Update on Anticoagulation and Reversals for Direct Oral Anticoagulants

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Cardiac Critical Care Pharmacist
Presbyterian Healthcare Services
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USA

Disclosures

<table>
<thead>
<tr>
<th>Research Support</th>
<th>North American Thrombosis Forum, McMaster University</th>
</tr>
</thead>
<tbody>
<tr>
<td>Employee</td>
<td>Presbyterian Healthcare Services</td>
</tr>
<tr>
<td>Consultant and/or Honoraria</td>
<td>New York Hospital Association, Anticoagulation Forum, Pharmacy Times, Point of Care Software Solutions, Janssen, Daiichi Sankyo, Boehringer-Ingelheim, Pfizer, Bristol-Myers Squibb, Eisai, Polymedix Inc., Leo Pharm,</td>
</tr>
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<td>McMaster University, Presbyterian Healthcare, American Society of Health System Pharmacists, National Quality Forum</td>
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<tr>
<td>Stockholder</td>
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<tr>
<td>Speakers Bureau</td>
<td>Janssen, Boehringer-Ingelheim, Pfizer, Bristol-Myers Squibb, Portola</td>
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<tr>
<td>Scientific Advisory Board</td>
<td>Daiichi-Sankyo, Boehringer-Ingelheim, Janssen, Pfizer, Leo, Eisai, Portola</td>
</tr>
</tbody>
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Objectives

- Identify Current Direct Anticoagulants and their pharmacokinetic and pharmacodynamic properties
- Discuss new DOAC studies and agents in
  - Extended medical thromboprophylaxis
  - Coronary/peripheral artery disease
  - Non-valvular Atrial fibrillation and PCI (cardiac stents)
  - and extended venous thromboembolism treatment
- Recognize current and investigational reversal agents for DOACs

The evolution of anticoagulant drugs
New anticoagulants

- Pegnivacogin
  - TTP889 - halted
- TFPI (tifacogin)
- NAPc2
- Indirect Xa
- Fondaparinux
- Ifrabiotaparinux?
- Semuloparin
- M118
- Direct Xa
- Rivaroxaban
- Apixaban
- Edoxaban
- Betrixaban
- Otamixaban
- TAK 442
- SR123781A - halted
- Barexaban - halted
- DX-9065a - halted

- APC (drotrecogin alfa) - Withdrawn from market
- Recombolin TB-402
- Indirect Xa
- Fondaparinux
- Idrabiotaparinux?
- Semuloparin M118

- Fibrinogen
- AT Dependent
- Newer Targets
- Factor IX - Pegnivacogin
- Factor XI - ISIS 416858 antisense oligonucleotide, antibodies, aptamers
- Factor XII - antisense oligonucleotides, antibodies, aptamers

2. Weitz et al. CHEST 2012

DOACs: Approved Indications

<table>
<thead>
<tr>
<th>Agent</th>
<th>EU</th>
<th>US</th>
<th>Canada</th>
<th>Japan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td>NVAF, VTE OrtPX, VTE TX, ACS</td>
<td>NVAF, VTE OrtPX, VTE TX</td>
<td>NVAF, VTE OrtPX, VTE TX</td>
<td>NVAF, VTE OrtPX, VTE TX</td>
</tr>
<tr>
<td>Apixaban</td>
<td>NVAF, VTE OrtPX</td>
<td>NVAF, VTE OrtPX VTE TX</td>
<td>NVAF, VTE OrtPX</td>
<td>NVAF</td>
</tr>
<tr>
<td>Betrixaban</td>
<td>Under Review</td>
<td>Medical Thrombo-prophylaxis</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>NVAF, VTE OrtPX VTE TX</td>
<td>NVAF, VTE TX VTE OrtPX</td>
<td>NVAF, VTE OrtPX</td>
<td>NVAF</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>NVAF VTE TX</td>
<td>NVAF VTE TX</td>
<td>NVAF VTE TX</td>
<td>NVAF VTE TX</td>
</tr>
</tbody>
</table>

ACS = acute coronary syndrome; NVAF = non-valvular atrial fibrillation; OrtPX = Ortho prophylaxis; TX = treatment; VTE = venous thromboembolism

### US Indications and Dosage

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Apixaban</th>
<th>Rivaroxaban**</th>
<th>Edoxaban</th>
<th>Betrixaban</th>
</tr>
</thead>
</table>
| Non-valvular atrial fibrillation | 150 mg PO BID
75 mg PO BID* CrCl <15 mL/min Avoid use | 5 mg PO BID 2.5 mg PO BID* | 20 mg PO daily 15 mg PO daily*
CrCl <15 mL/min Avoid use | 60 mg PO daily 30 mg PO daily
CrCl <15 mL/min Avoid use | N/A |
| VTE prophylaxis (orthopedic) | 110 mg x1, then 220 mg daily | 2.5 mg PO BID | 10 mg PO daily
CrCl <30 mL/min Avoid use | N/A | N/A |
| VTE treatment and prevention of recurrence | 150 mg PO BID after 5-10 days of parenteral anticoagulation
CrCl <30 mL/min Avoid use | 10 mg PO BID x 7 days then 5 mg PO BID
Ext: 2.5 mg PO BID | 15 mg PO BID x 21 days, then 20 mg PO daily
Ext: 20 mg or 10 mg?
CrCl <30 mL/min Avoid use | 60 mg PO BID after 5-10 days of parenteral anticoagulation
Ext: not studied
CrCl <30 mL/min Avoid use | N/A |
| VTE prophylaxis in acute medical illness | N/A | N/A | Under Investigation Results likely in Summer 2018 | N/A | 160 mg PO x 1 then 80 mg PO QDay or 80 mg
PO x 1 then 40 mg Qday*** CrCl <15 mL/min Avoid use |

* Adjusted for renal impairment, drug interactions, age, low weight or a combination of these factors
** Treatment doses of rivaroxaban should be taken with largest meal of the day
*** For CrCl 15-30 mL/min or with concurrent use of strong P-GP Inhibitors – Duration 35-42 days

### Pharmacokinetics of DOACs

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
<th>Betrixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct factor inhibition</td>
<td>IIa</td>
<td>Xa</td>
<td>Xa</td>
<td>Xa</td>
<td>Xa</td>
</tr>
<tr>
<td>Onset of Action, minutes</td>
<td>&lt; 30 min</td>
<td>&lt; 30 min</td>
<td>&lt; 30 min</td>
<td>&lt; 30 min</td>
<td>&lt; 30 min</td>
</tr>
<tr>
<td>Bioavailability (F_rel)</td>
<td>6%</td>
<td>80%</td>
<td>80%</td>
<td>&gt; 50%</td>
<td>50%</td>
</tr>
<tr>
<td>Peak action (t_max)</td>
<td>1–3 hr</td>
<td>1–3 hr</td>
<td>1–3 hr</td>
<td>1–2 hr</td>
<td>3–4 hr</td>
</tr>
<tr>
<td>Protein binding</td>
<td>35%</td>
<td>92 – 95%</td>
<td>84%</td>
<td>55%</td>
<td>60%</td>
</tr>
<tr>
<td>Renal clearance</td>
<td>80%</td>
<td>36%</td>
<td>27%</td>
<td>35 - 39%</td>
<td>5 – 11%</td>
</tr>
<tr>
<td>Duration of Action, hours</td>
<td>24 – 36</td>
<td>24</td>
<td>≥ 24</td>
<td>≤ 24</td>
<td>~ 36-48 hrs</td>
</tr>
<tr>
<td>Elimination half life – varying renal function</td>
<td>13.8 - 27.5 hr</td>
<td>8.3 -9.5 hr</td>
<td>15.1 - 17.3 hr</td>
<td>8.6 - 16.9 hrs</td>
<td>19 – 27 hrs</td>
</tr>
<tr>
<td>Effect of Food</td>
<td>None</td>
<td>Increases Absorption</td>
<td>None</td>
<td>None</td>
<td>Decreases Absorption</td>
</tr>
<tr>
<td>Drug Interactions</td>
<td>P-GP</td>
<td>P-GP and CYP-3A4</td>
<td>P-GP and CYP-3A4</td>
<td>P-GP</td>
<td>P-GP</td>
</tr>
<tr>
<td>Antidote</td>
<td>Idarucizumab</td>
<td>Andexanet</td>
<td>Andexanet</td>
<td>Andexanet</td>
<td>Andexanet</td>
</tr>
</tbody>
</table>

