Managing Thrombosis in Cardiovascular Disease
New Anticoagulants: What You Need to Know

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Disclosures
- I have no disclosures relevant to the content of this presentation.

AF and Stroke
- AF increases stroke risk ~5-fold
- Incidence of all-cause stroke in patients with AF is 5%
- 15% of all strokes in the US caused by AF

AF and Stroke
- Patients with AF-related stroke have a 1.8-fold increase in mortality when compared with those who experience a stroke unrelated to AF
  - possibly because AF-related strokes tend to be larger in size and more often lead to hemorrhagic transformation.

VTE: Incidence and Impact in the United States
- Approximately 2 million VTEs occur every year¹
- Each year 1 person in 1000 will experience VTE in the US²
  - One third manifest PE with or without DVT
- Death within 1 month of diagnosis³:
  - 6% of DVT cases; 12% of PE cases
- Recurrent DVT:
  - 17% of DVT patients 2 years after initial treatment⁴
  - 30% of DVT patients 8 to 10 years after initial treatment⁴

Other indications for OAC
- Mechanical heart valves
- Hypercoagulable states
- LVAD (HeartMate II)
- Intracavitary thrombus (LV aneurysm)
The Ideal Oral Anticoagulant

- Bioavailable, predictable dose response (no monitoring)
- High efficacy to safety index
- Rapid onset of action
- Available antidote
- Minimal interactions with food or other drugs

Limitations of Vitamin K Antagonists

<table>
<thead>
<tr>
<th>Limitations</th>
<th>Clinical Implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slow onset &amp; offset of action</td>
<td>Need to bridge</td>
</tr>
<tr>
<td>Individual variability in anticoagulant effect</td>
<td>Variable dosing</td>
</tr>
<tr>
<td>Narrow therapeutic index</td>
<td>Need to monitor</td>
</tr>
<tr>
<td>Similar dose for treatment and prophylaxis</td>
<td>Over anticoagulation</td>
</tr>
<tr>
<td>Food and drug interaction</td>
<td>Restrictions, frequent monitoring</td>
</tr>
<tr>
<td>Reduced synthesis of natural anticoagulants: PC, PS</td>
<td>Risk of skin necrosis with PC deficiency</td>
</tr>
</tbody>
</table>

Models of Care: Warfarin Therapy

- **Routine medical care**
  - a physician or office staff manage warfarin dosing based on INRs obtained from blood draws in a laboratory or via a point-of-care device in the clinic.
- **Anticoagulation clinics**
  - managed by dedicated healthcare professionals that have systematic policies to manage and dose patients, using either point-of-care or laboratory-based INRs.
- **Patients using a point-of-care monitor at home**
  - measure their INRs and then report back to the personnel in a clinic to alter the dose.

INR Variability in AF Patients

- Data suggest that patients on warfarin maintain a therapeutic INR only 63% of the time at best, with even worse results being observed in community practices.¹

- It is important to maintain a minimum INR of 2.0 to obtain effective stroke prevention during warfarin therapy.²⁻⁵

INR Variability in AF Patients

- Patients using warfarin who had a therapeutic INR at least 67% of the time had a composite event rate of 5.3%/yr
  - lower than event rate with dabigatran
- Patients who were in the therapeutic range less than 54% of the time had an event rate of 12%/yr
  - much worse than event rate with dabigatran


INR Variability in AF Patients

- Patients using warfarin who had a therapeutic INR at least 67% of the time had a composite event rate of 5.3%/yr
  - lower than event rate with dabigatran
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  - much worse than event rate with dabigatran

Self-Monitoring of INR Levels

- Self-testing may provide a better way to maintain INR levels within a narrow therapeutic window.
  - THINRS trial suggested beneficial trends in mortality, major bleeding, and stroke when patients performed self-testing for monitoring and managing their anticoagulation therapy.¹⁻³
  - In the STOARM2 trial, INR management improved with automated self-monitoring, with INR values < 1.5 or > 5 seen in only 0.47% of patients.⁴


Some of the New Anticoagulants

**Anti-FXa**
- Rivaroxaban (o)
- Apixaban (o)
- Edoxaban (o)
- Otamixaban (p)
- LY-517717 (o)
- DX-9065a (p)
- Betrixiban (o)
- TK-442 (o)

**Anti-FIIa (anti-thrombin)**
- Dabigatran (o)
- Odiparcil (o)
- Flovagatran (p)
- Pegmusirudin (p)
- Peg-hirudin (p)
- Desirudin (p)

O:Oral, P:Parenteral

Targeting Specific Coagulation Factors

- Newer oral anticoagulants target specific points in the coagulation cascade:
  - Factor Xa inhibitors (eg, rivaroxaban, apixaban) prevent the conversion of prothrombin to thrombin.
  - Direct thrombin (factor IIa) inhibitors (eg, dabigatran, ximelagatran) block the conversion of fibrinogen to fibrin.

