DISCLOSURES

Research Support:

BiO₂ Medical; Boehringer-Ingelheim; BMS; BTG EKOS; Daiichi; Janssen; NHLBI; Thrombosis Research Institute

Consultant:

Agile; Bayer; Boehringer-Ingelheim; BMS; Daiichi; eXlthera; Janssen; Portola; Zafgen
A novel NOAC, betrixaban, prevents PE, DVT, and stroke in hospitalized medically ill patients, during hospitalization and in the vulnerable first 5 weeks after hospital discharge (APEX Trial—NEJM 2016).
VTE AFTER HOSPITAL DISCHARGE

- Despite in-hospital VTE prophylaxis with UFH or LMWH, > 400,000 VTE events occur in this patient population annually.

- About half occur within 6 weeks of discharge. No agents are currently approved or guideline recommended for thromboprophylaxis.
OUT-OF-HOSPITAL VTE

Despite in-hospital VTE prophylaxis, 75% of VTEs present out-of-hospital—37% have been hospitalized within the 3 months preceding the diagnosis of VTE.

Figure. Timing of diagnosis of venous thromboembolism (VTE) relative to the preceding hospital discharge among individuals who developed VTE as an outpatient.

(Arch Intern Med 2007;167:1471)
RISK OF VTE EXTENDS POST-HOSPITAL DISCHARGE

Observational study of >11,000 hospitalized medical patients

EXTENDED VTE PROPHYLAXIS: MEDICAL PATIENTS

<table>
<thead>
<tr>
<th>Study</th>
<th>Study conclusion</th>
<th>Net clinical benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXCLAIM--LMWH (n = 5,963)</td>
<td>VTE↓ Major bleeding↑</td>
<td>Marginal</td>
</tr>
<tr>
<td>MAGELLAN--Riva (n = 8,101)</td>
<td>VTE↓ Major bleeding↑</td>
<td>No</td>
</tr>
<tr>
<td>ADOPT--Apixaban (n = 6,528)</td>
<td>VTE↔ Major bleeding↑</td>
<td>No</td>
</tr>
</tbody>
</table>

Ann Intern Med 2010; 153: 8-18
POST-DISCHARGE VTE: MEDICAL PATIENTS

- The rate of symptomatic VTE > doubles over 21 days post discharge.
- The risk of fatal VTE increases 5 fold.

<table>
<thead>
<tr>
<th>MAGELLAN</th>
<th>Incidence of VTE related death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10d</td>
</tr>
<tr>
<td>Lovenox 10D</td>
<td>0.2%</td>
</tr>
<tr>
<td>Riva 35D</td>
<td>0.1%</td>
</tr>
</tbody>
</table>
Extended Thromboprophylaxis with Betrixaban in Acutely Ill Medical Patients

Alexander T. Cohen, M.D., Robert A. Harrington, M.D., Samuel Z. Goldhaber, M.D., Russell D. Hull, M.B., B.S., Brian L. Wiens, Ph.D., Alex Gold, M.D., Adrian F. Hernandez, M.D., and C. Michael Gibson, M.D., for the APEX Investigators*

(NEJM 2016; 375: 534-544)
BETRIXABAN

- Factor Xa inhibitor
- 19-25 hour half life
- Low peak-to-trough ratio
- 17% renal clearance
- Antidote (Andexanet)
PROPERTIES OF BETRIXABAN

- Rapid onset of action with $C_{\text{max}}$ achieved at 3 – 4 hours
- Stable plasma concentration and anti-thrombotic effect at steady state
- Long half life
- Low renal clearance
- Lack of CYP450 interactions