Venous Thromboembolism Prevention in the Medical Patient

VTE Prevention Medical Patients – 9th ACCP Recommendations

Risk Stratification for bleeding and VTE then:

At-risk for VTE, Low Bleed Risk
- Low molecular weight heparin (LMWH) (1B)
- Low dose unfractionated heparin (LDUH) BID or TID (1B)
- Fondaparinux (1B)

At-risk for VTE, High Bleed Risk or actively bleeding
- Optimal use of graduated compression stockings (GCS) or intermittent pneumatic compression (IPC) (2C)
- When bleeding risk subsides and if VTE risk persists, pharmacologic TP as above. (2B)

We suggest against extending the duration of thromboprophylaxis beyond the period of patient immobilization or acute hospital stay (2B)

Kahn et al. CHEST 2012;141:E195S-E226S
**IMPROVE (IMPACT-ILL) RAM for VTE - evidence based derivation**

<table>
<thead>
<tr>
<th>VTE Risk Factor</th>
<th>Points For the Risk Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMmobilization ≥7 days</td>
<td>1</td>
</tr>
<tr>
<td>Previous VTE</td>
<td>3</td>
</tr>
<tr>
<td>Age &gt; 60 years</td>
<td>1</td>
</tr>
<tr>
<td>Current cancer</td>
<td>2</td>
</tr>
<tr>
<td>Thrombophilia</td>
<td>2</td>
</tr>
<tr>
<td>ICU/CCU stay</td>
<td>1</td>
</tr>
<tr>
<td>Lower Limb paralysis</td>
<td>2</td>
</tr>
</tbody>
</table>

Three-Tiered Risk Assessment Model
0-1 Points = Low Risk, 2-3 Points = Moderate Risk, ≥ 4 points = High Risk

1. Spyropoulos AC et al., *CHEST* 2011 Sep;140(3):706-14

**Extended-duration DOACs for VTE Prevention in Hospitalized Medical Patients:**

- **EXCLAIM**: enoxaparin
- **ADOPT**: apixaban
- **MAGELLAN**: rivaroxaban
- **APEX**: betrixaban
- **MARINER**: rivaroxaban
Summary of Extended Med Prevention Trials

**EXCLAIM**
Enoxaparin

RRR = 38.0%
p < 0.042

**ADOPT**
Apixaban

RRR = 12.9%
p = 0.44

**MAGELLAN**
Rivaroxaban

RRR = 22.8%
p = 0.02

**APEX**
Betrexaaban

RRR = 24.0%
p = 0.006

Incidence

<table>
<thead>
<tr>
<th>Study</th>
<th>Incidence</th>
<th>Major Bleeding</th>
<th>Net Clinical Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXCLAIM – enoxaparin N=5,963</td>
<td>VTE ↓ Major Bleeding ↑</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>MAGELLAN – rivaroxaban N=8,101</td>
<td>VTE ↓ Major Bleeding ↑</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>ADOPT – apixaban N=6,528</td>
<td>VTE ↔ Major Bleeding ↑</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>APEX – betrixaban N = 7513</td>
<td>VTE ↓ Major Bleeding ↔</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>
Failures of Earlier Phase 3 Trials
Extended Thromboprophylaxis

- Not enough benefit
  - How do we select an “at risk” subgroup of heterogeneous medical patients that would benefit from extended thromboprophylaxis?

- Too much harm
  - How do we minimize harm to key patient subgroups, especially given excellent safety profile of LMWH and Placebo?

WHY would we need Extended-duration DOACs for VTE Prevention in Hospitalized Medical Patients?
Baseline Dd ROC (MAGELLAN)

An important finding from the Magellan study was that D-dimer may also be used as a biomarker or risk factor for the development of future VTE in medical patients.


Hospital Length of Stay has Decreased Over Time in Countries Targeted for Participation in the Study

Average length of stay in hospital for all causes, 2000 and 2010 (or nearest year)

- Lengths of hospital stay have SIGNIFICANTLY shortened in the last 15-20 years
- US averages 3-4 days where original VTE prophylaxis trials were 6-14 days

Source: OECD Health Data 2012; Eurostat Statistics Database; WHO European Health For All Database.
Post-Discharge Thromboprophylaxis in Medical Patients – US Data

- N = 141,628 from US claims analysis
- Mean/median LOS days (SD) – 5.9/4.0 days
- 3.9% received post-discharge TP (92% warfarin)
  - Hospital Px use did NOT reduce risk of post-discharge VTE (p = 0.398)
- Overall Sx VTE at 90 days – 1.9%

Claims analysis: predictors of post-discharge venous thromboembolism (VTE) N = 141,628.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥65 years</td>
<td>1.27*</td>
<td>1.17-1.38</td>
</tr>
<tr>
<td>History of VTE</td>
<td>3.95*</td>
<td>3.33-4.80</td>
</tr>
<tr>
<td>Thrombophilia</td>
<td>1.65*</td>
<td>1.34-1.97</td>
</tr>
<tr>
<td>Varicose veins</td>
<td>1.36*</td>
<td>1.08-1.76</td>
</tr>
<tr>
<td>Malignancy without intravenous chemotherapy</td>
<td>1.36*</td>
<td>1.15-1.45</td>
</tr>
<tr>
<td>Length of hospital stay ≥3 days</td>
<td>1.02</td>
<td>0.91-1.15</td>
</tr>
<tr>
<td>All-cause re-hospitalization</td>
<td>3.87*</td>
<td>3.65-4.17</td>
</tr>
</tbody>
</table>

*p ≤ 0.05, yes vs. no VTE prophylaxis

Spyropoulos AC et al. Chest 2011; 10.1378;10-194

Shorter Durations of Thromboprophylaxis May be Inadequate

May need 35-45 days of thromboprophylaxis in this population

Spyropoulos AC et al. Chest 2011; 10.1378;10-194
APEX Design – Target Patients

**HOSPITALIZED FOR ACUTE MEDICAL ILLNESS FOR 3 DAYS**
- Heart Failure, Respiratory Failure, Infectious Disease, Rheumatic Disease, or Ischemic Stroke

**EXPECTED MODERATE / SEVERE IMMOBILITY**
- Expected severe immobilization for 24h during hospitalization and moderate and/or severe immobilization 23 days after admission with anticipated survival of ≥8 weeks

