 66%

Lancet 2010;376:975-83
Time to primary outcome in each quartile of center’s mean TTR

- **cTTR <57.1%**
  - Dabigatran 110 mg
  - Dabigatran 150 mg
  - Warfarin

- **cTTR 57.1-65.5%**

- **cTTR 65.5-72.6%**

- **cTTR >72.6%**

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>Dabigatran 110 mg</th>
<th>Dabigatran 150 mg</th>
<th>Warfarin</th>
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<tbody>
<tr>
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<td>Follow-up (years)</td>
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<td>0.5</td>
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<td>Dabigatran 110 mg</td>
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<td>Dabigatran 150 mg</td>
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<td>Warfarin</td>
<td>1504</td>
<td>1445</td>
<td>1395</td>
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</table>
Time to major bleeding event in each quartile of center’s mean TTR

- **cTTR <57-1%**
  - Dabigatran 110 mg
  - Dabigatran 150 mg
  - Warfarin

- **cTTR 57-65.5%**

- **cTTR 66.5-72.6%**

- **cTTR >72.6%**

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<td>1504</td>
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<td>1509</td>
<td>1448</td>
<td>1399</td>
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<tr>
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<th>Warfarin</th>
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<tr>
<td>Warfarin</td>
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<td>1430</td>
<td>1371</td>
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TTR in RE-LY by country

Threshold above warfarin superior to dual antiplatelet Rx

US: 66%

Below dabigatran superior to warfarin

Above no difference

Lancet 2010;376:975-83
# Pharmacist Run Anticoagulation Clinical Data

## Measures of Anticoagulation Control

<table>
<thead>
<tr>
<th>Measure</th>
<th>Usual Care Model</th>
<th>Nurse Model</th>
<th>Pharmacist Model</th>
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</thead>
<tbody>
<tr>
<td>INR time in range (%)*</td>
<td>57.4</td>
<td>71.8</td>
<td>83.6</td>
</tr>
<tr>
<td>INR values in range (%)*</td>
<td>49.4</td>
<td>67.3</td>
<td>74.9</td>
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<tr>
<td>INR &gt; 5.0 (%)*</td>
<td>2.9</td>
<td>2.0</td>
<td>1.2</td>
</tr>
<tr>
<td><strong>Hospitalizations</strong></td>
<td></td>
<td></td>
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<tr>
<td>Rate (#/100)*</td>
<td>13.9</td>
<td>12.3</td>
<td>5.4</td>
</tr>
<tr>
<td>Relative Risk (95% CI)†</td>
<td>2.59 (1.29-5.18)</td>
<td>2.29 (1.23-4.25)</td>
<td>----</td>
</tr>
<tr>
<td><strong>ED visits</strong></td>
<td></td>
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<tr>
<td>Rate (#/100)*</td>
<td>5.6</td>
<td>5.6</td>
<td>1.2</td>
</tr>
<tr>
<td>Relative Risk (95% CI)†</td>
<td>4.40 (1.24-15.59)</td>
<td>4.45 (1.42-13.98)</td>
<td>----</td>
</tr>
</tbody>
</table>

* p < 0.05 for all comparisons vs pharmacist
† p < 0.01 for all comparisons vs. pharmacists

Stroke prevention in afib--rivaroxaban

- ROCKET AF
  - Rivaroxaban 20 mg daily (15 mg daily for CrCl 30-49) vs. adjusted dose warfarin 2.0-3.0
  - Mean CHADS$_2$ score 3.48 (rivaroxaban), 3.46 (warfarin)
  - Median TTR 57.8
  - Vascular death, stroke, embolism
    - On treatment event rate: rivaroxaban 3.11, warfarin 3.63; HR 0.86 (0.74-0.99)
    - ITT: rivaroxaban 4.51, warfarin 4.81; HR 0.94 (0.84-1.05)
  - No difference bleeding rates

Presented at the AHA meeting, November 2010
TTR in RE-LY by country

Threshold above warfarin superior to dual antiplatelet Rx

US: 66%

Below dabigatran superior to warfarin

Above no difference

TTR in ROCKET AF

Country

Mean time in therapeutic range (%)
**Stroke prevention in afib--apixaban**

- **AVERROES**
- Patients “unsuitable” for VKA
- Apixaban 5 mg BID vs. ASA 81-324 mg daily
- Mean CHADS\textsubscript{2} 2.0 (apixaban), 2.1 (ASA)
- Primary outcome stroke or systemic embolism
  - 51 apixaban, 113 ASA HR 0.45 (0.32-0.62)
- No difference in bleeding
- Terminated early due to benefit of apixaban

*NEJM 2011;364:806-17*
Stroke prevention in afib--apixaban

- ARISTOTLE
  - Apixaban vs. warfarin
  - Ongoing
Cost effectiveness/utility

- Perspective
  - Society, patient, provider, payer
- What are the costs?
  - Cost of the drug
  - Costs of monitoring
  - Costs of events
- Effectiveness/utility
- Time horizon
Effectiveness vs. Utility

- **Cost effectiveness**
  - Dollars expended for particular benefit
  - I.e., life years gained

- **Cost utility**
  - Dollars expended for value gained
  - I.e., QALY
Cost effectiveness/utility--dabigatran in afib

- Target population:
  - age ≥ 65, non-valvular a fib, CHADS ≥ 1
- Perspective: society
- Time horizon: lifetime (35 years)
- Markov decision model
- Data from RE-LY
- Cost of dabigatran estimated based on UK pricing