  - The goal is, in part, to offer more specific targeting and to afford more predictable responses than current anticoagulant therapies, such as warfarin, can offer.

New Anticoagulants

<table>
<thead>
<tr>
<th>TF-VIIa</th>
<th>Factor Xa Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>IXa</td>
<td>Indirect (via AT):</td>
</tr>
<tr>
<td>VIII</td>
<td>Fondaparinux (subQ)</td>
</tr>
<tr>
<td>X</td>
<td>Direct: Oral</td>
</tr>
<tr>
<td>Xa</td>
<td>Rivaroxaban</td>
</tr>
<tr>
<td>Va</td>
<td>Apixaban</td>
</tr>
<tr>
<td>PL</td>
<td>Betrixiban</td>
</tr>
<tr>
<td>II</td>
<td>Direct Thrombin Inhibitors (DTI)</td>
</tr>
<tr>
<td></td>
<td>Oral: Dabigatran</td>
</tr>
<tr>
<td></td>
<td>Ximelagatran</td>
</tr>
<tr>
<td></td>
<td>IV: Argatroban</td>
</tr>
<tr>
<td></td>
<td>Lepirudin</td>
</tr>
<tr>
<td></td>
<td>Bivalirudin</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td></td>
</tr>
<tr>
<td>Fibrin</td>
<td></td>
</tr>
</tbody>
</table>

Issues with Newer Oral Anticoagulants not shared with warfarin

- A shorter half-life with rapid offset and potential attendant clotting risk
- No reversal agent (antidote) in cases of acute bleeding or at the time of emergent procedures
- No validated tests to assay their anticoagulant effect
  - More difficult to assess patient compliance

Issues with Newer Oral Anticoagulants not shared with warfarin

- No data on long-term adverse effects beyond bleeding
- No head-to-head comparisons between new agents
Cost-Effectiveness

• Cost-effectiveness analyses of newer OAC in preventing stroke in AF are limited
  – At a cost of $7–$9/day (two capsules), dabigatran use may cost an estimated $10,000 per year of life saved.
  – This analysis does not consider direct comparisons against the cost of maintaining patients on warfarin under current models of care.

• Further studies are needed to better analyze the relative cost-effectiveness of warfarin versus that of any of the newer OAC

Pink J, et al. BMJ. 2011;343:d5333

Dabigatran Etexilate

• Specific, competitive, reversible univalent thrombin inhibitor
• Pro-drug converted to active form
• Rapid onset within 2-3 hours
• Low bioavailability, 6.5%
• Low protein binding
• Half life 12-17 hours
• Renal clearance as glucuronic acid conjugate: 80%
• Metabolized by esterase catalyzed hydrolysis and P-Gp transport mechanisms

Pradaxa®

RE-LY: Non-Inferiority Trial
Stoke Prevention
18,113 patients, F/U 2 years

Dabigatran 110 mg bid vs Warfarin
Dabigatran 150 mg bid vs warfarin

Non-inferiority Superiority
p-value p-value
<0.001 0.34
Margin = 1.46

0.50 0.75 1.00 1.25 1.50
Dabigatran better HR (95% CI) Warfarin better


Dabigatran Etxilate 150-220 mg vs Enoxaparin 40-60 mg in Major Orthopedic Surgery

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Efficacy</th>
<th>Safety Major Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-MODEL</td>
<td>TKR 2,076 6-10 days</td>
<td>Non-Inferior</td>
<td>Equivalent</td>
</tr>
<tr>
<td>RE-MOBILIZE</td>
<td>TKR 2,615 12-15 days</td>
<td>Enox, 30 mg bid</td>
<td>Superior p=0.02</td>
</tr>
<tr>
<td>RE-NOVATE</td>
<td>THR 3,494 28-351 days</td>
<td>Non-Inferior</td>
<td>Equivalent</td>
</tr>
</tbody>
</table>

