Warfarin 2016: New State of the Art for an Old Drug

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Objectives:
• Plan an evidence-based method to choose the initiation dose of warfarin to minimize the risk of a bleeding complication
• Identify a strategy to manage supratherapeutic INR values in patients taking warfarin to minimize the risk of bleeding complication
• Discuss the Time in Therapeutic Range measurement and apply this information to the clinical management of patients taking warfarin
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Department of Pharmacotherapy
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Conflicts of Interest Disclosure

• I have no conflicts to disclose
• I will not be discussing unlabeled indications
Learning Objectives

• Devise an evidence-based method to choose the initiation dose of warfarin for patients with acute venous thromboembolism.

• Employ a strategy to manage supratherapeutic INR values in patients taking warfarin to minimize the risk of a bleeding complication.

• Interpret the Time in Therapeutic Range measurement and apply this information to the clinical management of a patient taking warfarin.
• Despite six decades of experience evidence support many operational aspects of warfarin is not strong

• Warfarin management often suboptimal

• Consequences of poor warfarin management:
  • Bleeding
  • VTE recurrence
  • Prolonged duration of LMWH
  • Increased LOS
  • Higher cost
Warfarin Guidance Questions

- Who are good candidates for warfarin?
- How should warfarin be initiated?
- How can I optimize anticoagulation control?
- How do I manage warfarin during invasive procedures?
- How do I manage over anticoagulation and bleeding?
- How do I manage low INRs and recurrent VTE?
- How do I manage drug interactions?
- How do I switch between anticoagulants?
- What is an appropriate follow up & care transition strategy?
- How do I manage challenging situations?
Patients with Renal Dysfunction

• Little is known about DOAC use in patients with CrCl <30 mL/min
• Warfarin preferred
• UFH preferred at initiation
• Cockroft-Gault vs. other?
• Vigilant monitoring
• Bleeding risk assessment
Poor Medication Adherence

- INR monitoring—blessing or curse?
- Once daily vs. twice daily
- DOAC dose transitions
- Slow vs. rapid offset of anticoagulant effect
- Warfarin preferred if access to monitoring
Patients with Bleeding Risk Factors

• Things to consider...
  • Less bleeding with DOACs in some trials
  • Patients at high bleeding risk excluded from DOAC trials
  • Reversal agent availability

• No clear preference
Other Scenarios

• Patients taking drugs known to interact
  • Warfarin preferred—INR response can monitored, dose titrated
  • Avoid aspirin

• Patient preference and affordability
  • Thorough discussion of pros & cons, selection criteria

• Patients who are pregnant or breastfeeding
  • Avoid warfarin (and DOACs) in pregnancy
  • Warfarin preferred for breastfeeding mothers

• Patients with APLA
  • For now warfarin preferred—trials ongoing
Warfarin Guidance Questions

• Who are good candidates for warfarin?
• **How should warfarin be initiated?**
• How can I optimize anticoagulation control?
• How do I manage warfarin during invasive procedures?
• How do I manage over anticoagulation and bleeding?
• How do I manage low INRs and recurrent VTE?
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• How do I switch between anticoagulants?
• **What is an appropriate follow up & care transition strategy?**
• How do I manage challenging situations?
Warfarin Initiation for VTE

- Initiate warfarin & parenteral agent on same day
- 5 or 10 mg will work for most patients
- At least 5 days of overlap with parenteral therapy & INR of at least 2.0
INR Frequency During Initiation

• **Daily INRs** beginning on day 3 of warfarin therapy until INR 2.0 or more
• **Weekends are a pain!**
• **If daily monitoring not possible** DOACs may be preferred

Of the 1629 patients who received warfarin therapy, the total duration of parenteral therapy overlap days could be definitively determined for 1439 (88%). Of these, 1405 (98%) had at least 5 days of overlapping therapy (mean overlap duration of \(6.2 \pm 1.8\) days). An INR value was

*Annals of Pharmacotherapy*  
2015, Vol. 49(8) 869–875
Pharmacogenomic Testing

• Suggest *against* using pharmacogenomic testing to determine initial warfarin doses in most patients

Median time = 21 days
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Computer-aided Dosing

• When determining warfarin doses during VTE treatment suggest using computer-aided dosing programs or validated dosing algorithms over ad hoc approach

<table>
<thead>
<tr>
<th></th>
<th>Total number of events</th>
<th>Events per 100 patient-years</th>
<th>Adjusted* incidence rate ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall results</td>
<td>1068</td>
<td>5.7</td>
<td>0.90 (0.80–1.02)†</td>
</tr>
<tr>
<td>Results by clinical indication‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AF</td>
<td>479</td>
<td>5.1</td>
<td>0.93 (0.78–1.12)</td>
</tr>
<tr>
<td>DVT/PE</td>
<td>267</td>
<td>7.5</td>
<td>0.67 (0.52–0.85)</td>
</tr>
<tr>
<td>Mechanical heart valves</td>
<td>170</td>
<td>6.3</td>
<td>1.04 (0.77–1.40)</td>
</tr>
<tr>
<td>Other indication</td>
<td>152</td>
<td>5.0</td>
<td>1.20 (0.87–1.65)</td>
</tr>
</tbody>
</table>

