Novel Oral Anticoagulants (NOACs)

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Dean, Hudson College of Public Health
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## Disclosures for Dr. Gary Raskob

<table>
<thead>
<tr>
<th>Category</th>
<th>Disclosures</th>
</tr>
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<tbody>
<tr>
<td>Research Support</td>
<td>None</td>
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<td>Employee</td>
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<tr>
<td>Consultant</td>
<td>Bayer HealthCare, BMS, Boehringer-Ingelheim, Daiichi-Sankyo, Eli Lilly, Janssen, Johnson and Johnson, Merck, Pfizer, Portola, Tetherex</td>
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<tr>
<td>Patents</td>
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<td>Honorarium</td>
<td>Bayer, BMS, Daiichi, Janssen, Pfizer</td>
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<td>Bayer HealthCare, BMS, Daiichi-Sankyo, Janssen, Johnson and Johnson, Merck, Pfizer, Portola</td>
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Goals of Presentation

• Describe the burden of disease from thrombosis
• Review the evidence for efficacy and safety of NOACs for stroke prevention in patients with AF and for treatment of VTE
• Discuss recent evidence for efficacy and safety of NOACs for:
  - prevention of VTE after hospitalization for medical illness
  - chronic treatment of stable CAD or PAD
• Discuss key concepts re reversal of NOAC anticoagulation
• Practical considerations in the choice of NOACs for anticoagulant therapy
• Describe the future directions for clinical research in anticoagulant therapy
Not discussed today

• Antithrombotic therapy in interventional cardiology
• Antithrombotic therapy for acute stroke
• Role of NOACs for prevention of VTE in surgical patients
• Role of NOACs for treatment of cancer-associated VTE
• Role of NOACs for prevention of VTE in ambulatory cancer patients
• Role of NOACs in patients with end stage renal disease
• Role of ASA in cardiovascular disease prevention
• ? NOACs for primary prevention of major adverse cardiovascular events
Thrombosis 1 in 4 Global Deaths

GBD 2015 Study WHO, World Bank

55.8 million deaths 2015
39.8 million, 71%, non-communicable disease

Ischemic heart disease
8.9 million deaths
17% increase since 2005

Cerebrovascular disease
6.3 million deaths
2.9 million ischemic stroke
8% increase since 2015

VTE deaths not specifically assessed
Estimated several million

Source: Lancet 2016; 388 pg. 1459-1544
Disease Burden of VTE

• 3 episodes per 1,000 population
• 2 to 7 per 1,000 population age > 70 yrs
• 547,596 hospitalizations with VTE in US 2007- 2009
• Estimated 900,000 cases per year in US
• 100,000 to 300,000 VTE-related deaths in US each year
• 684,000 DVT, 434,000 PE, and 543,000 VTE-related deaths in European Union 2004 (pop 454.4 million)
• VTE a leading cause of hospital - associated premature death and disability (DALY) world wide

Disease Burden of Atrial Fibrillation

• 33.5 million people globally 2010 (3 to 5 million in US), 4.7 million new cases each year

• Age-adjusted incidence 2010 (per 1,000 person years)
  o Marked age dependence and regional variation
  o Highest in North America, lowest in Asia Pacific region
  o Developed > 2 to 3 fold developing countries

<table>
<thead>
<tr>
<th></th>
<th>North America, Men</th>
<th>Asia Pacific, Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-54</td>
<td>2.4</td>
<td>0.5</td>
</tr>
<tr>
<td>60-64</td>
<td>6.9</td>
<td>1.2</td>
</tr>
<tr>
<td>70-74</td>
<td>17.7</td>
<td>1.7</td>
</tr>
<tr>
<td>80+</td>
<td>45.7</td>
<td>3.6</td>
</tr>
</tbody>
</table>

• Major cause of stroke (OXVASC study UK, 44% of disabling strokes AF-related)

Novel Anticoagulants

**Xa inhibition**
- Direct
  - Rivaroxaban
  - Apixaban
  - Edoxaban
  - Betrixaban

- Indirect
  - Idraparinux
  - Idrabiotaparinux

**Thrombin (IIa) inhibition**
- Dabigatran

Adapted from Weitz J et al Chest 2012;141: e120s-e151s
NOACs (novel oral anticoagulants) are now called DOACs (direct oral anticoagulants).

