DISCLOSURES

None of the planners or presenters of this session have disclosed any conflict or commercial interest.
Understanding anticoagulation and antithrombotic therapy

• OBJECTIVES:

1. Review diseases requiring anticoagulations or antithrombotics.
2. Explain the various categories of medication choices with a focus on the pharmacological variations.
What are these new drugs called?

- NOAC: “Novel” Oral Anticoagulant
- NOAC: “New” Oral Anticoagulant
- NOAC: “Non-vitamin K” Oral Anticoagulant
- TSOAC: Target-specific Oral Anticoagulant
- DOAC: Direct Oral Anticoagulants

4 currently available worldwide:
- Dabigatran (Pradaxa®)
- Apixaban (Eliquis®)
- Edoxaban (Savaysa®)
- Rivaroxaban (Xarelto®)
The “Ideal” Anticoagulant

- Oral, fixed dose
- Rapid onset and offset
- Predictable, reliable anticoagulant effect
- Wide therapeutic range
- No need for renal or hepatic dosing adjustments
- No need for routine anticoagulation monitoring
- Minimal, if any, drug interactions
- Easily, rapidly, effectively reversed
- Cheap
Patient Case

• DL is a 68-year-old man with permanent atrial fibrillation presents for routine follow-up

• PMH:
  • Hypertension
  • Hyperlipidemia
  • TIA, 2 years ago

• Weight = 87 kg
• Still working full time
Patient Case

- **Laboratory values:** (checked 9 months ago)
  - Creatinine: 1.0 mg/dL
  - Hemoglobin: 14.4 g/dL
  - Hematocrit: 40%

- **Medications:**
  - Aspirin 81 mg daily
  - HCTZ 25 mg daily
  - Lisinopril 10 mg daily
  - Atorvastatin 20 mg daily
  - Ibuprofen 400 mg PRN
    - knee pain

- Review of refill history reveals DL picks up his medications regularly
Which of the following stroke prevention therapies would you recommend?

A. No therapy
B. Aspirin 325 mg daily
C. Dual antiplatelet therapy
D. DOAC
E. Warfarin

D. DOAC
IF DL was taking a DOAC rather than warfarin, which of the following would be the most important to assess during this visit?

A. Adherence
B. Creatinine
C. Blood pressure
D. Coagulation test
E. Not sure
Thromboembolic stroke in patients with Atrial Fibrillation

- Stroke Mortality within 1st year:
  - 64% for AF vs. 32% for all other strokes

- Greater disability:
  - OR = 1.43 (95% CI 1.18-1.80)

- Longer hospitalization stay
  - 40 days vs. 50 days

- Lower hospital d/c to home rates

Lamassa M et al. Stroke 2001;32:392-8
Jorgensen HS et al. Stroke 1996;27:1760-4
Warfarin is underused in AF patients

11,082 pts with AF, no contraindications to Warfarin

OAC is still under prescribed in 2016

NCDR PINNACLE Registry: 429, 417 patients

Hsu JC et al. JAMA 2016;1:55-62
Practical Guide to Monitoring DOACs

• A: Adherence
• B: Bleeding
• C: Creatinine
• D: Drug Interactions
• E: Examination
• F: Final Assessment and Follow-up

Adherence

• Assess:
  • “Some patients have trouble remembering to take their medications.”
  • “In an average week, how many doses would you typically miss for one reason or another?”

• Adherence is facilitate when:
  • Patients understand their disease:
    • Anticoagulation = “stroke prevention therapy”
  • Believe in their therapy
  • Trust their clinician
Adherence and Outcomes: Daily vs. BID

- Study of adherence and outcomes from US MarketScan databases from March 2010 – January 2015
- 36,868 patients total receiving either daily or BID DOACs
- Adherence was defined as proportion-of-days covered (PDC)
  - Poor adherence = < 80% PDC

- Adherence was better with daily dosing:
  - 27.2% suboptimal adherence with daily vs. 32.5% for BID (p<0.001)

- Poor adherence was associated with 50% increased hazard for ischemic stroke

Adherence: Clinical Pearls

• Apixaban and Dabigatran:
  • Take ASAP if < 6 hours before next dose due

• Rivaroxaban and Edoxaban:
  • Take ASAP if < 12 hours before next dose due

• Dabigatran: Store in original bottle
• Rivaroxaban: Take with food

• Schedule regular follow-up visits
• Address and stress adherence at each visit

If DL were to experience a GI bleed while on a DOAC instead of warfarin, which of the following outcomes statement is most supported by published data?

A. More likely to need reversal therapy, worse outcome
B. More likely to need reversal therapy, similar outcome
C. Less likely to need reversal therapy, better outcome
D. Less likely to need reversal, similar outcome

D. Less likely to need reversal, similar outcome
If DL were to taking dabigatran, and needed a colonoscopy, how long would we have to wait to perform this procedure if he took is dose last night? Assume his CLcr is 85mL/min.