Ansell J Hematology 2010, p 221

Dabigatran Treatment of VTE: RECOVER-1

• Randomized trial, 2564 pts comparing Dabigatran 150 mg bid vs Warfarin in the treatment of VTE for 6M after initial Rx with parenteral anticoagulant (9D)
• Primary Efficacy: Non-Inferior
• Safety: Lower rate of any bleeding: 16.1% vs 21.9% (P<0.001)

Major bleed: comparable
• Death, ACS and LFTs: comparable

Schulman S. et al. NEJM 2009, 361:2342
Dabigatran: FDA Status

• Pradaxa® trade name; Boehringer Ingelheim

• For the prevention of DVT/PE after orthopedic surgery:
  – FDA approval pending
  – Pradaxa approved in EU and Canada

• For the prevention of stroke in patients with non-valvular atrial fibrillation (SPAF):
  – Pradaxa 150 mg Bid FDA approved (Oct. 2010)
  – Pradaxa approved in EU, Canada and Japan

Rivaroxaban

• Direct, specific, competitive factor Xa inhibitor

• Rapid onset within 2-4 hours

• Half life 7-11 h, od or bid dosing

• High bioavailability of >80%

• Metabolized via the CYP3A4, CYP211, and P-gp transport mechanisms

• See interactions with drugs using the same metabolic pathways

• Renal and liver/fecal elimination

Rivaroxaban 10 mg/D Vs Enoxaparin 40 mg/D In Major Orthopedic Surgery

<table>
<thead>
<tr>
<th>Study</th>
<th>Population: n</th>
<th>Efficacy</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>RECORD-1</td>
<td>THR 4,541</td>
<td>Riv. Superior p&lt;0.001</td>
<td>Equivalent</td>
</tr>
<tr>
<td>RECORD-2</td>
<td>THR 2,509</td>
<td>Riv. Superior p&lt;0.001</td>
<td>Equivalent</td>
</tr>
<tr>
<td>RECORD-3</td>
<td>TKR 2,531</td>
<td>Riv. Superior p&lt;0.001</td>
<td>Equivalent</td>
</tr>
<tr>
<td>RECORD-4</td>
<td>TKR 3,148</td>
<td>Riv. Superior p&lt;0.001</td>
<td>Equivalent</td>
</tr>
</tbody>
</table>

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Primary Efficacy Outcome

Stroke and non-CNS Embolism

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban Event Rate</th>
<th>Warfarin Event Rate</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>On Treatment N=1,162</td>
<td>1.70</td>
<td>2.15</td>
<td>0.79</td>
<td>(0.65, 0.95)</td>
</tr>
<tr>
<td>ITT N=1,171</td>
<td>2.12</td>
<td>2.42</td>
<td>0.88</td>
<td>(0.74, 1.03)</td>
</tr>
</tbody>
</table>

Rivaroxaban better Warfarin better

Patel et al. NEJM 2011

Primary Safety Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban Event Rate</th>
<th>Warfarin Event Rate</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major and non-major Clinically Relevant</td>
<td>14.91</td>
<td>14.52</td>
<td>1.03 (0.96, 1.11)</td>
<td>0.442</td>
</tr>
<tr>
<td>Major</td>
<td>3.60</td>
<td>3.45</td>
<td>1.04 (0.96, 1.20)</td>
<td>0.576</td>
</tr>
<tr>
<td>Non-major Clinically Relevant</td>
<td>11.80</td>
<td>11.37</td>
<td>1.04 (0.96, 1.13)</td>
<td>0.345</td>
</tr>
<tr>
<td>Fatal Bleeding</td>
<td>0.2</td>
<td>0.5</td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td>Intracranial Hemorrhage</td>
<td>55 (0.49)</td>
<td>84 (0.74)</td>
<td>0.67 (0.47, 0.94)</td>
<td>0.019</td>
</tr>
</tbody>
</table>

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

ROCKET-AF: Clinical Trial Outcomes

• Efficacy
  – Rivaroxaban: non-inferior to warfarin for SPAF
  – Rivaroxaban: superior to warfarin while patients were taking study drug

• Safety
  – Similar rates of bleeding and adverse events
  – Less ICH and fatal bleeding with rivaroxaban

• Conclusion
  – Rivaroxaban is a potential alternative to warfarin for moderate or high risk AF patients
Patients with acute symptomatic PE with or without DVT

Predefined treatment period of 3, 6, or 12 months

Objectively confirmed PE & DVT

Day 21

Rivaroxaban

Enoxaparin bid for at least 5 days, plus VKA INR 2.5 (range 2.0-3.0)

20 mg od

30-day post-study treatment period

rivaroxaban showed:

