Disclosure

- Kevin Schleich reports no actual or potential conflicts of interest associated with this presentation

Learning Objectives

- Review tricks of the trade for safely and effectively managing warfarin therapy including initiation, bridging, and drug interactions
- Compare and contrast the direct oral anticoagulants (DOACs)
- Utilize case-based learning to highlight important topics related to both warfarin and direct oral anticoagulants
AF is a 54-year-old male with a PMH significant for hypertension, gout, and chronic back pain who presents to the ETC for "palpitations and a racing heart." An EKG is ordered and confirms atrial fibrillation.

Current Medications
- Acetaminophen 1000 mg as needed
- Allopurinol 300 mg daily
- Amlodipine 10 mg daily
- Lisinopril 20 mg daily

CHADS2 = 1
CHA2DS2-VASc = 1

Warfarin Initiation
- **Starting Dose:** 5 mg for everyone except when you should consider lower doses (elderly patients, prior bleed history, heart failure, liver dysfunction, interacting medications)
- For patients sufficiently healthy to be treated as outpatients, we suggest "initiating VKA therapy with warfarin 10 mg daily for the first 2 days followed by dosing based on INR measurements..." (Grade 2C)
- Why I recommend AGAINST initiating warfarin 10 mg x 2 days:
  - for patients with an acute ischemic event, a minimum of a 5-day overlap with heparin or low-molecular-weight heparin is required regardless of how quickly the INR reaches the therapeutic range
  - Difficult to interpret trending INR
  - Many patients require < 5 mg/day

Trending INR
- When starting at 5 mg daily, like to see the INR increase by 0.1 to 0.2 points per day
- Elderly patients often have a delayed effect ("slow responder"), therefore the full effect of warfarin may not be seen for up to 7 days

Follow-Up
- During initiation phase, follow-up every 3-4 days to monitor the trending INR until you can establish a weekly dose requirement
- Monday:Thursday; Tuesday:Friday
Warfarin Dosage Adjustment

For weekly dose adjustments, try to make a 5-15% adjustment to the weekly dose.

Previous example:
- 2.5 mg MF; 5 mg 5 d/wk (30 mg/wk)
  - Try changing one day first: 2.5 mg M; 5 mg 6 d/wk (32.5 mg/wk)
  - 32.5/30 (~8% change)

Situation where changing one day/week may not be appropriate:

- Very high doses: 20 mg MWF; 25 mg 4 d/wk (160 mg/wk)
  - 20 mg MF, 25 mg 5 d/wk (165 mg/wk) 165/160 = 3% change

- Very low doses: 1 mg M; 0.5 mg 6 d/wk (4 mg/wk)
  - 1 mg MF, 0.5 mg 5 d/wk (4.5 mg/wk) 13% change

Follow-up

Onset of Action: depends on half-life of the Vitamin K-dependent clotting factors

<table>
<thead>
<tr>
<th>Protein Factor</th>
<th>Half-Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor VII</td>
<td>8 hours</td>
</tr>
<tr>
<td>Protein C</td>
<td>8 hours</td>
</tr>
<tr>
<td>Factor IX</td>
<td>24 hours</td>
</tr>
<tr>
<td>Protein S</td>
<td>24 hours</td>
</tr>
<tr>
<td>Factor X</td>
<td>24 hours</td>
</tr>
<tr>
<td>Factor I</td>
<td>60 hours</td>
</tr>
</tbody>
</table>

Factor II has the longest half-life
- 60 hours x 5 half-lives = 300 hours = 12.5 days

Steady-state is reached in 10-14 days, so follow-up in 2 weeks after steady dosage changes
LJ is a 22-year-old female diagnosed with bilateral DVTs after a car ride to Panama City, FL over spring break. She is a current smoker, and has been taking estrogen-containing oral contraceptives. Her past medical history is otherwise insignificant.

**Current Medications**
- Portia-28® (EE 30 mcg; L-organethel 0.15 mg)
- Weight: 81 kg
- CrCl: > 90 mL/min

**Warfarin: Heparin Bridging**
- Bridging to a therapeutic INR
  - All patients with thrombotic events may consider for atrial fibrillation patients with elevated CHADS2 score
- Bridge with a therapeutic dose of low-molecular weight heparin
  - Enoxaparin 1 mg/kg twice daily; 1.5 mg/kg once daily
  - For a minimum of 5 days and until the INR is > 2.0
  - Consider restarting LMWH bridge therapy if INR drops below 2.0 during the first four weeks of therapy
CP is a 47 year-old male with a past medical history significant for morbid obesity (BMI = 73.6 kg/m²), hypertension, and type 2 diabetes mellitus. He was found to have a seemingly unprovoked RLE DVT on venous duplex ultrasound.

Current Medications
- Chlorthalidone 25 mg daily
- Metformin 1000 mg twice daily
- Insulin glargine 45 units twice daily
- Insulin aspart 30 units 3 times daily with meals
- Lisinopril 30 mg daily
- Metoprolol XL 50 mg daily

Enoxaparin dose should be based on actual body weight, with no maximum dose established—Patients weighing up to 210 kg have been enrolled in clinical studies evaluating enoxaparin for VTE treatment.

