The Evolving History of Anticoagulation: The DOAC Era?

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Objectives

• Discuss the evolution of anticoagulation therapy
• Compare and contrast the place in therapy for anticoagulants used in the outpatient setting
• Identify when parenteral anticoagulant bridge may be warranted in patients on warfarin with atrial fibrillation and/or venous thromboembolism
• Determine optimal oral anticoagulant based on patient-specific characteristics
• Recommend appropriate monitoring for direct oral anticoagulants
Evolution of Anticoagulation

Hirudo medicinalis → Heparin
180 A.D. → 1939
1952
1985-1993
1997-2000
2001
2003
2008-2015

Parenteral
DTIs
Fondaparinux
Ximelagatran

VKA = Vitamin K Antagonist
LMWH = Low-Molecular-Weight Heparin
DTI = Direct Thrombin Inhibitor
DOAC = Direct Oral AntiCoagulant

TF/VIIa

Initiation

Warfarin

Apixaban
Betrixaban
Edoxaban
Rivaroxaban
LMWH (via ATIII)

Xa

Amplification

Dabigatran

IIa

Propagation

Fibrinogen → Fibrin

# FDA Approved Oral Anticoagulants

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Warfarin (Coumadin®, Jantoven®)</th>
<th>Dabigatran (Pradaxa®)</th>
<th>Rivaroxaban (Xarelto®)</th>
<th>Apixaban (Eliquis®)</th>
<th>Edoxaban (Savaysa™)</th>
<th>Betrixaban (Bevyxxa™)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevent SSE in NVAF</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>VTE Treatment</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>VTE Secondary Prevention</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>VTE Prevention after hip or knee replacement</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>VTE Prevention in acutely ill medical patients</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>After Cardiac Valve Replacement</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>In CAD and PAD (with ASA)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

**SSE** = Stroke and Systemic Embolism, NVAF = Non-Valvular Atrial Fibrillation

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## Oral Anticoagulants Comparison

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Warfarin</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half life</td>
<td>40 h</td>
<td>12-14 h</td>
<td>7-13 h</td>
<td>8-13 h</td>
<td>10-14 h</td>
</tr>
<tr>
<td>Peak effect</td>
<td>4-5 days</td>
<td>1.5-3 h</td>
<td>2-4 h</td>
<td>1-3 h</td>
<td>1-2 h</td>
</tr>
<tr>
<td>Renal elimination</td>
<td>None</td>
<td>80%</td>
<td>33%</td>
<td>25%</td>
<td>35-50%</td>
</tr>
<tr>
<td>VTE Initial Phase: Oral Only?</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>VTE Secondary Phase Dosing</td>
<td>Once daily</td>
<td>BID</td>
<td>BID x21 days then Once daily</td>
<td>BID (reduced dose after 7 days)</td>
<td>Once daily</td>
</tr>
<tr>
<td>Antidote</td>
<td>Vitamin K</td>
<td>Idarucizumab</td>
<td>Andexanet alfa</td>
<td>Andexanet alfa</td>
<td>Andexanet alfa</td>
</tr>
</tbody>
</table>

*J Thromb Thrombolysis 2016;41,15-31.*
DOACs vs Warfarin for VTE

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran (RE-COVER)</th>
<th>Rivaroxaban (EINSTEIN)</th>
<th>Apixaban (AMPLIFY)</th>
<th>Edoxaban (Hokusai-VTE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent Symptomatic VTE or VTE-related Death</td>
<td>Equal</td>
<td>Equal*</td>
<td>Equal</td>
<td>Equal*</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>Equal</td>
<td>↓</td>
<td>↓</td>
<td>Equal</td>
</tr>
<tr>
<td>Major and Clinically Relevant Non-Major Bleeding</td>
<td>↓</td>
<td>Equal</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

*Did not include VTE-related death

- GI bleeding event rates were too low to draw definite conclusions (consider extrapolation from afib trials)
- Low rates of intracranial hemorrhage with DOACs compared to warfarin

VTE Treatment Guidelines

2016 CHEST

In patients with DVT of the leg or PE and no cancer, as long-term anticoagulant therapy, we suggest DOAC over VKA therapy (grade 2B)

2019 ASCO

For long-term anticoagulation, LMWH, edoxaban, or rivaroxaban for at least 6 months are preferred over VKA

2020 ASH

AF Stroke Prevention Guidelines

For patients with AF and an elevated CHA\textsubscript{2}DS\textsubscript{2}-VASc score of $\geq 2$ in men or $\geq 3$ in women, oral anticoagulants are recommended.