- Non-inferiority to LMWH/VKA for efficacy (first symptomatic recurrent VTE):
  - 2.1% vs. 1.8%; HR=1.12 (0.75–1.69);
  - \( \rho_{\text{non-inferiority}} = 0.0026 \) for non-inferiority margin of 2.0
- Superiority for major bleeding:
  - 1.1% vs. 2.2%; HR=0.49 (0.31–0.79) \( p=0.0032 \)

Rivaroxaban: FDA Status

- Xarelto trade name; Janssen Pharmaceuticals
- Nonvalvular Atrial Fibrillation:
  - with CrCl >50 mL/min: 20 mg once daily
  - with CrCl 15 - 50 mL/min: 15 mg once daily
- Treatment of DVT, PE, and Reduction in the Risk of Recurrence of DVT and of PE:
  - 15 mg twice daily for the first 21 days then 20 mg once daily for the remaining treatment
- Prophylaxis of DVT Following Hip or Knee Replacement Surgery:
  - 10 mg once daily

Apixaban

- Direct, reversible FXa inhibitor
- Rapid onset, peak within 3 hrs
- Bioavailability of 51-85%
- Long half life (8-14 hrs), slightly longer in elderly (15 hrs)
- Multiple elimination pathways
  - 25% renal
  - 75% biliary
- Metabolism via CYP2A4, SULT1AA pathways

Apixaban 2.5 mg bid vs Enoxaparin 40-60 mg/D in Major Orthopedic Surgery

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Efficacy</th>
<th>Safety Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADVANCE-1</td>
<td>TKR 3,195</td>
<td>9.0% vs 8.9%</td>
<td>Apix - Safer</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>ADVANCE-2</td>
<td>TKR 1,873</td>
<td>Apix - Superior</td>
<td>Equivalent</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Full 8001</td>
</tr>
<tr>
<td>ADVANCE-3</td>
<td>THR 6,407</td>
<td>Apix - Superior</td>
<td>Equivalent</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Full 8001</td>
</tr>
</tbody>
</table>

Ansell J Hematology 2010, p 221
Study Outcomes

- Treatment with apixaban (5 mg bid) as compared to warfarin in patients with AF (n>18,000) and at least one additional risk factor for stroke:
  - Reduces stroke and systemic embolism by 21% (p=0.01)
  - Reduces major bleeding by 31% (p<0.001)
  - Reduces mortality by 11% (p=0.047)
  - Consistent effects across all major subgroups
  - Fewer drug discontinuations on apixaban than on warfarin, consistent with good tolerability

Granger CB, et al. NEJM 2011;365

Apixaban: FDA Status

- Eliquis® trade name; Bristol-Myers Squibb & Pfizer
- For the prevention of DVT/PE after orthopedic surgery:
  - No FDA approval yet
- For the prevention of stroke in patients with atrial fibrillation:
  - No FDA approval yet
  - June 2012: FDA requested additional information
  - September 2012: NDA resubmitted

Edoxaban: FDA Status

- Lixiana® trade name; Daiichi-Sankyo
- For the prevention of DVT/PE after orthopedic surgery:
  - No FDA approval yet
  - Edoxaban approved in Japan
- For the prevention of stroke in patients with atrial fibrillation:
  - No approvals

The New Oral Anticoagulants: Similar Yet Different

<table>
<thead>
<tr>
<th>Features</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Dabigatran</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trade name</td>
<td>Xarelto</td>
<td>Eliquis</td>
<td>Pradaxa</td>
</tr>
<tr>
<td>Target</td>
<td>Xa</td>
<td>Xa</td>
<td>Ila</td>
</tr>
<tr>
<td>Prodrug</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Bioavailability (%)</td>
<td>80</td>
<td>50</td>
<td>6</td>
</tr>
<tr>
<td>Time to peak (h)</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>9</td>
<td>9-14</td>
<td>12-17</td>
</tr>
<tr>
<td>Renal excretion (%)</td>
<td>65</td>
<td>25</td>
<td>80</td>
</tr>
</tbody>
</table>

Practical Considerations

- P-Glycoprotein/CYP3A4
  - Inhibitors
    - Azoles, protease inhibitors
  - Inducers
    - Carbamazepine, phenytoin, rifampin
- P-Glycoprotein inhibitor with moderate renal impairment (CrCl 30-50 ml)
  - e.g. Dronedarone, systemic ketoconazole
  - Reduce the dose of Dabigatran
Non-Valvular AF