**AGE AND ADDITIONAL VTE RISK FACTORS**

<table>
<thead>
<tr>
<th>≥75 years</th>
<th>60 to 74 years</th>
<th>40 to 59 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligible</td>
<td>2 Additional Risk Factors OR D-Dimer ≥ 2x ULN</td>
<td>2 Additional Risk Factors OR D-Dimer ≥ 2x ULN</td>
</tr>
<tr>
<td></td>
<td>+ History of VTE OR History of Cancer</td>
<td>+ History of VTE OR History of Cancer</td>
</tr>
</tbody>
</table>

- Patients with CrCl ≥ 15 and < 30 mL/min were included

**Additional Risk Factors:**
- Previous VTE or superficial vein thrombosis
- History of NYHA Class III or IV HF
- Concomitant acute infection
- Obesity (BMI >35)
- History of cancer
- Inherited or acquired thrombophilia
- Current use of erythropoiesis stimulating agent
- Hormone therapy

ULN: Upper Limit of Normal

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APEX Study Design

**Objective**
Demonstrate the superiority of extended duration (35-42 days) anticoagulation with betrixaban compared to standard of care anticoagulation with enoxaparin (6-14 days)

<table>
<thead>
<tr>
<th>Enoxaparin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median length of treatment: 9 days</td>
<td>Median length of treatment: 36 days</td>
</tr>
</tbody>
</table>

**Dosing adjustments:**
- In severe renal insufficiency (CrCl 15 to <30 mL/min): Betrixaban 40 mg (80 mg loading dose) and enoxaparin 20 mg SC daily
- In patients taking concomitant strong P-gp inhibitors: Betrixaban 40 mg (80 mg loading dose), no dose adjustment for enoxaparin
APEX Primary Efficacy Endpoint
mITT population

**PRIMARY COMPOSITE ENDPOINT: VTE at Day 42 ***

<table>
<thead>
<tr>
<th></th>
<th>Enoxaparin/Placebo</th>
<th>Betrixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event Rate (%)</td>
<td>6.0%</td>
<td>4.4%</td>
</tr>
<tr>
<td>Event Rate (%)</td>
<td>223 / 3720</td>
<td>165 / 3721</td>
</tr>
</tbody>
</table>

Composite of asymptomatic proximal DVT between day 32 and day 47, symptomatic proximal or distal DVT, symptomatic nonfatal PE, or death from vVTE between day 1 and day 42.

* Asymptomatic DVT measured up to Day 47

mITT=modified intent-to-treat; RRR=relative risk reduction.

APEX Safety Results: Major Bleeding

**SAFETY (PRIMARY ENDPOINT) MAJOR BLEEDING**

<table>
<thead>
<tr>
<th></th>
<th>Enoxaparin (N=3716) n (%)</th>
<th>Betrixaban (N=3716) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Bleeding</td>
<td>21 (0.57)</td>
<td>25 (0.67)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>9 (0.24)</td>
<td>19 (0.51)</td>
</tr>
<tr>
<td>Intracranial</td>
<td>7 (0.19)</td>
<td>2 (0.05)</td>
</tr>
<tr>
<td>Intraocular</td>
<td>1 (0.03)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (0.11)</td>
<td>4 (0.11)</td>
</tr>
<tr>
<td>Fatal Bleeding *</td>
<td>1 (0.03)</td>
<td>1 (0.03)</td>
</tr>
</tbody>
</table>

Other major bleeding includes hematoma, pericardial, rectal, epistaxis

* One pericardial fatal bleed in the betrixaban group and one ICH fatal bleed in the enoxaparin group

No significant difference in major bleeding with extended duration betrixaban for a median of 36 days vs. standard duration enoxaparin for a median of 9 days

Extended duration betrixaban associated with non-significant reduction in rate of intracranial hemorrhage (ICH) vs. standard duration enoxaparin

Safety Population includes all patients who received active study drug

1: Major bleeding is based on ISTH criteria: Schulman et al. T Thromb Haemost 2005;3:692-4
**APEX Rate of Stroke or Transient Ischemic Attack (TIA)**

**SAFETY (SECONDARY SAFETY ENDPOINT)**

<table>
<thead>
<tr>
<th>Event Rate (%)</th>
<th>ISCHEMEIC STROKE</th>
<th>RR=0.59</th>
<th>(95% CI 0.35-0.97)</th>
<th>P=0.03</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Stroke or TIA</td>
<td>1.10%</td>
<td>41/3716</td>
<td>0.65%</td>
<td>24/3716</td>
</tr>
<tr>
<td>New Ischemic Stroke</td>
<td>0.91%</td>
<td>34/3716</td>
<td>0.48%</td>
<td></td>
</tr>
</tbody>
</table>

- In safety population, extended duration betrixaban reduced risk of ischemic stroke, all strokes, and all strokes or TIA vs. standard duration enoxaparin.
- There was 1 hemorrhagic stroke in each group.
- All stroke includes ischemic and hemorrhagic stroke.

Gibson C et al. *Circulation*. 2016;134:00-00

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**Post-Hoc Analysis: Fatal or Irreversible Outcomes**

<table>
<thead>
<tr>
<th>Event</th>
<th>Enoxaparin/Placebo</th>
<th>Betrixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Through Visit 3</td>
<td>HR = 0.71 (95% CI: 0.56, 0.91)</td>
<td>NNT = 85</td>
</tr>
<tr>
<td>ARR = 1.18%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Through End of Trial</td>
<td>HR = 0.70 (95% CI: 0.57, 0.88)</td>
<td>NNT = 65</td>
</tr>
<tr>
<td>ARR = 1.53%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Extended duration betrixaban reduced rate of fatal or irreversible events vs. standard duration enoxaparin at visit 3 and through the end of the trial.

All Randomized Patients

Gibson CM et al. *J Am Heart Assoc*. 2017;6(e006015*
Extended duration betrixaban significantly reduced symptomatic VTE vs. standard duration enoxaparin in the overall study population.

*End of trial defined as final follow-up visit (30 + 5 days after Visit 3).

mITT Population
HR=hazard ratio; ARR=absolute risk reduction; NNT=number needed to treat.

AEPX Net Clinical Benefit (PEOP Population)

COMPOSITE OF THE PRIMARY EFFICACY OUTCOME (Symptomatic or Asymptomatic VTE*) AND PRIMARY SAFETY OUTCOME

\[ RR = 0.78 \]
\[ (95\% CI 0.65-0.95) \]
\[ P = 0.01 \]
\[ NNT = 67 \]

\[ RR = 0.71 \]
\[ (95\% CI 0.57-0.89) \]
\[ P = 0.002 \]
\[ NNT = 48 \]

*VTE defined as asymptomatic proximal DVT, symptomatic proximal or distal DVT, symptomatic non-fatal PE, or VTE-related death

Cohort 1: RRR=18% (95% CI 0.66, 1.01; p=0.07); Cohort 2: RRR=18% (95% CI 0.68, 1.00; p=0.05)


RRrelative risk.
Primary Efficacy Endpoint: Composite of Symptomatic VTE or VTE-Related Death
Use of Rivaroxaban 10 mg or 7.5 mg with CrCl 30-50 ml/min

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 alpha</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>

