ADVANCES IN ANTICOAGULATION

WHERE DO THE NEW ANTICOAGULANTS FIT IN?

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Cardiologist
• Indications for anticoagulants

• Review - Physiology of Hemostasis

• Types of anticoagulants

• New anticoagulants – Where do they fit in?
  ■ Focus on the new oral anticoagulants
    • Dabigatran
    • Apixaban
    • Rivoroxaban
INDICATIONS

- **ARTERIAL THROMBOEMBOLIC DISEASE**
  - Acute coronary syndromes
  - Reduce stroke risk in Atrial Fibrillation
  - *Antiphospholipid antibody syndrome*
  - Pulmonary arterial Embolism (PE)

- **VENOUS THROMBOEMBOLIC DISEASE**
  - Deep vein thrombosis (DVT)

- **INTRACARDIAC THROMBOEMBOLIC DISEASE**
  - Prosthetic (Mechanical) valves
  - Intra-cardiac thrombus
Figure 1. (A) The apical four-chamber view showing a huge thrombus in the right atrium. (B) The parasternal short-axis view showing both thrombi in the right atrium and the main pulmonary artery. RV: Right ventricle; PA: Pulmonary artery; T: Thrombus.
Anticoagulation

- Inhibition of the coagulation cascade to induce blood thinning and prevent thrombus formation or extension

**FULL ANTICOAGULATION**

- Full inhibition of the coagulation cascade in high risk patients
- Target Therapeutic INR or AaPTT or anti-Xa levels

**PARTIAL ANTICOAGULATION**

- Prophylaxis in patients at high risk for thrombus
OVERVIEW OF HEMOSTASIS

- HEMOSTASIS - Blood clot formation at the site of vessel injury. The clot is eventually lysed, followed by tissue remodeling.
- Abnormal bleeding or clotting may occur from disorder of this process

COMPONENTS OF HEMOSTASIS
- Initiation and formation of platelet plug
- Propagation of clotting by coagulation cascade
- Termination of clotting by antithrombotic control mechanisms
- Clot removal by fibrinolysis
Coagulation cascade initiated by tissue factor release at the site of tissue injury

A Initiation
TF complexes with factor VIIα formed at the site of tissue injury; the subsequent activation of factor X and factor IX generate small amounts of thrombin.

B Amplification
Thrombin activates platelets and cofactors (V, VII); coagulation factors and cofactors assemble on surface of activated platelets (VIIα, Va, IXα); multiple feedback loops amplify the process.

C Propagation
Assembled complexes continue cascade on surface of activated platelets; the prothrombinase complex converts prothrombin to thrombin which then converts fibrinogen to fibrin; this is followed by clot stabilization.

Factors in squares are inactive forms, whereas factors in circles are active enzymes.
PT: prothrombin; Th: thrombin.
Coagulation pathways

Intrinsic pathway
- Contact factors, XI, XII
  - VIII → IX
  - X, V, phospholipids
  - Prothrombin (factor II) → Thrombin
  - Fibrinogen (factor I)
    - Initial fibrin clot
      - Factor XIII
        - Cross-linked fibrin clot

Extrinsic pathway
- Tissue factor
  - VII
  - Extrinsic pathway

Common pathway

Schematic representation of the intrinsic (in red), extrinsic (in blue), and common (in green) coagulation pathways. In the clinical laboratory, the intrinsic (and common) pathway is assessed by the activated partial thromboplastin time (aPTT) and the extrinsic (and common) pathway by the prothrombin time (PT). The thrombin time (TT) assesses the final step in the common pathway, the conversion of fibrinogen to fibrin, following the addition of exogenous thrombin. Fibrin is crosslinked through the action of factor XIII, making the final fibrin clot insoluble in 5 Molar urea or monochloroacetic acid. This latter function is not tested by the PT, aPTT, or TT.
SITE OF ACTION ANTICOAGULANTS

**Coagulation cascade**

**Extrinsic pathway**
- VII → VIIa → TF → VIIIa/TF → Xa → VIII
- Ca²⁺/PL → IXa → VIIIa/TF → Xa → VIII
- PT → PL → TH → Fibrinogen → Fibrin monomer → Fibrin polymer → Crosslinked fibrin polymer

**Intrinsic pathway**
- XI → IX → VIII
- XIa → VIII
- Ca²⁺/PL → IXa → VIII
- XI → IX → VIII

**Warfarin**
Inhibits VII, IX, X

**Heparins**

**Direct Thrombin Inhibitors**

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Schematic representation of the coagulation cascade including our improved understanding of the role of the tissue factor (TF) pathway in initiating clotting; interactions between pathways; and the role of thrombin in sustaining the cascade by feedback activation of coagulation factors. HK: high-molecular-weight kininogen; PK: prekallikrein; PL: phospholipid; PT: prothrombin; TH: thrombin.

