Pearls in Thrombosis

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Conflict Disclosures

• Faculty: Alan Bell MD CCFP

• Relationships with commercial interests:
  • Grants/Research Support: AstraZeneca, Boehringer Ingelheim, Bayer, Amgen, Takeda, Daiichi Sankyo
  • Speakers Bureau/Honoraria: AstraZeneca, Merck, Takeda, Forest, BMS, Pfizer, Amgen, Sanofi, Boehringer Ingelheim
  • Consulting Fees: AstraZeneca, Merck, Takeda, Forest, BMS, Pfizer, Amgen, Sanofi
  • Other: Thrombosis Canada, Canadian Cardiovascular Society
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  - Other: Thrombosis Canada
Thrombosis Pearls

• This program has not received financial support from any commercial or non-commercial organizations

• Potential for conflict(s) of interest:
  • Drs. Alan and Benjamin Bell are executive members of Thrombosis Canada (non-profit, unpaid)
Thrombosis Pearls

Bias has been mitigated by the following:

• All program content was developed by the speakers

• All clinical recommendations are based on clinical guidelines and peer-reviewed evidence.

• No commercial or other non-commercial organization has had any input to the content of this program
Learning Objectives

After attending this session, participants will be more skilled at:

• Appropriate dosing of anticoagulants in atrial fibrillation
• Diagnosis and management of venous thromboembolic disorders (VTE) including deep vein thrombosis and pulmonary embolism
• Duration of therapy in VTE for secondary prevention
• Perioperative management of anticoagulants
Thrombosis Canada

- **Our Mission:**
  - To further education and research in the prevention and treatment of thrombotic vascular disease

- **Who are we?**
  - Established in 1991
  - Nationally registered non-profit organization of internationally recognized thrombosis experts
  - Our membership is comprised of thrombosis experts from many disciplines across Canada, including internal medicine, hematology, stroke neurology, cardiology, pharmacy, nursing, laboratory medicine, emergency medicine and primary care
Clinical Guides

New/Novel Oral Anticoagulants (NOACs): Coagulation Tests

Novel Oral Anticoagulants, Perioperative management

To describe the effect of the new/novel direct oral anticoagulants (NOACs) on laboratory coagulation tests which are widely available: prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (aPTT), and thrombin clotting time (TCT), and to discuss how clinicians should use and interpret coagulation tests in patients who are bleeding or require elective surgery or an invasive procedure.

New/Novel Oral Anticoagulants (NOACs): Comparison and Frequently-Asked Questions

Novel Oral Anticoagulants

To provide a comparison of the new/novel oral anticoagulants (NOACs) currently available in Canada, and to address frequently-asked questions regarding NOACs.

New/Novel Oral Anticoagulants (NOACs): Management of Bleeding

Novel Oral Anticoagulants

To assist clinicians in the management of bleeding in patients receiving new/novel oral anticoagulants (NOACs).

New/Novel Oral Anticoagulants (NOACs): Peri-Operative Management

Novel Oral Anticoagulants, Perioperative management
How Can I Find This Information?

www.thrombosiscanada.ca

CLINICAL GUIDES
Thrombosis Canada has developed practical and actionable guides related to the treatment and management of thrombosis.

View Guides!
Click to view or download!
Acetyl Salicylic Acid

Anticoagulant and Antithrombotic Drugs

To provide information on the use of acetyl salicylic acid in the treatment and prevention of vascular events.
ATRIAL FIBRILLATION
The Impact of Stroke

- **Globally**:1
  - The 3rd most common cause of death in developed countries
  - 15 million strokes annually
    - 5 million deaths
    - 5 million people permanently disabled
- **Each year in Canada**:2
  - 50,000 people have a stroke – one every 10 minutes
  - 14,000 people die from stroke – the 3rd leading cause of death
- **Stroke costs the Canadian economy $2.7 billion annually**3

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1. World Health Organization. 2004
3. Canadian Stroke Network.
Atrial fibrillation affects approximately 350,000 Canadians
Atrial Fibrillation: Major Risk Factor for Stroke