MARINER – KEY FEATURES SUMMARY

- Use of a post-discharge design to focus on the key clinical question given that the burden of VTE in the acutely ill hospitalized medical patient population is shifting to the post-discharge setting given shortening hospital LOS
- Use of a validated risk scoring tool and biomarker Dd to identify high risk subgroups that has potential to answer a significant unmet clinical need
- Using a 45 day duration of treatment based on recent epidemiologic data to suggest the period of greatest VTE risk in this population
- Decreasing the bleeding risk by delaying randomization until hospital discharge, excluding patients who have had a bleeding event during hospitalization, excluding active cancer subgroups, and lowering the dose in patients with moderate renal impairment, as well and several other factors that will improve the bleeding profile
- Using symptomatic VTE and VTE-related death as the primary efficacy endpoint heightens the importance of clinically relevant endpoints assessed compared to prior studies in the field
- Results due in late 2018
EINSTEIN CHOICE Rivaroxaban

- In patients without reversible risk factors, the risk of recurrent venous thromboembolism is up to 10% in the first year if anticoagulation therapy is stopped1–5
- Although extended anticoagulation therapy is effective for the prevention of recurrent venous thromboembolism,1–5 concerns about bleeding often lead to a reluctance to continue anticoagulant treatment beyond 6 to 12 months
- Attempts to reduce the risk of bleeding when treatment is extended include the use of lower dose anticoagulant therapy and the use of aspirin in place of an anticoagulant 2,6–8


Einstein Choice Study Design

- Aim: Compare efficacy and safety of rivaroxaban 20 mg or 10 mg with aspirin 100mg in patients at equipoise regarding the need for continued anticoagulation
- Randomized, double-blind, active-comparator, event-driven, superiority study

![Einstein Choice Study Design Diagram](attachment:image.jpg)

Einstein Choice
Main Study Outcomes

- Efficacy outcomes:
  - **Primary**: Composite of symptomatic recurrent fatal or nonfatal VTE and unexplained death where PE cannot be excluded
  - Symptomatic recurrent VTE, MI, ischemic stroke or systemic embolism
  - Death from any cause
  - Symptomatic recurrent VTE or death from any cause
  - Symptomatic recurrent VTE or venous thrombosis in other locations
  - Symptomatic recurrent VTE, MI, ischemic stroke or systemic embolism or venous thrombosis in other locations

- Safety outcomes
  - **Principal**: Major bleeding (ISTH)
  - Clinically relevant non-major bleeding
  - Composite of major bleeding and clinically relevant nonmajor bleeding
  - Non-major bleeding associated with study drug interruption for >14 days


---

Einstein Choice Patient Flow

Randomized N=3396

1121 assigned to rivaroxaban 20 mg
1136 assigned to rivaroxaban 10 mg
1139 assigned to aspirin 100 mg

1046
14 Did not take study medication
182 prematurely discontinued study treatment
8 died
14 withdrew consent
3 were lost to follow-up

1063
1069
143 prematurely discontinued study treatment
7 died
16 withdrew consent
4 were lost to follow-up

Included in ITT & safety analyses

1107
1127
1131


**ITT (Intention to treat)**: all randomized patients who received at least one dose of study medication
### Einstein Choice Prespecified Efficacy Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban 20 mg (n=1107)</th>
<th>Rivaroxaban 10 mg (n=1127)</th>
<th>Aspirin 100 mg (n=1131)</th>
<th>Rivaroxaban 20 mg vs aspirin</th>
<th>Rivaroxaban 10 mg vs aspirin</th>
<th>Rivaroxaban 20 mg vs 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE</td>
<td>17 (1.6)</td>
<td>13 (1.2)</td>
<td>10 (0.9)</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>DVT</td>
<td>9 (0.8)</td>
<td>7 (0.6)</td>
<td>10 (0.9)</td>
<td>0.34 (0.20–0.57)</td>
<td>0.32 (0.19–0.54)</td>
<td>1.08 (0.57–2.09)</td>
</tr>
<tr>
<td>PE</td>
<td>6 (0.6)</td>
<td>5 (0.4)</td>
<td>13 (1.7)</td>
<td>0.42 (0.26–0.68)</td>
<td>0.27 (0.15–0.47)</td>
<td>1.57 (0.82–3.00)</td>
</tr>
<tr>
<td>PE+/DVT</td>
<td>3 (0.3)</td>
<td>1 (0.1)</td>
<td>2 (0.2)</td>
<td>0.35 (0.21–0.58)</td>
<td>0.28 (0.16–0.48)</td>
<td>1.28 (0.66–2.50)</td>
</tr>
<tr>
<td>Fatal VTE</td>
<td>2 (0.2)</td>
<td>1 (0.1)</td>
<td>2 (0.2)</td>
<td>0.35 (0.22–0.57)</td>
<td>0.33 (0.20–0.54)</td>
<td>1.07 (0.59–1.95)</td>
</tr>
</tbody>
</table>

Recurrent VTE, MI, ischaemic stroke or SE 17 (1.6) 13 (1.2) 50 (4.4) 0.34 (0.20–0.59) P<0.001 0.26 (0.14–0.47) P<0.001 1.34 (0.65–2.75) P<0.001

Recurrent VTE, all-cause mortality 19 (1.7) 18 (1.6) 26 (2.3) 0.42 (0.26–0.68) P<0.001 0.27 (0.15–0.47) 1.57 (0.82–3.00) P=0.18

Recurrent VTE, venous thrombosis in other locations 20 (1.8) 16 (1.4) 57 (5.0) 0.42 (0.26–0.68) 0.27 (0.15–0.47) 1.57 (0.82–3.00) P=0.18

Recurrent VTE, MI, ischaemic stroke, SE, venous thrombosis in other locations 22 (2.0) 21 (1.9) 63 (5.6) 0.42 (0.26–0.68) 0.27 (0.15–0.47) 1.57 (0.82–3.00) P=0.18

HR, hazard ratio; CI, confidence interval; VTE venous thromboembolism; MI, myocardial infarction; SE, systemic embolism

---

### Einstein Choice Prespecified Safety Outcome

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban 20 mg (n=1107)</th>
<th>Rivaroxaban 10 mg (n=1127)</th>
<th>Aspirin 100 mg (n=1131)</th>
<th>Rivaroxaban 20 mg vs aspirin</th>
<th>Rivaroxaban 10 mg vs aspirin</th>
<th>Rivaroxaban 20 mg vs 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>6 (0.5)</td>
<td>5 (0.4)</td>
<td>3 (0.3)</td>
<td>2.01 (0.30–8.04)</td>
<td>1.64 (0.39–6.84)</td>
<td>1.23 (0.37–4.03)</td>
</tr>
<tr>
<td>Major bleeding, fatal, n (%)</td>
<td>1 (0.1)</td>
<td>0 (0.0)</td>
<td>1 (0.1)</td>
<td>2.01 (0.30–8.04)</td>
<td>1.64 (0.39–6.84)</td>
<td>1.23 (0.37–4.03)</td>
</tr>
<tr>
<td>Non-fatal bleeding in a critical site, n (%)</td>
<td>4 (0.4)</td>
<td>2 (0.2)</td>
<td>1 (0.1)</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>
<tr>
<td>Intracranial, n (%)</td>
<td>3 (0.3)</td>
<td>1 (0.1)</td>
<td>1 (0.1)</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>

Major or clinically relevant non-major bleeding 36 (3.3) 27 (2.4) 23 (2.0) 1.59 (0.94–2.69) 1.16 (0.67–2.03) 1.37 (0.83–2.26)