Warfarin: Drug Interactions
- Enoxaparin dose should be based on actual body weight, with no maximum dose established
- Patients weighing up to 210 kg have been enrolled in clinical studies evaluating enoxaparin for VTE treatment
Warfarin: Drug Interactions

- 472 drug-drug interactions in Micromedex®
- Only 2 drugs require prophylactic dose adjustments
  - Sulfamethoxazole-trimethoprim
  - Metronidazole
  - Decrease warfarin dose by ~20%
- Other antibiotics/antifungals require closer monitoring:
  - Fluoroquinolones, doxycycline, clindamycin, fluconazole

- Interesting drug-drug interactions
  - Amiodarone (↑ INR)
  - Rifampin (↓ INR)
  - Carbamazepine (↓ INR)
  - Nafcillin (↓ INR, up to 30 days post op)

Direct Oral Anticoagulants (DOACs)

- Factor Xa Inhibitors
  - Rivaroxaban
  - Apixaban
  - Edoxaban

- Direct Thrombin Inhibitor
  - Dabigatran

Warfarin also inhibits
- Protein C
- Protein S
Direct Oral Anticoagulants (DOACs)

**Indications**

<table>
<thead>
<tr>
<th></th>
<th>VTE Prevention</th>
<th>VTE Treatment</th>
<th>Atrial Fibrillation</th>
<th>Mechanical Heart Valve</th>
<th>MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>Y</td>
<td>Y</td>
<td></td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Y</td>
<td>Y</td>
<td></td>
<td>Y</td>
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</tr>
<tr>
<td>Rivaroxaban</td>
<td>Y</td>
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<td>Y</td>
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<td>Y</td>
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<td></td>
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</table>

Safety and efficacy compared to warfarin

- **Ischemic Stroke Prevention**
  - Dabigatran: Y
  - Rivaroxaban: Y
  - Apixaban: Y
  - Edoxaban: Y

- **Stroke Prevention in AF Patients**
  - Dabigatran: Y
  - Rivaroxaban: Y
  - Apixaban: Y
  - Edoxaban: Y

- **Oral Bleeding**
  - Dabigatran: Y
  - Rivaroxaban: Y
  - Apixaban: Y
  - Edoxaban: Y

- **Ischemic Stroke**
  - Dabigatran: Y
  - Rivaroxaban: Y
  - Apixaban: Y
  - Edoxaban: Y

- **Major Bleeding**
  - Dabigatran: Y
  - Rivaroxaban: Y
  - Apixaban: Y
  - Edoxaban: Y

**Trial**

- **RE-LY**
- **ROCKET-AF**
- **ARISTOTLE**
- **ENGAGE-AF**

**Note:** ROCKET-AF trial only reported crude numbers without statistical evaluation for GI bleed events.

Switching from warfarin to DOAC

- **Dabigatran:** based on renal function
- **Rivaroxaban, apixaban:** discontinue and initiate parenteral anticoagulant and warfarin at the time next TSOA dose is due
- **Edoxaban:** reduce dose by 50% (15, 30, 60 mg tablets), initiate warfarin, and continue 50% dosed edoxaban until INR > 2.0

Switching from DOAC to warfarin

- **Dabigatran:** based on renal function

<table>
<thead>
<tr>
<th>CrCl (mL/min)</th>
<th>When to start warfarin</th>
</tr>
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<tbody>
<tr>
<td>&lt; 15</td>
<td>No recommended available</td>
</tr>
<tr>
<td>15-49</td>
<td>3 days before stopping dabigatran</td>
</tr>
<tr>
<td>50-89</td>
<td>2 days before stopping dabigatran</td>
</tr>
<tr>
<td>&gt; 90</td>
<td>1 day before stopping dabigatran</td>
</tr>
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- **Rivaroxaban, apixaban:** discontinue and initiate parenteral anticoagulant and warfarin at the time next TSOA dose is due

- **Edoxaban:** reduce dose by 50% (15, 30, 60 mg tablets), initiate warfarin, and continue 50% dosed edoxaban until INR > 2.0
BD is a 81 year-old white female with a history of recurrent DVTs requiring indefinite anticoagulation. She is extremely compliant with her medications, but transportation is an issue and she can no longer reliably have transportation for INRs. She would like to switch to one of the anticoagulants that does not requiring routine monitoring.