DOACs are recommended over VKA in DOAC-eligible patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve).

The Future of Anticoagulation?

References:

Adverse Drug Reactions (ADRs)

WHO Database
- 39,972 reports in patients with NVAF
- 51% dabigatran, 28% warfarin, 19% rivaroxaban, 2% apixaban
- 204 ADRs with a reporting odds ratio > 1

FAERs Database
- 42,964 cases
- Rivaroxaban with highest rate per prescription for each ADR
- Dabigatran had the highest reported rates of ischemic stroke
- Warfarin with lowest rate per prescription for each ADR


Limitations of DOAC Use

- Mechanical heart valves
- Antiphospholipid syndrome
- Pregnancy and breastfeeding
- Moderate or severe hepatic impairment (Child-Pugh B or C)
- CYP3A4 and P-gp strong inducers/inhibitors
  - Examples of P-gp inducers: carbamazepine, rifampin, St. John’s Wort
  - Examples of P-gp inhibitors: amiodarone, azithromycin, ketoconazole, ritonavir, verapamil
Choice of Anticoagulant: Example Approach

FDA-approved Indication for DOAC

Does patient meet ≥1 of the following?
□ Able to obtain DOAC longitudinally
□ Likely to be compliant to medication
□ Not pregnant or breastfeeding
□ No clinically significant drug interactions
□ No altered GI absorption
□ Adequate renal/hepatic function
□ No extremes of weight?

Yes
DOAC candidate
Select DOAC based on patient characteristics and preferences

No
NOT a DOAC candidate
Warfarin or LMWH

Parenteral Anticoagulant Bridging for Warfarin

Intermediate Thromboembolic Risk
Consider based on individual risks/patient preferences

Atrial Fibrillation: CHA<sub>2</sub>DS<sub>2</sub>-VASc score 5-6 with prior stroke/TIA/SSE or prior history of embolic ischemic CVA/TIA/SSE

VTE: Bridging NOT recommended
VTE within past 3-12 months, Heterozygous factor V Leiden, Prothrombin 20210 mutation, recurrent VTE, active cancer

High Thromboembolic Risk
Bridging Advised

CHA<sub>2</sub>DS<sub>2</sub>-VASc score 7-9, Recent TE event (within 3 months) if procedure cannot be delayed, Rheumatic valvular disease, Recent (<4 weeks) cardioversion or AF ablation

Consider delaying procedure
Recent (within 3 months) TE event, Severe thrombophilia (protein C or S or antithrombin deficiency, APS)
## DOACs in Renal Impairment

<table>
<thead>
<tr>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CrCl</strong></td>
<td><strong>Dose</strong></td>
<td><strong>CrCl</strong></td>
<td><strong>Dose</strong></td>
</tr>
<tr>
<td>≥30</td>
<td>150 mg BID</td>
<td>&gt;50</td>
<td>5 mg BID (VTE: 10 mg BID x7 day load)</td>
</tr>
<tr>
<td>29-15</td>
<td>75 mg BID (Avoid in VTE)</td>
<td>50-15</td>
<td>2 of 3: ≥80 y, Scr &gt; 1.5 mg/dL, Weight ≤60 kg</td>
</tr>
<tr>
<td>&lt;15</td>
<td>Avoid</td>
<td>&lt;15</td>
<td>AF: 2.5 mg BID</td>
</tr>
<tr>
<td>HD</td>
<td>Avoid</td>
<td>HD</td>
<td>5 mg BID?</td>
</tr>
</tbody>
</table>

*CrCl in mL/min

*labeling suggests rivaroxaban may be administered to patients on HD at a dose of 15 mg, however, not adequately studied in large-scale clinical trial