• Every 10% increase in following algorithm predicted:
  • 6% increase in TTR
  • 8% increase in adverse events

* Adjusted for age, sex, body weight, type of VTE, and concomitant medications.
‡ Clinical indications include atrial fibrillation (AF), deep vein thrombosis (DVT), pulmonary embolism (PE), mechanical heart valves, and other indications.
### Anticoagulation Management Services

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Events in AMS/patients (%)</th>
<th>Events in UC/patients (%)</th>
<th>Risk ratio (95% CI)</th>
<th>I² (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCTs</td>
<td>5/367 (1)</td>
<td>10/368 (3)</td>
<td>0.64 (0.18–2.36)</td>
<td>12.2</td>
</tr>
<tr>
<td>Non-RCTs</td>
<td>49/4619 (1)</td>
<td>91/4595 (2)</td>
<td>0.49 (0.26–0.93)</td>
<td>46.7</td>
</tr>
<tr>
<td>Thromboembolic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCTs</td>
<td>8/367 (2)</td>
<td>11/368 (3)</td>
<td>0.79 (0.33–1.93)</td>
<td>0.0</td>
</tr>
<tr>
<td>Non-RCTs events</td>
<td>44/5335 (1)</td>
<td>133/5250 (3)</td>
<td>0.37 (0.26–0.53)</td>
<td>3.7</td>
</tr>
<tr>
<td>All cause mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCTs</td>
<td>10/299 (3)</td>
<td>11/299 (4)</td>
<td>0.93 (0.41–2.13)</td>
<td>0.0</td>
</tr>
<tr>
<td>Non-RCTs</td>
<td>5671/88,480 (6)</td>
<td>44,763/633,499 (7)</td>
<td>0.85 (0.37–1.98)</td>
<td>15.7</td>
</tr>
</tbody>
</table>

*J Thromb Thrombolysis (2016) 41:187–205*

- Suggest enrolling patients with VTE in an AMS, or implement a similar structured care process
Patient Self Testing/Management

• Not much data in VTE patients
• Reimbursement issues
  • For Medicare must have completed 3 months of therapy
  • Weekly testing may be mandated by 3rd party vendors
• Accuracy vs. venipuncture INRs
• Reserve for motivated patients who can demonstrate competency with self-testing equipment
Slightly Out-of-Range INRs

In summary, we found that warfarin dose management varied widely in similar clinical situations. This variation in practice had implications for INR control; extremes of management were associated with lower TTR than management closer to the mean. Our simulation suggests that, when the target range is 2.0–3.0, optimal management of warfarin would be to change the warfarin dose only when the INR is 1.7 or lower/3.3 or higher; a smaller tolerance for slightly out-of-range values seems to destabilize the INR through excessive dose adjustments. Finally, our study suggests that in addition to offering warfarin to as many optimal candidates as possible, we also need to optimize warfarin dose management to fully realize the benefits of anticoagulation.

*Journal of Thrombosis and Haemostasis, 7: 94–101*

- **Watchful waiting if stable INR control and +/- 0.3 of range**
- **Suggest against routine use of boost/skipped doses**
Warfarin Guidance Questions

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Invasive Procedures

• Arthur Allen will cover this topic in his presentation
Warfarin Guidance Questions

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Without Bleeding

- Hold warfarin +/- 1.25-2.5mg oral vit K for INR 4.5-10
- 2.5 mg oral vit K for INR >10
- What is the difference between an INR of 9.9 and an INR of 10.1 (or 20.1 for that matter)?

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**Outcome**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Vitamin K Group [95% CI], n (%)</th>
<th>Placebo Group [95% CI], n (%)</th>
<th>Risk Difference (95% CI), percentage points</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any bleeding event</td>
<td>56 (15.8 [12.1 to 20.0])</td>
<td>60 (16.3 [12.6 to 20.4])</td>
<td>−0.5 (−6.1 to 5.1)</td>
<td>0.86*</td>
</tr>
<tr>
<td>Major bleeding event</td>
<td>9 (2.5 [1.2 to 4.8])</td>
<td>4 (1.1 [0.3 to 2.8])</td>
<td>1.5 (−0.8 to 3.7)</td>
<td>0.22+</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>4 (1.1 [0.3 to 2.9])</td>
<td>3 (0.8 [0.2 to 2.4])</td>
<td>0.3 (−1.4 to 2.0)</td>
<td>0.72+</td>
</tr>
<tr>
<td>Death</td>
<td>7 (2.0 [0.8 to 4.0])</td>
<td>7 (1.9 [0.8 to 3.9])</td>
<td>0.1 (−2.2 to 2.4)</td>
<td>0.94+</td>
</tr>
</tbody>
</table>

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Ann Intern Med. 2009;150:293-300

Thromb Haemost 2010; 104: 118–121
With Bleeding

Rapid & continuous assessment/reassessment of patient’s condition:
- Intubation/fluid/blood
- Transfer to ICU (if necessary)
- Measure activity of coagulation system, hemoglobin, platelets,