Current Medications
- Amlodipine 5 mg daily
- Calcium carbonate 500 mg twice daily
- Levothryoxine 90 mcg daily
- Lisinopril 5 mg daily
- Vitamin D 1000 units daily
- Warfarin 2.5 mg daily

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trade Name</th>
<th>Target</th>
<th>Time to Peak</th>
<th>Half-Life</th>
<th>Renal Clearance</th>
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<td>2 hours</td>
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<td>80% Renal</td>
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<td>Rivaroxaban</td>
<td>Xarelto®</td>
<td>Xa</td>
<td>2.5-4 hours</td>
<td>9-13 hours</td>
<td>66% Renal</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Eliquis®</td>
<td>Xa</td>
<td>3 hours</td>
<td>8-11 hours</td>
<td>25% Renal</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Savaysa®</td>
<td>Xa</td>
<td>1-2 hours</td>
<td>10-14 hours</td>
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DOACs: Elderly/Renal

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DOACs: Elderly/Renal

**Pharmacokinetics**

- Dabigatran
  - Target: IIa
  - Time to Peak: 2 hours
  - Half-Life: 12-17 hours
  - Renal Clearance: 80% Renal

- Rivaroxaban
  - Target: Xa
  - Time to Peak: 2.5-4 hours
  - Half-Life: 9-13 hours
  - Renal Clearance: 66% Renal

- Apixaban
  - Target: Xa
  - Time to Peak: 3 hours
  - Half-Life: 8-11 hours
  - Renal Clearance: 25% Renal

- Edoxaban
  - Target: Xa
  - Time to Peak: 1-2 hours
  - Half-Life: 10-14 hours
  - Renal Clearance: 35% Renal

**Renal Dosing**

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- **Dabigatran**: No dose adjustment required for patients with CrCl 30-50 mL/min.
- **Rivaroxaban**: No dose adjustment required for patients with CrCl 30-50 mL/min.
- **Apixaban**: Dose reduced to 2.5 mg twice daily in patients 80 years of age and older if:
  - SCr > 1.5 mg/dL
  - Body weight < 60 kg

**References**

DOACs: Acute VTE Treatment

VTE Dosing

<table>
<thead>
<tr>
<th>Drug</th>
<th>Heparin Bridge</th>
<th>Loading Dose</th>
<th>Maintenance Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>5–10 days prior to starting</td>
<td>150 mg twice daily*</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>15 mg twice daily for 21 days</td>
<td>20 mg daily</td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>5–10 days prior to starting</td>
<td>10 mg twice daily for 7 days</td>
<td>5 mg twice daily</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>5–10 days prior to starting</td>
<td>60 mg daily¥</td>
<td>60 mg daily¥</td>
</tr>
</tbody>
</table>

* Dabigatran not recommended for VTE treatment with CrCl < 30 mL/min
¥ Reduce dose to 30 mg daily with CrCl 15–50 mL/min or concurrent P-gp inhibitors

DOAC Reversal

Idarucizumab (Praxbind®)

- All patients who meet above criteria, will receive 5 gm of idarucizumab given as 2 back-to-back 2.5 gm IV push/bolus infusions
- Binding of dabigatran and reduction in dilute thrombin time/earcin clotting time occurs immediately
- RE-VERSE AD trial: median time to bleeding cessation was 11.4 hours
- 5 gm dose = $3500

Direct Oral Anticoagulants (DOACs)

- Idarucizumab (Praxbind®)

- Kidney function CrCl: 
  - >15 mg/min: Up to 48 hours (2 days) from time of administration of recent recent dabigatran dose
  - 5–15 mg/min: Up to 72 hours (3 days) after time of administration of most recent dabigatran dose
  - 3–5 mg/min: Up to 144 hours (6 days) after time of administration of most recent dabigatran dose

* Creatinine clearance (CrCl) is calculated using the Cockcroft-Gault formula.

- Start the presentation to activate live content.
Direct Oral Anticoagulants (DOACs)

Reversal
- Historically, fresh frozen plasma (FFP), prothrombin complex concentrates (PCCs), and activated factor VIIa have been used with relatively poor results.
- Currently, 2 reversal agents in either phase II or III trials.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>Structure</th>
<th>Route</th>
<th>MOA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andexanet alfa</td>
<td>Xa inhibitors</td>
<td>Recombinant factor Xa</td>
<td>IV</td>
<td>Binds to factor Xa inhibitors with similar affinity as native factor Xa</td>
</tr>
<tr>
<td>Aripazine</td>
<td>All agents</td>
<td>Small synthetic molecule</td>
<td>IV</td>
<td>Binds to TSOA and heparin leading to reversal of anticoagulant effect</td>
</tr>
</tbody>
</table>

When to expect other reversal agents on the market?
- Andexanet alfa designated by the FDA as "breakthrough therapy" in phase III trials.
- Andexanet alfa expected Fall 2016...
- Aripazine has a number of phase II trials underway.

Good DOAC Candidate
- Excellent medication adherence
- Unable to reliably have INR drawn frequently
- Fluctuating INRs due to dietary changes or medication interactions
- Younger age
- Good renal function

Poor DOAC Candidate
- Poor medication adherence
- INR fluctuations due to poor adherence
- Elderly
- Poor renal function, or susceptible to declining renal function
- Occupation with high bleed risk
- Obesity
- BMI > 40 kg/m^2
- Weight > 120 kg

Summary
- Warfarin remains a mainstay of anticoagulation therapy, and if managed effectively, is a very safe medication.
- The direct oral anticoagulants provide a viable option for anticoagulation therapy in appropriately selected patients.
- Each direct oral anticoagulant has unique pharmacokinetic properties, and thus has unique dosing strategies for initiation, bridging and discontinuation.
- Comprehensive patient education is essential for safe anticoagulation regardless of which agent is prescribed.
THANK YOU!

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