A Brief History of the World of Anticoagulation

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Disclosures

None
Objectives

Discuss the evolution of anticoagulation therapy

Recognize increasing need for anticoagulants

Describe the primary role(s) in therapy for each class of anticoagulants

Explain key changes in the therapeutic landscape of anticoagulation

Summarize ongoing and future investigational areas pertaining to anticoagulants
Mechanism of Action

Phase of coagulation

Initiation
- TF/VIIa
- Pl, Ca²⁺
- IXa

Amplification
- Va
- Xa
- VIIIa
- TF

Propagation
- Fibrinogen
- Fibrin

Drugs
- Warfarin
- Heparin + AT
- LMWH + AT
- Fondaparinux + AT
- Apixaban
- Edoxaban
- Rivaroxaban
- Argatroban
- Bivalirudin
- Dabigatran
Impact of AC Evolution

- Linear pharmacokinetics
- Increased specificity & predictability
- Fewer adverse effects and interactions
- Ability to give fixed doses
- Reduced routine monitoring
- Increased convenience and satisfaction
- Increased comfort in prescribing
Increasing Need for AC

Atrial Fibrillation

VTE

Figure 2. Projected number of persons with AF in the United States between 2000 and 2050, assuming no further increase in age-adjusted AF incidence (solid curve) and assuming a continued increase in incidence rate as evident in 1980 to 2000 (dotted curve).


Figure 2. Prevalence and projected estimates of VTE prevalence in the U.S. population (2002–2050).

Global Burden of Thrombosis

• 1 in 4 deaths is caused by arterial or venous thrombosis

**Parenteral Anticoagulants**

### Unfractionated heparin

#### Disadvantages
- Non-linear kinetics, non-specific binding, low predictability
- Frequent monitoring of anticoagulant activity
- HIT in 1-5% of exposed patients

#### Advantages
- Minimal renal elimination
- Short-half life (approximately 1-1.5 hours)
- Reversibility- 100% with protamine

#### Common roles in therapy
- Cardiac indications (e.g. ACS, PCI, cardiothoracic surgery)
- Conventional VTE treatment (with warfarin)
- VTE prophylaxis
- ECMO, hemodialysis, CRRT
Parenteral Anticoagulants

**Low molecular weight heparins (LMWHs)**

- Dalteparin, enoxaparin

**Disadvantages**

- Renal elimination (~40%)
- Requires injection
- Only partially reversible with protamine (50-60%)

**Advantages**

- No routine monitoring of anticoagulant activity
- Longer half-life (4-7 hours)
- Pre-filled syringes and SQ administration
- Lower incidence of HIT (<1%)

**Common roles in therapy**

- ACS
- Conventional VTE treatment (with warfarin)
- Cancer-associated VTE (monotherapy)
- VTE prophylaxis
Parenteral Anticoagulants

Fondaparinux (pentasaccharide)

Disadvantages
• Requires injection
• Long half-life (~20 hours)
• Heavily reliant on renal elimination (>70%)
• Not reversible

Advantages
• No routine monitoring of anticoagulant activity
• Synthetic (pork allergy, religious beliefs)
• Pre-filled syringes and SQ administration
• Fixed-dose, once daily administration

Common roles in therapy
• Conventional VTE treatment (with warfarin)
• VTE prophylaxis
• ACS (Non-US > US)
• HIT
**Parenteral Anticoagulants**

### Parenteral DTIs
- Argatroban, bivalirudin

### Disadvantages
- Short half-life requires continuous infusion
- Frequent monitoring of anticoagulant activity
- Can affect INR (argatroban > bivalirudin)

### Advantages
- Do not interact with platelet factor 4 (PF-4)
- Do not require AT co-factor (can bind clot-bound & unbound thrombin)

### Common roles in therapy
- HIT
- PCI with or without HIT (bivalirudin > argatroban)
- Need for anticoagulation and heparin contraindication (e.g. ECMO, CRRT)
# Oral Anticoagulants

<table>
<thead>
<tr>
<th>Common/approved uses</th>
<th>Warfarin</th>
<th>DOACs</th>
</tr>
</thead>
</table>
| • Any thrombotic condition requiring oral anticoagulation | • NVAF | • VTE TX  
|  | • VTE ppx |  |

| PK | Non-linear | Linear |
| Onset/offset | Slow | Rapid |
| Specificity and predictability | Low | High |
| Dosing | Variable, based on INR | Fixed |
| Renal elimination | No | Yes (% varies by DOAC) |
| Interactions | Numerous | Fewer |
| Routine monitoring | Yes | No |
| Readily available reliable assay | Yes (INR) | No |
| Antidote(s) | Yes (PCC, vitamin K) | Dabigatran-yes  
|  | Fxa inhibitors- no |  |
### Metanalyses:
**DOACs vs. Warfarin for NVAF and VTE**