- Hemodynamically significant valve disease

- Prosthetic heart valve
  - annuloplasty with or without ring, commissurotomy and/or valvuloplasty permitted

New OACs: ‘Real Life’ Experience

- Populations not studied in the clinical trials:
  - Elderly, pediatrics
  - Pregnant
  - Chronically ill

- Common patient characteristics that influence the drug PKs and safety/efficacy of NOACs:
  - Co-morbid illnesses
  - Reduced renal function
  - Reduced hepatic function
  - Altered metabolism, gastric pH, intestinal motility, protein binding
  - Extremes in body weight
  - Rx drugs, dietary supplements, herbs

Special populations

- Pregnancy (Category C)/lactation
  - Discontinue

- Renal failure, dialysis, CrCl <15 ml/min
  - Pradaxa: no dosing recommendation for
  - Xarelto: avoid use

- Liver failure
  - Avoid in Child-Pugh B and C

Practical Considerations

- Assess renal function
- Switching from warfarin:
  - Stop warfarin, initiate once INR <2.0
- Switching to Warfarin:
  - Start warfarin with bridging at the time of next dose OR:
  - Start warfarin before stopping:

<table>
<thead>
<tr>
<th>CrCl (ml/min)</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50</td>
<td>Day -3</td>
<td>Day -4</td>
</tr>
<tr>
<td>31-50</td>
<td>Day -2</td>
<td>Day -3</td>
</tr>
<tr>
<td>15-30</td>
<td>Day -1</td>
<td>Day -2</td>
</tr>
</tbody>
</table>

Practical Considerations

- Monitoring effect of dabigatran
  - Not routinely needed, not done in trials
  - Can raise INR, aPTT, & thrombin time
    - No clear association with therapeutic effect
    - Drug present/absent (compliance, safe to proceed with surgery)
  - Hemoclot uses standard amount of thrombin (quantitative)
    - Canada/Europe; not for patient use in US
    - Therapeutic range for dabigatran 50-320
Laboratory Monitoring

- An anti-factor Xa level may be used to evaluate the therapeutic effects of rivaroxaban or apixaban.
- These assays are not as quickly obtained or as widely available as is the INR.
- Therapeutic ranges for these laboratory tests remain to be determined.

Practical Considerations

how to manage bleeding

- Stop the drug (time; short half-life)
- Evaluate severity and need for surgery
  - Local measures
- Fluid and blood product support
- General hemostatic agents
- Hemodialysis
  - Dabigatran: low protein binding: dialyzable
  - ~2/3 removed in a 4-hour session
  - Rivaroxaban: high protein binding: not dialyzable

Practical Considerations

how to manage mild bleeding

- Hold one dose
- If bleeding continues
  - Stop concomitant antiplatelets if possible
  - Investigate for a local cause
  - Check for drug accumulation
    - Measure PTT; Creatinine Clearance
- Consider reducing dose or stopping the drug

Practical Considerations

how to manage mod/sev bleeding

- Stop treatment / investigate the source
- If within 2 hours of the dose, consider activated charcoal
- Consider administration of platelets
  - If thrombocytopenia or long-acting antiplatelet drugs have been used
- Maintain adequate diuresis, consider hemodialysis/hemofiltration
- Control bleeding surgically

Reversal of new OAC

- A specific reversal agent for dabigatran/rivaroxaban is not available.
- Recombinant factor VIIa (rVIIa)
  - 90 μg/kg
- Prothrombin complex concentrates (PCC)
  - II, VII, IX, X [Canada, Europe; US → 3 factors]
  - 40 IU/kg
- Activated prothrombin complex concentrates (aPCC): FEIBA 50 IU/kg

PCC in healthy subjects on Rivaroxaban

PCC in healthy subjects on Dabigatran


Timing of interrupting therapy before procedures & surgeries

<table>
<thead>
<tr>
<th>Calculated creatinine clearance, mL/min</th>
<th>Half-life, hours</th>
<th>Standard risk of bleeding*</th>
<th>High risk of bleeding†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran &gt; 80</td>
<td>13 (11-22)</td>
<td>24 h</td>
<td>2 d</td>
</tr>
<tr>
<td>&gt; 50-0 80</td>
<td>15 (12-34)</td>
<td>24 h</td>
<td>2 d</td>
</tr>
<tr>
<td>&gt; 30-50</td>
<td>18 (13-23)</td>
<td>2 d</td>
<td>4 d</td>
</tr>
<tr>
<td>&lt; 30</td>
<td>27 (22-35)</td>
<td>4 d</td>
<td>6 d</td>
</tr>
<tr>
<td>Dabigatran &gt; 30</td>
<td>12 (11-13)</td>
<td>24 h</td>
<td>2 d</td>
</tr>
<tr>
<td>&lt; 30</td>
<td>Unknown</td>
<td>2 d</td>
<td>4 d</td>
</tr>
</tbody>
</table>