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## Apixaban in Hemodialysis

**Mavrakanas et al, 2017**
- PK study
- N = 7
- At steady state, apixaban 5 mg BID increased exposure 2-5.7 times relative to 2.5 mg BID

**Siontis et al, 2018**
- Retrospective cohort study
- N = 25 523 with AF on HD or PD
- Apixaban 5 mg BID was associated with lower TE and major bleeding compared to warfarin

**RENAL-AF, 2019**
- Prospective randomized controlled trial (stopped early)
- N = 154 with AF on HD
- Apixaban 5 mg BID had similar rates of bleeding and stroke as warfarin (TTR ~44%) among patients with ESRD on HD
### DOACs in Obesity

**2016 ISTH SSC**

We suggest that DOACs should not be used in patients with a BMI > 40 kg/m² or a weight > 120 kg

<table>
<thead>
<tr>
<th>DOAC</th>
<th>Trial</th>
<th>Indication</th>
<th>Weight or BMI Cutoff</th>
<th>Proportion of Obese Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>RE-COVER I/II</td>
<td>VTE</td>
<td>≥ 35 kg/m²</td>
<td>12.1</td>
</tr>
<tr>
<td></td>
<td>RE-LY</td>
<td>AF</td>
<td>≥ 100 kg</td>
<td>17.1</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>EINSTEIN DVT/PE</td>
<td>VTE</td>
<td>&gt; 100 kg</td>
<td>14.3</td>
</tr>
<tr>
<td></td>
<td>ROCKET-AF</td>
<td>AF</td>
<td>&gt; 90 kg, ≥ 35 kg/m²</td>
<td>28.5, 13.6</td>
</tr>
<tr>
<td>Apixaban</td>
<td>AMPLIFY</td>
<td>VTE</td>
<td>≥ 35 kg/m²</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>ARISTOTLE</td>
<td>AF</td>
<td>&gt; 30 kg/m²</td>
<td>40</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>HOKUSAI VTE</td>
<td>VTE</td>
<td>&gt; 100 kg</td>
<td>14.8</td>
</tr>
<tr>
<td></td>
<td>ENGAGE AF-TIMI 48</td>
<td>AF</td>
<td>None</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR = Not Reported

### DOACs in Morbidly Obese

<table>
<thead>
<tr>
<th>Study, Year</th>
<th>N</th>
<th>Indication</th>
<th>Weight, kg</th>
<th>BMI, kg/m²</th>
<th>Anticoagulant</th>
<th>Efficacy Outcome</th>
<th>Safety Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kido et al, 2019</td>
<td>128</td>
<td>AF</td>
<td>&gt; 120</td>
<td>&gt; 40</td>
<td>DOAC (D, R, A) Warfarin</td>
<td>1.75%/y p = 0.77</td>
<td>2.18%/y p = 0.09</td>
</tr>
<tr>
<td>Kushnir et al, 2019</td>
<td>429</td>
<td>AF</td>
<td>&gt; 40</td>
<td>&gt; 40</td>
<td>DOAC (R, A) Warfarin</td>
<td>1.8% p = 1.0</td>
<td>2.9% p = 0.087</td>
</tr>
<tr>
<td>Kushnir et al, 2019</td>
<td>366</td>
<td>VTE</td>
<td>&gt; 40</td>
<td>&gt; 40</td>
<td>DOAC (R, A) Warfarin</td>
<td>2.0% p = 0.69</td>
<td>1.5% p = 0.60</td>
</tr>
<tr>
<td>Kalani et al, 2019</td>
<td>180</td>
<td>VTE and AF</td>
<td>≥ 120</td>
<td>≥ 40</td>
<td>DOAC (D, R, A) Warfarin</td>
<td>12.2% p = 0.82</td>
<td>2.2% p = 0.65</td>
</tr>
<tr>
<td>Coons et al, 2020</td>
<td>1840</td>
<td>VTE</td>
<td>100-300</td>
<td>(&gt; 40 ~ 43-45%)</td>
<td>DOAC (D, R, A) Warfarin</td>
<td>6.5% p = 0.93</td>
<td>1.7% p = 0.31</td>
</tr>
</tbody>
</table>