## Direct Oral Anticoagulants

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Enzyme Target</th>
<th>Renal Clearance</th>
<th>Half Life (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>Pradaxa</td>
<td>Thrombin</td>
<td>80%</td>
<td>14 - 17</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Xarelto</td>
<td>Xa</td>
<td>33%</td>
<td>7 - 11</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Eliquis</td>
<td>Xa</td>
<td>25%</td>
<td>8 - 12</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Savaysa</td>
<td>Xa</td>
<td>35%</td>
<td>8 - 10</td>
</tr>
<tr>
<td>Betrixaban</td>
<td>Bevyxxa</td>
<td>Xa</td>
<td>11%</td>
<td>19 - 27</td>
</tr>
</tbody>
</table>

Clinical Trials of Anticoagulants for Stroke Prevention in AF

- **Warfarin vs. Placebo**
  - 2,900 Patients
  - 6 Trials of Warfarin vs. Placebo 1989-1993

- **DOACs vs. Warfarin**
  - 71,683 Patients
  - ROCKET AF (Rivaroxaban) 2010
  - ENGAGE AF-TIMI 48 (Edoxaban) 2013

- **RE-LY (Dabigatran)** 2009
- **ARISTOTLE (Apixaban)** 2011
DOAC Trials: Stroke or Systemic Embolism

Risk Ratio (95% CI)

- RE-LY [Dabigatran 150 mg] 0.66 (0.53 - 0.82)
- ROCKET AF [Rivaroxaban 20/15 mg] 0.88 (0.75 - 1.03)
- ARISTOTLE [Apixaban 5/2.5 mg] 0.80 (0.67 - 0.95)
- ENGAGE AF-TIMI 48 [Edoxaban 60/30 mg] 0.88 (0.75 - 1.02)
- Combined [Random Effects Model] 0.81 (0.73 - 0.91) p=<0.0001

Heterogeneity p=0.13

DOACs vs. Warfarin: Secondary Efficacy Outcomes

- **Ischemic Stroke**: Risk Ratio (95% CI) 0.92 (0.83 - 1.02), p=0.10
- **Hemorrhagic Stroke**: Risk Ratio (95% CI) 0.49 (0.38 - 0.64), p<0.0001
- **MI**: Risk Ratio (95% CI) 0.97 (0.78 - 1.20), p=0.77
- **All-Cause Mortality**: Risk Ratio (95% CI) 0.90 (0.85 - 0.95), p=0.0003

Heterogeneity p=NS for all outcomes

DOACs vs. Warfarin: Intracranial Hemorrhage

- Dabigatran 110 mg BID
- Dabigatran 150 mg BID
- Rivaroxaban 20 mg QD
- Apixaban 5 mg BID
- Edoxaban 30 mg
- Edoxaban 60 mg

Superiority

- Warfarin better
- DOAC better

DOACs vs. Warfarin: ISTH Major Bleeding

- Dabigatran 110 mg BID
- Dabigatran 150 mg BID
- Rivaroxaban 20 mg QD
- Apixaban 5 mg BID
- Edoxaban 30 mg
- Edoxaban 60 mg

Superiority p-value:
- 0.003
- 0.31
- 0.58
- <0.001
- <0.001
- <0.001

DOACs vs. Warfarin: Secondary Safety Outcomes

- **ICH**:
  - Risk Ratio (95% CI): 0.48 (0.39 - 0.59)
  - Heterogeneity: ICH, p=0.22
  - Favors Warfarin (p<0.0001)

- **GI Bleeding**:
  - Risk Ratio (95% CI): 1.25 (1.01 - 1.55)
  - Heterogeneity: GI Bleeding, p=0.009
  - Favors DOAC (p=0.043)

Conclusions from Clinical Trials of DOACs for Stroke Prevention in Atrial Fibrillation

- All are at least as effective as warfarin
- All reduce the risk of intracranial bleeding
- Most regimens reduced major bleeding
- Heterogeneity for GI bleeding
- Achieve a 10% relative risk reduction in mortality
- Drugs given in fixed doses without anticoagulant monitoring
## Treatment of Venous Thromboembolism