Clinically relevant non-major bleeding 30 (2.7) 22 (2.0) 20 (1.8) 1.53 (0.87–2.69) 1.09 (0.59–2.00) 1.40 (0.81–2.43)

Non-major bleeding with study drug interruption ≥14 days 17 (1.5) 12 (1.1) 12 (1.1) 1.44 (0.69–3.02) 0.99 (0.44–2.20) 1.46 (0.70–3.06)

All P Values are Not Significant

Weitz JI et al, N Engl J Med 2017

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**Weitz JI et al, N Engl J Med 2017**
Einstein Choice Summary

- In patients with symptomatic DVT/PE with equipoise for continued anticoagulation, continued treatment with rivaroxaban 20 or 10 mg showed:
  - Superior reduction vs aspirin for the primary and other efficacy outcomes
  - Number needed to treat (NNT) for rivaroxaban to prevent one episode of recurrent nonfatal or fatal VTE without increasing the risk of bleeding is 30 for rivaroxaban 10mg and 33 for rivaroxaban 20 mg*
  - Rate of bleeding with rivaroxaban similar to aspirin

*NNT compared with aspirin for primary efficacy outcome up to 1 year
Weitz JI et al, N Engl J Med 2017

Atrial Fibrillation and Need for Percutaneous Coronary Intervention
PIONEER PCI Overview – Atrial Fibrillation requiring cardiac stents

- This trial compared standard therapy (dual antiplatelet therapy plus a vitamin K antagonist) with two regimens containing rivaroxaban plus antiplatelet therapy in patients with atrial fibrillation undergoing percutaneous coronary intervention (PCI) with placement of stents.

- The rivaroxaban groups had reduced rates of bleeding and similar efficacy in preventing cardiovascular events.


PIONEER PCI Stratification, Randomization, and Follow-up.

**Group 1** - low-dose rivaroxaban (15 mg once daily) plus a P2Y_{12} inhibitor for 12 months

- 440 Patients were screened for eligibility
- 111 Did not meet eligibility criteria
- 329 Were enrolled in the trial
- 128 Were in the DAPT (dual antiplatelet therapy) arm
- 201 Were in the rivaroxaban arm
- 128 Were assigned to group 1

**Group 2** - very-low-dose rivaroxaban (2.5 mg twice daily) plus DAPT for 1, 6, or 12 months

- 440 Patients were screened for eligibility
- 111 Did not meet eligibility criteria
- 329 Were enrolled in the trial
- 128 Were in the DAPT (dual antiplatelet therapy) arm
- 201 Were in the rivaroxaban arm
- 128 Were assigned to group 2

**Group 3** - standard therapy with a dose-adjusted vitamin K antagonist (once daily) plus DAPT for 1, 6, or 12 months

- 440 Patients were screened for eligibility
- 111 Did not meet eligibility criteria
- 329 Were enrolled in the trial
- 128 Were in the DAPT (dual antiplatelet therapy) arm
- 201 Were in the rivaroxaban arm
- 128 Were assigned to group 3

Cumulative Incidence of the Primary Safety End Point and a Secondary Efficacy End Point.


Cumulative Incidence of the Primary Safety End Point and Its Components, with Stratification According to Intended Duration of DAPT.

<table>
<thead>
<tr>
<th>Table 1. Cumulative Incidence of the Primary Safety End Point and Its Components, with Stratification According to Intended Duration of DAPT.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>No. of Patients with Events</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)</td>
</tr>
<tr>
<td>P Value</td>
</tr>
</tbody>
</table>

* Data are for all patients who underwent randomized assignment (n=186) and survived at least one dose of the trial regimen during the treatment period. Participants in group 1 were assigned to receive aspirin (325 mg daily) plus clopidogrel (75 mg daily) for at least 12 months, and those in group 7 were assigned to receive oral anticoagulant therapy with a heparin derivative (intravenous unfractionated heparin or low-molecular-weight heparin) for at least 6 months. Participants in group 2 were assigned to receive aspirin (325 mg daily) plus clopidogrel (75 mg daily) for at least 6 months. Participants in group 8 were assigned to receive aspirin (325 mg daily) plus clopidogrel (75 mg daily) for at least 3 months. Participants in group 3 were assigned to receive aspirin (325 mg daily) plus clopidogrel (75 mg daily) for at least 1 month. Participants in group 4 were assigned to receive aspirin (325 mg daily) plus ticagrelor (180 mg daily) for at least 6 months. Participants in group 5 were assigned to receive aspirin (325 mg daily) plus ticagrelor (180 mg daily) for at least 3 months. Participants in group 6 were assigned to receive aspirin (325 mg daily) plus ticagrelor (180 mg daily) for at least 1 month. Participants in group 7 were assigned to receive aspirin (325 mg daily) plus clopidogrel (75 mg daily) for at least 1 year. Participants in group 9 were assigned to receive aspirin (325 mg daily) plus clopidogrel (75 mg daily) for at least 6 months. Participants in group 10 were assigned to receive aspirin (325 mg daily) plus clopidogrel (75 mg daily) for at least 3 months. Participants in group 11 were assigned to receive aspirin (325 mg daily) plus clopidogrel (75 mg daily) for at least 1 month. Participants in group 12 were assigned to receive aspirin (325 mg daily) plus aspirin (325 mg daily) for at least 1 year. Participants in group 13 were assigned to receive aspirin (325 mg daily) plus aspirin (325 mg daily) for at least 6 months. Participants in group 14 were assigned to receive aspirin (325 mg daily) plus aspirin (325 mg daily) for at least 3 months. Participants in group 15 were assigned to receive aspirin (325 mg daily) plus aspirin (325 mg daily) for at least 1 month. Participants in group 16 were assigned to receive aspirin (325 mg daily) plus aspirin (325 mg daily) for at least 1 year. Participants in group 17 were assigned to receive aspirin (325 mg daily) plus aspirin (325 mg daily) for at least 6 months. Participants in group 18 were assigned to receive aspirin (325 mg daily) plus aspirin (325 mg daily) for at least 3 months. Participants in group 19 were assigned to receive aspirin (325 mg daily) plus aspirin (325 mg daily) for at least 1 month.
PIONEER PCI Conclusions

• In participants with atrial fibrillation undergoing PCI with placement of stents, the administration of either low-dose rivaroxaban plus a P2Y_{12} inhibitor for 12 months or very-low-dose rivaroxaban plus DAPT for 1, 6, or 12 months was associated with a lower rate of clinically significant bleeding than was standard therapy with a vitamin K antagonist plus DAPT for 1, 6, or 12 months.

• The three groups had similar efficacy rates, although the observed broad confidence intervals diminish the surety of any conclusions regarding efficacy.

