MANAGING ORAL ANTICOAGULANT-ASSOCIATED BLEEDING: Lessons from Warfarin

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Disclosures

**Grants/Research Support:** CIHR, HSFO, CFI, ORF

**Consultant:** Bristol-Myers Squibb, Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, Bayer, Janssen, and Portola
Overview

Anticoagulant conundrum

Scope of problem

NOACs versus warfarin

Warfarin reversal
The Anticoagulant Conundrum

Clotting

Bleeding

<table>
<thead>
<tr>
<th>Medication</th>
<th>Annual National Estimate of Hospitalizations (N=99,628)</th>
<th>Proportion of Emergency Dept. Visits Resulting in Hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Most commonly implicated medications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>33,171</td>
<td>33.3 (28.0-38.5)</td>
</tr>
<tr>
<td>Insulins</td>
<td>13,854</td>
<td>13.9 (9.8-18.0)</td>
</tr>
<tr>
<td>Oral antiplatelet agents</td>
<td>13,263</td>
<td>13.3 (7.5-19.1)</td>
</tr>
<tr>
<td>Oral hypoglycemic agents</td>
<td>10,656</td>
<td>10.7 (8.1-13.3)</td>
</tr>
<tr>
<td>Opioid analgesics</td>
<td>4,778</td>
<td>4.8(3.5-6.1)</td>
</tr>
</tbody>
</table>

Budnitz DS et al. *NEJM*, 2011
<table>
<thead>
<tr>
<th>Therapeutic category and Adverse-event manifestations</th>
<th>Annual National Estimate of Hospitalizations</th>
<th>Proportion of Emergency Dept. Visits Resulting in Hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematologic agents</strong></td>
<td>% (95% CI)</td>
<td>%</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>5.6 (2.1-9.1)</td>
<td>99.7</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>2.0 (1.1-2.8)</td>
<td>73.6</td>
</tr>
<tr>
<td><strong>Gastrointestinal hemorrhage</strong></td>
<td><strong>40.8 (29.9-51.7)</strong></td>
<td><strong>84.7</strong></td>
</tr>
<tr>
<td>Genitourinary hemorrhage</td>
<td>4.7 (3.2-6.2)</td>
<td>42.4</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>6.1 (4.3-8.0)</td>
<td>10.6</td>
</tr>
<tr>
<td>Skin or wound hemorrhage</td>
<td>6.8 (4.5-9.1)</td>
<td>24.5</td>
</tr>
<tr>
<td>Other type of hemorrhage</td>
<td>5.3 (2.7-8.0)</td>
<td>27.5</td>
</tr>
</tbody>
</table>

Budnitz DS et al. *NEJM*, 2011
New Oral Anticoagulants vs. Warfarin: Intracranial Hemorrhage

- Dabigatran 110 mg BID
- Dabigatran 150 mg BID
- Rivaroxaban 20 mg QD
- Apixaban 5 mg BID
- Edoxaban 30 mg QD
- Edoxaban 60 mg QD

Comparative HR (95% CI):
- Warfarin better
- Comparator better

Superiority p-value:
- Dabigatran 110 mg BID: <0.001
- Dabigatran 150 mg BID: <0.001
- Rivaroxaban 20 mg QD: 0.02
- Apixaban 5 mg BID: <0.001
- Edoxaban 30 mg QD: <0.001
- Edoxaban 60 mg QD: <0.001

New Oral Anticoagulants vs. Warfarin: ISTH Major Bleeding

Dabigatran 110 mg BID
Dabigatran 150 mg BID
Rivaroxaban 20 mg QD
Apixaban 5 mg BID
Edoxaban 30 mg QD
Edoxaban 60 mg QD

Superiority p-value
0.003
0.31
0.58
<0.001
<0.001
<0.001

New Oral Anticoagulants vs. Warfarin: GI Bleeding

- Dabigatran 110 mg BID: HR (95% CI) = 0.43
- Dabigatran 150 mg BID: HR (95% CI) = 0.002
- Rivaroxaban 20 mg QD: HR (95% CI) < 0.001
- Apixaban 5 mg BID: HR (95% CI) = 0.37
- Edoxaban 30 mg QD: HR (95% CI) < 0.001
- Edoxaban 60 mg QD: HR (95% CI) = 0.03

NOACs Versus Warfarin

NOACs are replacing warfarin for many indications.