<table>
<thead>
<tr>
<th>Initial (acute) treatment</th>
<th>Long term treatment</th>
<th>Extended treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin</td>
<td>Vitamin K Antagonists</td>
<td>Vitamin K Antagonists</td>
</tr>
<tr>
<td>LMWH</td>
<td>LMWH</td>
<td>ASA 100 mg</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>Oral XaI or dabigatran</td>
<td>Oral XaI or dabigatran</td>
</tr>
<tr>
<td>Thrombolysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombus Removal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVC filter</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Rivaroxaban
- Apixaban

- **5 to 10 days**
- **3 to 6 months**
- **> 6 months**
## VTE Treatment Studies Direct Oral Anticoagulants

<table>
<thead>
<tr>
<th></th>
<th>Hokusai-VTE</th>
<th>AMPLIFY</th>
<th>EINSTEIN-DVT</th>
<th>RE-COVER I</th>
<th>RE-COVER II</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug</strong></td>
<td>Edoxaban</td>
<td>Apixaban</td>
<td>Rivaroxaban</td>
<td>Dabigatran</td>
<td></td>
</tr>
<tr>
<td><strong>Study design</strong></td>
<td>Double-blind</td>
<td>Double-blind</td>
<td>Open label</td>
<td>Double-blind</td>
<td></td>
</tr>
<tr>
<td><strong>Heparin lead-in</strong></td>
<td>At least 5 days</td>
<td>None</td>
<td>None</td>
<td>At least 5 days</td>
<td></td>
</tr>
</tbody>
</table>
| **Dose**              | 60 mg qd  
30 mg qd  
(CrCl, bw, P-gp) | 10 mg bid x 7 days then 5 mg bid | 15 mg bid x 3 wk then 20 mg qd | 150 mg bid |
| **Non-inferiority margin** | 1.5     | 1.8     | 2.0          | 2.75       |
| **Sample size**       | 8,292       | 5,400   | 3,449        | 2,564      | 2,568      |
| **Treatment duration**| Flexible  
3 to 12 months | 6 months | Pre-specified  
3, 6, or 12 months | 6 months |

Source: Adapted from Raskob et al. J Thromb Haemost 2013; 11: 1287 - 1294
Recurrent VTE and VTE-related Death

<table>
<thead>
<tr>
<th>Medication</th>
<th>HR (95% CI)</th>
<th>P-value (non-inferiority)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>1.00</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>1.00</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Apixaban</td>
<td>1.00</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>1.00</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Major Bleeding

- Dabigatran
- Rivaroxaban
- Apixaban
- Edoxaban

P-value (superiority)

- NS
- <0.002
- <0.001
- NS

Major and CRNB

- Dabigatran
- Rivaroxaban
- Apixaban
- Edoxaban

P-value

- <0.001
- 0.27
- <0.001
- 0.004

Conclusions from Clinical Trials of DOACs for VTE Treatment

All are at least as effective as warfarin

All reduce the risk of clinically relevant bleeding

Rivaroxaban and apixaban can be given as oral, single drug regimens

Given as a fixed dose, without routine anticoagulant monitoring
Anticoagulant Treatment of VTE
Risk-Benefit of DOAC vs. Vitamin K Antagonist

<table>
<thead>
<tr>
<th>Risk Event</th>
<th>DOAC</th>
<th>VKA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute risk of recurrent VTE</td>
<td>2.0 %</td>
<td>2.2 %</td>
</tr>
<tr>
<td>RR 0.90 (95% CI 0.77 to 1.06)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute risk of major bleeding</td>
<td>1.1 %</td>
<td>1.8 %</td>
</tr>
<tr>
<td>NNT = 147</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute risk of intracranial bleeding</td>
<td>0.1 %</td>
<td>0.3 %</td>
</tr>
<tr>
<td>NNT = 588</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute risk of fatal bleeding</td>
<td>0.1 %</td>
<td>0.2 %</td>
</tr>
<tr>
<td>NNT = 1,250</td>
<td></td>
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</tbody>
</table>

Clinical Presentations of VTE

• Provoked (70% of all patients)
  • Associated with known risk factors
  • Hospital, surgery, cancer, medical illness
  • Risk factors may be continuing (cancer, APLA)
  • If risk factor reversible (transient), 2% per year recurrence after 3 months of anticoagulant therapy

• Unprovoked (30% of all patients)
  • Absence of identifiable risk factor
  • Also called “idiopathic”
  • 7% to 11% per year recurrence for DVT or PE if anticoagulant therapy stopped after 3, 6, 12 or 24 months