Secondary Prevention of Cardiovascular Events in Coronary or Peripheral Arterial Disease
Rationale for Rivaroxaban in CAD/PAD

- Rivaroxaban alone or in combination with aspirin might be more effective than aspirin alone for vascular prevention in patients with stable coronary artery disease (CAD) or peripheral artery disease (PAD)
- Rivaroxaban has been shown in large RCTs to be effective for the prevention and treatment of VTE and for prevention of stroke or systemic embolism in patients with atrial fibrillation\(^1-4\)
- In patients with recent ACS, rivaroxaban at a dose of 2.5 mg or 5 mg twice daily reduced the risk of nonfatal and fatal CV events\(^5\)


COMPASS Study Design

- Phase III, event-driven, blinded, randomized controlled trial with a 3 x 2 partial factorial design
- During the 30-day run-in period, potentially eligible subjects (excluding those randomized after CABG surgery) received rivaroxaban placebo twice daily and aspirin 100 mg once daily
  - Pantoprazole/pantoprazole placebo was not administered during run-in
- Subjects who successfully completed the run-in period and who consented to continue in the study, as well as those enrolled after CABG were randomized in a 1:1 ratio to receive pantoprazole or pantoprazole placebo

\(^{1}\) Patients treated according to local standard of care; \(^{2}\) 350 days of the required prespecified number of events having occurred; \(^{3}\) Patients who were not receiving a proton pump inhibitor were randomized to pantoprazole or pantoprazole placebo; \(^{4}\) Defined as at least 80% adherence to treatment; \(^{5}\) CABG patients underwent same screening, followup, and wash out periods as other COMPASS trial participants except that they did not undergo a run-in; Bosch J, et al. Canadian J of Cardiology (2017), doi: 10.1016/j.cjca.2017.06.001.
COMPASS: Outcomes

Primary
- CV death, stroke, or MI

Secondary
- CHD death, ischemic stroke, MI, or ALI
- CV death, ischemic stroke, MI, or ALI
- Mortality

Safety and Net Clinical Benefit
- ISTH major bleeding (modified)
- Primary + fatal or critical organ bleeding

ClinicalTrials.gov NCT01776424.

COMPASS: Primary Endpoints
CV Death, Stroke, MI

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Riva + Aspirin (n=9152)</th>
<th>Riva (n=9117)</th>
<th>Aspirin (n=9126)</th>
<th>Riva + Aspirin vs Aspirin</th>
<th>Riva vs Aspirin</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>
</tbody>
</table>

Eikelboom JW. ESC 2017. FP 1154.
**COMPASS: Major Bleeding**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Riva + Aspirin (n=9152)</th>
<th>Riva (n=9117)</th>
<th>Aspirin (n=9126)</th>
<th>Riva + Aspirin vs Aspirin</th>
<th>Riva vs Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</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></td>
<td>p &lt; .0001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal</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>
<tr>
<td></td>
<td>p = 0.32</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal ICH*</td>
<td>21 (0.2)</td>
<td>32 (0.4)</td>
<td>19 (0.2)</td>
<td>1.10 (0.59, 2.04)</td>
<td>1.69 (0.96, 2.98)</td>
</tr>
<tr>
<td></td>
<td>p = 0.77</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal other critical organ*</td>
<td>42 (0.5)</td>
<td>45 (0.5)</td>
<td>29 (0.3)</td>
<td>1.43 (0.89, 2.29)</td>
<td>1.57 (0.98, 2.50)</td>
</tr>
<tr>
<td></td>
<td>p = 0.14</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


**COMPASS: Net Clinical Benefit**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Riva + Aspirin (n=9152)</th>
<th>Aspirin (n=9126)</th>
<th>Riva + Aspirin vs Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Net clinical benefit (primary + severe bleeding events)</td>
<td>431 (4.7)</td>
<td>534 (5.9)</td>
<td>0.80 (0.70, 0.91)</td>
</tr>
</tbody>
</table>

Eikelboom JW. ESC 2017. FP 1154.
Reversal of Direct Oral Anticoagulants

Major Bleeding: DOACs vs. Warfarin in NVAF

**Intracranial Hemorrhage (ICH): DOACs vs. Warfarin in NVAF**

<table>
<thead>
<tr>
<th></th>
<th>NOAC</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of events (%/yr)</td>
<td>HR</td>
</tr>
<tr>
<td>Dabi 1101,2</td>
<td>27 (0.23)</td>
<td>90 (0.76)</td>
</tr>
<tr>
<td>Dabi 1501,2</td>
<td>38 (0.32)</td>
<td>90 (0.76)</td>
</tr>
<tr>
<td>Rivaroxaban2</td>
<td>55 (0.5)</td>
<td>84 (0.7)</td>
</tr>
<tr>
<td>Apixaban</td>
<td>52 (0.33)</td>
<td>122 (0.80)</td>
</tr>
</tbody>
</table>

Not head-to-head comparisons – for illustrative purposes only

---

**Major Bleeding Case Fatality Rates in NVAF**

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>DOAC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>ROCKET AF</td>
<td>55/386</td>
<td>14%</td>
</tr>
<tr>
<td>Dabigatran systematic review</td>
<td>53/407*</td>
<td>13%</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>55/462</td>
<td>12%</td>
</tr>
<tr>
<td>ENGAGE AF-TIMI 48</td>
<td>59/524</td>
<td>11%</td>
</tr>
</tbody>
</table>

**Major bleeding with warfarin has a high risk of death that has not diminished over the last several decades**

Patel et al. NEJM 2011; Majeed et al. Circ 2013; Granger et al. NEJM 2011; Giugliano et al. NEJM 2013. *estimated from paper
Idarucizumab: An Antidote to Dabigatran

DEVELOPMENT
- Monoclonal mouse antibody with high dabigatran binding affinity
- Humanized & expressed as Fab fragment in hamster cells

PROPERTIES
- Binding affinity ~350 times higher than binding of dabigatran to thrombin
- No procoagulant or anticoagulant effects
- Short half life
- IV administration, immediate onset of action

EXPECTED LOW RISK OF ADVERSE REACTIONS
- No Fc receptor binding (cellular mediators of antibody functions)
- No endogenous targets


REVERSE-AD: Idarucizumab for Dabigatran Reversal

Prospective, multicenter cohort study – over 400 international centers
- Planned recruitment of 300 patients – increased to 503 patients

Target population: adult patients on dabigatran with one of the following
- Overt, uncontrollable or life-threatening bleeding requiring reversal (group A)
- Need for urgent surgical procedure that could not be delayed ≥ 8 hours (group B)

Intervention: 5 gm idarucizumab given as two 2.5 gm boluses ≤ 15 minutes apart

Primary objective: max % reversal of dabigatran effect measured by dilute thrombin time (dTT) or ecarin clotting time (ECT)

Idarucizumab was 100% effective in reversing the anticoagulant effect of dabigatran:

- among 300 patients with uncontrolled bleeding (median time to bleeding cessation, 2.5 hours)
- and among 200 patients who required an urgent procedure (median time to procedure initiation, 1.6 hours).