A. Tomorrow morning (1 day)
B. 3 days
C. 4 days
D. 5 days

Correct answer: A. Tomorrow morning (1 day)
B: Bleeding

- Bleeding while taking anticoagulants is unavoidable
- Strategies to minimize risks:
  - Avoid aspirin unless medically necessary (coronary stents)
  - Avoid Chronic NSAIDs (if needed, add PPI)
  - Assess proper dosing and renal function
  - Assess blood pressure at each visit
    - Treat hypertension aggressively to reduce risk of intracranial hemorrhage

B: Bleeding related to procedures

• Recommend appropriate duration of time to withhold DOACs prior to invasive procedures and surgery

• General concepts:
  • Balance risk of bleeding during procedure
  • Risk of thrombosis while not taking DOAC

## Interruption for surgery/procedures

<table>
<thead>
<tr>
<th>TSOAC</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>CLcr &gt; 50: stop 1 – 2 days prior to procedure</td>
</tr>
<tr>
<td></td>
<td>CLcr &lt; 50: stop 3 – 5 days prior to procedure</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Stop 24 – 48 hours prior to procedure</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Stop 24 – 48 hours prior to procedure</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Stop 24 – 48 hours prior to procedure</td>
</tr>
</tbody>
</table>
## Bleeding: Clinical Trial Experience: Apixaban

<table>
<thead>
<tr>
<th>Event</th>
<th>Apixaban</th>
<th>Warfarin</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization</td>
<td>1.05%</td>
<td>1.41%</td>
<td>0.0052</td>
</tr>
<tr>
<td>Fall Hgb 2g/dL</td>
<td>1.06%</td>
<td>1.44%</td>
<td>0.0035</td>
</tr>
<tr>
<td>Transfusions</td>
<td>0.89%</td>
<td>1.25%</td>
<td>0.0025</td>
</tr>
<tr>
<td>Medical or surgical consultation</td>
<td>1.54%</td>
<td>1.94%</td>
<td>0.0080</td>
</tr>
<tr>
<td>Medical or surgical intervention needed</td>
<td>0.65%</td>
<td>0.90%</td>
<td>0.012</td>
</tr>
<tr>
<td>Hemodynamic compromise</td>
<td>0.26%</td>
<td>0.38%</td>
<td>0.069</td>
</tr>
<tr>
<td>Required change in antithrombotic therapy</td>
<td>1.14%</td>
<td>1.47%</td>
<td>0.012</td>
</tr>
</tbody>
</table>

Death 30-days after major bleeding

# Clinical Trial Experience: Rivaroxaban

<table>
<thead>
<tr>
<th>Within 2-days post bleeding</th>
<th>Rivaroxaban</th>
<th>Warfarin</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin K</td>
<td>7.9%</td>
<td>14.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aminocaproic acid</td>
<td>0.5%</td>
<td>0.7%</td>
<td>NS</td>
</tr>
<tr>
<td>Tranexamic Acid</td>
<td>0.7%</td>
<td>3.4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prothrombin complex concentrates</td>
<td>0.9%</td>
<td>2.2%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Recombinant Factor VII concentrate</td>
<td>0%</td>
<td>0.2%</td>
<td>NS</td>
</tr>
<tr>
<td>Recombinant Factor IX concentrate</td>
<td>0%</td>
<td>0.7%</td>
<td>NS</td>
</tr>
</tbody>
</table>

Rivaroxaban: Real-world experience

- Xantus: real-world observational study
- 6784 patients with AF followed for 1-year
  - Mean CHADS-VASc = 3.4
  - Mean age: 71.5 years-old

- Major bleeding: 2.1% (128 patients)
  - GI Bleeding: 0.9%
  - ICH: 0.4%
  - Fatal bleeding: 0.2%

- PCC therapies required: 2 patients
  - Total of 5 patients received any type of reversal therapy

BIDMC Emergency Room

- Prospective observational study: 6 months
  - Patients admitted through the emergency department
  - Receiving either warfarin or dabigatran
  - Objective: describe the course of bleeding
    - Treatments
    - Length of stay
    - Type of bleeding

## Observations

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>Dabigatran</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td>123</td>
<td>15</td>
</tr>
<tr>
<td><strong>ICH</strong></td>
<td>32%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>GI Bleeding</strong></td>
<td>48%</td>
<td>80%</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>13%</td>
<td>12%</td>
</tr>
<tr>
<td><strong>Total Length of Stay</strong></td>
<td>6 days</td>
<td>3.5 days</td>
</tr>
<tr>
<td><strong>GI Bleeding Length of Stay</strong></td>
<td>8.4 days</td>
<td>4 days</td>
</tr>
<tr>
<td><strong>FFP transfusions</strong></td>
<td>1.1 units</td>
<td>0.3 units</td>
</tr>
<tr>
<td><strong>RBC transfusions</strong></td>
<td>2.3 units</td>
<td>1.1 units</td>
</tr>
<tr>
<td><strong>Reversal Therapy Administered</strong></td>
<td>3 patients</td>
<td>0 patients</td>
</tr>
</tbody>
</table>
Warfarin: Real world experience

  - 125,195 patients in Ontario, receiving chronic warfarin for stroke prevention in atrial fibrillation
  - Evaluated rates of major bleeding by hospitalization
  - Rate of major bleeding: 3.8%/person-year
    - Highest risk was within the first 30 days of therapy
    - ICH: 5.1%
    - Upper GI Bleeding: 26.1%
    - Lower GI Bleeding: 36.5%
    - Other major bleeding: 38.7%
  - Overall morality rate within 7 days of event: 18.1%
    - ICH mortality rate: 41.7%
    - GI Bleeding mortality: 14.4 – 15%