Management of Unprovoked VTE

Stop anticoagulant therapy

ASA therapy

3 months

Continue anticoagulant therapy

Identify selected patients at low risk to stop anticoagulant therapy
# AMPLIFY Extended Treatment Trial Recurrent VTE

## Cumulative Event Rates

<table>
<thead>
<tr>
<th>Months</th>
<th>No. at risk</th>
<th>Baseline</th>
<th>Month 3</th>
<th>Month 6</th>
<th>Month 9</th>
<th>Month 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>826</td>
<td>826</td>
<td>796</td>
<td>768</td>
<td>743</td>
<td>471</td>
</tr>
<tr>
<td>Apixaban 2.5 mg</td>
<td>813</td>
<td>807</td>
<td>769</td>
<td>791</td>
<td>743</td>
<td>471</td>
</tr>
<tr>
<td>Apixaban 5 mg</td>
<td>840</td>
<td>836</td>
<td>825</td>
<td>818</td>
<td>533</td>
<td>513</td>
</tr>
</tbody>
</table>

**NNT to prevent one recurrent event = 14**

<table>
<thead>
<tr>
<th>Event</th>
<th>Apixaban 2.5 mg N=840</th>
<th>Apixaban 5 mg N=811</th>
<th>Placebo N=826</th>
<th>Apixaban 2.5 mg vs placebo RR (95% CI)</th>
<th>Apixaban 5 mg vs placebo RR (95% CI)</th>
<th>Apixaban 2.5 mg vs 5 mg RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleed</td>
<td>2 (0.2)</td>
<td>1 (0.1)</td>
<td>4 (0.5)</td>
<td>0.49 (0.09, 2.64)</td>
<td>0.25 (0.03, 2.24)</td>
<td>1.93 (0.18, 21.25)</td>
</tr>
<tr>
<td>Clinically relevant non-major bleed</td>
<td>25 (3.0)</td>
<td>34 (4.2)</td>
<td>19 (2.3)</td>
<td>1.29 (0.72, 2.33)</td>
<td>1.82 (1.05, 3.18)</td>
<td>0.71 (0.43, 1.18)</td>
</tr>
<tr>
<td>Major or clinically relevant non-major bleeding</td>
<td>27 (3.2)</td>
<td>35 (4.3)</td>
<td>22 (2.7)</td>
<td>1.20 (0.69, 2.10)</td>
<td>1.62 (0.96, 2.73)</td>
<td>0.74 (0.46, 1.22)</td>
</tr>
</tbody>
</table>

Major Bleeds
- 2.5 mg: 2 events, both Intraocular
- 5.0 mg: 1 event, Gastrointestinal
- Placebo: 4 events, Intraocular, Stroke, Urogenital, Gastrointestinal

# EINSTEIN Choice Trial of Extended Treatment VTE

Rivaroxaban vs. ASA

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rivaroxaban 20 mg N= 1107</th>
<th>Rivaroxaban 10 mg N= 1127</th>
<th>ASA 100 mg N= 1131</th>
<th>Rivaroxaban 20 mg vs ASA HR (95% CI)</th>
<th>Rivaroxaban 10 mg vs ASA HR (95% CI)</th>
<th>Rivaroxaban 20 mg vs 10 mg HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE</td>
<td>17 (1.5%)</td>
<td>13 (1.2%)</td>
<td>50 (4.4%)</td>
<td>0.34 (0.20, 0.59)</td>
<td>0.26 (0.14, 0.47)</td>
<td>1.34 (0.65, 2.75)</td>
</tr>
<tr>
<td>Major bleed</td>
<td>6 (0.5%)</td>
<td>5 (0.4%)</td>
<td>3 (0.3%)</td>
<td>2.01 (0.50, 8.04)</td>
<td>1.64 (0.39, 6.84)</td>
<td>1.23 (0.37, 4.03)</td>
</tr>
<tr>
<td>Major or clinically relevant non-major bleeding</td>
<td>36 (3.3%)</td>
<td>27 (2.4%)</td>
<td>23 (2.0)</td>
<td>1.59 (0.94, 2.69)</td>
<td>1.16 (0.67, 2.03)</td>
<td>1.37 (0.83, 2.26)</td>
</tr>
</tbody>
</table>

