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Medical Director of Lifeblood: the thrombosis charity
@bhwords
The principles of bridging

• Need to bridge with level of anticoagulation commensurate with level of thrombotic risk

• Ideally create a narrow window of normal/near normal haemostasis for the surgeon

• E.g. mechanical valves. High thrombotic risk. Need UF heparin, stop and restart as sewing up

• E.g. Atrial fibrillation. Can stop and restart DOAC/warfarin on night of surgery….
Do you need to bridge at all?!
BRIDGE Study Design.

# THE BRIDGE STUDY - Study Outcomes of patients with atrial fibrillation.

Table 3. Study Outcomes.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No Bridging (N=918)</th>
<th>Bridging (N=895)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial thromboembolism</td>
<td>4 (0.4)</td>
<td>3 (0.3)</td>
<td>0.01*, 0.73†</td>
</tr>
<tr>
<td>Stroke</td>
<td>2 (0.2)</td>
<td>3 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>2 (0.2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>12 (1.3)</td>
<td>29 (3.2)</td>
<td>0.005†</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>5 (0.5)</td>
<td>4 (0.4)</td>
<td>0.88†</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>7 (0.8)</td>
<td>14 (1.6)</td>
<td>0.10†</td>
</tr>
<tr>
<td>Deep-vein thrombosis</td>
<td>0</td>
<td>1 (0.1)</td>
<td>0.25†</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>0</td>
<td>1 (0.1)</td>
<td>0.25†</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>110 (12.0)</td>
<td>187 (20.9)</td>
<td>&lt;0.001†</td>
</tr>
</tbody>
</table>

*P value for noninferiority.
†P value for superiority.
Conclusions from the BRIDGE study

• In patients with atrial fibrillation who had warfarin treatment interrupted for an elective operation or other elective invasive procedure, forgoing bridging anticoagulation was noninferior to perioperative bridging with low-molecular-weight heparin for the prevention of arterial thromboembolism and decreased the risk of major bleeding.
What are you up against in 2018?

**Antiplatelet drugs**
- Aspirin
- (Non-steroidal anti-inflammatory drugs)
- Clopidogrel + others

**Anticoagulants**
- Vitamin K antagonists
- UF Heparin
- LMW heparins
- Fondaparinux
- The “not-so-new” direct oral anticoagulants (DOACs)
<table>
<thead>
<tr>
<th>Day at Start of Risk Analysis</th>
<th>Aspirin†</th>
<th>Placebo†</th>
<th>Absolute Increase in Risk with Aspirin</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day of surgery</td>
<td>311/4953 (6.3)</td>
<td>254/4978 (5.1)</td>
<td>1.2%</td>
<td>0.01</td>
</tr>
<tr>
<td>Day 1 after surgery</td>
<td>191/4832 (4.0)</td>
<td>129/4852 (2.7)</td>
<td>1.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Day 2 after surgery</td>
<td>138/4779 (2.9)</td>
<td>92/4813 (1.9)</td>
<td>1.0%</td>
<td>0.002</td>
</tr>
<tr>
<td>Day 3 after surgery</td>
<td>102/4741 (2.2)</td>
<td>59/4777 (1.2)</td>
<td>1.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Day 4 after surgery</td>
<td>73/4710 (1.6)</td>
<td>33/4748 (0.7)</td>
<td>0.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Day 5 after surgery</td>
<td>59/4693 (1.3)</td>
<td>27/4739 (0.6)</td>
<td>0.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Day 6 after surgery</td>
<td>43/4674 (0.9)</td>
<td>25/4736 (0.5)</td>
<td>0.4%</td>
<td>0.03</td>
</tr>
<tr>
<td>Day 7 after surgery</td>
<td>39/4667 (0.8)</td>
<td>22/4731 (0.5)</td>
<td>0.3%</td>
<td>0.03</td>
</tr>
<tr>
<td>Day 8 after surgery</td>
<td>20/2623 (0.8)</td>
<td>14/2662 (0.5)</td>
<td>0.3%</td>
<td>0.29</td>
</tr>
<tr>
<td>Day 9 after surgery</td>
<td>15/2617 (0.6)</td>
<td>14/2660 (0.5)</td>
<td>0.1%</td>
<td>0.82</td>
</tr>
<tr>
<td>Day 10 after surgery</td>
<td>14/2614 (0.5)</td>
<td>12/2657 (0.5)</td>
<td>0.0%</td>
<td>0.67</td>
</tr>
</tbody>
</table>