Cost effectiveness/utility--dabigatran in afib

Assumptions:

Costs:
- Drug treatment costs for warfarin included:
  - 14 INR tests (sensitivity analysis add’l 8 tests)
  - Medicare reimbursement for “anticoagulation management”
- Costs of treatment for stroke, hemorrhage, MI, death

Utility:
- Taking the medications (and associated monitoring)
- Neurologic events, MI
- Temporary states: major and minor bleeding

Cost effectiveness/utility--dabigatran in afib

- Cost effectiveness sensitive to cost of drug:
  - No longer cost effective:
    - Above $9.36 for 110 mg BID
    - Above $13.70 for 150 mg BID
- Much benefit derived from lower rates of ICH with dabigatran (costly and low utility)
- Increasing risk of stroke or ICH, resulting in dabigatran being more cost effective
- Current US pricing $7.90/day 150 mg dose

New oral anticoagulants--will they be cost effective?

- Cost utility of new agents dependent upon:
  - Cost of drug
  - Institution’s TTR (higher TTR associated with better performance of warfarin)
  - Individual patient risk for clotting and bleeding (more cost effective for higher risk patients)
  - Confirmed performance of these new medications over warfarin
Need for monitoring

- Patients with low body weights or obese patients
- Pediatric patients
- Renal or hepatic impairment
- Accidental or deliberate overdose
- To measure adherence
- To evaluate patients with hemorrhagic or thrombotic complications

Ther Drug Monit 2010;32:673-679
Monitoring/effects on coagulation tests--dabigatran

- Affect on coagulation assays dependent on timing of administration of the drug
- PTT--relationship non-linear (plateaus) can detect presence of AC activity, but not suitable to quantify AC effect
  - On chronic therapy median peak 2x, trough 1.5x
- PT--least sensitive, little effect at clinically relevant doses (INR 2 at supratherapeutic doses)
- ACT--similar to PTT, relationship curvilinear

Thromb Haemost 2010;103:1116-1127
Monitoring/effects on coagulation tests--dabigatran

- Thrombin time--sensitive, available, linear relationship, not standardized across labs
- Ecarin clotting time--best to assess bleeding risk, not widely available
- Hemoclot thrombin inhibitor assay--dilute thrombin time, sensitive, standard reagents; dabigatran specific assay in development

Thromb Haemost 2010;103:1116-1127
Monitoring/effects on coagulation tests--rivaroxaban

- PT/INR--effect of rivaroxaban on PT is transient and changes over time after administration
  - Therapeutic drug concentration 12-19 (trough) to 152-201 (peak) ng/mL
  - PT insensitive, lacks accuracy and precision at trough levels; can detect at concentrations 50-700 ng/mL
  - INR correction not appropriate for rivaroxaban (can exacerbate effects of different reagents with rivaroxaban and PT)

*Ther Drug Monit* 2010;32:673-679
Monitoring/effects on coagulation tests--rivaroxaban

- aPTT--rivaroxaban has weaker affect on aPTT than PT
- Affect short lived
- Different reagents used in aPTT have different sensitivities to rivaroxaban
- No information on the affect on the ACT
- Hep Test (clot based anti-Factor Xa assay)--rivaroxaban has paradoxical affects
- Prothrombinase-induced Clotting time--paradoxical effects

THER Drug Monit 2010;32:673-679
Monitoring/effects on coagulation tests--rivaroxaban

- Anti-Factor Xa assays:
  - sensitivity varies among available assays
  - One commercially available assay appears to be able to detect rivaroxaban in concentrations 0-500 ng/mL
  - To be useful, standard curves will need to be developed

Ther Drug Monit 2010;32:673-679
Monitoring/effects on coagulation tests--apixaban

- Limited information available
- Minimal impact on PT and aPTT at therapeutic concentrations
- Factor Xa assays can detect the presence of drug
Potential advantages of new oral anticoagulants over VKAs

- Oral administration
- Rapid onset of action
  - May replace IV anticoagulants for certain indications
  - May eliminate need for 2 AC regimen (ie heparin and warfarin)
- Predictable therapeutic effect with fixed dosing
  - No routine coagulation monitoring

Thromb Haemost 2010;103:34-39
Potential advantages of new oral anticoagulants over VKAs

- Limited or no food or drug interactions
- Short half-life
  - Effect wears off more quickly than VKAs
- No need for bridging for invasive procedures
- More convenient for the patient
  - No routine monitoring, no dietary interactions, limited drug interactions
- More convenient for physician
  - No routine monitoring

Thromb Haemost 2010;103:34-39
Potential advantages of new oral anticoagulants over VKAs

- Potential for greater use
  - Barriers removed that limit more widespread use
- Potentially more cost effective
  - No routine monitoring
  - Fewer adverse events
- Possible superior efficacy
- Possible superior safety

Thromb Haemost 2010;103:34-39
Potential disadvantages of new oral anticoagulants over VKAs

- No routine coagulation monitoring
  - Cannot titrate dose
  - Determination of failure of therapy vs. poor compliance
- Short half-life
  - AC effect declines quickly if compliance poor
  - Poor compliance may affect efficacy more than with VKAs

Thromb Haemost 2010;103:34-39
Potential disadvantages of new oral anticoagulants vs VKAs

- No antidotes
- No monitoring lab marker available to measure drug activity if needed
- Potential dose adjustment for renal or hepatic dysfunction
- Cost

Thromb Haemost 2010;103:34-39