Type of Major Bleeds
- Fatal, 1 rivaroxaban 20 mg, 1 ASA
- Intracranial, 3 rivaroxaban 20 mg, 1 rivaroxaban 10 mg, 2 ASA
- GI: 1 rivaroxaban 20 mg, 2 rivaroxaban 10 mg, 1 ASA

At rest or at risk?
Importance of Thromboprophylaxis

Hospitalization increases the risk of VTE 6- to 13-fold

About 1.7% of medical patients develop VTE within 3 months of hospitalization

Up to 60% of patients with VTE have a history of recent hospitalization and 75% of fatal PE occur in medical patients

PE is the number one cause of preventable death in hospitalized patients

Anticoagulant Prophylaxis of VTE in Hospital 2007 Meta-analysis

<table>
<thead>
<tr>
<th>Outcome to prevent</th>
<th>RRR (RRI)</th>
<th>ARR (ARI)</th>
<th>NNT (NNH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic DVT</td>
<td>0.47 (0.22-1.00)</td>
<td>0.51</td>
<td>196</td>
</tr>
<tr>
<td>Symptomatic PE (fatal + non-fatal)</td>
<td>0.43 (0.26-0.69)</td>
<td>0.29</td>
<td>345</td>
</tr>
<tr>
<td>Fatal PE</td>
<td>0.38 (0.21-0.69)</td>
<td>0.25</td>
<td><strong>400</strong></td>
</tr>
<tr>
<td>Asymptomatic DVT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- any</td>
<td>0.51 (0.39-0.67)</td>
<td>2.6</td>
<td>36</td>
</tr>
<tr>
<td>- proximal</td>
<td>0.45 (0.31-0.65)</td>
<td>1.8</td>
<td>55</td>
</tr>
<tr>
<td>Bleeding</td>
<td>(1.32 [0.73-2.37])</td>
<td>(0.14)</td>
<td>(714)</td>
</tr>
</tbody>
</table>

Call-to-Action for VTE Risk Assessment by the ISTH Steering Committee for World Thrombosis Day

• A global call to action for VTE risk assessment in hospitalized patients by the ISTH Steering Committee for World Thrombosis Day

• Utilize the following VTE RAMs based on best available evidence
  • NHS England Tool
  • Caprini Tool for surgical patients
  • IMPROVE Tool for medical patients

Effective January 1, 2017 the Centers for Medicare and Medicaid Services (CMS) emphasized VTE risk assessment
MARINER Study Design

Screening Phase+

Randomization

Stratum 1
Subjects with CrCl ≥30 and <50 mL/min
1:1 ratio

Rivaroxaban 7.5 mg daily

Placebo

Stratum 2
Subjects with CrCl ≥50 mL/min
1:1 ratio

Rivaroxaban 10 mg daily

Placebo

Double-Blind Treatment Phase

Post-treatment Phase

30 follow-up

Day -10

Day 1

Day 45 (EOT)

Day 75 (EOT)

Acute medical condition plus: 1. Total IMPROVE VTE Risk Score ≥4 or 2. Total IMPROVE VTE Risk Score of 2 or 3 and elevated D-dimer (>2x ULN)

Primary Efficacy Endpoint: Composite of symptomatic VTE or VTE-related death
Secondary Efficacy Endpoint: VTE-related death (hierarchical design)
Primary Safety Endpoint: Major Bleeding (ISTH Definition)

Estimated Sample Size – Event Driven Study

<table>
<thead>
<tr>
<th>Sample size</th>
<th>Placebo</th>
<th>RRR</th>
<th>Events</th>
<th>Power for superiority</th>
<th>2 sided α</th>
</tr>
</thead>
<tbody>
<tr>
<td>12,000</td>
<td>2.5%</td>
<td>40%</td>
<td>161</td>
<td>90%</td>
<td>5%</td>
</tr>
</tbody>
</table>

## Key Inclusion and Exclusion Criteria

### Key inclusion criteria*
- Patients ≥ 40 years hospitalized for 3-10 days with thromboprophylaxis (LMWH or UFH) prior to randomization for one of the following acute medical conditions
  - Heart failure
  - Acute respiratory insufficiency or acute exacerbation of COPD
  - Acute ischemic stroke
  - Acute infectious diseases
  - Inflammatory diseases, including rheumatic disease
- Total modified IMPROVE VTE Risk Score ≥ 4 OR total modified IMPROVE VTE Risk Score 2 or 3 and D dimer > 2x ULN during index hospitalization