† Among patients who were alive and had not already had life-threatening or major bleeding, we determined the risk of the composite of life-threatening or major bleeding until day 30, starting on the day of surgery and then on each subsequent day. We also determined the absolute increase in risk among patients in the aspirin group and the P value for the comparison between aspirin and placebo. This allows the inference that, for example, if aspirin is started on the day of surgery, the cumulative incremental risk of bleeding attributable to aspirin over the next 30 days is 1.2%. If aspirin had been started on day 4 after surgery, the cumulative incremental risk over the next 26 days would be 0.9%, and so forth. Starting on day 8 after surgery, the sample was restricted to patients in the initiation stratum because all patients in the continuation stratum stopped taking the study drug in the aspirin trial on day 8 after surgery and resumed their regular aspirin regimen.

† Percentages were calculated with the use of the Kaplan–Meier method.

10,000 aspirin vs placebo, (clonidine vs placebo)
Antiplatelet drugs and surgery

• If recent coronary artery stenting, then discussion with their Cardiologist is OBLIGATORY
• Most will request continuation of both aspirin & clopidogrel
• Ideally stop clopidogrel....
• BUT emerging data only need dual antiplatelets for first 6/12

See Kedhi et al Brit Med J 2018 Oct 2; 365:k3793-1100 patients randomised to single vs double antiplatelet agents 6/12 after a drug-eluting stent: end point mortality/MI/stroke/bleed – 6/12 was non inferior
Reversal of the antiplatelet effect of aspirin & clopidogrel

Li et al. JTH 2012; 10: 521-528

Conclusion:
Platelet aggregation recovers
Within 4 days of stopping aspirin
BUT
10 days within stopping clopidogrel

If a bleeding & known platelet dysfunction then give one pool of platelets?
You are waiting for platelets?
1) tranexamic acid 1gm STAT
2) Consider desmopressin 0.3ug/Kg
Coumarins - discovered 1930s
> 1 million in UK at peak use

- Unpredictable pharmacokinetics
- Narrow therapeutic window
- High perception of incidence and severity of bleeding and side effects
- Many food and drug interactions
- High inter and intra patient variability
- Reversible

Convenience
- Dose adjustment required
- Slow on-set and off-set of action
- Routine coagulation monitoring required

Efficacy

Yes

Safety
Reversal of warfarin
a major cause of iatrogenic admission
see Hunt BJ, Levi M Briti Med J 2017

IMMEDIATE
• Prothrombin complex concs (Factor II, VII, IX and X) =PCC
• Fresh frozen plasma (but need to give large volumes & may not fully reverse)
• And Vitamin K

WITHIN 6 HOURS
• Stop warfarin
• Give vitamin K 1-2mgs orally/IV (takes 6 hours)
• NB may need more vitamin K after 24-48 hrs

ELECTIVE
• Stop day -4 and bridge with UF/LMWH/nothing –dependant on patient’s thrombotic risk
UF heparin

Yes

Efficacy

Unpredictable pharmacokinetics
HITT
Osteoporosis
Reversible

Safety

Convenience

No oral form
Needs monitoring

Bridging = Switch off 4 hours pre op
LMW heparin

- Predictable pharmacokinetics!
- ↓HITT
- ↓Osteoporosis
- Partially reversible

Yes

Efficacy

Safety

Convenience

- No oral form
- No monitoring unless BMI or renal failure
Bridging LMWH

• stop full dose 24 hrs pre-op
• stop thromboprophylactic 12 hrs pre-op
• if on renal replacement therapy then will need much longer
• In an emergency consider the use of protamine but will only PARTIALLY reverse effect (awaiting andexanet licensing)
Fondaparinux

- Predictable pharmacokinetics!
- No HITT
- No osteoporosis
- Irreversible
- $T \frac{1}{2} 17$ hrs

Convenience

- Yes
- Efficacy
- Safety

No oral form
- No monitoring unless BMI or renal failure
- Costly in low doses!!
Long t1/2 so most recommendations say NO to Epidural/spinal

Yes

Efficacy

Safety

No osteoporosis
Irreversible
T ½ 17 hrs

Convenience

No oral form
No monitoring unless BMI or renal failure
Costly in low doses!!
Fondaparinux