WHY ARE DOAC BLEEDING OUTCOMES SIMILAR OR BETTER

Why does lack of antidote or true “reversal” not translate clinically?
## Comparative PK/PD of TSOACs

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>Ila (thrombin)</td>
<td>Xa</td>
<td>Xa</td>
<td>Xa</td>
</tr>
<tr>
<td><strong>Hours to C&lt;sub&gt;max&lt;/sub&gt;</strong></td>
<td>1-3</td>
<td>2-4</td>
<td>3-4</td>
<td>1-2</td>
</tr>
<tr>
<td><strong>Half-life, hours</strong></td>
<td>12-17</td>
<td>11-13</td>
<td>12</td>
<td>10-14</td>
</tr>
<tr>
<td><strong>Renal Clearance, %</strong></td>
<td>80</td>
<td>33</td>
<td>27</td>
<td>50</td>
</tr>
<tr>
<td><strong>Transporters</strong></td>
<td>P-gp</td>
<td>P-gp</td>
<td>P-gp</td>
<td>P-gp</td>
</tr>
<tr>
<td><strong>CYP Metabolism, %</strong></td>
<td>None</td>
<td>32</td>
<td>&lt;32</td>
<td>&lt;4</td>
</tr>
</tbody>
</table>

CYP = cytochrome P450; P-gp = P-glycoprotein

Pradaxa [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc. 2013
ELIQUIS Summary of Product Characteristics. Bristol Myers Squibb/Pfizer EEIG, UK
DOAC ANTIDOTES

The future is (almost) now....
Dabigatran Antidote

- Idarucizumab (Praxbind®)
- FDA Approved October 16, 2015
  - Monoclonal antibody
  - Binds to Dabigatran
    - 350 x dabigatran binding to thrombin
    - Binds free and thrombin bound dabigatran
- 5 gram dose
  - 2.5 g/50mL x 2 doses, 15 min apart

Idarucizumab preparation

- Vials are 2.5g/50 mL of buffered isotonic solution
- Administration:
  - Two consecutive infusions -or-
  - Two consecutive bolus injections
  - Pre-existing lines must be flushed with 0.9% sodium chloride
  - Once vial injected, must be used within 1 hour
REVERSE-AD Trial

A Dilute Thrombin Time in Group A

A Concentration of Unbound Dabigatran in Group A

Factor Xa antidote: Andexanet Alfa
ANNEXA –A and ANNEXA-R Results

C Apixaban Study, Andexanet Bolus plus Infusion

D Rivaroxaban Study, Andexanet Bolus plus Infusion

C: Creatinine Clearance

- ALL DOACs are renally eliminated
- Clinical trials, patients with CLcr ≤30 mL/min excluded
  - CLcr ≤ 25 mL/min for Apixaban
- Impaired renal function is a risk for bleeding with ALL oral anticoagulants (including warfarin)

### C: Creatinine Clearance

<table>
<thead>
<tr>
<th>DOAC</th>
<th>Renal dose recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>2.5 mg po BID if 2 of 3: Age ≥ 80, weight ≤ 60 kg, creatinine ≥ 1.5 mg/dL</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>CLcr 15 – 30 mL/min: 75 mg po BID</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>CLcr 15 – 50 mL/min: 30 mg daily <strong>Do not use if CLcr &gt; 95 mL/min</strong></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>CLcr 15 – 50 mL/min: 15 mg daily</td>
</tr>
</tbody>
</table>

C: Creatinine Clearance: Monitoring

- Every 6 – 12 months is recommended
- Can be more frequently depending upon the patient
  - Dehydrating illness
  - Known early CKD (Stage II)
    - Patient baseline CLcr < 50 mL/min

For patients with eGFR < 50 mL/min:
- Calculate CLcr using Cockroft-Gault
  - \((140 - \text{age})(\text{body weight})\)
    \(\frac{(72 \times \text{creatinine})}{(72 \times \text{creatinine})}\)
  - **multiply by 0.85 for females**

Xantus: Rivaroxaban dosing

• CLcr was reported in 65.6% of 6784 patients
  • 14.4% had CLcr < 50 mL/min

• Of the 3812 patients with CLcr > 50 mL/min
  • 15% received 15 mg daily (reduced dose)

• Of the 640 patients with CLcr < 50 mL/min
  • 36% received 20 mg daily

• How much of this is intentional vs. unintentional?
  • Area for pharmacists to educate and/or improve dosing?
Doses of apixaban and rivaroxaban prescribed in real-world United States cardiology practices compared to registration trials

- I.M.S. Prescription Database from 9/2014-9/2015
  - Roughly 14.5 million patients included
  - Only evaluated DOACs prescribed by U.S. Cardiologists

Which if the following medications is not recommended with any DOAC, and would require DL to take warfarin?