*cardiac catheterization, ablation therapy, colonoscopy without removal of large polyps, and uncomplicated laparoscopic procedures, such as cholecystectomy; †major cardiac surgery, insertion of pacemakers or defibrillators (resulting from the risk for pocket hematoma), neurosurgery, large hernia surgery, and major cancer/urologic/vascular surgery.


Dabigatran and MI: Metaanalysis

N=30, 514

Mortality OR 0.89; 95% CI 0.80-0.99

Uchino K et al. Arch Intern Med 2012

MI occurred at annual rates of 0.82% and 0.81% with dabigatran 110 or 150 mg BID compared with 0.64% with warfarin (P=NS)

There was a nonsignificant increase in MI with dabigatran compared with warfarin, but other myocardial ischemic events were not increased.

Circulation. 2012;125:669-676

Efficacy and Safety of the Novel Oral Anticoagulants in Atrial Fibrillation

A Systematic Review and Meta-analysis of the Literature

Francisco Dalili, MD, Noorita Riva, MD, Mark Crowther, MD, Alexander G. Tapio, MD, Gregory Y.H. Lip, MD, Walter Agnelli, MD

12 studies; 54,875 patients; dabigatran, rivaroxaban, apixaban, edoxaban vs. warfarin

<table>
<thead>
<tr>
<th></th>
<th>NOAC</th>
<th>Warfarin</th>
<th>RR</th>
<th>CI</th>
<th>CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>5.61</td>
<td>6.02</td>
<td>0.89</td>
<td>0.83-0.96</td>
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<tr>
<td>CV Mortality</td>
<td>3.45</td>
<td>3.65</td>
<td>0.89</td>
<td>0.82-0.98</td>
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</tr>
<tr>
<td>Stroke/embolism</td>
<td>2.40</td>
<td>3.13</td>
<td>0.77</td>
<td>0.70-0.86</td>
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<tr>
<td>Major bleeding</td>
<td>4.90</td>
<td>5.54</td>
<td>0.86</td>
<td>0.72-1.02</td>
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<tr>
<td>ICH</td>
<td>0.59</td>
<td>1.30</td>
<td>0.46</td>
<td>0.39-0.56</td>
<td></td>
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<tr>
<td>MI</td>
<td>1.29</td>
<td>1.29</td>
<td>0.99</td>
<td>0.85-1.15</td>
<td></td>
</tr>
</tbody>
</table>

Circulation. 2012;126:2381-2391

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
Regulatory Approvals

- Orthopedic surgery (THR/TKR/Hip fracture):
  - Dabigatran: EU, Canada
  - Rivaroxaban: EU, Canada, US
  - Apixaban: EU
  - Edoxaban: Japan
- Non-ortho surgery, medical patients:
  - No approvals
- Treatment of DVT/PE
  - Rivaroxaban: US, EU
- SPAF:
  - Dabigatran: US, EU, Canada, Japan
  - Rivaroxaban: US and EU

The Future of Warfarin

1. Excellent efficacy
2. Low cost
3. Long track record (since 1954)
4. Centralized Anticoagulation Clinics that maintain TTRs > 60%
5. INR validated for warfarin relation to bleeding risk
6. Point-of-care testing

Conclusions

1. New OAC are now clinically available and additional drugs are being developed.
2. New OAC provide more options for the management of VTE; however, these drugs are not superior to the standard of care.
3. For VTE prevention, heparins and warfarin will remain the standard of care for some time, especially in medical patients.

Conclusions

4. For atrial fibrillation (SPAF) the new OAC appear to have a superior safety and efficacy profile.
5. Additional clinical trials are needed to assess them beyond the ‘clinical trial’ populations.
6. Warfarin’s low cost, efficacy, and track record will prolong its life. Its use may decrease but it will remain for years to come.

Conclusions

- The best use of these new drugs may need to be determined based on:
  - Patient specific factors
  - The efficacy of individual centers in managing INRs
    - The ability to safely maintain a therapeutic INR range
  - Current lack of a clear methodology for monitoring or reversing the anticoagulant effects of these new agents