The NLNOACs
(No Longer Novel Oral Anticoagulants):
Use and Misuse

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Targets for Pharmacologic Measures

PLATELETS

Anti-platelet agents: ASA, Plavix

FIBRIN STRANDS

vWf

FIBRIN CLOT via thrombin conversion of fibrinogen to fibrin

Inactivation of thrombin via ATIII by heparin (SUH, LMWH) or by direct thrombin inhibition (argatroban, bivalirudin, dabigatran)

Depletion of clotting proteins by Warfarin

Inactivation of Fxa by rivaroxaban or apixiban

Endothelial cells
Limitations of Warfarin (VKA)

- Requires frequent Monitoring
- Genotype testing
- Complicates Management Of:
  - Bleeding patient
  - Patient with High INR
- Periprocedural Anticoagulation Difficult
- Narrow Therapeutic Index & Drug/Diet Interactions
- Long Half-Life
- Slow Onset of Action

Anticoag. Clinics

Requires frequent Monitoring

? Genotype testing

Heparin “overlap” often necessary

Periprocedural Anticoagulation Difficult
Poor Control of Anticoagulation with Warfarin: Assessing Time in Therapeutic Range (TTR)

- Quest Diagnostics database, inclusive of all 50 states, was queried for all outpatient INR testing for patients ≥ 18 years of age
- Overall, 187,573 individuals were included (74% with AF), with a total of 3,493,443 INR measurements.
  - For AF, 58% TTR
  - For VTE, 52% TTR
- Conclusion: The TTR data demonstrate suboptimal anticoagulation in a substantial proportion of INR visits, suggesting that a large proportion of Americans with AF and VTE are not receiving the optimum warfarin effect

ASH #103 Anticoagulant Management of Atrial Fibrillation In the United States: Findings From a Large National Database of Clinical Test Results
Events per 100 Patient-Years According to International Normalized Ratio Control

<table>
<thead>
<tr>
<th>Event</th>
<th>Total Events</th>
<th>Poor Control</th>
<th>Moderate Control</th>
<th>Good Control</th>
<th>P Value (Poor vs Good)</th>
<th>P Value (Moderate vs Poor)</th>
<th>P Value (Good vs Moderate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or systemic embolism</td>
<td>2.1</td>
<td>0.02</td>
<td>1.34</td>
<td>0.09</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death, all cause</td>
<td>4.2</td>
<td>&lt; .01</td>
<td>1.84</td>
<td>&lt; .01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death, stroke, or systemic embolism</td>
<td>5.98</td>
<td>&lt; .01</td>
<td>3.01</td>
<td>&lt; .01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>3.85</td>
<td>&lt; .01</td>
<td>1.96</td>
<td>&lt; .01</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The Future!

...is now !!!!-

The Novel Oral Anticoagulants....AKA the NOACs

initially Novel Oral Anticoagulants, then TSOACs (target-specific oral agents) then NOACS again (now Non-vitamin K Oral Anticoagulants) and now possibly DOACs !!!

(direct oral anticoagulants)
Anticoagulants In Development

Unfractionated Heparin

Low Molecular Weight Heparin

New Oral Xa Inhibitors
- Rivaroxaban
- Apixaban
- Edoxaban

New Oral IIa Inhibitors
- Ximelagatran
- Dabigatran etexilate

Fibrin Clot
Factor IIa Inhibitors

Dabigatran etexilate

Factor Xa Inhibitors

Rivaroxaban

Apixaban
<table>
<thead>
<tr>
<th>Target</th>
<th>Warfarin (Coumadin)</th>
<th>Dabigatran (Pradaxa)</th>
<th>Rivaroxaban (Xarelto)</th>
<th>Apixaban (Eliquis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VKORC1 Factors II, VII, IX, X</td>
<td>VKORC1 Factors II, VII, IX, X</td>
<td>Factor Iia (Thrombin)</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
</tr>
<tr>
<td>T (max)</td>
<td>72-96 h</td>
<td>2 h</td>
<td>2.5-4 h</td>
<td>3 h</td>
</tr>
<tr>
<td>Half-life</td>
<td>40 h</td>
<td>14-17 h</td>
<td>5-9 h healthy, 9-13 h elderly</td>
<td>8-15 h</td>
</tr>
<tr>
<td>Affected by diet?</td>
<td>Yes!!!!</td>
<td>No!!!!</td>
<td>No!!!!</td>
<td>No!!!!</td>
</tr>
<tr>
<td>Affected by meds?</td>
<td>Often</td>
<td>Rarely</td>
<td>Rarely</td>
<td>Rarely</td>
</tr>
<tr>
<td>Monitoring</td>
<td>INR-adjusted</td>
<td>Not needed</td>
<td>Not needed</td>
<td>Not needed</td>
</tr>
<tr>
<td>Administration</td>
<td>Once daily</td>
<td>Once or twice daily</td>
<td>Once daily</td>
<td>Twice daily</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Cytochrome P450</td>
<td>80% renal, 20% fecal</td>
<td>66% renal, 33% fecal</td>
<td>25% renal, 75% fecal,</td>
</tr>
<tr>
<td>Assay</td>
<td>PT/INR</td>
<td>Ecarin clotting time, Dilute Thrombin time (not available in NYS)</td>
<td>Anti-factor Xa, PiCT®, HepTest® (not available in NYS)</td>
<td>Anti-factor Xa (not available in NYS)</td>
</tr>
<tr>
<td>FDA approval</td>
<td>AF Acute VTE</td>
<td>AF Acute VTE</td>
<td>AF Acute VTE Ortho VTE prophy</td>
<td>AF ----</td>
</tr>
</tbody>
</table>
NEW ORAL ANTICOAGULANTS VS WARFARIN: STROKE RISK IN AF