Long t1/2 so most recommendations say NO to Epidural/spinal

Yes
Efficacy
Safety
No osteoporosis
Irreversible
T ½ 17 hrs

No reversing agent until andexanet licensed

Convenience

No oral form
No monitoring unless BMI or renal failure
Costly in low doses!!
Direct Oral AntiCoagulants

- predictable dose response
- no need for routine monitoring
- fixed dose
- no food interactions
- limited drug interactions
Direct oral coagulants versus warfarin in patients with non valvular AF

**Study**

<table>
<thead>
<tr>
<th>All-cause Stroke &amp; Systemic Embolism</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY</td>
<td>0.66 (0.53, 0.82)</td>
</tr>
<tr>
<td>ROCKET AF</td>
<td>0.88 (0.75, 1.03)</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>0.80 (0.67, 0.95)</td>
</tr>
<tr>
<td>Subtotal (I-squared = 55.9%, p = 0.104)</td>
<td>0.78 (0.67, 0.92)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ischaemic Stroke</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY</td>
<td>0.77 (0.61, 0.99)</td>
</tr>
<tr>
<td>ROCKET AF</td>
<td>0.91 (0.73, 1.13)</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>0.92 (0.75, 1.14)</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.522)</td>
<td>0.87 (0.77, 0.99)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Haemorrhagic Stroke</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY</td>
<td>0.26 (0.14, 0.50)</td>
</tr>
<tr>
<td>ROCKET AF</td>
<td>0.58 (0.37, 0.92)</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>0.51 (0.35, 0.75)</td>
</tr>
<tr>
<td>Subtotal (I-squared = 52.2%, p = 0.124)</td>
<td>0.45 (0.31, 0.68)</td>
</tr>
</tbody>
</table>

RE-LY: dabigatran; ROCKET AF: rivaroxaban; ARISTOTLE: apixaban

Miller SC et al. April 27, Am J Cardiol 2012
Pharmacodynamics of oral direct inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct factor inhibition</td>
<td>Xa</td>
<td>IIa</td>
<td>Xa</td>
</tr>
<tr>
<td>Bioavailability ($F_{rel}$)</td>
<td>80%</td>
<td>6%</td>
<td>80%</td>
</tr>
<tr>
<td>Peak action ($t_{max}$)</td>
<td>1–3 hr</td>
<td>1–3 hr</td>
<td>1–3 hr</td>
</tr>
<tr>
<td>Protein binding</td>
<td>84%</td>
<td>35%</td>
<td>92–95%</td>
</tr>
<tr>
<td>Renal clearance</td>
<td>25%</td>
<td>80%</td>
<td>33%</td>
</tr>
<tr>
<td>Elimination half life with creatinine clearance &gt; 80 ml/min</td>
<td>15.1 hr</td>
<td>13.8 hr</td>
<td>8.3 hr</td>
</tr>
<tr>
<td>Elimination half life with creatinine clearance 50–79 ml/min</td>
<td>14.6 hr</td>
<td>16.6 hr</td>
<td>8.7 hr</td>
</tr>
<tr>
<td>Elimination half life with creatinine clearance 30–49 ml/min</td>
<td>17.6 hr</td>
<td>18.7 hr</td>
<td>9.0 hr</td>
</tr>
<tr>
<td>Elimination half life with creatinine clearance &lt; 30 ml/min</td>
<td>17.3 hr</td>
<td>27.5 hr</td>
<td>9.5 hr</td>
</tr>
</tbody>
</table>

Taken from Kaatz et al Am J Hematol 2012;S141
### Anticoagulants for Prevention of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation

**Drug Use and Dosing Based on Kidney Function Estimation**

- **eCrCl (estimated creatinine clearance)**

#### CrCl >50 ml/min
- Any anticoagulant – no dose adjustment needed based on kidney function.

#### CrCl 30–49 ml/min
- Apixaban 5 mg twice daily or 2.5 mg twice daily if serum creatinine (SCr) ≥133 μmol/L with age ≥80 years or body weight ≥60 kg.
- Dabigatran 110 mg twice daily if high risk of bleeding (suggest use of HAS-BLED score to assess risk); otherwise 150 mg twice daily.
- Rivaroxaban 15 mg once daily.
- Warfarin: International normalised ratio (INR) dependent dose adjustment.