REVERSE AD Full Cohort

Conclusions

- In emergency situations, idarucizumab rapidly, durably, and safely reversed the anticoagulant effect of dabigatran.
- Idarucizumab has been available in the US since 2015 and was approved based off of the early interim analysis by the FDA.
Andexanet Alfa: Recombinant, Modified Version of Human Factor Xa Produced in CHO Cells

- Andexanet acts as a FXa decoy
- Andexanet was rationally designed to reverse anticoagulant effects of factor Xa inhibitors

CHO=Chinese hamster ovary. GLA=γ-carboxyglutamate.
**Andexanet Mechanism of Action – Direct Factor Xa Inhibitors**

1. FXa inhibitors block enzymatic activity of FXa
2. Andexanet directly binds and sequesters unbound FXa inhibitors with high affinity
3. Absence of GLA domain prevents assembly into prothrombinase complex on platelet surface
4. Restoration of FXa activity and normal thrombin generation


---

**ANNEXA—4 Study Design**

**Patient Screening**
- Patient presents with major bleed
- If last dose of FXa inhibitor was within 18 hours

**Bleeding and Laboratory Assessment**
- Andexanet Treatment
  - IV Bolus
  - 2-hour IV Infusion
  - After end of infusion
  - Safety follow-up visit

**Assessments**
- 1 hr 4 hr 8 hr 12 hr Day 1 Day 3 Day 30

**Primary Efficacy Measurements**
- Percent change in anti-FXa activity
- Hemostatic efficacy at 12 hours (assessed by independent endpoint adjudication committee as excellent, good, or poor/none)

**Secondary Efficacy Measurements**
- Relationship between decrease in anti-FXa activity and achievement of hemostatic efficacy

**Safety Measurements**
- Overall safety
- Thrombotic events
- Antibodies to FX, FXa, andexanet
- 30-day all-cause mortality

No lab tests required to enroll patients

Portola Data on File.
ANNEXA-4 Dosing and Administration

Andexanet administered as IV bolus, immediately followed by continuous infusion.

There are two possible dosing regimens:

<table>
<thead>
<tr>
<th>Andexanet Initial IV Bolus</th>
<th>Andexanet Follow-on 120-minute Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients on apixaban</td>
<td>400 mg at a target rate of 30 mg/min</td>
</tr>
<tr>
<td>Patients who received rivaroxaban &gt;7 hours ago</td>
<td>480 mg at a target rate of 4 mg/min x 2 hrs</td>
</tr>
<tr>
<td>Patients on enoxaparin or edoxaban</td>
<td>800 mg at a target rate of 30 mg/min</td>
</tr>
<tr>
<td>Patients who received rivaroxaban within ≤7 hours or at an unknown time*</td>
<td>960 mg at a target rate of 8 mg/min x 2 hrs</td>
</tr>
<tr>
<td>Patients who received a Factor Xa inhibitor but it is uncertain which one</td>
<td></td>
</tr>
</tbody>
</table>

*If there is a delay between medical presentation and start of andexanet of more than 7 hours, the patient should receive the dose for rivaroxaban >7 hours ago.

Portola Data on File.

ANNEXA-4 Preliminary Study Results

- ANNEXA-4 is an ongoing study and is expected to be completed by November 2022.

- This preliminary and descriptive report presents the 67 patients for whom data were complete as of June 17, 2016.
  - 67 patients were included in the safety analysis and 47 patients were included in the safety analysis

- It cannot be guaranteed that the future results, levels of activity, performance, or events and circumstances reflected in this preliminary analysis will be achieved or occur and therefore the conclusions of this preliminary analysis are limited.
Hemostatic Efficacy Overall and by Bleed Site


Hemostatic Efficacy by Andexanet Dose and by Anticoagulant

Effect of Andexanet on Rivaroxaban and Apixaban Anti-FXa Activity

- Andexanet rapidly decreased anti-FXa activity by 89-93% at end of bolus, which was sustained during infusion.
- Andexanet also rapidly decreased anti-FXa activity in the 10% of patients with the highest baseline anti-FXa levels by approximately 33% (from 487.1 ng/mL to 327.4 ng/mL).
- All of these patients were adjudicated as having excellent or good hemostasis.

Rivaroxaban (N=26)
Apixaban (N=20)

Boxplot values represent median, 25th and 75th percentiles; whiskers represent lowest or highest data point within 1.5 times the lower or upper quartile respectively. Dots represent outliers.


ANNEXA-4 Safety Outcomes in Bleeding Patients Treated with FXa Inhibitors

- No infusion reactions
- 15% (10/67) of patients died within 30 days
  - Mortality among ICH patients was 21% (6/28) at 30 days
  - Mortality among non-ICH patients was 10% (4/39) at 30 days
- 18% (12/67) of patients experienced a thrombotic event between 1 and 28 days after andexanet treatment
  - All but 1 patient was not re-started on a therapeutic dose of anticoagulation
  - Thrombotic events could be attributed to the patient’s underlying medical condition
- In an updated cohort of 105 patients receiving andexanet, 12% (13/105) of patients experienced a thrombotic event within 30 days of treatment.

Immunogenicity

- No antibodies to factors Xa or X
- No neutralizing antibodies to andexanet

Summary of ANNEXA-4 Preliminary Study Results

- Andexanet in patients with acute major bleeding associated with the use of FXa inhibitors:
  - Rapidly reversed anti-FXa activity
  - Not associated with serious side effects
- Effective hemostasis achieved 12 hours after an infusion of andexanet in 79% of the patients.
- Thrombotic events occurred in 12% of the patients in the safety population, and 15% of the patients died during follow-up.
- Andexanet has been resubmitted to the FDA on 8/3/2017 with a likely estimated 200 or more patients.


Single center retrospective analysis of consecutive patients who received FEIBA in DOAC reversal

- UC Davis, acute major bleeding in the presence of DOACs is managed with activated prothrombin complex concentrate (PCC) FEIBA.
- Early experience demonstrated a profound, rapid effect with doses around 8 units/kg, leading to an initial low dose (LD) with the option to titrate to effect with additional FEIBA.
- 54 patients; apixaban (n=18), dabigatran (n=13) and rivaroxaban (n=23) received LD (< 20 units/kg) aPCC (mean 10±3.5 units/kg; n=32) or MD (mean 24±2.4units/kg; n=22). CNS bleeds occurred in 20 patients.
- 9 patients expired prior to discharge. One TE occurred with MD. Follow-up CT exams did not reveal any clinically concerning active bleeding or hematoma expansion except one HD patient where CT showed slight worsening of massive multifocal ICH.
- LD aPCC titration strategy using an option to repeat, and MD aPCC, depending on the urgency of the situation, may be a management strategy for major DOAC bleeding events.

Dager W Abstract PB 1216 | DOAC Reversal with Low (< 20 Units/kg) or Moderate Dose (≥20 Units/kg) FEIBA in the Urgent Management of Major Bleeding. Special Issue: Abstracts of the XXVI Congress of the International Society on Thrombosis and Haemostasis, July 8–13, 2017 Volume 1, Issue S1 July 2017 Pages 1–1451
Conclusions

- Five direct oral anticoagulants are now available on the US market for various indications
- Betrixaban is a new FXa inhibitor approved for extended thromboprophylaxis in acutely ill medical patients and rivaroxaban is almost complete with the MARINER study in a similar population
- Several new DOAC studies have recently been published in NVAF and PCI, Secondary Prevention of cardiovascular events in CAD/PAD, and extended treatment of VTE
- Idarucizumab is FDA approved and available for the reversal of dabigatran
- Andexanet has been studied for reversal of Factor Xa inhibitors, has recently been resubmitted to the FDA, and may be soon available on the US Market to reverse Factor Xa inhibitors

Backup slides
Disadvantages of Warfarin

- Delayed onset/offset
- Unpredictable dose response
- Narrow therapeutic index
- Drug-drug, drug-food interactions
- Problematic routine monitoring
- High bleeding rate
- Slow reversibility (6-24 hours)
- Complicated peri-operative management