<table>
<thead>
<tr>
<th></th>
<th>BETRIX</th>
<th>RIVA</th>
<th>APIXA</th>
<th>EDOXA</th>
<th>ENOX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half Life</td>
<td>19-25 hrs</td>
<td>5-9 hrs</td>
<td>9-13 hrs</td>
<td>8-10 hrs</td>
<td>4.5-7 hrs</td>
</tr>
<tr>
<td>Renal Excretion</td>
<td>5-7%</td>
<td>36%</td>
<td>25%</td>
<td>28%</td>
<td>&gt;40%</td>
</tr>
<tr>
<td>CYP3A4 Interactions</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
APEX TRIAL (N=7,513)

- Extended prophylaxis megatrial in high risk, immobilized Medical Patients with CHF, respiratory failure, infection, stroke.
- A higher risk population is targeted than in prior extended prophylaxis megatrials.
- Double-blind RCT: 35 days of oral betrixaban 80 mg daily versus injected enoxaparin 40 mg daily for 6-10 days.
- Endpoint: VTE plus VTE-Related Death (NEJM 2016; 375: 534-544)
APEX STUDY DESIGN

Subjects enrolled (N=7,513)

Subjects enrolled (N=7,513)

Enoxaparin 40 mg

Placebo

Betrixaban 80 mg

Betrixaban 80 mg

Double blind, double dummy

Loading dose 160 mg

Ultrasound & Visit 3

Day 35 (+7 days)

Follow-up safety visit

30 Days After Visit 3 (+5 days)

(NEJM 2016; 375: 534-544)
## BASELINE CHARACTERISTICS: PRIMARY REASONS FOR HOSPITALIZATION

<table>
<thead>
<tr>
<th>Reason</th>
<th>Enoxaparin (n=3,754)</th>
<th>Betrixaban (n=3,759)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute CHF NYHA III-IV, % (n)</td>
<td>44.5% (1,672)</td>
<td>44.6% (1,677)</td>
</tr>
<tr>
<td>Acute infection, % (n)</td>
<td>28.2% (1,058)</td>
<td>29.6% (1,112)</td>
</tr>
<tr>
<td>Acute respiratory failure, % (n)</td>
<td>12.6% (474)</td>
<td>11.9% (448)</td>
</tr>
<tr>
<td>Acute ischemic stroke w/ immobilization, % (n)</td>
<td>11.5% (432)</td>
<td>10.9% (411)</td>
</tr>
<tr>
<td>Acute rheumatic disorder, % (n)</td>
<td>3.1% (117)</td>
<td>2.9% (109)</td>
</tr>
</tbody>
</table>

(NEJM 2016; 375: 534-544)
PRIMARY EFFICACY ENDPOINT

Asymptomatic Proximal DVT, Symptomatic Proximal/Distal DVT, nonfatal PE, VTE-related Death

RRR = 24.0%

* p=0.006
SYMPTOMATIC VTE EVENTS

RRR = 46%

Event rate (%)

- Enoxaparin: 1.80%, n=3,720
- Betrixaban: 0.99%, n=3,721

p = 0.003
### Table 5: Efficacy Outcomes in APEX Trial (mITT Population)

|                         | BEVYXXA N=3,721 | Enoxaparin N=3,720 | Relative Risk (95% CI) 
|-------------------------|-----------------|-------------------|--------------------------
| **Composite Outcome**   | 165 (4.4)       | 223 (6.0)         | 0.75 (0.61, 0.91)        |
| Asymptomatic Event      | 133 (3.6)       | 176 (4.7)         |                          |
| Symptomatic DVT         | 14 (0.4)        | 22 (0.6)          |                          |
| Non-fatal PE            | 9 (0.2)         | 18 (0.5)          |                          |
| VTE-related Death       | 13 (0.3)        | 17 (0.5)          |                          |
| **Symptomatic Events**  | 35 (0.9)        | 54 (1.5)          | 0.64 (0.42, 0.98)        |

1 Percentages and event rates are based on the total number of patients and events included in each treatment group.

2 Relative Risk (BEVYXXA arm versus enoxaparin arm) is based on the Mantel-Haenszel test stratified by the dosing strata and D-dimer status from the local laboratory. The analyses are not adjusted for multiplicity.