#### CrCl 15–29 ml/min
- Apixaban 2.5 mg twice daily.
- Dabigatran contraindicated.
- Rivaroxaban 16 mg once daily but caution – plasma concentrations significantly increased (average 1.6-fold), which may increase bleeding risk.
- Warfarin: INR dependent dose adjustment under expert advice and review.

#### CrCl <15 ml/min
- No anticoagulant use recommended in general use, take expert advice.

<table>
<thead>
<tr>
<th>SCr (μmol/L)</th>
<th>Women ≥60 kg eCrCl (ml/min) (NB do not use table if &lt;60 kg – see below)</th>
<th>Men ≥70 kg eCrCl (ml/min) (NB do not use table if &lt;70 kg – see below)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>120</td>
<td>168</td>
</tr>
<tr>
<td>45</td>
<td>114</td>
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<tr>
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<td>11</td>
</tr>
<tr>
<td>180</td>
<td>1</td>
<td>9</td>
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<td>185</td>
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<td>7</td>
</tr>
<tr>
<td>190</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>195</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>200</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

**Current evidence suggests that an absolute CrCl (Cockcroft & Gault), as used in drug licence dosing studies, should be used for dosing decisions, not normalised estimated glomerular filtration rate (eGFR), especially for older patients and for narrow therapeutic index and high-risk drugs.**

**The tables should not be used for patients in acute renal impairment, who are dehydrated or if under the stated weights when eCrCl should be calculated individually (manually using the Cockcroft & Gault equation in Box 2 or on e.g. SystmOne® clinical tools—renal calculations) *Average ideal body weight.**

**Based on data taken from the current Summaries of Product Characteristics (SmPCs). Available from: www.medicines.org.uk/emc/*
## Bridging DOACs
- timing of last dose

<table>
<thead>
<tr>
<th>Renal function (CrCl ml/min)</th>
<th>Low risk Anti Xas</th>
<th>High risk AntiXas</th>
<th>Low risk surgery Anti Ila</th>
<th>High risk surgery Dabigatran</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;80</td>
<td>24hrs</td>
<td>48hrs</td>
<td>24 hrs</td>
<td>48</td>
</tr>
<tr>
<td>50-80</td>
<td>24hrs</td>
<td>48hrs</td>
<td>36</td>
<td>72</td>
</tr>
<tr>
<td>30-50</td>
<td>36hrs</td>
<td>48hrs</td>
<td>48</td>
<td>96</td>
</tr>
</tbody>
</table>

Post op-Use LMWH to bridge until bleeding risk is low
Emergency reversal of anticoagulants ......
Can the lab help?

1) The time of last dose of DOAC should be determined and the half-life can be estimated from measurement of serum creatinine and calculation of CrCl

2) The anticoagulant activity can be determined semi-quantitively by
   PT/INR affected by anti Xas
   Thrombin time by dabigatran

3) BUT only rivaroxaban has a linear relationship with PT
   Some labs also can measure quantitative= functional activity – anti Xa activity (similar to LMWHs)

4) Coming through in 2019 “DOAsense” a urine assay which determines which DOAC is present in the patient
Effect of rivaroxaban on coagulation assays

Samama et al  Thromb Haemostas 2010;103:815
Emergency reversal

Assess patient

History & examination

Anticoagulant

Lab

Imaging

Help?

- Drug class
- Indication
- Last dose
- ½ life
- Clearance

FBC

PT/APTT/fibrinogen

Creatinine

LFTS

Thrombin time & anti

As indicated

Haematology expertise?
Is there a need to reverse DOAC? Or will the effect wear off?

- Schematic diagram showing pharmacokinetic/pharmacodynamic characteristics of VKA and rivaroxaban

Urgent reversal required

- Warfarin
- IIa inhibitor DOAC
- Xa inhibitor DOAC
- Vit K + PCC
- Idarucizumab
- PCC
- Andexanet

Goals of intervention
1. Fluid resuscitation
2. Provide usual blood product replacement
3. Reversal of anticoagulant effect
# DOAC reversing agents