D = Dabigatran R = Rivaroxaban A = Apixaban
**DOAC Drug Selection**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-oral therapy</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspepsia or GI issues</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>GI bleed</td>
<td></td>
<td>✓</td>
<td></td>
<td>✓ (low dose)</td>
</tr>
<tr>
<td>Significant CAD</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Poor compliance with BID dosing</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>CrCl &lt; 30 mL/min</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**DOAC Monitoring**

<table>
<thead>
<tr>
<th>Resource</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Heart Rhythm Association Non-valvular Atrial Fibrillation Guidelines (2015)</td>
<td>“Patients should return on a regular basis for ongoing review...preferably after 1 month initially and later every 3 months”</td>
</tr>
<tr>
<td>ACC/AHA/HRS Atrial Fibrillation Guidelines (2019)</td>
<td>“Renal function and hepatic function should be evaluated before initiation of a [DOAC] and should be re-evaluated at least annually”</td>
</tr>
<tr>
<td>ASH VTE Guidelines (2018)</td>
<td>• For patients with a CrCl &gt; 50 ml/min receiving DOAC therapy, renal function should be monitored every 6-12 months</td>
</tr>
<tr>
<td></td>
<td>• For patients with a CrCl &lt; 50 ml/min receiving DOAC therapy, renal function should be monitored every 3 months</td>
</tr>
</tbody>
</table>

Joint Commission’s National Patient Safety Goal 03.05.01
Reduce the likelihood of patient harm associated with the use of anticoagulant therapy
OSUWMC Pharmacy Anticoagulation Management Services

ANTICOAGULATION Centers of Excellence

7 sites, hospital and outpatient
Pharmacist-run
Collaborative and personalized care
DOAC, LMWH, warfarin management
Patient education
Quality monitoring and clinical outcomes

For more information:
https://wexnermedical.osu.edu/heart-vascular/clinical-pharmacist-services/anticoagulation-management

Summary: DOAC Double-Check!

✓ • Double-check the indication
D • Drug-Drug Interactions
O • Organ Function
A • Adjustments
C • Counsel!

ATRIUM Cardiology Collaborative.
Objectives

- Describe the role of aspirin and oral P2Y$_{12}$ inhibitors for patients with stable ischemic heart disease (SIHD) or acute coronary syndromes (ACS) with or without percutaneous coronary intervention (PCI)

- Evaluate the advantages and disadvantages of the different P2Y$_{12}$ inhibitors
Epidemiology

- Chest discomfort most frequent reason for ED visits
- Coronary heart disease kills about 360,000 per year
- Each year ~ 112,000 people die of a myocardial infarction
- Estimated annual incidence is 605,000 for new heart attacks and 200,000 recurrent heart attacks. Of these ~ 170,000 silent attacks.
- Myocardial infarction ($12.1 billion) and coronary heart disease ($9 billion) are 2 of the 10 most expensive conditions treated in US hospitals in 2013
- About every 40 seconds an American will suffer a heart attack

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Case # 1

62 YO F admitted to the Emergency Department (ED)
- Abdominal pain and nausea. A couple of days before she took a test capsule for GI study.
- Sudden urge to have a bowel movement.
- In bathroom had sudden onset of severe chest pain
  - EKG showed ST-elevation

PMH:
CAD – LAD stent (unknown type) 2016
Hyperlipidemia
Chronic diarrhea

PSH:
Cholecystectomy 1992
Case # 1

- Patient instructed to stop both clopidogrel (Plavix) and aspirin 9 days prior to GI workup

- STEMI alert
  - Acute thrombosis of previous LAD stent

  Left heart catheterization with successful thrombectomy and balloon angioplasty

Case # 2

57 YO M
- Admitted for an elective urology procedure

PMH
CAD with a history of 3 cardiac stents (unknown type) in 2017
Peyronie’s and Erectile Dysfunction