- Increases the risk of stroke by 5-fold\(^1,2,3\)
- Accounts for approximately 15-20% of all strokes nationally\(^1,4\)
  - Associated with a 50-90% increase in mortality risk after adjustment for co-existing cardiovascular conditions\(^2\)
  - Risk of stroke in atrial fibrillation patients who do not receive anticoagulation averages ~ 5% per year
- Risk of stroke in atrial fibrillation patients by age group
  - 1.5% in 50-59 year olds
  - 23.5% in 80-89 year olds

Atrial Fibrillation Patients Have Increased Post-Stroke Mortality and Morbidity


**Mortality**

<table>
<thead>
<tr>
<th></th>
<th>30 days</th>
<th>1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>With AF</td>
<td>32.5%</td>
<td>49.5%</td>
</tr>
<tr>
<td>Without AF</td>
<td>16.2%</td>
<td>27.1%</td>
</tr>
</tbody>
</table>

**Morbidity**

<table>
<thead>
<tr>
<th></th>
<th>With atrial fibrillation</th>
<th>Without atrial fibrillation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bedridden patients (%)</td>
<td>41.2%</td>
<td>23.7%</td>
</tr>
</tbody>
</table>
Atrial Fibrillation: Warfarin Benefit

Warfarin reduces the risk of AF related stroke by about 2/3

Treatment on Admission With Stroke

All High-Risk Atrial Fibrillation Patients
- No antithrombotics: 29%
- Dual antiplatelets: 29%
- Single antiplatelet: 29%
- Warfarin: therapeutic: 2%
- Warfarin: sub-therapeutic: 10%

High-Risk Atrial Fibrillation Patients with Previous Stroke or Transient Ischemic Attack
- No antithrombotics: 3%
- Dual antiplatelets: 15%
- Single antiplatelet: 3%
- Warfarin: therapeutic: 25%
- Warfarin: sub-therapeutic: 18%

1 Million Preventable Strokes

15 million strokes annually worldwide

20% of strokes due to atrial fibrillation\(^1,2\)

3 million are due to atrial fibrillation

Relative risk reduction (RRR) of 64% with warfarin\(^3\)

2 million are preventable with warfarin therapy

50% of eligible patients treated with warfarin\(^4\)

1 million strokes could have been prevented

1. Arch Intern Med 1994
### All NOACS: Stroke or SEE

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY [150 mg]</td>
<td>0.66 (0.53 - 0.82)</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>ROCKET AF</td>
<td>0.88 (0.75 - 1.03)</td>
<td></td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>0.80 (0.67 - 0.95)</td>
<td></td>
</tr>
<tr>
<td>ENGAGE AF-TIMI 48 [60 mg]</td>
<td>0.88 (0.75 - 1.02)</td>
<td></td>
</tr>
<tr>
<td>Combined [Random Effects Model]</td>
<td>0.81 (0.73 - 0.91)</td>
<td></td>
</tr>
</tbody>
</table>

N=58,541
Heterogeneity p=0.13
All NOACS: Major Bleeding

- **RE-LY [150 mg]**
  - Risk Ratio (95% CI): 0.94 (0.82 - 1.07)

- **ROCKET AF**
  - Risk Ratio (95% CI): 1.03 (0.90 - 1.18)

- **ARISTOTLE**
  - Risk Ratio (95% CI): 0.71 (0.61 - 0.81)

- **ENGAGE AF-TIMI 48 [60 mg]**
  - Risk Ratio (95% CI): 0.80 (0.71 - 0.90)

- **Combined [Random Effects Model]**
  - Risk Ratio (95% CI): 0.86 (0.73 - 1.00)

*N=58,498*, p=0.06, *Heterogeneity p=0.001*

Secondary Safety Outcomes

- **ICH**
  - Risk Ratio (95% CI): 0.48 (0.39 - 0.59)
  - p-value: <0.0001

- **GI Bleeding**
  - Risk Ratio (95% CI): 1.25 (1.01 - 1.55)
  - p-value: 0.043

Heterogeneity:
- **ICH**, p=0.22
- **GI Bleeding**, p=0.009

NOACs and Warfarin: High Efficacy in Atrial Fibrillation

Reduction of stroke/systemic embolism

ASA
19% vs. placebo

Warfarin
64% vs. placebo

Further
19% vs. warfarin

NOACs

Not intended as a cross trial comparison
Teaching Pearls

• AF is a major risk factor for stroke
• Strokes associated with AF are associated with excess morbidity and mortality
• There is a large treatment gap that YOU are well positioned to address
• Anticoagulation is a highly efficacious strategy to prevent AF strokes
Mr NG