A. Rifampin  
B. Ketoconazole  
C. Phenytoin  
D. Amiodarone  
E. Clarithromycin

A. B. C. D. E. 0% 0% 0% 0% 0%
D: Drug interactions: Recommendations

• Review all prescription and OTC medications with patient at each visit

• Assess need for concurrent antiplatelet therapy
  • Including Aspirin
    • Exceptions: Mechanical valves, stents, recent MI

# Drug Interactions: Inducers = do not use

<table>
<thead>
<tr>
<th>DOAC</th>
<th>Drug-interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>Rifampin + “other known potent inducers”</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Rifampin, Carbamazepine, Phenytoin, St. John’s Wart</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Rifampin, Carbamazepine, Phenytoin, St. John’s Wart</td>
</tr>
</tbody>
</table>
# Drug Interactions: Inhibitors

<table>
<thead>
<tr>
<th>DOAC</th>
<th>Drug-interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>CLcr 30-50: use 75mg BID with Dronedarone, Ketoconazole</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Use 2.5 mg BID with Ketoconazole, Itraconazole, Ritonavir, and Clarithromycin</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>None listed</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Do not use with: Ketoconazole, Itraconazole, Ritonavir</td>
</tr>
</tbody>
</table>
IF DL had his renal function examined 3 months ago, which of the following would be the most important to assess today?

A. Adherence
B. Creatinine
C. Blood pressure
D. Coagulation test
E. Not sure

C. Blood pressure
E: Examination

• Blood pressure should be examined at each visit
• Encourage home BP monitoring
  • Hypertension is the single greatest risk for ICH
  • Treat hypertension aggressively

• Be careful for hypotension:
  • Increases risk of falls
• Examine gait and balance:
  • Identify candidates for walking aids, rehabilitation to prevent falls

DIFFERENCES BETWEEN DOACS: TRIAL DIFFERENCES
## DOAC AF Trials

<table>
<thead>
<tr>
<th>Drug</th>
<th>RE-LY</th>
<th>ROCKET-AF</th>
<th>ARISTOTLE</th>
<th>ENGAGE AF</th>
</tr>
</thead>
<tbody>
<tr>
<td># Randomized</td>
<td>18,113</td>
<td>14,266</td>
<td>18,201</td>
<td>21,105</td>
</tr>
<tr>
<td>Dose (mg)</td>
<td>150, 110</td>
<td>20</td>
<td>5</td>
<td>60, 30</td>
</tr>
<tr>
<td>Frequency</td>
<td>Twice Daily</td>
<td>Once Daily</td>
<td>Twice Daily</td>
<td>Once Daily</td>
</tr>
<tr>
<td>Dose Adjustment</td>
<td>No</td>
<td>20 → 15</td>
<td>5 → 2.5</td>
<td>60 → 30 30 → 15</td>
</tr>
<tr>
<td>At Baseline</td>
<td>0</td>
<td>21%</td>
<td>5%</td>
<td>25%</td>
</tr>
<tr>
<td>After Randomization</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>&gt;9%</td>
</tr>
<tr>
<td>Target INR (Warfarin)</td>
<td>2.0-3.0</td>
<td>2.0-3.0</td>
<td>2.0-3.0</td>
<td>2.0-3.0</td>
</tr>
<tr>
<td>Blinded Warfarin?</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>Throughout Study</td>
<td>Throughout Study</td>
<td>Only for 2 days</td>
<td>Only for 3 days</td>
</tr>
</tbody>
</table>

# Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>RE-LY (Dabigatran)</th>
<th>ROCKET-AF (Rivaroxaban)</th>
<th>ARISTOTLE (Apixaban)</th>
<th>ENGAGE AF (Edoxaban)</th>
</tr>
</thead>
<tbody>
<tr>
<td># Randomized</td>
<td>18,113</td>
<td>14,264</td>
<td>18,201</td>
<td>21,105</td>
</tr>
<tr>
<td>Age, years</td>
<td>72 ± 9</td>
<td>73 [65-78]</td>
<td>70 [63-76]</td>
<td>72 [64-78]</td>
</tr>
<tr>
<td>Female, %</td>
<td>37</td>
<td>40</td>
<td>35</td>
<td>38</td>
</tr>
<tr>
<td>Mean CHADS</td>
<td>2.1</td>
<td>3.5</td>
<td>2.1</td>
<td>2.8</td>
</tr>
<tr>
<td>VKA naive</td>
<td>50</td>
<td>43</td>
<td>38</td>
<td>41</td>
</tr>
<tr>
<td>Aspirin Use</td>
<td>40</td>
<td>36</td>
<td>31</td>
<td>29</td>
</tr>
</tbody>
</table>

### CHADS$_2$

- **0-1**: 33, 13, 30, 53
- **2**: 35, 87, 36, 47
- **3-6**: 32, 13, 34, 47

DOACs Combined: Stroke or SEE

- **RE-LY** [150 mg]  
  Risk Ratio (95% CI): 0.66 (0.53 - 0.82)
  p = <0.0001

- **ROCKET AF**  
  Risk Ratio (95% CI): 0.88 (0.75 - 1.03)

- **ARISTOTLE**  
  Risk Ratio (95% CI): 0.80 (0.67 - 0.95)

- **ENGAGE AF-TIMI 48** [60 mg]  
  Risk Ratio (95% CI): 0.88 (0.75 - 1.02)

**Combined [Random Effects Model]**

Risk Ratio (95% CI): 0.81 (0.73 - 0.91)