### Key exclusion criteria*
- **Bleeding Risks**
  - Any bleeding within 3 months
  - Surgery, biopsy or trauma 4 weeks prior or planned
  - Active gastroduodenal ulcer
  - Active cancer
- **Required anticoagulation after discharge**
- **Use of dual antiplatelet therapy during the index hospitalization**
- **Concomitant Medications**
  - Combined P-gp and strong CYP3A4 inhibitors
  - Combined P-gp and strong CYP3A4 inducers

*Reflects I/E Criteria as of INT-7

MARINER Primary Efficacy Outcome

Symptomatic VTE and VTE related Death up to Day 45

HR 0.76
(95% CI 0.52 to 1.09)
24% RRR
0.27% ARR

Rivaroxaban (N=6007)

Placebo (N=6012)

P=0.136
Randomization Stratified by Baseline Renal Function

Symptomatic VTE and VTE-related Death up to Day 45

<table>
<thead>
<tr>
<th>Treatment</th>
<th>CrCl (ml/min)</th>
<th>Event Rate</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban 10 mg (N=4909)</td>
<td>≥50</td>
<td>0.65</td>
<td>0.075</td>
</tr>
<tr>
<td>Placebo (N=4913)</td>
<td></td>
<td>0.98</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban 7.5 mg (N=1098)</td>
<td>30 to 49</td>
<td>1.64</td>
<td>0.994</td>
</tr>
<tr>
<td>Placebo (N=1099)</td>
<td></td>
<td>1.64</td>
<td></td>
</tr>
</tbody>
</table>

Secondary Efficacy Outcomes up to Day 45

VTE-related Death

HR 0.93 (95% CI, 0.62 – 1.42)

P = 0.751

Symptomatic VTE

HR 0.44 (95% CI, 0.22 – 0.89)

P = 0.023

56% RRR, ARR 0.24%

Secondary Efficacy Outcomes up to Day 45

Symptomatic VTE and All-Cause Mortality

- Symptomatic VTE, MI, Ischemic Stroke and CV Death
- All-Cause Mortality

27% RRR
0.30% ARR

## COMPASS Trial of Rivaroxaban for Stable CVD

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rivaroxaban 2.5 mg bid + ASA 100 mg (N = 9152)</th>
<th>Rivaroxaban 5 mg bid (N = 9117)</th>
<th>ASA 100 mg (N = 9126)</th>
<th>Rivaroxaban + ASA vs ASA RR (95% CI)</th>
<th>Rivaroxaban vs ASA RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death, Stroke, or MI</td>
<td>379 (4.1%)</td>
<td>448 (4.9%)</td>
<td>496 (5.4%)</td>
<td>0.76 (0.66, 0.86)</td>
<td>0.90 (0.79, 1.03)</td>
</tr>
<tr>
<td>CV death</td>
<td>160 (1.7%)</td>
<td>195 (2.1%)</td>
<td>203 (2.2%)</td>
<td>0.78 (0.64, 0.96)</td>
<td>0.96 (0.79, 1.17)</td>
</tr>
<tr>
<td>Death (all causes)</td>
<td>313 (3.4%)</td>
<td>366 (4.0%)</td>
<td>378 (4.1%)</td>
<td>0.82 (0.71, 0.96)</td>
<td>0.97 (0.84, 1.12)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>288 (3.1%)</td>
<td>255 (2.8%)</td>
<td>170 (1.9%)</td>
<td>1.70 (1.40, 2.05)</td>
<td>1.51 (1.25, 1.84)</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>15 (0.2%)</td>
<td>14 (0.2%)</td>
<td>10 (0.1%)</td>
<td>1.49 (0.67, 3.33)</td>
<td>1.40 (0.62, 3.15)</td>
</tr>
</tbody>
</table>


---

**Outcome**

Rivaroxaban 2.5 mg bid + ASA 100 mg
N = 9152

Rivaroxaban 5 mg bid
N = 9117

ASA 100 mg
N = 9126

Rivaroxaban + ASA vs ASA
RR (95% CI)

Rivaroxaban vs ASA
RR (95% CI)