- 80-year-old man with hypertension, diabetes, mild chronic kidney disease (serum creatinine 134 µmol/L),
- His weight is 99 kg
- Presents for diabetes follow up and noted to have an irregular pulse
CCS AF Guidelines (2014)

**RECOMMENDATION**

5. We recommend that when OAC therapy is indicated for patients with nonvalvular AF, most patients should receive dabigatran, rivaroxaban, apixaban, or edoxaban (when approved) in preference to warfarin (Strong Recommendation, High-Quality Evidence).
Bleeding Risk Management

• Address reversible risk factors:
  ▪ Falling – provide mobility aid
  ▪ Hypertension – treat BP to target
  ▪ Alcohol – encourage abstinence
  ▪ Labile INR – use NOAC
  ▪ Drugs – replace NSAID with other analgesic, avoid ASA unless clearly indicated for secondary prevention
  ▪ GI bleeding – use PPI
Case of asymptomatic AF in an elderly patient with moderate CKD

Which anticoagulant would you use?

A) Warfarin, INR target 2 - 3
B) NOAC
C) Reduced dose NOAC
Canadian Dosing Recommendations for Stroke Prevention in AF

Dabigatran

Patient has risk factor for stroke

Estimate CrCl

<30 ml/min
- Contraindicated

30–49 ml/min
- Elderly or risk factors for bleeding
  - 110 mg BID

≥50 ml/min
- Age <75
  - 150 mg BID
- Age 75–80
  - 110 mg BID
- Age >80
  - 150 mg BID

One other risk factor for bleeding

Pradaxa® Canada Product Monograph
**Rivaroxaban**

Patient has risk factor for stroke

Estimate CrCl

- <30 ml/min: Not recommended
- 30–49 ml/min: 15 mg OD*
- ≥50 ml/min: 20 mg OD*

*Rivaroxaban 15 mg and 20 mg should be taken with food

Xarelto® Canada Product Monograph
Canadian Dosing Recommendations for Stroke Prevention in AF

Apixaban

Patient has risk factor for stroke

Estimate CrCl

<15 ml/min

<15 ml/min

<15 ml/min

≥15 ml/min

≥15 ml/min

≥25 ml/min

≥25 ml/min

≥25 ml/min

≥80 years

≥80 years

≥80 years

≤60 kg

≤60 kg

≤60 kg

≥133 μmol/l

≥133 μmol/l

≥133 μmol/l

2.5 mg BID

2.5 mg BID

2.5 mg BID

5 mg BID

5 mg BID

5 mg BID

*In patients with CrCl 15–24 ml/min, no dosing recommendation can be made as clinical data are very limited

Eliquis® Canada Product Monograph
Management Tools

Anticoagulant Dosing In Atrial Fibrillation

<table>
<thead>
<tr>
<th>Age (years)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum Creatinine (µmol/L)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Congestive Heart Failure History
- Hypertension History
- Diabetes Mellitus History
- Previous stroke or TIA
- History of macrovascular disease (coronary, aortic or peripheral)
- Patient has another indication for warfarin therapy (for example, mechanical heart valve, LV thrombus, rheumatic valvular heart disease)
- Female Patient

Calculators
- CHADS2 Score for Atrial Fibrillation Stroke Risk
- CHA2DS2-VASc Score for Atrial Fibrillation Stroke Risk
- Creatinine Clearance (Cockcroft-Gault Equation)
- HAS-BLED Score for Major Bleeding Risk
- PERC Rule for Pulmonary Embolism
- Pulmonary Embolism Severity Index (PESI)
- Simplified PESI (Pulmonary Embolism Severity Index)
- TIMI Risk Score for UA/NSTEMI
- TIMI Risk Score for STEMI

Brought to you by Thrombosis Canada
Teaching Pearls

• Oral anticoagulation is indicated for patients with atrial fibrillation over 65 or any other CHADS$_2$ risk factor
• Do not withhold anticoagulation unless bleeding risk extreme
• Address reversible bleeding risk factors
• NOACs are considered first line over warfarin, in most patients, but require appropriate dosing.
VENOUS THROMBOEMBOLISM
VTE: Clot Formation Within the Venous Circulation

Deep vein thrombosis (DVT)