N = 58,541

Heterogeneity p = 0.13

## DOAC VTE Trials

<table>
<thead>
<tr>
<th></th>
<th>RECOVER</th>
<th>EINSTEIN</th>
<th>AMPLIFY</th>
<th>HOKUSAI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Dabigatran</td>
<td>Rivaroxaban</td>
<td>Apixaban</td>
<td>Edoxaban</td>
</tr>
<tr>
<td># Randomized</td>
<td>5107</td>
<td>8282</td>
<td>5395</td>
<td>8240</td>
</tr>
<tr>
<td>Dose (mg)</td>
<td>150 BID</td>
<td>15 mg BID x 21 days, then 20 daily</td>
<td>10 mg BID x 7 days, then 5 mg BID</td>
<td>60 mg Daily</td>
</tr>
<tr>
<td>Bridging?</td>
<td>YES: &gt; 5 days</td>
<td>NO</td>
<td>NO</td>
<td>YES: &gt; 5 days</td>
</tr>
<tr>
<td>Dose Adjustment</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td># PE Patients</td>
<td>1602</td>
<td>4833</td>
<td>1836</td>
<td>3319</td>
</tr>
<tr>
<td>Recurrent VTE (DOAC)</td>
<td>2.4%</td>
<td>2.1%</td>
<td>2.3%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Recurrent VTE (Warfarin)</td>
<td>2.2%</td>
<td>2.3%</td>
<td>2.7%</td>
<td>3.5%</td>
</tr>
</tbody>
</table>

Major Bleeding in DOAC VTE trials

### F: Final Assessment and Follow-up

#### DIRECT ORAL ANTICOAGULANT (DOAC) MONITORING CHECKLIST

| Patient name: | \_
| --- | --- |
| Date | \_
| DOAC | \_
| Dose | \_
| Dosing Time(s) | \_
| Age / Weight | \_
| CHADS$_2$ / CHA$_2$DS$_{-}$VS$_c$ | \_

#### HEALTH STATUS SINCE LAST ASSESSMENT

<table>
<thead>
<tr>
<th>Any new relevant medical problems, ED visits/hospitalizations?</th>
<th>Y / N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any embolic events (stroke / TIA / systemic embolism)?</td>
<td>Y / N</td>
</tr>
</tbody>
</table>

#### A: ADHERENCE WITH DOAC THERAPY

1 or more missed doses in an average week?
- If yes, number of missed doses

#### B: BLEEDING RISK ASSESSMENT

NER: a YES to any of the following requires individualized assessment & does not imply that DOAC should be discontinued
- Severe epistaxis?
- Hemoptysis?
- Excessive or unusual bruising / hematoma(s)?
- GIB / melena / BRBPR / hematemesis?
- Hematuria?
- Abnormal vaginal bleeding?
- Concerning daily headache or subcutaneous hematoma symptoms?
- Decreasing hemoglobin or new anemia?
  - Latest hemoglobin:
  - ETOH overuse?
  - Falls, presyncope, syncope, or seizures?
  - Uncontrolled hypertension?

#### C: CREATININE CLEARANCE / RENAL FUNCTION

- Latest eGFR / creatinine:
  - Is eGFR less than 50ml/min?
  - If YES, calculate Ccr (see back)
- Any recent dehydrating illness or medications added/changed? i.e. diuretics

#### D: DRUG INTERACTIONS (review all concomitant medications)

- ASA / other antiplatelets?
- NSAID?
- Other drug interactions? (Review med list / OTCs; see back)

#### E: EXAMINATION

- Blood pressure:
  - Elevated BP? (sBP greater than 160 mmHg)
  - Symptomatic hypotension?
- Significant gait impairment / imbalance / high risk for falls?
Similarities between DOACs

- Predictable and reliable anticoagulant effect
  - Rapid onset (therapeutic effect on first dose)
  - Rapid offset (minimal effect at trough)
- Fixed dosing for most patients
- No routine laboratory monitoring required
- No dietary interactions
- Less drug-drug interactions
- All renally eliminated and have adjustments for ↓ renal function
  - need to calculate CLcr
- All have less intracranial hemorrhage compared with warfarin
- Most have more GI Bleeding compared with warfarin
  - Depends upon the disease state and patients studied
Differences between DOACs

• Target site of action:
  • Dabigatran binds to and inhibits Thrombin (Factor IIa)
  • Rivaroxaban, apixaban and edoxaban bind to and inhibit Factor Xa

• Kinetics are different:
  • Absorption – need to take with meals or not?
  • % Renally eliminated (hence, when to renally dose)
  • T ½ (important for transitioning to procedures, surgery)
  • Protein Binding (use of dialysis during emergency?)
  • Daily vs. BID

• Patients enrolled in clinical trials, trial designs:
  • Stroke risk in AF (CHADS score)
  • Definitions of major bleeding in AF trials
  • VTE trials:
    • Bridging mandatory vs. monotherapy
    • Duration of trials (6 months vs. 12 months)
    • % patients with Pulmonary Embolism

• Reversal:
  • Dabigatran = YES
  • Xa inhibitors = not yet (but probably soon)
Antiplatelet therapy

• Which agents do we use in addition to Aspirin?
  • Clopidogrel (Plavix)
  • Prasugrel (Effient)
  • Ticagrelor (Brilinta)

• Newer therapies:
  • Vorapaxar (Zontivity)
  • Cangrelor (Kangreal)

• How long do we continue Dual Antiplatelet Therapy (DAPT)
Targets for Platelet Inhibition

GP = glycoprotein; PAR = protease-activated receptor; TP = thromboxane A₂ / prostaglandin H₂.