PSH
Colonscopy

Post Procedure
Chest Pain and diaphoresis

EKG showed ST-elevation

Emgrent cath - 100% thrombotic occlusion of prox and mid RCA at site of previous stents
S/P thrombectomy and PCI with bare metal stent placement x 3

Patient instructed to discontinue aspirin for 10 days prior to procedure
Stent Evolution: Restenosis vs Stent Thrombosis

First Generation DES
Restenosis 5 – 15%

Second Generation DES
Restenosis < 5%

Risk of Mortality
Stent Thrombosis versus Bleeding

Mortality associated with stent thrombosis
Drug Eluting Stents: 17 - 45%
Bare Metal Stents: 9 - 21%

Mortality associated with bleeding after PCI at 12-24 months
7.3 - 13%
**Essentials of Thrombosis**

1. Tissue Factor
   1. Plasma Clotting cascade
   2. Prothrombin
      1. Factor Xa
      2. Thrombin
         1. Fibrinogen
         2. Fibrin

2. Collagen
   1. TXA₂
   2. ADP
   3. Platelet activation
   4. Platelet aggregation

**Sites of Antithrombotic Action**

1. Tissue Factor
   1. Plasma Clotting cascade
   2. Prothrombin
      1. Factor Xa
      2. Thrombin
         1. Fibrinogen
         2. Fibrin

2. Collagen
   1. TXA₂
   2. ADP
   3. Platelet activation
   4. Platelet aggregation

- **Antithrombotic Agents**
  - Aspirin
  - Clopidogrel
  - Prasugrel
  - Ticagrelor
  - Bivalirudin
  - LMWH
  - Heparin
  - LMWH
  - AT
  - Thrombolytics
  - GP IIb/IIIa Inhibitors

- **Thrombolytics**
- **GP IIb/IIIa Inhibitors**
- **LMWH**
## P2Y<sub>12</sub> Inhibitor Comparison

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel</th>
<th>Prasugrel</th>
<th>Ticagrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Loading Dose</strong></td>
<td>300-600 mg</td>
<td>60 mg</td>
<td>180 mg</td>
</tr>
<tr>
<td><strong>Maintenance Dose</strong></td>
<td>75 mg daily</td>
<td>10 mg daily</td>
<td>90 mg BID</td>
</tr>
<tr>
<td><strong>Prodrug</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Reversible</strong></td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>CYP 2C19</td>
<td>CYP 3A, 2B6</td>
<td>CYP 3A</td>
</tr>
<tr>
<td><strong>Time to 50% Platelet Inhibition (min)</strong></td>
<td>120-240 (600 mg)</td>
<td>60</td>
<td>30</td>
</tr>
<tr>
<td><strong>Maximal Platelet Inhibition (%)</strong></td>
<td>35</td>
<td>79</td>
<td>88</td>
</tr>
</tbody>
</table>

### Mechanism of Action of P2Y<sub>12</sub> Inhibitors

1. **ADP** stimulates the **GP IIb/IIIa** receptor, attracting **Fibrinogen** and leading to platelet aggregation.
2. **Clopidogrel** and **Prasugrel** bind to the **P2Y<sub>12</sub> Receptor**, inhibiting platelet aggregation.
3. **Ticagrelor** directly inhibits the **GP IIb/IIIa** receptor, preventing platelet aggregation.
Dual Antiplatelet Therapy (DAPT) Recommendations

**Bare metal stent for Acute Coronary Syndromes**
- Aspirin 81 mg by mouth daily uninterrupted lifelong
- Clopidogrel 75mg daily or prasugrel 10mg daily or ticagrelor 90mg twice daily for a **minimum of 1 month** (Class II) **ideally at least 12 months** (Class I)

**Drug eluting stent for Acute Coronary Syndromes**
- Aspirin 81 mg by mouth daily uninterrupted lifelong
- Clopidogrel 75mg daily or prasugrel 10mg daily or ticagrelor 90mg twice daily for a **minimum of 6 months** (Class II) **ideally at least 12 months** (Class I)

**Bare metal stent for Stable Ischemic Heart Disease**
- Aspirin 81 mg by mouth daily uninterrupted lifelong
- Clopidogrel 75mg daily for a **minimum of 1 month** (Class I) **consider up to 12 months** (Class II)