Thrombi form predominantly in venous valve pockets and other sites of presumed stasis

Pulmonary embolism (PE)

Thromboemboli detach and travel through the right side of the heart to block vessels in the lungs

Incidence of VTE in Canada

- An estimated 45,000 patients in Canada are affected by deep vein thrombosis (DVT) each year\(^1\)
- There are approximately 1-2 cases per 1,000 persons annually\(^1\)
- Among those who develop DVT\(^2\):
  - One-third will have long term complications such as chronic lower leg edema, post phlebitic syndrome, pain, pigment changes
  - One-third will develop a recurrent event within 10 years
- Despite adequate therapy, 1% to 8% of patients in whom pulmonary embolism develops, will die\(^2\)

1. Thrombosis Canada, 2013, Clinical Guides, Venous Thromboembolism; http://thrombosiscanada.ca/
2. Scarvelis et al, CMAJ 2006; 175(9) 1087-92
What Causes VTE?

- Hypercoagulability
- Stasis
- Endothelial injury

Dr. Rudolf Virchow 1856
What Causes VTE?

Provoked by a transient major risk factor
- Surgery
- Major trauma
- Hospitalization
- Lower extremity cast
- Immobilization ≥ 3 days
- Pregnancy and puerperium
- Estrogen therapy

Provoked by a minor risk factor
- Air travel
- Stuck in traffic
- Minor trauma

Unprovoked or provoked by an irreversible risk factor
- Cancer
- Immobilization

ACCP guidelines recommend at least 3 months’ anticoagulant therapy after provoked VTE with transient risk factors or longer after unprovoked (idiopathic) or VTE provoked by irreversible factors.

Annual recurrence risk off anticoagulation:
- 1%
- 5-10%
How is DVT diagnosed?

Clinical probability
- Unlikely
  - D-Dimer
    - Negative: No DVT
    - Positive: pCUS
      - Negative: No DVT
      - Positive: DVT
- Likely
  - pCUS
    - Positive: DVT
    - Negative: No DVT
  - D-Dimer
    - Negative: No DVT
    - Positive: Serial pCUS
Teaching Pearls

• Distal and proximal DVT are different entities

• One of the most important questions in VTE is whether the event was “provoked” or “unprovoked”

• Diagnostic strategy relies on pretest probability
Case 2

- 27F D&C following spontaneous abortion 1 month ago
- Otherwise healthy
- Presents to your office for routine follow-up
- You note left calf swelling and tenderness
- Normal BP, HR, RR, chest exam
- Discharge Cr 65, Hb 127, Plt 243
Wells' Criteria for DVT

Calculates Wells' Score for risk of DVT.

- Active cancer?
- Bedridden recently > 3 days or major surgery within four weeks?
- Calf swelling > 3cm compared to the other leg?
- Collateral (nonvaricose) superficial veins present?
- Entire leg swollen?
- Localized tenderness along the deep venous system?
- Pitting edema, greater in the symptomatic leg?
- Paralysis, paresis, or recent plaster immobilization of the lower extremity?
- Previously documented DVT?
- Alternative diagnosis to DVT as likely or more likely?

Score 4

High risk group for DVT. " Likely" according to Wells DVT studies.
Decision

How do you manage this patient?

A) Refer to ER
B) Confirm DVT with US prior to starting anticoagulation
C) Start anticoagulant empirically
2.2.1. In patients with a high clinical suspicion of acute VTE, we suggest treatment with parenteral anticoagulants compared with no treatment while awaiting the results of diagnostic tests (Grade 2C).

2.2.2. In patients with an intermediate clinical suspicion of acute VTE, we suggest treatment with parenteral anticoagulants compared with no treatment if the results of diagnostic tests are expected to be delayed for more than 4 h (Grade 2C).