Adapted from Ferguson et al, Eur Heart J 1998; Suppl 19:S.
LIMITATIONS OF WARFARIN AND HEPARIN

- Narrow therapeutic window
- Highly variable dose-response

UFH
- Competitive binding by other proteins
- Reduced ability to activate thrombin bound to fibrin and factor Xa bound to platelets
- Clots may continue to form on heparin therapy or reactivated clotting after stopping therapy
LIMITATIONS OF WARFARIN

- Delayed onset/offset
- Multiple food and drug interactions
- Genetic variability in metabolism
- Requires frequent monitoring of INR because of limited therapeutic index
Efficacy and Safety of Warfarin

Odds Ratio vs. INR

- Ischemic Stroke
- Intracranial Haemorrhage
## PROPERTIES OF AN IDEAL ANTICOAGULANT

<table>
<thead>
<tr>
<th>PROPERTIES</th>
<th>BENEFIT</th>
</tr>
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<tbody>
<tr>
<td>Oral, once-daily dosing</td>
<td>Ease of administration</td>
</tr>
<tr>
<td>Rapid onset of action</td>
<td>No need for parenteral anticoagulant</td>
</tr>
<tr>
<td>Minimal food or drug interactions</td>
<td>Simplified dosing</td>
</tr>
<tr>
<td>Predictable anticoagulant effect</td>
<td>No Coagulation monitoring</td>
</tr>
<tr>
<td>Extra renal clearance</td>
<td>Safe in patients with renal disease</td>
</tr>
<tr>
<td>Rapid offset in action</td>
<td>Simplifies mgt in case of bleeding or intervention</td>
</tr>
<tr>
<td>Antidote</td>
<td>For emergencies</td>
</tr>
</tbody>
</table>
NEW ANTICOAGULANTS

ORAL

TF/VIIa

Rivaroxaban
Apixaban
Edoxaban
Darexaban

PARENTERAL

NAPc2F

Otamixaban (IV)

Semuloparin

Xa

X

IX

IXa

II

IIa

Dabigatran

Fibrinogen → Fibrin
## PK/PD OF 3 NOVEL ORAL AGENTS

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Apixaban</th>
<th>Rivoroxaban</th>
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<tbody>
<tr>
<td><strong>Target</strong></td>
<td>IIa(Thrombin)</td>
<td>Xa</td>
<td>Xa</td>
</tr>
<tr>
<td><strong>Hours to C&lt;sub&gt;max&lt;/sub&gt;</strong></td>
<td>2</td>
<td>1-3</td>
<td>2-4</td>
</tr>
<tr>
<td><strong>CYP metabolism</strong></td>
<td>None</td>
<td>15%</td>
<td>32%</td>
</tr>
<tr>
<td><strong>Half life</strong></td>
<td>12-14hrs</td>
<td>8-15hrs</td>
<td>9-13hrs</td>
</tr>
<tr>
<td><strong>Renal Elimination</strong></td>
<td>80%</td>
<td>25%</td>
<td>66%</td>
</tr>
</tbody>
</table>

Guiliano RP. *Hot topics in Cardiology* 2011
WHERE DO THE NEW ORAL ANTICOAGULANTS FIT IN?

- INDICATIONS
  - Stroke prevention in Non-valvular Atrial Fibrillation
  - DVT prophylaxis in high risk patients
  - Treatment of DVT and Pulmonary embolism

- Not indicated in the following
  - Mechanical heart valves
  - Stroke prevention in valvular AF
STROKE PREVENTION IN ATRIAL FIBRILLATION
### CHADS\textsubscript{2} VS CHADS\textsubscript{2} VASC

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>SCORE (Points)</th>
<th>Prevalence (%)</th>
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<tbody>
<tr>
<td>CHF</td>
<td>1</td>
<td>32</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td>65</td>
</tr>
<tr>
<td>Age &gt; 75 years</td>
<td>1</td>
<td>28</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
<td>18</td>
</tr>
<tr>
<td>S\textsubscript{2}TROKE OR TIA</td>
<td>2</td>
<td>10</td>
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</table>

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>SCORE</th>
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<tbody>
<tr>
<td>CHF/EF&lt;40%</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age &gt; 75 years</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
</tr>
<tr>
<td>S\textsubscript{2}TROKE</td>
<td>2</td>
</tr>
<tr>
<td>Vascular</td>
<td>1</td>
</tr>
<tr>
<td>Age 65-74</td>
<td>1</td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
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Nieuwlaat R, et al. Eur Heart J. 2006;27;3018-3026
<table>
<thead>
<tr>
<th>RISK FACTOR</th>
<th>RECOMMENDED THERAPY</th>
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</thead>
<tbody>
<tr>
<td>No risk factors CHADS$_2$ = 0</td>
<td>ASA 81- 325 mg OD</td>
</tr>
<tr>
<td>One moderate risk factor CHADS$_2$ =1</td>
<td>ASA 81-325 OR Warfarin (INR 2.0-3.0)</td>
</tr>
<tr>
<td>Any High Risk factor or CHADS$_2$ &gt;=2</td>
<td>Warfarin INR 2.0-3.0</td>
</tr>
<tr>
<td>Prosthetic Valve</td>
<td>Warfarin INR 2.5-3.5</td>
</tr>
</tbody>
</table>
## PHASE 3 AF TRIALS

