Bridging the Gap: How to Transition from the NOACs to Warfarin

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Amanda Styer, Pharm.D.
Marion General Hospital, OhioHealth
Objectives:

1. Review labeling regarding transition from NOACs (rivaroxaban, apixaban, edoxaban, dabigatran) to warfarin
2. Discuss the trial data that led to the black box warning regarding interruption of NOAC therapy
3. Provide guidance to prescribers on how to safely transition patients from NOACs to warfarin
Patient Case

- RM is a 66 year old male recently discharged from your facility with a diagnosis of nonvalvular atrial fibrillation. After 3 weeks of taking rivaroxaban 20mg once daily, the patient realizes he will not be able to afford this medication. The physician decides to switch the patient to warfarin.
Question

What is the most appropriate way to transition this patient from rivaroxaban to warfarin?

a) Stop rivaroxaban and start warfarin when the next dose of rivaroxaban is due
b) Stop rivaroxaban and start warfarin simultaneously, bridge with enoxaparin until the INR is 2-3
c) Overlap rivaroxaban and warfarin for 2 days then stop rivaroxaban
d) Overlap rivaroxaban and warfarin until the INR is between 2-3, then stop rivaroxaban
US Labeling Answer:

What is the most appropriate way to transition this patient from rivaroxaban to warfarin?

a) Stop rivaroxaban and start warfarin when the next dose of rivaroxaban is due
b) Stop rivaroxaban and start warfarin simultaneously, bridge with enoxaparin until the INR is 2-3
c) Overlap rivaroxaban and warfarin for 2 days then stop rivaroxaban
d) Overlap rivaroxaban and warfarin until the INR is between 2-3, then stop rivaroxaban
Canadian Labeling Answer:

What is the most appropriate way to transition this patient from rivaroxaban to warfarin?

a) Stop rivaroxaban and start warfarin when the next dose of rivaroxaban is due
b) Stop rivaroxaban and start warfarin simultaneously, bridge with enoxaparin until the INR is 2-3
c) Overlap rivaroxaban and warfarin for 2 days then stop rivaroxaban
d) Overlap rivaroxaban and warfarin until the INR is between 2-3, then stop rivaroxaban
Why the Discrepancy?

repeat after me...
"I am the best."

I AM THE BEST!!
Literature Review

• Major clinical trials that evaluated a specific NOAC for the purpose of stroke and systemic embolism prevention in patients with nonvalvular AFib
  – ROCKET-AF (rivaroxaban)
  – ARISTOTLE (apixaban)
  – ENGAGE AF TIMI-48 (edoxaban)
• Patients followed 30 days after the end of study (EOS) to evaluate risk during transition to warfarin
Literature Review: ROCKET AF EOS

End of Study Transitional Design

Rivaroxaban (n=4591)

Warfarin (n=4657)

End of Study (day 0)

INR #1 (day 3)

Warfarin 92.2%

25% had INR over 2

60% had INR over 2

Warfarin + enoxaparin bridge 1.8%

Warfarin + enoxaparin bridge 1.2%

Warfarin 98.2%

Warfarin 98.8%
Literature Review: ROCKET AF EOS

Number of events following discontinuation of study anticoagulant during transition to warfarin (days 3-30)

- Stroke/Systemic Embolism: Rivaroxaban (HR 3.72), Warfarin
- Major Bleeding: Rivaroxaban (HR 3.62), Warfarin
FDA Black Box Warning

- Premature discontinuation of NOAC (rivaroxaban, dabigatran, apixaban, edoxaban) increases the risk of thrombotic events. Premature discontinuation of any oral anticoagulant, including an NOAC, increases the risk of thrombotic events. To reduce this risk, consider coverage with another anticoagulant if the NOAC is discontinued for a reason other than pathological bleeding or completion of a course of therapy.
Literature Review: ARISTOTLE EOS

End of Study Transitional Design

48 hr overlap

Apixaban (n=6809)