2.2.3. In patients with a low clinical suspicion of acute VTE, we suggest not treating with parenteral anticoagulants while awaiting the results of diagnostic tests, provided test results are expected within 24 h (Grade 2C).
Signs and Symptoms of VTE

**DVT**
- Unilateral leg swelling
- Palpable cord
- Leg pain

**PE**
- DVT
- Pleuritic chest pain

**Nonspecific!**
- ACS?
- Pneumonia?
- Malignancy?
- Esophageal spasm?
- Reactive airways?
- Sepsis?
- Pericarditis?
- Pleuritis?
- Pneumothorax?
Treatment Options in 2015

Bridge

(LMWH)H → Warfarin

Single agent (LMWH/rivaroxaban/apixaban)

NOAC → NOAC

Switch (dabigatran/edoxaban*)

LMWH → NOAC

*when HC approved
Published between 2009-2013
n=27,075
# The Bottom Line: Acute Treatment

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosing</strong></td>
<td>Variable</td>
<td>150 mg BID*</td>
<td>15 mg BID x 3 weeks then 20 mg OD</td>
<td>10 mg BID x 7 days then 5 mg BID</td>
<td>60 mg OD (30 mg OD for CKD, wt &lt;60)</td>
</tr>
<tr>
<td><strong>Initial LMWH Rx</strong></td>
<td>Required</td>
<td>Required</td>
<td>Not required</td>
<td>Not required</td>
<td>Required</td>
</tr>
<tr>
<td><strong>Efficacy v warfarin</strong></td>
<td>Same</td>
<td>Same</td>
<td>Same</td>
<td>Same</td>
<td>Same</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeds</td>
<td>Same</td>
<td>Less</td>
<td>Less</td>
<td>Same</td>
<td></td>
</tr>
<tr>
<td>Clinically sig bleeds</td>
<td>Less</td>
<td>Same</td>
<td>Less</td>
<td>Less</td>
<td></td>
</tr>
<tr>
<td><strong>Health Canada Approved</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Renal clearance</strong></td>
<td>85%</td>
<td>33%</td>
<td>25%</td>
<td>35%</td>
<td></td>
</tr>
</tbody>
</table>

*110 mg BID if age >80 or additional RF for bleeding*
Home treatment
VTE recurrence: 0.61 (0.42-0.90)
Mortality: 0.72 (0.45-1.15)
Major bleeding: 0.67 (0.33-1.36)

2.7. In patients with acute DVT of the leg and whose home circumstances are adequate, we recommend initial treatment at home over treatment in hospital (Grade 1B).
Patients who should be admitted

- Iliofemoral DVT
- Phlegmasia or venous ischemia
- Severe CKD (CrCl <30)
- Suspicion for high risk PE
- High bleeding risk
- Significant comorbid disease
Teaching Pearls

• The differential of DVT is not a dangerous group
• The NOACs have non-inferior efficacy and superior safety than a LMWH-warfarin bridge
• Home therapy is appropriate for the vast majority of patients with DVT and the NOACs allow family physicians to treat entirely in their office without involving the hospital
PERI-PROCEDURAL ANTICOAGULANT MANAGEMENT
Mr. JF

- 75-year-old retired lawyer
- Referred for GI endoscopy to investigate altered bowel habit
- Non-valvular AF
- Dabigatran 150 mg bid
- CHADS$_2$ = 3 (hypertension, diabetes, age)
- Serum creatinine 122 µmol/L
- Weight 92 kg
GI endoscopy required in patient on NOAC
How should the NOAC be managed?

A) Continued throughout the procedure
B) Hold for 5 days prior to the procedure and restart day following
C) Hold for 2 days prior to the procedure and restart day following
D) Hold the NOAC for 5 days but provide LMWH bridging
E) I don’t know and I admit it
Does not yet address perioperative management of NOACs
Where Does this Leave the Clinician?
Management Tools

**Perioperative Anticoagulant Management Algorithm**

**Procedural Bleeding Risk**

- Low (minor non-dental procedure)
- Low (minor dental procedure)
- Moderate
- High

Reset

Brought to you by Thrombosis Canada
Teaching Pearls

• Periprocedural management of anticoagulants is a very common yet complex clinical issue often left to the family physician

• Correct management is critically important to prevent bleeding and thrombotic events

• Tools are available to ensure optimized dosing – DON’T GUESS
QUESTIONS?
Too bad we don’t have time to talk about…

NOAC REVERSAL AGENTS
How to reverse NOACs

- **Coagulation factors?**
  - **FEIBA** for dabigatran: 50 IU/kg
  - 4-factor **PCC** for oral Xa-inhibitors: 2,000 IU-3,000 IU

- **Remove drug: Dialysis**
  - **Yes** for dabigatran (not highly protein bound)
  - **No** for oral Xa inhibitors (highly protein bound)

- **Neutralize drug: Antidote**
  - **Andexanet-α**: Human rfXa variant, decoy molecule that competes with native fXa to bind oral Xa inhibitors
  - **Idarucizumab**: Humanized Fab fragment, attracts dabigatran with > 300-times affinity than thrombin

Idarucizumab was designed as a specific reversal agent for anticoagulant activity of dabigatran (monoclonal Ab).