CV death, Stroke, or MI:
- Rivaroxaban: 379 (4.1%)
- ASA: 496 (5.4%)
- RR: 0.76 (0.66, 0.86)

CV death:
- Rivaroxaban: 160 (1.7%)
- ASA: 203 (2.2%)
- RR: 0.78 (0.64, 0.96)

Death (all causes):
- Rivaroxaban: 313 (3.4%)
- ASA: 378 (4.1%)
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Major bleeding:
- Rivaroxaban: 288 (3.1%)
- ASA: 170 (1.9%)
- RR: 1.70 (1.40, 2.05)

Fatal bleeding:
- Rivaroxaban: 15 (0.2%)
- ASA: 10 (0.1%)
- RR: 1.49 (0.67, 3.33)
## Which DOAC should be used?

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Drug Choice</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl 30-50 ml/min</td>
<td>Rivaroxaban, Apixaban, Edoxaban</td>
<td>Less affected by renal impairment than dabigatran</td>
</tr>
<tr>
<td>Dyspepsia or upper GI complaints</td>
<td>Rivaroxaban, Apixaban, Edoxaban</td>
<td>Dyspepsia with dabigatran in up to 10% of patients</td>
</tr>
<tr>
<td>History of GI bleeding</td>
<td>Apixaban</td>
<td>More GI bleeding with dabigatran, rivaroxaban and edoxaban</td>
</tr>
<tr>
<td>Significant CAD or PAD</td>
<td>Rivaroxaban</td>
<td>22% RRR in CVD in COMPASS Small increase in MI with dabigatran</td>
</tr>
<tr>
<td>All oral, single drug preferred for VTE treatment</td>
<td>Rivaroxaban, Apixaban</td>
<td>Dabigatran, edoxaban require heparin lead - in</td>
</tr>
<tr>
<td>Once daily dosing preferred</td>
<td>Rivaroxaban, Edoxaban</td>
<td>Only agents given once-daily</td>
</tr>
</tbody>
</table>
Reasons to use Warfarin

- Stable on warfarin, monitoring not a burden
- Mechanical heart valves
- Creatinine clearance < 30 ml/min
Reversal of DOAC Anticoagulation

**Idarucizumab**

- Mab fragment highly specific for dabigatran, given IV
- Rapid, complete reversal of anticoagulant effect within 4 hrs
- Median time to cessation of bleeding 2.5 hrs
- Median time to initiation of procedure 1.6 hr
- Peri-procedural hemostasis normal > 90%
- Chronic treatment of heart failure associated with CAD
- No apparent excess of subsequent thrombotic events
- No serious adverse safety signal

Andexanet Alfa

- Recombinant, modified human Factor Xa decoy protein
- Designed for reversal all FXa inhibitors
- IV bolus, then 2hr infusion, dose based on time of last FXa inhibitor dose
- Post bolus median anti-Fxa activity decreased by 89% for rivaroxaban
- Post bolus median anit-FXa activity decreased by 93% for apixaban
- 4 hrs post infusion 30% to 39% decrease in anti-Fxa activity
  (redistribution of DOAC)
- Clinical hemostasis 12 hrs post infusion good/excellent in 79%
- Thrombotic events in 12 of 67 patients (18%) at 30 day follow up

Novel anticoagulants - the Future

**Xa inhibition**
- **Direct**
  - Rivaroxaban
  - Apixaban
  - Edoxaban
  - Betrixaban
- **Indirect**
  - Idraparinux
  - Idrabiotaparinux

**Thrombin (IIa) inhibition**
- Dabigatran

**Factor XI target**
- Mab to F XI
- Mab to F XIa
- Small molecule Direct F XIa inhibitor

Adapted from Weitz J et al Chest 2012;141: e120s-e151s
Summary

• DOACs have transformed anticoagulant therapy
  - improved safety (reduced bleeding)
  - ease of use for clinician and patient
• DOACs preferred for most patients with AF or treatment of VTE
• Risk-benefit calculus shifting to extended anticoagulation in VTE
• For hospitalized medical patients, risk-benefit of thromboprophylaxis extended after discharge is fine trade off, population effect important
• Chronic anticoagulation with DOAC (rivaroxaban) likely indicated for many patients with stable CVD (awaiting FDA decision, Europe approved)
• DOAC reversal available, ultimate clinical role to be defined
• F XI is a promising target for future anticoagulant development