Withdraw anticoagulation therapy (remove from bedside)

Give appropriate dose of antidote (if one exists)

Address mechanical causes of bleeding:
- Radiological interventions
  - Endoscopy
  - Surgery

Consider prohemostatic agent(s):
- Tranexamic acid/amniocaproic acid
- Desmopressin (DDAVP)
- Recombinant factor VIIa

Consider interventions to remove anticoagulant:
- Dialysis
- Hemoperfusion, and/or
- Plasmapheresis

Vit K 5-10 mg IV + 4-factor PCC if life-threatening bleeding
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Low INRs

- Reestablish therapeutic INR without bridge therapy for most VTE patients
Recurrent VTE

- Medication adherence?
- INR control prior to recurrence?
- Presence of cancer?
- Proximity to initial VTE?

- Switch to alternative anticoagulant—LMWH preferred
- Increase target INR range
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Drug Interactions - Antibiotics

- Increase the frequency of INR monitoring, titrate dose
Drug Interactions

- The literature supporting warfarin drug interactions is poor
- Increase the frequency of INR monitoring, titrate dose
- Avoid pre-emptive dose adjustments
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Switching Between Anticoagulants

### Warfarin to DOAC

<table>
<thead>
<tr>
<th>DOAC</th>
<th>Start when INR &lt; 2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Start when INR &lt; 3.0</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Start when INR &lt; 2.0</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Start when INR &lt; 2.6</td>
</tr>
</tbody>
</table>

### DOAC to Warfarin

<table>
<thead>
<tr>
<th>DOAC</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>Start warfarin &amp; overlap with dabigatran:</td>
</tr>
<tr>
<td></td>
<td>CrCl &gt; 50 mL/min, overlap 3 days</td>
</tr>
<tr>
<td></td>
<td>CrCl 30-50 mL/min, overlap 2 days</td>
</tr>
<tr>
<td></td>
<td>CrCl 15-30 mL/min, overlap 1 day</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Stop DOAC, start warfarin &amp; LMWH at time of</td>
</tr>
<tr>
<td></td>
<td>next scheduled DOAC dose and bridge</td>
</tr>
<tr>
<td>Apixaban</td>
<td>until INR 2.0 or more</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>For 60 mg dose reduce dose to 30 mg &amp; start</td>
</tr>
<tr>
<td></td>
<td>warfarin</td>
</tr>
<tr>
<td></td>
<td>For 30 mg dose reduce dose to 15 mg &amp; start</td>
</tr>
<tr>
<td></td>
<td>warfarin</td>
</tr>
<tr>
<td></td>
<td>Overlap warfarin &amp; edoxaban—stop edoxaban</td>
</tr>
<tr>
<td></td>
<td>when INR 2.0 or more</td>
</tr>
</tbody>
</table>
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• What is an appropriate follow up & care transition strategy?
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## INR Recall Interval

<table>
<thead>
<tr>
<th>Situation</th>
<th>INR Recall Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin dose change for INR &gt;3.9 or &lt;1.6</td>
<td>7 days</td>
</tr>
<tr>
<td>Warfarin dose change for INR 3.1-3.9 or 1.6-1.9</td>
<td>14 days</td>
</tr>
<tr>
<td>Following INR &gt;5.0</td>
<td>Within 3 days</td>
</tr>
<tr>
<td>Following vitamin K administration for high INR</td>
<td>Next day</td>
</tr>
<tr>
<td>During LMWH overlap at therapy initiation</td>
<td>Daily (starting on day 3)</td>
</tr>
<tr>
<td>Stable INR during first 3 months of therapy</td>
<td>Not &gt;6 weeks</td>
</tr>
<tr>
<td>Stable INR after first 3 months of therapy</td>
<td>Not &gt;12 weeks</td>
</tr>
</tbody>
</table>

- INR recall interval is a key driver of TTR
- Shorter recall intervals following dose changes
- Longer recall intervals during stability

![INR recall interval graph](image)
Transitions Between Healthcare Sites

- When patients receiving warfarin transition between healthcare sites suggest dedicated anticoagulation providers assume responsibility for care coordination using a structured approach
Patient Education

• All patients and their caregivers should receive patient-centered education regarding warfarin use for VTE treatment at the initiation of treatment and periodically thereafter.
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Liver Disease

• Suggest against warfarin in patients with multiple comorbidities & unable to closely monitor INR

• Suggest starting dose of 1 mg daily with careful dose titration

• Suggest banding of esophageal varices prior to beginning therapy when possible
Nonadherence

• Suggest use of a systematic tracking process
• Use non-threatening reminders for those who miss INR tests
• Explore the use of pillboxes, calendars, diaries, electronic reminders & written instructions
Travel

• Ensure a sufficient supply of warfarin is available for duration of travel
• Make arrangements for INR monitoring
• Ensure a plan for ongoing communication is in place
Is Warfarin Dead?

your friend here is only mostly dead.

mostly dead is slightly alive