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>DOACs</th>
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<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding (%)</td>
<td>4.65</td>
<td>4</td>
<td>RR 0.72 [0.62-0.85]; p&lt;0.01</td>
</tr>
<tr>
<td>Case fatality rate from major bleeding (%)</td>
<td>11.05</td>
<td>7.57</td>
<td>p=0.001</td>
</tr>
<tr>
<td>ICH (%)</td>
<td>1.08</td>
<td>0.51</td>
<td>RR 0.43 [0.37-0.5]; p&lt;0.01</td>
</tr>
<tr>
<td>Fatal bleeding (%)</td>
<td>0.52</td>
<td>0.30</td>
<td>RR 0.53 [0.43-0.64]; p&lt;0.01</td>
</tr>
</tbody>
</table>

## DOAC Antidotes

<table>
<thead>
<tr>
<th>Antidote</th>
<th>Classification</th>
<th>Reverses</th>
<th>Mechanism</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idarucizumab¹</td>
<td>Drug-specific</td>
<td>Dabigatran</td>
<td>Antibody fragment</td>
<td>FDA approved 2015</td>
</tr>
<tr>
<td>Andexanet alfa²</td>
<td>Class-specific</td>
<td>FXa inhibitors • Apixaban • Edoxaban • Rivaroxaban</td>
<td>Decoy Xa molecule</td>
<td>Under FDA review</td>
</tr>
<tr>
<td>Ciraparantag³</td>
<td>Universal</td>
<td>• UFH • LMWH • Fondaparinux • Dabigatran • FXa inhibitors</td>
<td>Anticoagulant binding via non-covalent hydrogen bonds and charge-charge interactions</td>
<td>Phase II</td>
</tr>
</tbody>
</table>

¹ Pollack CV et al. NEJM 2015; 373:511-20
² Connolly SJ et al. NEJM 2016; 375:1131-41
DOAC or Warfarin?

<table>
<thead>
<tr>
<th>DOAC if patient meets criteria</th>
<th>Adequately studied indication and population</th>
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<tbody>
<tr>
<td></td>
<td>No contraindications to DOAC (e.g. mechanical valve)</td>
</tr>
<tr>
<td></td>
<td>Adequate renal and hepatic function</td>
</tr>
<tr>
<td></td>
<td>No major drug-drug interactions</td>
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<tr>
<td></td>
<td>High likelihood of adherence</td>
</tr>
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<td>Ability to access DOAC for duration of therapy</td>
</tr>
<tr>
<td></td>
<td>Amenable to therapy with DOAC</td>
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</tbody>
</table>
New prescriptions for oral anticoagulants

% Market Share

Source: IMS NPA Market Dynamics | Data to: Mar 10 2017
US Prescribing Patterns-OACs

Total prescriptions for oral anticoagulants

% Market Share

Source: IMS NPA Weekly | Data to: Mar 10 2017
Source: IMS DDD Weekly 3/03/2017, 1Q’14 CVI Targeted Accounts – Hospital Non Government
Ongoing Investigations: DOACs*

- Cancer
- NVAF + PCI
- Heart failure
- Cryptogenic stroke
- CVT
- APLA
- CAD
- PAD
- Medical prophylaxis
- Cardioversion
- Pediatric VTE
- Ablation

* List is not exhaustive
Learning to Optimize Anticoagulation

- Sometimes less may be more...
  - BRIDGE\(^1\)
  - WOEST\(^2\), PIONEER\(^3\)
  - EINSTEIN CHOICE\(^4\), AMPLIFY EXT\(^5\)

- And sometimes less may just be less...\(^6,7\)

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**Off-Label Dosing of Non-Vitamin K Antagonist Oral Anticoagulants and Adverse Outcomes**

The ORBIT-AF II Registry

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**Real-life treatment of venous thromboembolism with direct oral anticoagulants: The influence of recommended dosing and regimens**

Javier Trujillo-Santos\(^1\); Pierpaolo Di Micco\(^2\); Francesco Dentali\(^3\); James Douketis\(^4\); José Antonio Díaz-Peromingo\(^5\); Manuel Jesús Núñez\(^6\); Inmaculada Cañas\(^7\); Daniela Mastroiacovo\(^6\); Marta Saraiva De Sousa\(^8\); Manuel Monreal\(^9\); RIETE Investigators*
Evolution continues...

- **Future anticoagulants**
  - Betrixaban?
  - FXIa inhibitor?

- **Increasing use of antithrombotic cocktails**
  - PCI + NVAF
  - Endovascular TX of ischemic stroke

- **Increasing use of advanced therapies**
  - Thrombolysis of PE

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**Antithrombosis**

- **Anticoagulants**
- **Antiplatelets**
- **Thrombolytics**
Conclusions

Anticoagulation therapies have dramatically evolved over the last century.

Both conventional and newer anticoagulants have important roles in therapy.

NVAF and VTE expected to double by 2050, increasing the need for anticoagulants.

Practice is expanding to include a wider variety of procedures and antithrombotic agents.

Anticoagulation clinicians will continue to serve an important and expanded role.