IMPROVE RAM Validation

<table>
<thead>
<tr>
<th></th>
<th>LOW (Score 0-1)</th>
<th>MODERATE (Score 2-3)</th>
<th>HIGH (Score ≥ 4)</th>
<th>TOTAL Population</th>
<th>MODERATE and HIGH RISK Population</th>
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</thead>
<tbody>
<tr>
<td>IMPROVE VTE</td>
<td>47 / 10179</td>
<td>87 / 3795</td>
<td>147 / 5991</td>
<td>145 / 15123</td>
<td>148 / 4766</td>
</tr>
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<td>Incidence</td>
<td>0.45%</td>
<td>1.3%</td>
<td>16.74%</td>
<td>16.95%</td>
<td>12.7%</td>
</tr>
<tr>
<td>VALOUR VTE</td>
<td>28 / 17451</td>
<td>86 / 6307 (1.05%)</td>
<td>47 / 1109</td>
<td>139 / 20067</td>
<td>113 / 7416</td>
</tr>
<tr>
<td>Incidence</td>
<td>0.21%</td>
<td>1.05%</td>
<td>6.44%</td>
<td>6.88%</td>
<td>1.52%</td>
</tr>
</tbody>
</table>

COMPASS Background: CAD/PAD

– Cardiovascular (CV) disease is responsible for approximately one-third of deaths in 2013\(^1\)

- Estimated 17.3 million people worldwide died of CV disease in 2012
  - Projected to increase to 23.6 million per year by 2030\(^1\)
- Coronary artery disease (CAD) and peripheral arterial disease (PAD) are strong predictors of risk for future CV events \(^1,2\)
- Long-term aspirin prevents vascular events but is only modestly effective\(^3,4\)


COMPASS Background: Therapeutic Strategies

- Aspirin, statins, angiotensin modulators, and β-blockers are effective and widely used for CV prevention in patients with CAD, and the first 3 classes of drugs are effective in patients with PAD
- Despite use of these therapies, as many as 5% of patients experience recurrent vascular events each year\(^1\)

Aspirin reduces the risk of myocardial infarction (MI), stroke, or CV death by one-fifth in patients with CAD, cerebrovascular disease, or PAD\(^1\)

Aspirin is also effective for prevention of graft failure after coronary artery bypass graft (CABG) surgery,\(^1\) but despite its use as many as 40% of patients have at least 1 obstructed graft within 1 year\(^2\)
- Graft failure is an independent predictor of MI and death

Compared with aspirin, clopidogrel produced a reduction in MI, stroke, or CV death\(^3\)
- The combination of aspirin and clopidogrel did not reduce major adverse CV events compared with aspirin alone,\(^4\) but a benefit was evident in the subgroup of patients with a history of symptomatic disease\(^5\)

Long-term treatment with the combination of aspirin and dipyridamole or aspirin and ticagrelor compared with aspirin alone, or the combination of vorapaxar with standard antiplatelet therapy also yielded benefits without significant reductions in mortality\(^6-8\)

**COMPASS Evidence for Anti-platelet Efficacy**


**Select APEX Exclusion Criteria**

**Kidney Function**

- End stage renal disease with CrCl <15 mL/min, or requiring dialysis, or severe renal insufficiency (i.e., CrCl between ≥ 15 mL/min and < 30 mL/min) and requiring concomitant use of strong P-gp inhibitor.

**Liver Function**

- Known abnormality of liver function tests (> 3x ULN for serum glutamic-oxaloacetic transaminase (SGOT)/aspartate aminotransferase (AST), serum glutamate pyruvate transaminase (SGPT)/alanine transaminase (ALT) or alkaline phosphatase (ALP), or > 2 x ULN for total bilirubin in the absence of Gilbert’s syndrome), active liver disease, or hepatic dysfunction (e.g., cirrhosis).

**Bleeding Risk**

- History of clinically significant bleeding within 6 months prior to enrollment.
- History of any significant gastrointestinal, pulmonary or urogenital bleeding, ongoing chronic peptic ulcer disease or ongoing or acute gastritis within 2 years prior to enrollment.

**Anticoagulant Use**

- Contraindication to anticoagulant therapy
- Current intake of dual antiplatelet therapy
- Anticipated need for prolonged anticoagulation
- Greater than 96 hours of administration of the following immediately prior to receiving study treatment (enoxaparin or another low molecular weight heparin, fondaparinux, unfractionated heparin)

APEX Efficacy Analyses for FDA Label Were Performed Based on the Modified Intent-to-Treat (mITT) Population

The mITT population consisted of all patients who had taken at least one dose of study drug and had follow-up assessment of one or more primary or secondary efficacy outcome components. Rationale for pre-specified mITT analyses:

- Minimizes the magnitude of any missing data and any bias due to informative censoring in evaluation of study results
- A larger sample size provides a more robust estimate of the efficacy of betrixaban

The FDA used the mITT analysis as the basis for Betrixaban approval because:

- It minimizes the magnitude of any missing data in evaluation of study results
- It is based on a larger sample size that provides a better estimate of the efficacy of betrixaban

NOTE: Prior to the completion of the study the FDA requested that the statistical analysis plan (SAP) include and predefine the mITT analysis for the assessment of efficacy results

APEX Study Publications

Extended Thromboprophylaxis with Betrixaban in Acutely Ill Medical Patients.

The safety and efficacy of full versus reduced-dose betrixaban in the Acute Medically Ill VTE Prevention With Extended-Duration Betrixaban (APEX) trial.

When academic research organizations and clinical research organizations disagree: Processes to minimize discrepancies prior to unblinding of randomized trials.

Extended-Duration Betrixaban Reduces the Risk of Stroke Versus Standard-Dose Enoxaparin Among Hospitalized Medically Ill Patients

Comparison of Fatal or Irreversible Events With Extended-Duration Betrixaban Versus Standard Dose Enoxaparin in Acutely Ill Medical Patients: An APEX Trial Substudy
Gibson CM, et al. J Am Heart Assoc. 2017;6(7)

Look for Reduced Rehospitalization Data with betrixaban. Will be Forthcoming
Pharmacokinetics of Andexanet

Drug Properties
- 40 KDa protein
- Rapid onset of action
- PD/effective half-life ~1 hour and elimination half-life of ~5-7 hours
- Anticoagulants don't affect PK of andexanet (they clear separately)
- PK in elderly is same as in younger subjects

Clearance/Metabolism
- Like other large proteins, andexanet is broken down by proteolytic cleavage mechanisms into small peptides
- Clearance likely occurs via hepatic and renal mechanisms
  - Size is within molecular weight range for filtration through glomerulus and excretion in urine
  - In clinical trials, no intact drug was detected in urine

ANNEXA 4 Preliminary Types of Anticoagulants and Bleeds

<table>
<thead>
<tr>
<th>Type of Anticoagulant</th>
<th>Type of Bleed</th>
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</thead>
<tbody>
<tr>
<td>Rivaroxaban (n=32)</td>
<td>GI 49%</td>
</tr>
<tr>
<td>Apixaban (n=31)</td>
<td>Other 9%</td>
</tr>
<tr>
<td>Enoxaparin (n=4)</td>
<td>ICH 42%</td>
</tr>
<tr>
<td></td>
<td>Subarachnoid 39%</td>
</tr>
<tr>
<td></td>
<td>Intracerebral 50%</td>
</tr>
<tr>
<td></td>
<td>Subdural 11%</td>
</tr>
</tbody>
</table>

GI: gastrointestinal
ICH: intracranial hemorrhage