UP AND COMING
ANTICOAGULANTS AND
HEMOSTASIS AGENTS

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Overview

Advances in thrombosis
New indications for NOACs
New targets, new drugs

Advances in hemostasis
Reversal agents for NOACs
Rebalancing therapy for hemophilia
Advances in Thrombosis

New indications for NOACs
New Indicators for NOACs

<table>
<thead>
<tr>
<th>Indication</th>
<th>Trial</th>
<th>Treatment</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embolic stroke of uncertain source</td>
<td>NAVIGATE-ESUS NCT 02313909</td>
<td>Rivaroxaban or aspirin</td>
<td>7000</td>
</tr>
<tr>
<td></td>
<td>RESPECT-ESUS NCT 02239120</td>
<td>Dabigatran or aspirin</td>
<td>6000</td>
</tr>
<tr>
<td>Heart failure</td>
<td>COMMADER-HF NCT 01877915</td>
<td>Rivaroxaban or placebo</td>
<td>5000</td>
</tr>
<tr>
<td>CAD or PAD</td>
<td>COMPASS NCT 01776424</td>
<td>Rivaroxaban, rivaroxaban plus aspirin, or aspirin</td>
<td>27,400</td>
</tr>
</tbody>
</table>

CAD, coronary artery disease; PAD, peripheral artery disease;
Advances in Thrombosis

New targets
Why Do We Need New Targets?

Holy grail of anticoagulant therapy is to attenuate thrombosis without increasing the risk of bleeding.

Less intracranial bleeding with NOACs, but annual rate of major bleeding remains at 2% to 3% in the AF population.
Triggers of Coagulation Activation

- Tissue factor
- Contact (e.g., stents, valves, catheters)
- Thrombin

Intrinsic Pathway:
- XIIa
- Xla

Extrinsic Pathway:
- VIIa

Common Pathway:
- Xa

Clot formation

(e.g., plaque rupture)
Why the Focus on the Intrinsic Pathway?

New initiators of the intrinsic pathway identified

Attenuated thrombosis in mice deficient in FXII or FXI

Minimal alteration in hemostasis with FXII- or FXI-directed therapies
New Initiators of the Intrinsic Pathway

Leukocytes → NETs
Activated/damaged cells → DNA/histones RNA → Activate FXII
Platelets → Inorganic polyphosphates → Promote FXI activation

Promote platelet activation → Thrombosis
## New Drugs That Target the Intrinsic Pathway

<table>
<thead>
<tr>
<th>Target</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyphosphates</td>
<td>Dendrimers, PdSP15, DNase</td>
</tr>
<tr>
<td>FXII</td>
<td>ASO, Antibodies</td>
</tr>
<tr>
<td>FXI</td>
<td>ASO, Antibodies, Small molecules</td>
</tr>
</tbody>
</table>
## Failure of Dabigatran Compared with Warfarin in Patients with Mechanical Heart Valves

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Dabigatran (n=168)</th>
<th>Warfarin (n=84)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>TIA</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>7</td>
<td>2</td>
</tr>
</tbody>
</table>

CTI Attenuates Valve Leaflet-induced Thrombin Generation

Mechanical Valve Leaflet-induced Thrombin Generation is Factor XI-dependent

Comparison of the Effects of FXII, FXI or FVII Knockdown on Catheter Thrombosis in Rabbits

Phase II Trial Comparing FXI ASO with Enoxaparin for Thromboprophylaxis

Elective TKR

Enoxaparin (40 mg OD starting after surgery)

ASO (200 or 300 mg starting 35 d prior to surgery)

**Comparison of the Efficacy and Safety of FXI ASO and Enoxaparin**

<table>
<thead>
<tr>
<th></th>
<th>FXI ASO, 200 mg n=144</th>
<th>FXI ASO, 300 mg n = 77</th>
<th>Enoxaparin n=72</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE</td>
<td>27%</td>
<td>4%</td>
<td>30%</td>
</tr>
<tr>
<td>Major or non-major bleeding</td>
<td>3%</td>
<td>3%</td>
<td>8%</td>
</tr>
</tbody>
</table>

Potential New Indications

Prevention of medical device-associated thrombosis (e.g., mechanical heart valves)

Prevention or treatment of thrombosis in patients at high risk for bleeding (e.g., AF in patients with ESRD)

Safer platform therapy for patients receiving dual antiplatelet therapy
Advances in Hemostasis

Reversal agents for NOACs
Need for Reversal Agents for NOACs

Annual rate of major bleeding remains at 2-3% in AF population

Even with NOACs, annual rate of intracranial hemorrhage is 0.1-0.5% in AF population

Some patients require reversal because of trauma or need for urgent surgery
### Specific Reversal Agents

<table>
<thead>
<tr>
<th>Structure</th>
<th>Idarucizumab</th>
<th>Andexanet alfa</th>
<th>Ciraparantag</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humanized Fab fragment</td>
<td>Human rFXa variant</td>
<td>Synthetic small molecule</td>
<td></td>
</tr>
<tr>
<td>Target</td>
<td>Dabigatran</td>
<td>FXa inhibitors</td>
<td>Universal</td>
</tr>
<tr>
<td>Binding</td>
<td>Non-competitive</td>
<td>Competitive</td>
<td>Non-covalent hydrogen bonds</td>
</tr>
<tr>
<td>Phase 2 results</td>
<td>Rapid, complete reversal</td>
<td>Rapid, complete reversal</td>
<td>Complete reversal</td>
</tr>
<tr>
<td>Phase 3 trial</td>
<td>Licensed, but trial ongoing</td>
<td>Ongoing</td>
<td>Awaited</td>
</tr>
</tbody>
</table>