DAPT: How did we get here?

Syndrome

What are we treating?

ACS

The Stent

1 Year

CAD

The Patient
CURE

NSTEMI presenting within 24 hours of symptom onset (n = 12562)

Clopidogrel 300mg load then 75mg daily + aspirin 75-325 mg daily for 3-12 months (n=6259)

Placebo + aspirin 75-325 mg daily (n= 6303)

Primary endpoint: CV death + stroke + MI
Mean follow-up: 9 months

## CURE: Efficacy results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Clopidogrel</th>
<th>Placebo</th>
<th>RRR</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death/MI/Stroke (primary endpoint)</td>
<td>9.3%</td>
<td>11.8%</td>
<td>20%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>MI</td>
<td>5.2%</td>
<td>6.7%</td>
<td>23%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.2%</td>
<td>1.4%</td>
<td>14%</td>
<td>NS</td>
</tr>
<tr>
<td>CV Death</td>
<td>5.1%</td>
<td>5.5%</td>
<td>7%</td>
<td>NS</td>
</tr>
</tbody>
</table>

Number needed to treat to prevent one primary endpoint event = 40 patients for 9 months

---

## CURE: Safety results

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Clopidogrel</th>
<th>Placebo</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>3.7%</td>
<td>2.7%</td>
<td>0.001</td>
</tr>
<tr>
<td>Life-threatening bleeding</td>
<td>2.2%</td>
<td>1.8%</td>
<td>NS</td>
</tr>
<tr>
<td>Non life-threatening bleeding</td>
<td>1.5%</td>
<td>0.9%</td>
<td>0.002</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>5.1%</td>
<td>2.4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Transfusion of ≥ 2 units blood</td>
<td>2.8%</td>
<td>2.2%</td>
<td>0.02</td>
</tr>
<tr>
<td>Total bleeding complications</td>
<td>8.5%</td>
<td>5%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Number needed to harm = 100**

Major bleeding episodes were defined as substantially disabling bleeding, intraocular bleeding leading to the loss of vision, or bleeding necessitating the transfusion of at least 2 units of blood.

Minor bleeding: other hemorrhages that led to interruption of study medication.

---

Clopidogrel Activation

Pro-drug

Hydrolysis
(Esterases)

Oxidation
(Cytochrome P450)

85% Inactive
Metabolites
Esterases

Genetic Factors
- Polymorphisms of CYP
- Polymorphisms of GPIa
- Polymorphisms of P2Y_{12}
- Polymorphisms of GPIIla

Cellular Factors
- Accelerated platelet turnover
- Reduced CYP3A metabolic activity
- Increased ADP exposure
- Up-regulation of the P2Y_{12} pathway
- Up-regulation of the P2Y_{1} pathway
- Up-regulation of P2Y–independent pathways (collagen, epinephrine, TXA_{2}, thrombin)

Clinical Factors
- Failure to prescribe/poor compliance
- Under-dosing
- Poor absorption
- Drug-drug interactions involving CYP3A4
- Acute coronary syndrome
- Diabetes mellitus/insulin resistance
- Elevated body mass index

Genetic Factors
- Polymorphisms of CYP
- Polymorphisms of GPIa
- Polymorphisms of P2Y_{12}
- Polymorphisms of GPIIla

Clopidogrel Response Variability
Pharmacology: Clopidogrel vs. Prasugrel

**Prasugrel**

**Pro-drug**

**Hydrolysis** (Esterases)

**Oxidation** (Cytochrome P450)

**Active Metabolite**

**85% Inactive Metabolites**

**Esterases**

**Clopidogrel**

**Active Metabolite**

Potency: Clopidogrel vs. Prasugrel

Mean IPA (%) vs. Day/Hour Post Dosing

- Prasugrel (40 mg LD/5 mg MD)
- Prasugrel (40 mg LD/7.5 mg MD)
- Prasugrel (60 mg LD/10 mg MD)
- Prasugrel (60 mg LD/15 mg MD)
- Clopidogrel (300 mg LD/75 mg MD)

Jernberg, T et al EHJ 2006
TRITON-TIMI 38

Primary endpoint: CV death + MI + Stroke
Primary safety endpoint: Total major bleeding

6–15-month exposure

UA/NSTEMI (moderate-to-high-risk) or STEMI all with scheduled PCI (N=13,608)

