Anticoagulation
Past, present, and future

Werkgroep Cardiologische centra Nederland (WCN)
1e Dunselman Lecture

1952-2017
Anticoagulant drug development: from serendipity to designer drugs
Lessons learned from the trials

1. The efficacy and safety of anticoagulants is vascular-bed specific
2. Bleeding is a key determinant of thromboembolic outcomes
3. Breakthrough thromboembolic events that occur despite therapeutic anticoagulation are driven by novel mechanisms
Vascular bed-specific anticoagulant efficacy

<table>
<thead>
<tr>
<th>Indication</th>
<th>Efficacy: thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous thrombosis</td>
<td>decreased by 80-90%</td>
</tr>
<tr>
<td>Stroke in atrial fibrillation</td>
<td>decreased by 70-80%</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>decreased by 50%</td>
</tr>
<tr>
<td>Atherothrombosis</td>
<td>decreased by 20-40%</td>
</tr>
</tbody>
</table>
# Vascular bed-specific bleeding

<table>
<thead>
<tr>
<th>Organ / vascular bed</th>
<th>Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal tract</td>
<td>Increased by 30%</td>
</tr>
<tr>
<td>Brain</td>
<td>Decreased by 50%</td>
</tr>
<tr>
<td>Uterus</td>
<td>Increased by 200%*</td>
</tr>
<tr>
<td>Other</td>
<td>Decreased by 30%</td>
</tr>
</tbody>
</table>

*Anti-Xa agents
Why was this not recognized previously?

• Historically we thought that bleeding did not matter (inconvenient but reversible)
• More recently bleeding recognized as independent predictor of morbidity and mortality
• NOAC trials have had greater power to detect organ-specific effects
  • Large numbers of patients
  • Better characterization of sites of bleeding (e.g., routine endoscopy, routine brain imaging)
Historical thinking is reflected in approach to bleeding risk prediction and definition

- HAS-BLED
- HAEMORR\textsubscript{2}HAGES
- ATRIA, ORBIT
- ABC bleeding score
- ISTH
- GUSTO
- TIMI
- PLATO
- BARC

No “organ specificity”
Why might the bleeding effects be organ / vascular-bed specific?

Two possible mechanisms:

• Drug specific
  • Local concentration
  • Mechanism of action

• Vascular bed
  • Expression of procoagulant / anticoagulant mediators
## High concentration of NOACs in the gut

<table>
<thead>
<tr>
<th></th>
<th>Active drug in gut?</th>
<th>Intraluminal levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>Yes (prodrug activated by gut esterases)</td>
<td>80%</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Yes</td>
<td>35%</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Yes</td>
<td>30%</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Yes</td>
<td>50%</td>
</tr>
<tr>
<td>Warfarin</td>
<td>No</td>
<td>&lt;5%</td>
</tr>
</tbody>
</table>

ICH and cerebral microbleeds

Koennecke, HC. Neurology 2006; 66; 165-171.
Warfarin reduces thrombin generation by reducing formation of factor VII/TF

Coagulation activation

blocks thrombin generation

Tissue factor

(high concentration in basement membrane and adventitia)

VII, X, IX, prothrombin

Warfarin

thrombin
Mechanism of reduced intracranial bleeding with NOACs

• There are high concentrations of tissue factor surrounding cerebral vessels
• Experimental evidence supports hypothesis that NOACs are less effective than warfarin at blocking tissue factor-mediated thrombin generation

Dabigatran is overwhelmed by excess thrombin

**Coagulation activation**

**Tissue factor**

(high concentration in basement membrane and adventitia)

VII, X, IX, prothrombin

Thrombin in excess overwhelms dabigatran

thrombin
dabigatran
Summary and clinical implications

- NOAC trials have shown organ specific differences of anticoagulants on bleeding (and thromboembolic events)
- This knowledge can impact choice of anticoagulant (e.g., GI: apixaban, dabigatran 110; ICH: NOAC; menstrual: dabigatran)
Research implications

- Can improved understanding of organ specific effects help to more effectively predict and prevent bleeding? Do we need new bleeding scores for different organs?
- Can better understanding of mechanisms help in development of safer anticoagulants? (e.g., factor XI inhibitors?)
INTERBLEED: a study of risk factors for and outcomes after GI bleeding

Case-control
Risk factors for bleeding

Prospective cohort
Reasons why bleeding results in adverse outcome

Case → 3 months (phone) → 12 months (phone)
Control → 3 months (phone) → 12 months (phone)
Lessons learned from the trials

1. The efficacy and safety of anticoagulants is vascular-bed specific

2. **Bleeding is a key determinant of thromboembolic outcomes**

3. Breakthrough thromboembolic events that occur despite therapeutic anticoagulation are driven by novel mechanisms
Bleeding and thromboembolism in orthopedic VTE prevention trials

Bleeding and thromboembolism in stroke prevention in AF trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Stroke</th>
<th>Stroke CHADS$_2$ 3+</th>
<th>Any Bleeding</th>
<th>Maj. bleeding</th>
<th>Maj. bleed CHADS$_2$ 3+</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARISTOTLE (5/2.5mg bid)</td>
<td>1.3%</td>
<td>2.0%</td>
<td>18%</td>
<td>2.1%</td>
<td>2.9%</td>
</tr>
<tr>
<td>ENGAGE (60/30 mg od)</td>
<td>1.5%</td>
<td>-</td>
<td>14%</td>
<td>2.8%</td>
<td>-</td>
</tr>
<tr>
<td>RELY (150 mg bid)</td>
<td>1.1%</td>
<td>1.9%</td>
<td>16%</td>
<td>3.3%</td>
<td>4.8%</td>
</tr>
<tr>
<td>ROCKET (20/15mg od)</td>
<td>1.7%</td>
<td>-</td>
<td>15%</td>
<td>3.6%</td>
<td>-</td>
</tr>
</tbody>
</table>