Group A: Uncontrolled bleeding + dabigatran-treated

Group B: Emergency surgery or procedure + dabigatran-treated

5 g idarucizumab (two separate infusions of 2.5 g)

0–15 minutes

0–24 hours

90 days follow-up

Hospital arrival

Pre-1st vial

Pre-2nd vial

~20 min 1 h 2 h 4 h 12 h 24 h 30 d 90 d

Blood samples

Pollack C et al. Thromb Haemost. 2015 May 28;114 [Epub ahead of print]
Normalization of dTT and ECT with Idarucizumab

Group A

Group B

Secondary Endpoint: Clinical Outcomes

**Group A**
- 51 Patients
- Assessable in 38 patients
- Median local investigator-determined time to bleeding cessation 11.4 hours*

**Group B**
- 39 Patients
- Surgery performed in 36 patients
- Intraoperative hemostasis:
  - 33 normal
  - 2 mildly abnormal
  - 1 moderately abnormal

*Assessment of bleeding cessation may be difficult with internal bleeding into confined spaces such as intramuscular or intracranial bleeding

Idarucizumab

Licensed in the United States

Available in 2000 Emergency Departments across the country

Costs about $3500 per dose
Time Courses of Anti-Factor Xa Activity Before and After Andexanet Administration

A Apixaban Study, Andexanet Bolus

B Rivaroxaban Study, Andexanet Bolus

C Apixaban Study, Andexanet Bolus plus Infusion

D Rivaroxaban Study, Andexanet Bolus plus Infusion

Andexanet

Phase III study in patients with serious bleeding is ongoing

Andexanet likely to be licensed in 2016

Not currently being tested in patients requiring urgent reversal prior to surgery
Advances in Hemostasis

Rebalancing therapy in hemophilia
Bleeding

Clotting

↓ FVIII
↓ FIX
Bleeding

\[
\downarrow \text{FVIII} \\
\downarrow \text{FIX}
\]

\text{Clotting}

\text{Bleeding}

\[
\downarrow \text{AT} \\
\downarrow \text{TFPI} \\
\downarrow \text{aPC}
\]
Unmet Needs in Hemophilia

Prophylaxis is expensive and burdensome even with long-acting clotting factor.

Management of bleeding in patients with inhibitors is problematic.
Approaches to Rebalancing Therapy

- siRNA knockdown of antithrombin (Fitusiran)
- TFPI-directed aptamer (BAX499) or antibody (conziumab)
- Bispecific antibody to factors IXa and X (ACE910)
Interim Fitusiran Phase 1 Study Results*

Thrombin Generation, Part B & C

Post hoc analysis of thrombin generation by AT lowering quartiles

<table>
<thead>
<tr>
<th>AT Lowering</th>
<th>N</th>
<th>Peak Thrombin Generation, nM (Mean ± SD)</th>
<th>% Increase in Peak Thrombin Generation (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25%</td>
<td>24</td>
<td>18 ± 9</td>
<td>20 ± 72%</td>
</tr>
<tr>
<td>25-50%</td>
<td>21</td>
<td>26 ± 12</td>
<td>48 ± 61%</td>
</tr>
<tr>
<td>50-75%</td>
<td>18</td>
<td>47 ± 29</td>
<td>218 ± 272%</td>
</tr>
<tr>
<td>&gt;75%</td>
<td>9</td>
<td>62 ± 27**</td>
<td>285 ± 165%**</td>
</tr>
</tbody>
</table>

**p < 0.001, compared with AT lowering less than 25%

Sorensen B, et al., ISTH 2015
Interim Fitusiran Phase 1 Study Results*

- Exploratory Analysis of Bleed Events, Parts B & C
  - Post hoc analysis of bleed events by AT lowering quartiles

### Table: ABR Estimate, Mean (SEM)

<table>
<thead>
<tr>
<th>AT Lowering</th>
<th>Patients†</th>
<th>Cumulative Days</th>
<th>Cumulative Bleeds</th>
<th>ABR‡, Mean (SEM)</th>
<th>ABR, Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>AT Lowering &lt;25%</td>
<td>24</td>
<td>602</td>
<td>43</td>
<td>34 ± 10</td>
<td>13</td>
</tr>
<tr>
<td>AT Lowering 25-50%</td>
<td>21</td>
<td>838</td>
<td>34</td>
<td>20 ± 7</td>
<td>11</td>
</tr>
<tr>
<td>AT Lowering 50-75%</td>
<td>18</td>
<td>862</td>
<td>35</td>
<td>14 ± 4</td>
<td>10</td>
</tr>
<tr>
<td>AT Lowering &gt;75%</td>
<td>9</td>
<td>304</td>
<td>3</td>
<td>6 ± 3</td>
<td>0</td>
</tr>
</tbody>
</table>

**p<0.05  

†Number of patients with time spent in quartile

‡For each subject, the ABR in each quartile is calculated by 365.24*(number of bleed events/number of days in quartile).

**Based on negative binomial regression model

Sørensen B, et al., ISTH 2015
Futisaran-mediated AT Knockdown

Durable knockdown with once-monthly subcutaneous injection

Thrombin generation increased by up to 300% and post-hoc analysis suggests that annualized bleeding rates decrease in a dose-dependent manner with AT knockdown

Sorensen B, et al., ISTH 2015
Conclusions

Rapid advances in thrombosis and hemostasis

Licensing of reversal agents will enhance the safety profile of the NOACs and eliminate the final barrier to their uptake

Rebalancing therapy for hemophilia appears promising