Clopidogrel
300 mg loading dose then 75 mg daily maintenance

Prasugrel
60 mg loading dose then 10 mg daily maintenance

## TRITON-TIMI 38 Results: Primary and Secondary Endpoints

<table>
<thead>
<tr>
<th></th>
<th>Prasugrel (n=6813)</th>
<th>Clopidogrel (n=6795)</th>
<th>HR for (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary objective, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV death + MI + stroke</td>
<td>643 (9.9)</td>
<td>781 (12.1)</td>
<td>0.81 (0.73–0.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Secondary objectives, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total death + MI + stroke</td>
<td>692 (10.7)</td>
<td>822 (12.7)</td>
<td>0.83 (0.75-0.92)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CV death + MI + stroke + rehospitalization for ischemia</td>
<td>797 (12.3)</td>
<td>938 (14.6)</td>
<td>0.84 (0.76-0.92)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Myocardial infarction</strong></td>
<td>475 (7.3)</td>
<td>620 (9.5)</td>
<td>0.76 (0.67–0.85)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CV death</td>
<td>133 (2.1)</td>
<td>150 (2.4)</td>
<td>0.89 (0.70-1.12)</td>
<td>0.31</td>
</tr>
<tr>
<td>Stroke</td>
<td>61 (1.0)</td>
<td>60 (1.0)</td>
<td>1.02 (0.71-1.45)</td>
<td>0.93</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>188 (3.0)</td>
<td>197 (3.2)</td>
<td>0.95 (0.78-1.16)</td>
<td>0.64</td>
</tr>
</tbody>
</table>

TRITON-TIMI 38

Bleeding End Points

<table>
<thead>
<tr>
<th></th>
<th>No of patients</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Non-CABG)</td>
<td>146</td>
<td>21</td>
<td>244</td>
<td>24</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>146</td>
<td>21</td>
<td>244</td>
<td>24</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>111</td>
<td>5</td>
<td>182</td>
<td>6</td>
</tr>
<tr>
<td>Fatal Bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>requiring PRBC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(CABG)</td>
<td>146</td>
<td>21</td>
<td>244</td>
<td>24</td>
</tr>
</tbody>
</table>

P < 0.001

Prasugrel Subgroups

Prior Stroke / TIA
- Yes
- No

Age
- >=75
- < 75

Wgt
- < 60 kg
- >=60 kg

OVERALL

Risk (%)
- +37
- 16
- 1
- 16
- 1
- 1
- 3
- 14
- 13

P_int = 0.006
P_int = 0.18
P_int = 0.36

HR
- Prasugrel Better
- Clopidogrel Better

0.5 to 2

MCPHS UNIVERSITY
Ticagrelor: An oral reversible P2Y$_{12}$ antagonist

Ticagrelor is a cyclo-pentyl-triazolo-pyrimidine (CPTP)

- **Direct acting**
  - Not a prodrug; does not require metabolic activation
  - Rapid onset of inhibitory effect on the P2Y$_{12}$ receptor
  - Greater inhibition of platelet aggregation than clopidogrel

- **Reversibly bound**
  - Degree of inhibition reflects plasma concentration
  - Faster offset of effect than clopidogrel
  - Functional recovery of all circulating platelets 2-3 days
Potency of maintenance doses of clopidogrel (C) and Ticagrelor (T): VerifyNow P2Y\textsubscript{12} assay

<table>
<thead>
<tr>
<th>Platelet reaction units (PRU)</th>
<th>C</th>
<th>T</th>
<th>C</th>
<th>T</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trough</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Storey RF et al. J Am Coll Cardiol 2010;56(18):1456-62
PLATO Study Design

**Primary endpoint:** CV death + MI + Stroke

**Primary safety endpoint:** Total major bleeding

**6–12-month exposure**

**Clopidogrel**
If pre-treated, no additional loading dose; if naive, standard 300 mg loading dose, then 75 mg daily maintenance; (additional 300 mg allowed pre PCI)

**Ticagrelor**
180 mg loading dose, then 90 mg bid maintenance; (additional 90 mg pre-PCI)

**NSTE-ACS (moderate-to-high risk) or STEMI (if primary PCI)**
Clopidogrel-treated or -naive; randomised within 24 hours of index event (N=18,624)

### PLATO Results: Primary and Secondary Endpoints

<table>
<thead>
<tr>
<th>All patients</th>
<th>Ticagrelor (n=9,333)</th>
<th>Clopidogrel (n=9,291)</th>
<th>HR for (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary objective, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV death + MI + stroke</td>
<td>864 (9.8)</td>
<td>1,014 (11.7)</td>
<td>0.84 (0.77–0.92)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Secondary objectives, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total death + MI + stroke</td>
<td>901 (10.2)</td>
<td>1,065 (12.3)</td>
<td>0.84 (0.77–0.92)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CV death + MI + stroke + ischemia + TIA + arterial thrombotic events</td>
<td>1,290 (14.6)</td>
<td>1,456 (16.7)</td>
<td>0.88 (0.81–0.95)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Myocardial infarction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>504 (5.8)</td>
<td>593 (6.9)</td>
<td>0.84 (0.75–0.95)</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td><strong>CV death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>353 (4.0)</td>
<td>442 (5.1)</td>
<td>0.79 (0.69–0.91)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>125 (1.5)</td>
<td>106 (1.3)</td>
<td>1.17 (0.91–1.52)</td>
<td>0.22</td>
<td></td>
</tr>
<tr>
<td><strong>All-cause mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>399 (4.5)</td>
<td>506 (5.9)</td>
<td>0.78 (0.69–0.89)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Non-CABG and CABG-related Major Bleeding