Apixaban + Warfarin 84.3%

Warfarin

Placebo + Warfarin 84.8%

Warfarin

End of Study (day 0) (day 2)

Warfarin

Warfarin
Literature Review: ARISTOTLE EOS

Number of events following discontinuation of study anticoagulant during transition to warfarin (days 0-30)

- **Stroke/Systemic Embolism**
  - Apixaban: (HR 4.06)
  - Warfarin: 5

- **Major Bleeding**
  - Apixaban: (HR 2.5)
  - Warfarin: 10

Comparison between Apixaban and Warfarin shows a higher risk of stroke/systemic embolism and major bleeding for Warfarin.
Thromboembolic Risk

- Long half-life of Factor II and early decreases in circulating proteins C and S, warfarin initiation in warfarin naïve patients creates a temporary hypercoagulable state.
- Patients in both ROCKET AF and ARISTOTLE had a CHADS<sub>2</sub> score of ≥ 2 with the patients experiencing thromboembolism having a disproportionately higher median score
  - Patients with a CHADS<sub>2</sub> score of ≥ 2 have a predicted 4 - 18.5% risk of thromboembolic event if not anticoagulated
Major Bleeding Risk

• Increase in bleeding reflects warfarin initiation risk for warfarin naïve patients versus patients stabilized on warfarin
  – Patients experience highest risk of bleeding within the first 3 months of warfarin initiation

• Similar increases noted at the beginning of the ARISTOTLE trial when warfarin naïve patients were initiated on warfarin
Literature Review: ENGAGE AF-TIMI 48 EOS

End of Study Transitional Design

14 day overlap or until INR ≥ 2

Edoxaban 30mg (n=3107)

- Edoxaban 60mg (n=3050)
- Warfarin (n=3147)

- Edoxaban 15mg + warfarin 67.4%

- Edoxaban 30mg + warfarin 67.4%

- Placebo + warfarin 69.9%

- Warfarin
Literature Review: ENGAGE AF-TIMI 48 EOS

Number of events following discontinuation of study anticoagulant during transition to warfarin (days 0-30)

- edoxaban 30mg
- edoxaban 15mg
- warfarin

Number of Patient Events

<table>
<thead>
<tr>
<th></th>
<th>Stroke/Systemic Embolism</th>
<th>Major Bleeding</th>
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</thead>
<tbody>
<tr>
<td>edoxaban 30mg</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>edoxaban 15mg</td>
<td>7</td>
<td>18</td>
</tr>
<tr>
<td>warfarin</td>
<td>7</td>
<td>11</td>
</tr>
</tbody>
</table>
Dabigatran

- No EOS transitional data
- US Labeling (no mention in Canadian Labeling)

Conversion to warfarin: Since dabigatran contributes to INR elevation, warfarin’s effect on the INR will be better reflected only after dabigatran has been stopped for ≥2 days. Start time must be adjusted based on CrCl:

- **CrCl >50 mL/min**: Initiate warfarin 3 days before discontinuation of dabigatran
- **CrCl 31 to 50 mL/min**: Initiate warfarin 2 days before discontinuation of dabigatran
- **CrCl 15 to 30 mL/min**: Initiate warfarin 1 day before discontinuation of dabigatran (dabigatran use is contraindicated in Canadian labeling when CrCl <30 mL/minute).
Question

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- Stop rivaroxaban and start warfarin simultaneously, bridge with enoxaparin until the INR is 2-3
- Overlap rivaroxaban and warfarin for 2 days then stop rivaroxaban
- Overlap rivaroxaban and warfarin until the INR is between 2-3, then stop rivaroxaban
Summary

• Stopping an NOAC in patients with atrial fibrillation is expected to return the patient to the same risk category associated with their CHADS$_2$ score
• Patients should have transitional therapy to decrease thromboembolic risk
• Method of transition (injectable vs. oral) based upon clinician and patient preference
• Obtain INRs early and often, just prior to the next scheduled dose of NOAC to minimize effect
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Speaker: Amanda Styer, PharmD
Clinical Pharmacist, Marion General Hospital

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