GASTROINTESTINAL EMERGENCIES IN ENDOSCOPY - SHOULD I STAY OR SHOULD I GO?
September 2016

ANTICOAGULATION AND BLEEDING MANAGEMENT

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BLEEDING WHILE ON AN ANTICOAGULANT: WHAT HAVE WE LEARNT?

Less critical bleeding with NOACs
Different bleeding pattern with NOACs
Patient characteristics drive bleeding
Proactive measures to reduce bleeding risk
Guidance to manage bleeding

NOACs vs VKA: Improved Clinical outcomes

<table>
<thead>
<tr>
<th>Event</th>
<th>VKA (W/O DO)</th>
<th>NOAC (W/O DO)</th>
<th>RR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischaemic stroke</td>
<td>665/29,292</td>
<td>724/29,221</td>
<td>0.92 (0.83–1.02)</td>
<td>0.10</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>130/29,292</td>
<td>263/29,221</td>
<td>0.49 (0.38–0.64)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>413/29,292</td>
<td>432/29,221</td>
<td>0.97 (0.78–1.20)</td>
<td>0.77</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>2022/29,292</td>
<td>2245/29,221</td>
<td>0.90 (0.85–0.95)</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

Relative risk difference (%) (95% CI)

Favours NOAC  favours warfarin

SAFE

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VKAs VERSUS NOACs:
ORGAN-SPECIFIC PATTERNS OF BLEEDING

Meta-analysis: ARISTOTLE, ENGAGE AF, RE-LY and ROCKET AF

<table>
<thead>
<tr>
<th>Event</th>
<th>Relative risk difference (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial bleeding</td>
<td></td>
</tr>
<tr>
<td>Other major bleeding</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td></td>
</tr>
</tbody>
</table>

Favours NOAC  favours warfarin

The patient on antithrombotics
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**Risk of GI Bleeding Varies Between Populations**

<table>
<thead>
<tr>
<th>Study Populations</th>
<th>Mean CHADS2 Score</th>
<th>Major GI Bleeding Event Rate/Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized clinical trial</td>
<td>n=7111</td>
<td>2.0%</td>
</tr>
<tr>
<td>Prospective registry</td>
<td>Dresden NOAC3,4</td>
<td>2.4%</td>
</tr>
<tr>
<td>Observational study</td>
<td>XANTUS5</td>
<td>2.1%</td>
</tr>
<tr>
<td>Randomized clinical trial</td>
<td>ARISTOTLE6,7</td>
<td>2.1%</td>
</tr>
</tbody>
</table>

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**Risk Factors for Bleeding**

- Age
- Male sex
- High blood pressure
- Use of platelet inhibitors
- History of GI bleeding
- Anaemia

Treat

Avoid

PPI

Assess

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**Initial Management of Serious Bleeding Events**

Identify and control source of bleeding

Supportive care to stabilize patient

Assess (anti)coagulation

How much drug is on board? Which and when?

PT/aPTT and renal function

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WHAT CAN WE LEARN FROM ROUTINE COAGULATION TESTS?

FXa-inhibitors (riva, apixa, edo):
Prothrombin Time (PT)

- **Prolonged**
  - suggests on-therapy levels (or above)
  - (riva > edo > apixaban)

- **Normal**
  - does not exclude on-therapy
  - high levels unlikely (riva > edo > apixaban)

WHAT CAN WE LEARN FROM ROUTINE COAGULATION TESTS?

Dabigatran: aPTT

- **Prolonged**
  - suggests on-therapy levels (or above)

- **Normal**
  - does not exclude on-therapy
  - high levels unlikely

HOW TO SUPPORT HAEMOSTASIS?

Non-specific support of haemostasis
- Procoagulants (PCCs)
- Antifibrinolytics
- Reversal agents
  - Idarucizumab
  - Andexanet

PHASE I STUDY SHOWED REVERSAL OF RIVAROXABAN-INDUCED ANTICOAGULATION WITH PCC

20 mg rivaroxaban was administered bid followed by PCC (Cofact®, 50 U/kg bodyweight)

- Prolongation of PT was reversed completely by PCC

STANDARD CLINICAL MEASURES SUFFICIENT TO MANAGE MAJOR BLEEDING IN THE MAJORITY OF CASES

Dresden NOAC registry

| Approach (%) | RBC | Cryoprecipitate | FFP | PCC | V/K | FVIII-
|--------------|-----|----------------|-----|-----|-----|---|

Major bleeding events mostly treated in the real world

NOAC reversal agents in development

- **Idarucizumab**
  - Target: dabigatran
  - Phase I: Phase II: Phase III: Approved by EMA/FDA

- **Andexanet alfa**
  - Target: FXa inhibitors
  - Phase I: Phase II: Phase III: Approved

NOAC reversal agents are investigational compounds under development and have not been approved for use in the EU.