3 Symptomatic events include symptomatic DVT, non-fatal PE or VTE-related death.
INDICATIONS AND USAGE

BEVYXXA is a factor Xa (FXa) inhibitor indicated for the prophylaxis of venous thromboembolism (VTE) in adult patients hospitalized for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE. (1)

Limitations of Use:
Safety and efficacy of BEVYXXA have not been established in patients with prosthetic heart valves because this population has not been studied. (1)
MORE THAN HALF OF VTE OCCURS AFTER 10 DAYS OF PROPHYLAXIS

<table>
<thead>
<tr>
<th></th>
<th>ADOPT</th>
<th>MAGELLAN</th>
<th>APEX</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptomatic</strong></td>
<td>1.6%</td>
<td>3.1%</td>
<td>1.5%</td>
</tr>
<tr>
<td><strong>Asymptomatic</strong></td>
<td>3.1%</td>
<td>2.7%</td>
<td>0.24%</td>
</tr>
<tr>
<td><strong>VTE (%)</strong></td>
<td></td>
<td>5.7%</td>
<td></td>
</tr>
<tr>
<td><strong>Days</strong></td>
<td>0 - 10</td>
<td>0 - 35</td>
<td>0 - 35</td>
</tr>
<tr>
<td><strong>Days</strong></td>
<td>0 - 35</td>
<td>0 - 35</td>
<td>0 - 35</td>
</tr>
</tbody>
</table>
## Rate of Stroke or TIA
### mITT Population

<table>
<thead>
<tr>
<th>Stroke Type</th>
<th>Enoxaparin N=3716</th>
<th>Betrixaban N=3716</th>
<th>Relative Risk Reduction (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Stroke</td>
<td>36 (0.97%)</td>
<td>20 (0.54%)</td>
<td>0.44 (0.04-0.68)</td>
<td>0.032</td>
</tr>
<tr>
<td>Ischemic</td>
<td>34 (0.91%)</td>
<td>18 (0.48%)</td>
<td>0.47 (0.06-0.70)</td>
<td>0.026</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>1 (0.03%)</td>
<td>1 (0.03%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Uncertain Type</td>
<td>1 (0.03%)</td>
<td>1 (0.03%)</td>
<td>0.00 (-14.98-0.94)</td>
<td>1.000</td>
</tr>
<tr>
<td>TIA</td>
<td>5 (0.13%)</td>
<td>4 (0.11%)</td>
<td>0.20 (-1.98-0.79)</td>
<td>0.739</td>
</tr>
<tr>
<td>Any Stroke or TIA</td>
<td>41 (1.10%)</td>
<td>24 (0.65%)</td>
<td>0.41 (0.03-0.65)</td>
<td>0.034</td>
</tr>
</tbody>
</table>

(Gibson et. al. AHA 2016 – November 14, 2016)
Ischemic Stroke or CHF as Index Event

- Enoxaparin
- Betrixaban

HR = 0.45 (0.24, 0.87)
ARR = 0.75%
NNT = 133

P = 0.014

Gibson et al. AHA 2016 – November 14, 2016
PRIMARY SAFETY ENDPOINT: MAJOR BLEEDING

- Enoxaparin (N=3,716): 0.57% (n=21)
- Betrixaban (N=3,716): 0.67% (n=25)

p = 0.55

(NEJM 2016; 375: 534-544)
FATAL BLEEDING AND ICH: Safety Population

Event rate (%)

Fatal Bleeding

Enoxaparin (N=3,716) 0.03% (n=1)
Betrixaban (N=3,716) 0.03% (n=1)

ICH

Enoxaparin (N=3,716) 0.19% (n=7)
Betrixaban (N=3,716) 0.05% (n=2)

Safety population defined as patients who received at least one dose of active study drug. Analysis by actual treatment.