**Drug-eluting stent for Stable Ischemic Heart Disease**
- Aspirin 81 mg by mouth daily uninterrupted lifelong
- Clopidogrel 75mg daily for a **minimum of 3-6 months** (Class I) **consider up to 12 months** (Class II)

**Medical management of Acute Coronary Syndromes**
- Aspirin 81 mg by mouth daily uninterrupted lifelong
- Clopidogrel 75 mg daily or Ticagrelor 90 mg twice daily for **ideally at least 12 months** (Class I)

Find the Balance

<table>
<thead>
<tr>
<th><strong>Increased Ischemic Risk/Risk of Stent Thrombosis</strong></th>
<th><strong>Increased Bleeding Risk</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced age</td>
<td>Advanced age</td>
</tr>
<tr>
<td>Acute coronary syndrome presentation</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Extensive coronary artery disease</td>
<td>History of prior bleeding</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Oral anticoagulant therapy</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>Female sex</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>Low body weight</td>
</tr>
<tr>
<td>Prior stent thrombosis</td>
<td>Chronic kidney disease</td>
</tr>
<tr>
<td>Heart failure</td>
<td>Liver disease</td>
</tr>
<tr>
<td>Current smoker</td>
<td>Anemia</td>
</tr>
<tr>
<td>Multi-vessel disease</td>
<td>Chronic steroid or NSAID therapy</td>
</tr>
<tr>
<td>Stent undersizing or underexpansion</td>
<td></td>
</tr>
<tr>
<td>Small stent diameter</td>
<td></td>
</tr>
<tr>
<td>Long stent length (&gt;60 mm)</td>
<td></td>
</tr>
<tr>
<td>Short stent length (&lt;3mm)</td>
<td></td>
</tr>
<tr>
<td>Bifurcation stents</td>
<td></td>
</tr>
<tr>
<td>in-stent restenosis</td>
<td></td>
</tr>
<tr>
<td>Multiple stents (≥ 3 stents)</td>
<td></td>
</tr>
<tr>
<td>First-generation drug-eluting stent</td>
<td></td>
</tr>
</tbody>
</table>

Levine GN. Circulation 2016;68:1082-1115
### Tools to find the balance

<table>
<thead>
<tr>
<th>Time of use</th>
<th>PRECISE-DAPT Score</th>
<th>DAPT Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>At time of coronary stenting</td>
<td>Short DAPT (3-6 months) vs Standard/long DAPT (12-24 months)</td>
<td>After 12 months of uneventful DAPT vs Standard DAPT (12 months) vs Long DAPT (30 months)</td>
</tr>
</tbody>
</table>

#### Score calculator

<table>
<thead>
<tr>
<th>Score range</th>
<th>Decision making cut-off</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 100 points</td>
<td>≥25 → 3-6 months of DAPT &lt;25 → 12-24 months of DAPT</td>
</tr>
<tr>
<td>-2 to 10 points</td>
<td>≥2 → Long DAPT &lt;2 → Standard DAPT</td>
</tr>
</tbody>
</table>

#### Score factors
<table>
<thead>
<tr>
<th>Score Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
</tbody>
</table>

#### Limitations
- Clopidogrel 88%
- Validated in PLATO cohort (Ticagrelor)
- Excluded patients on long term anticoagulation

### Benefits of DAPT in Acute Coronary Syndromes

<table>
<thead>
<tr>
<th>Study</th>
<th>Indication</th>
<th>Duration (months)</th>
<th>Antiplatelet Therapy</th>
<th>Incidence of Primary Composite Endpoint* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CURE</td>
<td>ACS</td>
<td>12</td>
<td>Aspirin vs Aspirin + Clopidogrel</td>
<td>11.4 vs 9.3 p&lt;0.001</td>
</tr>
<tr>
<td>Triton-TIMI 38</td>
<td>ACS/PCI</td>
<td>15</td>
<td>Aspirin + Clopidogrel vs Aspirin + Prasugrel</td>
<td>12.1 vs 9.9 p&lt;0.001</td>
</tr>
<tr>
<td>PLATO</td>
<td>ACS</td>
<td>12</td>
<td>Aspirin + Clopidogrel vs Aspirin + Ticagrelor</td>
<td>11.7 vs 9.8 p&lt;0.001</td>
</tr>
</tbody>
</table>