1. Adapted from Greinacher A et al. Thromb Haemost 2015;113:931–42;
4. ClinicalTrials.gov Identifier: NCT02329327; 5. ClinicalTrials.gov Identifier: NCT02207257

*Approved by EMA/FDA Phase III: Patients requiring urgent surgery and/or major bleeding within 24 h after dosing.
*Not approved for use in the EU.
Idarucizumab for Dabigatran Reversal

Charles V. Pollack, Jr., M.D., Paul A. Reilly, Ph.D., John Ellenboom, M.B., B.S.,
Stephen Glund, Ph.D., Peter Verhamme, M.D., Richard A. Bernstein, M.D., Ph.D.,
Robert Judil, Pharm.D., Memn V. Huismen, M.D., Ph.D., Elaine M. Hylek, M.D.,
Peter W. Kamphuisen, M.D., Ph.D., Jörg Kreuzer, M.D., Jérôme H. Levy, M.D.,
Frank W. Sollie, M.D., Joachim Stangier, Ph.D., Thorsten Steiner, M.D., M.M.E.,
Bush Wang, Ph.D., Chik-Wah Lam, M.D., and Jeffrey I. Witzt, M.D.

NEJM, Aug 6th 2015

Idarucizumab showed immediate, complete, and sustained reversal of dabigatran anticoagulation in a healthy volunteer study

Idarucizumab: specific reversal agent for dabigatran

Idarucizumab to reverse dabigatran in patients with bleeding: interim results

Reversal was also evident on aPTT results

Idarucizumab levels
The patient on antithrombotics
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Target: dabigatran

Andexanet alfa (PRT064445)
Target: FXa inhibitors

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Andexanet: Designed to Reverse Activity of direct and indirect Factor Xa Inhibitors

- fXa decoy to bind molecules that target and inhibit fXa
- Np catalytic activity
- No GLA domain

Andexanet: Reversal of Rivaroxaban

Siegel, N Engl J Med 2015

Anti-factor Xa Activity: Apixaban

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Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors

Stuart J. Connolly, M.D., Truman J. Milling, Jr., M.D., John W. Eikelboom, M.D., C. Michael Gibson, M.D., John T. Curnette, M.D., Ph.D., Alex Gold, M.D., Michele D. Bronson, Ph.D., Geminin Lu, Ph.D., Pamela B. Conley, Ph.D., Peter Verhamme, M.D., Ph.D., Jeannot Schmidt, M.D., Saskia Middeldorp, M.D., Alexander T. Cohen, M.D., Jan Breyer-Westendorf, M.D., Pierre Albulujio, M.D., Jose Lopez-Sendon, M.D., Shelly Goodman, Ph.D., Janet Ede, Ph.D., Brian L. Wiens, Ph.D., Deborah M. Sigel, M.D., Elena Zotova, Ph.D., Brandi Meeks, B.E., Juliet Nakamura, Ph.D., W. Ting Lin, M.Sc., and Mark Crowther, M.D., for the ANNEXA-4 Investigators

Sept 22, 2016

The patient on antithrombotics

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The NOAC-brothers
Dabigatran (Pradaxa)
Rivaroxaban (Xarelto)
Apixaban (Eliquis)
Edoxaban (Lixiana)

<table>
<thead>
<tr>
<th>PK/PD</th>
<th>DABIGATRAN 150/110 BD</th>
<th>RIVAROXABAN 20/15 OD</th>
<th>APIXABAN 5/2.5 BD</th>
<th>EDOXABAN 60/30 OD</th>
</tr>
</thead>
<tbody>
<tr>
<td>target</td>
<td>thrombine</td>
<td>fXa</td>
<td>fXa</td>
<td>fXa</td>
</tr>
<tr>
<td>t1/2 Cmax</td>
<td>2h</td>
<td>2h</td>
<td>2h</td>
<td>2h</td>
</tr>
<tr>
<td>Renal clearance</td>
<td>80%</td>
<td>1/3</td>
<td>1/3</td>
<td>1/2</td>
</tr>
<tr>
<td>Half-life</td>
<td>12h</td>
<td>12h</td>
<td>12h</td>
<td>12h</td>
</tr>
</tbody>
</table>