Gibson et al. ISTH SSC 2016 – May 27, 2016
FATAL OR IRREVERSIBLE OUTCOMES

Through Visit 3
HR = 0.71 (95% CI: 0.55-0.90)
ARR = 1.18%
NNT = 85

Through End of Trial*
HR = 0.70 (95% CI: 0.57-0.88)
ARR = 1.53%
NNT = 65

(Gibson et al. J Am Heart Assoc. 2017;6(7) doi: 10.1161/JAHA.117.006015.)
## REHOSPITALIZATION DATA

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Enoxaparin (N = 3716)</th>
<th>Betrixaban (N = 3716)</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE-related rehospitalization or VTE-related mortality</td>
<td>1.64% (58)</td>
<td>0.87% (31)</td>
<td>0.53 (0.35–0.83)</td>
<td>0.0042</td>
</tr>
<tr>
<td>VTE-related rehospitalization</td>
<td>1.04% (36)</td>
<td>0.45% (16)</td>
<td>0.44 (0.25–0.80)</td>
<td>0.0055</td>
</tr>
<tr>
<td>VTE-related mortality</td>
<td>0.75% (26)</td>
<td>0.41% (15)</td>
<td>0.58 (0.31–1.09)</td>
<td>0.09</td>
</tr>
<tr>
<td>Net clinical benefit †</td>
<td>1.81% (64)</td>
<td>1.46% (52)</td>
<td>0.81 (0.56–1.17)</td>
<td>0.27</td>
</tr>
</tbody>
</table>

† Composite of VTE-related rehospitalization, VTE-related mortality, bleeding-related rehospitalization, and bleeding-related mortality

(Circulation 2017; in press)
VTE-RELATED REHOSPITALIZATION

HR = 0.44
(0.25-0.80)
ARR = 0.59%
NNT = 170

P = 0.0055

(Circulation 2017; in press)
VTE-RELATED MORTALITY

HR = 0.58
(0.31-1.09)

P = 0.09

0.41%

0.75%

(AHA Scientific Sessions 2017)
VTE-Related Rehospitalization and VTE-Related Death

HR = 0.53 (0.35-0.83)
ARR = 0.77%
NNT = 130

P = 0.0042

HR = 0.53 (0.35-0.83)
ARR = 0.77%
NNT = 130

Circulation 2017; in press
Primary Efficacy Outcome by History of VTE

**HISTORY OF VTE**
RR = 0.57 (0.38-0.86)  
p = 0.006  
NNT = 12

**NO HISTORY OF VTE**
RR = 0.79 (0.64-0.99)  
p = 0.042  
NNT = 100

P interaction = NS

(Yee et al. J Thromb Thrombolysis 2017; in press)
SUMMARY

• Betrixaban: 24% reduction in VTE (p=0.006).
• Betrixaban: 46% reduction in symptomatic VTE (p=0.003).
• Betrixaban: 56% reduction in stroke (p=0.32)
• Betrixaban: no increase in major or fatal bleeding.
• Betrixaban: favorable net clinical benefit.
SUMMARY: SUBSTUDIES

- Betrixaban: 29% reduction in fatal or irreversible outcomes
- Betrixaban: 56% reduction in VTE-related rehospitalization
- Betrixaban: 42% reduction in VTE-related death
- Betrixaban: 47% reduction in VTE-related rehospitalization and VTE-related death
TRANSITIONS OF CARE: HOSPITAL PERSPECTIVES

- Reduce 30-day readmissions to reduce CMS financial penalties and to boost quality of care
- Reduce post-discharge PE, DVT, and stroke
- Improve coordination of inpatient/outpatient care
FUTURE PERSPECTIVES:
MENU OF INTERVENTIONS

- Patient and HCP education
- Boost medication adherence
- Telephone support/telemonitoring
- First outpatient visit soon after hospital discharge
- Home visits or virtual visits for medically high risk patients