### Antiplatelet and Anticoagulant Therapy: Oral Antiplatelet Agents

<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 for P2Y$_{12}$ inhibition treatment in patients with NSTE-ACS treated with an early invasive strategy and/or coronary stenting.</td>
<td>Ila</td>
<td>B</td>
</tr>
<tr>
<td>It is reasonable to choose prasugrel over clopidogrel for P2Y$_{12}$ treatment in patients with NSTE-ACS who undergo PCI who are not at high risk of bleeding complications.</td>
<td>Ila</td>
<td>B</td>
</tr>
</tbody>
</table>

## Oral P2Y$_{12}$ inhibitor Comparisons

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pro-Drug?</th>
<th>P2Y$_{12}$ Inhibition</th>
<th>Time to Peak (hours)</th>
<th>Mean Platelet Inhibition</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel (Plavix®)</td>
<td>YES (2-step conversion)</td>
<td>Irreversible</td>
<td>2 – 4</td>
<td>40 – 60 %</td>
<td>300 – 600 mg x 1 75 mg Daily</td>
</tr>
<tr>
<td>Prasugrel (Effient®)</td>
<td>YES (1-step conversion)</td>
<td>Irreversible</td>
<td>1</td>
<td>70%</td>
<td>60 mg x 1 5 – 10 mg daily</td>
</tr>
<tr>
<td>Ticagrelor (Brilinta®)</td>
<td>NO</td>
<td>Reversible</td>
<td>2 – 4</td>
<td>95%</td>
<td>180 mg x 1 90 mg BID</td>
</tr>
</tbody>
</table>

P2Y$_{12}$ Inhibitors: Clinical Pearls

- **Prasugrel:**
  - *should not be administered* to patients with a history of prior stroke or transient ischemic attack.
  - Generally not recommended in patients with age $\geq 75$ years old

- **Ticagrelor:**
  - the recommended maintenance dose of aspirin to be used with is *81 mg daily*. 

---

- Effient (prasugrel) prescribing information. Indianapolis, IN: Eli Lilly and Company; 2013 Nov.
Cangrelor (Kangreal)

- Intravenous P2Y12 Inhibitor
- Plasma half-life 3-5 minutes
- Full recovery of platelet function <60 minutes
Cangrelor Dosing and Transitions

• Dosing:
  • 30 mcg/kg IV Bolus
  • 4 mcg/kg/min IV Infusion

• Transition to PO Therapy:
  • Ticagrelor: 180 mg po x 1 anytime during cangrelor infusion or after stopping
  • Prasugrel: 60 mg po x 1 immediately after discontinuation
  • Clopidogrel: 600 mg po x 1 immediately after discontinuation

• DO NOT give prasugrel or clopidogrel before discontinuation of cangrelor!
Vorapaxar: Thrombin Receptor Antagonist

Vorapaxar:
- First-in-class
- Oral PAR-1 inhibitor
- 2.5 mg once daily

- Metabolism:
  - Primarily hepatic via CYP 3A4
  - Terminal half-life: ~126–269 hrs

- Contraindications:
  - Prior Stroke/TIA
DAPT Study Design

12 Month observational period: Open label ASA + Thienopyridine (n: 25,682)

THIENOPYRIDINE + ASPIRIN (n: 5020)

PLACEBO + ASPIRIN (n: 4941)

3-Month observational period: On ASA, off Thienopyridine

Time in months after index stent procedure

0 12 30 33

Thienopyridine: Clopidogrel (65%), Prasugrel (35%) of patients enrolled

Results: MACCE Endpoint

Primary Analysis Period

12-30 Months:
HR 0.71 (0.59-0.85)
4.3% vs. 5.9%
P<0.001
Results: Stent Thrombosis

Results: Myocardial Infarction

55% of these events were NOT RELATED to stent thrombosis

DAPT: Safety results

DAPT Score: New risk tool to help?

• Objective:
  - To develop a decision tool to identify whether a patient is more or less likely to benefit from prolonged DAPT beyond 1 year
  - Account for risks of recurrent ischemia and bleeding simultaneously

• Derived from patients in DAPT trial
  - Those that tolerated DAPT for at least one year
  - Remember DAPT exclusion criteria
    • These patients would not apply to the risk scoring system

• www.daptstudy.org
# DAPT Score

## Patient Characteristics

<table>
<thead>
<tr>
<th>Age:</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 75 years-old</td>
<td>- 2</td>
</tr>
<tr>
<td>65 – 74</td>
<td>- 1</td>
</tr>
<tr>
<td>≤ 64</td>
<td>0</td>
</tr>
</tbody>
</table>

| Diabetes                    | 1     |
| Current cigarette smoker    | 1     |
| Prior PCI or prior MI       | 1     |
| CHF or LVEF < 30%           | 2     |

## Index Procedure Characteristic

| MI at presentation          | 1     |
| Vein graft PCI              | 2     |
| Stent Diameter < 3 mm       | 1     |

**TOTAL SCORE**

-2 – 10 points
DAPT Score

- DAPT score may help identify patients where:
  - Ischemic benefits outweigh the risks of bleeding
  - Bleeding outweighs risk of ischemic events

- Low DAPT Score (< 2)
  - NNT to prevent ischemia = 153
  - NNH to cause bleeding = 64

- High DAPT Score ≥ 2
  - NNT to prevent ischemia = 34
  - NNH to cause bleeding = 272

www.daptstudy.org
THANK YOU!