- Humanized Fab fragment
- Binding affinity \( \sim 350 \times \) higher than dabigatran to thrombin
- No intrinsic procoagulant or anticoagulant activity
- IV dosing by bolus or rapid infusion; immediate onset of action

Schiele et al. Blood 2013
Andexanet-α was designed as a specific reversal agent for anticoagulant activity of FXa inhibitors (Decoy Molecule)

**Background**

- Andexanet alfa reduces the non-protein-bound free fraction of the Factor Xa inhibitor \( \Rightarrow \) anticoagulant effect caused by a direct Factor Xa inhibitor is rapidly neutralized by administration of andexanet alfa

- Andexanet alfa is inactivated Factor Xa
  - Lower molecular weight owing to truncated chain
  - No GLA domain
  - Mutated serine
  - Active binding site to Factor Xa substrates

- The molecule has no catalytic activity and does not bind to the protaminase complex
- Intact binding site allows binding to:
  - Direct Factor Xa inhibitors, e.g. rivaroxaban

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**Normal Factor Xa molecule**

- Serine in protease catalytic triad
- GLA domain

**PRT064445**

- Mutated serine in protease catalytic triad
- Truncated chain
- No GLA domain

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*Lu et al., 2013
Gold AM, et al. ACC 2015, abstract # 912-08.*

GLA, gamma-carboxyglutamic acid-rich
• 51 patients on dabigatran with acute bleeding (Group A)
• 39 patients on dabigatran requiring urgent surgery (Group B)
• All administered 5 g IV Idarucizumab
RE-VERSE AD Trial Results

- Median maximum reversal within 4 hours was **100% for both dTT and ECT (95% CI, 100–100)**, evident after first vial of idarucizumab
- dTT normalized in 98% and 93% of Group A and B patients, respectively*
- ECT normalized in 89% and 88% of Group A and B patients, respectively*
- Sustained reversal of dabigatran effect over 12 hours was observed in at least 90% of patients
- Similar results with aPTT and TT

ANNEXA™ Phase 3 Studies: Andexanet Alfa Antidote to the Anticoagulant Effects of fXA Inhibitors in Healthy Volunteers

- **Part 1 Complete**
  - **Apixaban**
    - Andexanet bolus only
    - Apixaban – 400 mg Andexanet
    - Placebo
  - **Rivaroxaban**
    - Rivaroxaban – 800 mg Andexanet

- **Part 2 Ongoing**
  - **Apixaban**
    - Andexanet bolus + infusion
    - Apixaban – 400 mg + 4 mg/min Andexanet
    - Placebo
  - **Rivaroxaban**
    - Rivaroxaban – 800 mg + 8 mg/min Andexanet

5 mg BID Apixaban/ 20 mg OD Rivaroxaban administered over 3 days and morning of 4th day prior to administration of Andexanet or Placebo.
ANNEXA™-A (Apixaban, Part I)
Primary Endpoint: Anti-fXa

- **Met Primary Endpoint:**
  - Percent change anti-fXa from baseline to nadir (≈ 94%)
    - $p < 0.0001$

- **Met first Secondary Endpoint:**
  - Number of subjects with > 80% reversal: andexanet (100%) vs. placebo (0%)
    - $p < 0.0001$

- All andexanet subjects achieved ≥ 90% reversal

Data plotted as Mean±SEM
Met primary efficacy endpoint:
- Mean % change in anti-FXa from baseline to post-infusion nadir: 92%
  - \( p<0.0001 \) vs placebo

Met 1\textsuperscript{st} secondary endpoint:
- Mean % change in anti-FXa from baseline to post-bolus nadir: 93%
  - \( p<0.0001 \) vs placebo

Met 2\textsuperscript{nd} secondary endpoint:
- Occurrence of subjects with \( \geq 80\% \) reduction in anti-FXa activity post-infusion nadir
  - Andexanet (23/23) vs placebo (0/8): \( p<0.0001 \)