<table>
<thead>
<tr>
<th>Point</th>
<th>Idarucizumab</th>
<th>Andexanet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical structure</td>
<td>Human monoclonal antibody fragment</td>
<td>Recombinant truncated human Factor Xa variant (decoy)</td>
</tr>
<tr>
<td>Onset</td>
<td>&lt; 5 mins</td>
<td>2 mins</td>
</tr>
<tr>
<td>Half-life</td>
<td>Initial 47 mins</td>
<td>Terminal- 6 hrs</td>
</tr>
<tr>
<td></td>
<td>Terminal 10.3 hrs</td>
<td></td>
</tr>
<tr>
<td>Elimination</td>
<td>Kidney</td>
<td>Not reported</td>
</tr>
<tr>
<td>Binding</td>
<td>Non competitive binding to dabigatran</td>
<td>Competitive binding to direct &amp; indirect Factor Xa inhibitors</td>
</tr>
<tr>
<td>Target affinity</td>
<td>X350 affinity for dabigatran than IIa</td>
<td>Affinitiy for Direct FXa inhibitor similar to that of native FXa</td>
</tr>
<tr>
<td>Storage</td>
<td>Refrigerate</td>
<td>Refrigerate</td>
</tr>
</tbody>
</table>
12 healthy men - rivaroxaban 20mg BD
- dabigatran 150mg BD for 2.5 days each
Given a single bolus of 50iu/Kg PCC

Rivaroxaban  PT prolonged (15 sec vs baseline 12)
Completely reversed by PCC
Normalised thrombin potential

Dabigatran APTT, ecarin clotting time & thrombin time prolonged
Not restored by PCC
Emergency Room Coagulation Monitoring for the patient with no history

<table>
<thead>
<tr>
<th></th>
<th>Vit K Antagonist</th>
<th>Anti Xa DOAC</th>
<th>Anti Iia DOAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT</td>
<td>↑↑↑↑</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Anti Xa (LMWH)</td>
<td></td>
<td>↑↑↑↑</td>
<td></td>
</tr>
<tr>
<td>TT/Haemaclot</td>
<td></td>
<td>↑↑↑↑</td>
<td>↑↑↑↑</td>
</tr>
</tbody>
</table>

- **Laboratory tests**
  - PT/APTT/Fibrinogen concentration
  - DOAC plasma concentrations
  - Platelet number

- **TEG ® / ROTEM® not helpful**

- **(DOAsense)**
What to do with an unconscious bleeding patient known to be taking an anticoagulant but uncertain which?

• No clarity
• No publications (yet)
• No guidelines

• Most laboratories do not have specific DOAC anti-Xa assays set up & if they do turn around times too slow

• Need to establish a fast generic anti Xa assay for all DOACs (van Pelt et al, Thrombosis Research 2018;168: 63-66
Idarucizumab mode of action

Idarucizumab alters the equilibrium – dabigatran dissociates from thrombin

Idarucizumab rapidly binds to dabigatran in the plasma

Dabigatran inhibiting thrombin

Dabigatran bound to plasma proteins

Unbound dabigatran

Thrombin

Dabigatran molecule

Antidote (idarucizumab)
Intravenous idarucizumab, an antibody fragment of a human antibody specific for dabigatran, produced rapid reversal of the anticoagulant effect in patients with bleeding or an urgent surgical indication with no apparent toxic effects or rebound hypercoagulable state.
Idarucizumab dosing schedule

- Administer dose undiluted IV bolus. Infusion of each vial should take 5 - 10 minutes with the second vial of 2.5 g administered no later than 15 minutes after the end of the first 2.5 g vial.

- Baseline aPTT (at presentation), repeat at 2 hours postexposure (if exposure time is known) or post-presentation (if exposure time is unknown) and every 12 hours thereafter until aPTT returns to normal.

- 2.5 gm/50 mL (50 mL): $2100.00
Thrombotic events or death within 30 days
Idarucizumab (cohort n=90)

5 patients had thrombotic events

2 days post Rxment: DVT/PE
9 days post Rxment: DVT/PE/Left Atrial thrombus
7 days post Rxment: DVT
13 days post Rxment: NSTEMI
26 days post Rxment: Stroke

Mechanism of Action of Andexanet alfa
Effect of Andexanet on the Anti-Xa Activity of Rivaroxaban

Crowther M. et al., ASH 2013 (Abstract 3636)
Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors

MAJOR BLEEDING CRITERIA

1. Potentially life-threatening
2. Acute overt bleeding with signs or symptoms of hemodynamic compromise (e.g., severe hypotension, poor skin perfusion, mental confusion, or low cardiac output that could not otherwise be explained)
3. Acute overt bleeding associated with a decrease in hemoglobin of at least 2 g or a hemoglobin level of 8 g or less if no baseline hemoglobin level was available
4. Acute symptomatic bleeding in a critical area or organ (e.g., retroperitoneal, intraarticular, pericardial, intracranial, or intramuscular with the compartment syndrome).
**Andexanet dosing schedule**