Adverse consequences of bleeding

Bleeding reduced by 38%  
Deaths reduced by 17%

## OASIS-5: link between bleeds and deaths

Number of deaths at 180 days

<table>
<thead>
<tr>
<th></th>
<th>Enoxaparin</th>
<th>Fondaparinux</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Bleeds</td>
<td>526</td>
<td>523</td>
<td>+3</td>
</tr>
<tr>
<td>Minor bleeds</td>
<td>33</td>
<td>13</td>
<td>+20</td>
</tr>
<tr>
<td>Major bleeds</td>
<td>79</td>
<td>38</td>
<td>+41</td>
</tr>
<tr>
<td>Total</td>
<td>638</td>
<td>574</td>
<td>+64</td>
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### Weighing the importance of bleeding

<table>
<thead>
<tr>
<th>Event</th>
<th>Death HR (95% CI)</th>
<th>Weight</th>
</tr>
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<tr>
<td>Ischemic stroke</td>
<td>6.5 (5.9-7.1)</td>
<td>1.00</td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>5.8 (4.7-7.3)</td>
<td>0.90</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>21.3 (17.6-25.7)</td>
<td>3.29</td>
</tr>
<tr>
<td>Subdural bleeding</td>
<td>5.1 (3.8-6.9)</td>
<td>0.79</td>
</tr>
<tr>
<td><strong>Extracranial Bleeding</strong></td>
<td><strong>4.6 (4.2-5.1)</strong></td>
<td><strong>0.71</strong></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>6.2 (5.4-7.1)</td>
<td>0.96</td>
</tr>
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Why is bleeding associated with thromboembolic events and death?

Bleeding → Death

- Direct adverse effects of bleeding (e.g., hypovolemic, acute stress)
- Discontinuation of effective antithrombotic therapies
- Treatments for bleeding (e.g., antifibrinolytic therapy, red blood cell transfusion)

Summary and clinical implications

• Bleeding independently predicts subsequent CV events and death
• Mechanism remains poorly understood
• Major bleeding should weight similarly to thromboembolic events when considering the net benefit of a treatment
Research implications

• Can prevention of bleeding by targeting risk factors help to prevent CV events and death?
• Can improved treatment of bleeding help to prevent CV events and death?
• Can targeting the mechanisms linking bleeding with subsequent CV events and death help to prevent these complications?
Pantoprazole to prevent upper GI bleeding…and related CV events

Outcome: upper GI complications
Mean follow up: 3-4 years

INTERBLEED: a study of risk factors for and outcomes after GI bleeding

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Case --→ 3 months (phone) --→ 12 months (phone)

Control --→ 3 months (phone) --→ 12 months (phone)
Lessons learned from the trials

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Breakthrough thromboembolic events

- 1 in 50 AF patients experience stroke each year despite therapeutic anticoagulation
- 1 in 20 mechanical valve patients experience thromboembolism despite therapeutic anticoagulation with dabigatran
Why do thrombotic events occur despite OAC treatment?

• Anticoagulant effect of the drugs is weak
  • low drug levels (dose, compliance)

• Stimulus for thrombogenesis overcomes or is non-responsive to anticoagulants
  • AF: inflammation (blood - IL-6, CRP; LA wall inflammation) and up-regulation of procoagulant molecules (e.g., TF, PAI-1)
  • Valves: contact activation
Persistent coagulation activation despite OAC treatment in AF

Persistent coagulation activation independently predicts stroke

Potential for anti-inflammatory treatment to improve response to OAC

• Colchicine
  • Targets neutrophils, monocytes
  • Lowers CRP
• Inflammation linked with coagulation activation
Anti-inflammatory therapy to suppress coagulation activation
OASIS 5/6: Catheter thrombosis

Event rate (%)

Mechanism of catheter thrombosis

Catheter-induced clotting

- Heparin
- Enoxaparin
- Fondaparinux

Heart attack-induced clotting

- Heparin
- Enoxaparin
- Fondaparinux

Anticoagulants for heart valves

RE-ALIGN: Stroke/valve thrombosis

Contact-induced coagulation activation

Modulating contact-induced coagulation activation by targeting factors XI or XII

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<th>Strategy</th>
<th>Mechanism of action</th>
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<tr>
<td>Antisense oligonucleotides</td>
<td>Reduce hepatic synthesis of factor XII or factor XI</td>
</tr>
<tr>
<td>Aptamers</td>
<td>Bind factor XII or factor XI and block activity</td>
</tr>
<tr>
<td>Antibodies</td>
<td>Bind factor XII or factor XI and block activation or activity</td>
</tr>
<tr>
<td>Small molecules</td>
<td>Bind reversibly to active site of factor XIIa or factor Xla and block activity</td>
</tr>
<tr>
<td>Polyanion antagonists</td>
<td>Neutralize polyphosphates or nucleic acids via ionic interactions, thereby attenuating contact pathway activation</td>
</tr>
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Conclusion

• Recent dramatic advances in anticoagulant therapy have revolutionized medicine
• In addition to informing efficacy and safety, RCTs have provided insights into mechanisms of thrombosis and bleeding
• Improved insights offer potential to develop unique approaches to thrombosis prevention and treatment