Annual rate of major bleeding with NOACs is about 3%.
Warfarin Reversal

General principles

Warfarin-specific agents

Outcome
General Principles for Management of Anticoagulant-related Bleeding

1. Stop drug
2. Investigate and treat cause
3. Administer antidote
4. Test integrity of coagulation system
5. Use non-specific blood thickeners
6. Transfuse to replace deficient factors or if transfusion reverses drug
7. Consider dialysis or other maneuvers to remove drug
8. By the time all this is done, most drugs will have cleared

Crowther M et al, Blood 2008
Specific Management of Warfarin-associated Bleeding

Vitamin K (antidote to warfarin)

Replace vitamin K-deficient clotting factors with PCC or FFP
Oral Versus IV Vitamin K

4F-PCC versus FFP

### Hemostatic Efficacy (Intention-to-Treat Efficacy Population)

<table>
<thead>
<tr>
<th>Primary Rating</th>
<th>No. (%) of Patients [95% CI]</th>
<th>Difference 4F-PCC Minus Plasma, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4F-PCC (n=98)</td>
<td>Plasma (n=104)</td>
</tr>
<tr>
<td>Hemostatic efficacy rating by category*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excellent</td>
<td>44† (44.9)</td>
<td>45 (43.3)</td>
</tr>
<tr>
<td>Good</td>
<td>27 (27.6)</td>
<td>23 (22.1)</td>
</tr>
<tr>
<td>Poor/none</td>
<td>27 (27.6)</td>
<td>36 (34.6)</td>
</tr>
<tr>
<td>Noneffective</td>
<td>25 (25.5)</td>
<td>33 (31.7)</td>
</tr>
<tr>
<td>Missing primary rating</td>
<td>2 (2.0)</td>
<td>3 (2.9)</td>
</tr>
<tr>
<td>Effective hemostasis</td>
<td>71 (72.4) [63.6 to 81.3]</td>
<td>68 (65.4) [56.2 to 74.5]</td>
</tr>
</tbody>
</table>

Sarode R et al, *Circulation* 2013;128:1234-1243
Hemostatic Efficacy by Time of Rating (Post Hoc Analysis; Intention-to-Treat Efficacy Population)

<table>
<thead>
<tr>
<th>No. of bleeds assessed for hemostatic efficacy at 4 h (visible, musculoskeletal)</th>
<th>Treatment Group</th>
<th>Difference 4F-PCC Minus Plasma, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4F-PCC (n=98)</td>
<td>Plasma (n=104)</td>
</tr>
<tr>
<td>No. (%) of patients with effective hemostasis</td>
<td>23</td>
<td>28</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. of bleeds assessed for hemostatic efficacy at 24 h (gastrointestinal, intracranial, other nonvisible)</th>
<th>Treatment Group</th>
<th>Difference 4F-PCC Minus Plasma, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>75</td>
<td>76</td>
</tr>
</tbody>
</table>

| No. (%) of patients with effective hemostasis | 52 (69.3) | 54 (71.1) | |

Sarode R et al, *Circulation* 2013;128:1234-1243
Risk of VKA Reversal After GIB

P=.002, log-rank test

(3/182 had fatal stroke)

Benefit of VKA Reversal After GIB

Warfarin-Associated ICH: Poor Prognosis Despite Anticoagulation Reversal

Canadian PCC (prothrombin complex concentrate) Registry:
- N=141 anticoagulation associated intracerebral hemorrhages
- 72% with INR < 1.5 within < 1h; yet 42% mortality (50% of cases)
Bleeding with NOACs

Patients are different from those treated with warfarin – younger, better renal function, less ICH, and more GI bleeding

NOACs are different than warfarin – shorter half-life and more dependence on renal function, particularly dabigatran
Conclusions

Bleeding is a common complication of anticoagulant therapy

Management of major bleeding is complicated and requires a dedicated and informed team of clinicians