- **Apixaban or rivaroxaban > 7 hours before**
  - Bolus dose: 400 mg [15-30 min]
  - Infusion dose: 480 mg [over 2 hrs]

- **Enoxaparin, edoxaban, or rivaroxaban < 7 hours or less before or an Unknown time.**
  - Bolus dose: 800 mg [15-30 min]
  - Infusion dose: 960 mg [over 2 hrs]
Anti–Factor Xa Activity and Percent Change from Baseline in Patients Receiving Rivaroxaban and Apixaban (Efficacy Population).

A Rivaroxaban (N=26)

- Baseline: 277.0
- End of Bolus: 16.8
- End of Infusion: 30.6
- 4 Hr: 177.7
- 8 Hr: 127.1
- 12 Hr: 97.9

Median Percent Change (95% CI)
- Baseline: 16.8 (-95 to -94)
- End of Bolus: 30.6 (-55 to -93)
- End of Infusion: -39 (-27 to -45)
- 4 Hr: -49 (-43 to -57)
- 8 Hr: -64 (-51 to -70)

B Apixaban (N=20)

- Baseline: 249.7
- End of Bolus: 10.3
- End of Infusion: 12.5
- 4 Hr: 103.0
- 8 Hr: 107.1
- 12 Hr: 100.2

Median Percent Change (95% CI)
- Baseline: 10.3 (-87 to -94)
- End of Bolus: 12.5 (-85 to -94)
- End of Infusion: -30 (-23 to -46)
- 4 Hr: -28 (-19 to -38)
- 8 Hr: -31 (-27 to -41)
### Subgroup Analysis of Hemostatic Efficacy

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>Percent Adjudicated as Excellent or Good Hemostasis (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients with efficacy analyses</td>
<td>47</td>
<td>79 (64–89)</td>
</tr>
<tr>
<td>Drug</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>26</td>
<td>81 (61–93)</td>
</tr>
<tr>
<td>Apixaban</td>
<td>20</td>
<td>77 (51–91)</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>24</td>
<td>71 (49–87)</td>
</tr>
<tr>
<td>Female</td>
<td>23</td>
<td>87 (66–97)</td>
</tr>
<tr>
<td>Site of bleeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>25</td>
<td>84 (64–96)</td>
</tr>
<tr>
<td>Intracranial</td>
<td>20</td>
<td>80 (56–94)</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>7</td>
<td>71 (29–96)</td>
</tr>
<tr>
<td>65–75 yr</td>
<td>9</td>
<td>89 (52–100)</td>
</tr>
<tr>
<td>≥75 yr</td>
<td>31</td>
<td>77 (59–90)</td>
</tr>
<tr>
<td>Andexanet dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>42</td>
<td>76 (61–88)</td>
</tr>
<tr>
<td>High</td>
<td>5</td>
<td>100 (48–100)</td>
</tr>
<tr>
<td>Anti–factor Xa &lt;75 ng/ml or &lt;0.5 IU/ml</td>
<td>17</td>
<td>82 (57–96)</td>
</tr>
</tbody>
</table>

Thrombotic Events or Death during the 30-Day Study Period.

Summary

- Management strategies in DOAC-treated patients who have bleeding complications or require surgical procedures are dependent on the agent involved, the location and severity of the bleeding, and/or the urgency of the invasive procedure.

- Management of such clinical situations has typically involved temporary removal of the DOAC and supportive care, with the addition of clotting factor supplements when urgent reversal of anticoagulant activity is required.
For more information..

Engineering Reversal — Finding an Antidote for Direct Oral Anticoagulants

Beverley J. Hunt, M.D., and Marcel Levi, M.D., Ph.D.

Urgent reversal of vitamin K antagonists Hunt BJ, Levi M
BMJ 2018;360:j5424

Spotlight on reversing anti Factor Xa agents and the unmet needs in trauma patients. Hunt BJ, Neal MD, Stensbale J, Blood 2018 Oct 11
• Up to 1:1000 people are affected by VTE in the UK each year and up to 1:10 people who suffer a PE will die if not treated.
• Venous thromboembolism is the most common cause of preventable hospital deaths in the UK.

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