<table>
<thead>
<tr>
<th></th>
<th>RE-LY</th>
<th>ROCKET AF</th>
<th>ARISTOTLE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug</strong></td>
<td>Dabigatran</td>
<td>Rivaroxaban</td>
<td>Apixaban</td>
</tr>
<tr>
<td><strong>Dose (mg)</strong></td>
<td>150, 110</td>
<td>20(15^*)</td>
<td>5(2.5^*)</td>
</tr>
<tr>
<td><strong>Frequency</strong></td>
<td>BID</td>
<td>QID</td>
<td>BID</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>18,113</td>
<td>14,266</td>
<td>18,206</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>PROBE</td>
<td>2x blind</td>
<td>2x blind</td>
</tr>
<tr>
<td><strong>%VKA-naive</strong></td>
<td>50%</td>
<td>38%</td>
<td>43%</td>
</tr>
</tbody>
</table>

* Dose adjusted in patients with low drug clearance

PROBE = Prospective Randomized, Open-label, Blinded Endpoint
ATRIAL FIBRILLATION
ATRIAL FIBRILLATION

A. Stroke or Systemic Embolism

Hazard ratio with apixaban, 0.45
(95% CI, 0.32–0.62)

Aspirin
Apixaban

P<0.001

No. at Risk
Aspirin 2791 2716 2530 2112 1543 628
Apixaban 2808 2758 2566 2125 1522 615

B. Major Bleeding

Hazard ratio with apixaban, 1.13
(95% CI, 0.74–1.75)

Aspirin
Apixaban

P=0.57

No. at Risk
Aspirin 2791 2716 2530 2112 1571 642
Apixaban 2808 2758 2566 2120 1521 622

A. Primary Outcome: Stroke or Systemic Embolism

Hazard ratio, 0.79 (95% CI, 0.66–0.95)
P<0.01

No. at Risk
Apixaban 9120 8726 8440 6051 3464 1754
Warfarin 9081 8620 8301 5972 3405 1768

B. Major Bleeding

Hazard ratio, 0.69 (95% CI, 0.60–0.80)
P<0.001

No. at Risk
Apixaban 9088 8103 7564 5365 3048 1515
Warfarin 9052 7910 7335 5196 2956 1491
Early trials with warfarin then dalteparin then ximelagatran – potential long term benefit
EINSTEIN-PE STUDY

Efficacy and safety results

4833 Patients underwent randomization

2420 Were assigned to receive rivaroxaban
1 Was excluded because of invalid informed consent
2419 Were included in the intention-to-treat analysis
7 Did not receive rivaroxaban
2412 Were included in safety analysis

2413 Were assigned to receive standard therapy
2413 Were included in the intention-to-treat analysis
8 Did not receive standard therapy
2405 Were included in safety analysis

A Primary Efficacy

B Clinically Significant Bleeding

C Major Bleeding
VENOUS THROMBOEMBOLISM

- Dabigatran 150 and 220 in both hip and knee arthroplasty vs Enoxaparin
  - RE-NOVATE I+II, RE-MOBILIZE AND RE-MODEL
  - 40 mg enox – non-inferior/60 mg enox superior, but more bleeding
- Rivaroxaban 10 mg – RECORD1-4
  - 1+2 – HIP – superior to enox 40
  - 3+4 – KNEE – superior to enox 40, but inferior to enox 60
- Apixaban 2.5 mg BD – ADVANCE 1-3
  - Non-inferiority vs enox 60 mg daily
  - Superior to enox 40 mg OD (European dosing)
- XAMOS - Registry
Cost effectiveness

- Cost of 1 months supply of “Dabigatran” – private pharmacy $17,000

- Cost of 1 months’ warfarin
  - Warfarin tablets - $463
  - Clinic visit – $3500
  - Transportation cost - $500
  - INR check - $1500
  - TOTAL(Per INR check and review) - $5500
  - 4INR checks/month $22,000
    - + Cost of multiple blood tests(PRICELESS!!)
PARTING QUESTIONS RE: NOVEL ANTICOAGULANTS

- Are they any better if patients are well controlled on warfarin?
- Will clinicians be comfortable with lack of ability to monitor the level of anticoagulation?
- How do we manage anti-coagulation peri-procedure?
- Is the fast offset a problem if patients are not compliant?
- How do we evaluate cost-effectiveness?
SUMMARY

- Anticoagulants have a major role in the prevention and treatment of diseases of the clotting system
- Heparins and warfarin are mainstay, but have significant limitations
- New and emerging therapies promise to mitigate the limitations of warfarin and heparins
- Newer treatments need the test of time to look at clinical outcomes and safety