*Primary Composite Endpoint – Death from Cardiovascular (CV) Causes, Non-fatal myocardial infarction (MI) or Non-fatal stroke

References:
Risks of DAPT in Acute Coronary Syndromes

<table>
<thead>
<tr>
<th>Study</th>
<th>Indication</th>
<th>Duration</th>
<th>Antiplatelet Therapy</th>
<th>Incidence of Major Bleeding (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CURE</td>
<td>ACS</td>
<td>12</td>
<td>Aspirin vs Aspirin + Clopidogrel</td>
<td>2.7 vs 3.7 p=0.001</td>
</tr>
<tr>
<td>Triton-TIMI 38</td>
<td>ACS/PCI</td>
<td>15</td>
<td>Aspirin + Clopidogrel vs Aspirin + Prasugrel</td>
<td>1.8 vs 2.4 p=0.03</td>
</tr>
<tr>
<td>PLATO</td>
<td>ACS</td>
<td>12</td>
<td>Aspirin + Clopidogrel vs Aspirin + Ticagrelor</td>
<td>2.2 vs 2.8 p=0.03</td>
</tr>
</tbody>
</table>

These rates are under the umbrella of a clinical trial NOT real world

Patients who require oral anticoagulation are excluded


P2Y$_{12}$ Recommendations in Acute Coronary Syndromes

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>It is reasonable to choose ticagrelor over clopidogrel in ACS patients treated with an early invasive strategy and/or PCI.</td>
<td>IIa</td>
<td>B-R</td>
</tr>
<tr>
<td>It is reasonable to choose prasugrel over clopidogrel in ACS patients who undergo PCI who are not at high risk for bleeding complications.</td>
<td>IIa</td>
<td>B-R</td>
</tr>
<tr>
<td>In ACS patients managed with medical therapy alone (without revascularization or fibrinolytic therapy) treated with DAPT, it is reasonable to use ticagrelor in preference to clopidogrel.</td>
<td>IIa</td>
<td>B-R</td>
</tr>
<tr>
<td>Prasugrel should not be administered to patients with a prior history of stroke or TIA.</td>
<td>III: Harm</td>
<td>B-R</td>
</tr>
</tbody>
</table>

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Factors Preventing Continuation of Ticagrelor

- Side Effects: Dyspnea, Bradycardia
- Drug Interactions: 3A4 Inducers, P-glycoprotein
- Indication for Oral Anticoagulation: Triple Therapy (Limited data)
- Patient Adherence: Once vs Twice Daily
- Cost: Insurance

Drug Interactions with Ticagrelor

- Ticagrelor is metabolized by CYP 3A
- Weak CYP 3A inhibitor

<table>
<thead>
<tr>
<th>Strong CYP 3A inhibitors</th>
<th>CYP 3A inducers</th>
<th>CYP 3A substrates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiretrovirals</td>
<td>Carbamazepine</td>
<td>Cyclosporine</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Rifampin</td>
<td>Tacrolimus</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Phenytoin</td>
<td>Amlodipine</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Dexamethasone</td>
<td>Diltiazem, Verapamil</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>Phenobarbital</td>
<td>Ator, simva, lovastatin</td>
</tr>
</tbody>
</table>

Simvastatin and lovastatin doses limited to no more than 40 mg

- Ticagrelor and active metabolite are P-glycoprotein (PgP) substrates and weak inhibitors PgP
  - Monitor digoxin levels
  - Dabigatran
Switching Between P2Y12 Inhibitors

### Conclusions

- Understanding the current recommendations for DAPT is critically important.
- Early discontinuation of DAPT is problematic.
- Patients should remain on at least one antiplatelet medication following stent placement.
- Patient education is key.
  - Pharmacists can be instrumental in providing this education.
- Work together with the patients cardiologist to ensure safe transitions of care.