Stroke or Systemic Embolism

- Dabigatran 110 mg BID: HR 1.00 (95% CI), p-value 0.29
- Dabigatran 150 mg BID: HR 1.00 (95% CI), p-value <0.001
- Rivaroxaban 20 mg QD: HR 1.12 (95% CI), p-value 0.12
- Apixaban 5 mg BID: HR 0.99 (95% CI), p-value 0.01

Ischemic Stroke

- Dabigatran 110 mg BID: HR 0.65 (95% CI), p-value 0.35
- Dabigatran 150 mg BID: HR 0.71 (95% CI), p-value 0.03
- Rivaroxaban 20 mg QD: HR 1.03 (95% CI), p-value 0.59
- Apixaban 5 mg BID: HR 1.13 (95% CI), p-value 0.42

Warfarin better

Comparators:

NEW ORAL ANTICOAGULANTS VS WARFARIN: BLEEDING RISK IN AF

Take home message - 1:300 ICH risk reduced to 1:600

**Intracranial Hemorrhage**
- Dabigatran 110 mg BID
- Dabigatran 150 mg BID
- Rivaroxaban 20 mg QD
- Apixaban 5 mg BID

**ISTH Major Bleeding**
- Dabigatran 110 mg BID
- Dabigatran 150 mg BID
- Rivaroxaban 20 mg QD
- Apixaban 5 mg BID

Comparator better | Warfarin better
---|---

### Table: Risk Factors and Hemorrhage Rate

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>HAS-BLED Score</th>
<th>CHADs2 (%/y)</th>
<th>CHA2DS2-VASc (%/y)</th>
<th>Bleeding rate (%/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension-1</td>
<td>0</td>
<td>1.9</td>
<td>0</td>
<td>1.1%</td>
</tr>
<tr>
<td>Abnl renal/hepatic function – 1 each</td>
<td>1</td>
<td>2.8</td>
<td>1.3</td>
<td>1.0%</td>
</tr>
<tr>
<td>Stroke-1</td>
<td>2</td>
<td>4</td>
<td>2.2</td>
<td>1.9%</td>
</tr>
<tr>
<td>Bleeding-1</td>
<td>3</td>
<td>5.9</td>
<td>3.2</td>
<td>3.7%</td>
</tr>
<tr>
<td>Labile INR-1</td>
<td>4</td>
<td>8.5</td>
<td>4.0</td>
<td>8.7%</td>
</tr>
<tr>
<td>Elderly &gt; 65 yrs-1</td>
<td>&gt;5</td>
<td>12.5</td>
<td>6.7</td>
<td>Insufficient data</td>
</tr>
<tr>
<td>Drugs or alcohol use- 1 each</td>
<td></td>
<td>18.2</td>
<td>9.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Tailoring the NOAC for the Specific Situation in AF -
Starting point is quantifying risk of stroke vs. risk of bleed.
<table>
<thead>
<tr>
<th>Specific clinical situation</th>
<th>General consideration</th>
<th>Specific consideration</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk of bleeding, i.e. HAS-BLED &gt; 3</td>
<td>Consider agent/dose with the lowest incidence of bleeding</td>
<td>Apixiban (in Canada Dabigatran 110 also)</td>
</tr>
<tr>
<td>Previous GI bleeding or high risk</td>
<td>Consider agent with the lowest reported incidence of GI bleeding</td>
<td>Apixiban</td>
</tr>
<tr>
<td>High risk of ischemic stroke but low bleeding risk</td>
<td>Consider agent/dose with the best reduction of ischemic stroke</td>
<td>Dabigatran 150</td>
</tr>
<tr>
<td>Previous stroke (secondary prevention)</td>
<td>Consider best investigated agent for greatest reduction of 2° stroke</td>
<td>Rivaroxaban Apixiban</td>
</tr>
<tr>
<td>CAD, previous MI or high risk for ACS/MI</td>
<td>Consider agent for postive effect in ACS</td>
<td>Rivaroxaban</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>Consider agent least dependent on renal function</td>
<td>Apixiban (least) Rivaroxaban</td>
</tr>
<tr>
<td>GI upset/disorders</td>
<td>Consider agent/dose with no reported GI effects</td>
<td>Apixiban Rivaroxaban</td>
</tr>
<tr>
<td>Patient preference</td>
<td>Consider once daily formulation</td>
<td>Rivaroxaban</td>
</tr>
</tbody>
</table>
“Hey, Dr. Kouides, when can we prescribe dabigatran or rivaraxaban for VTE?”

- Rivaroxaban? Yes….but know 3 relative contraindications:
  1. Poor renal function b/c………. The NOACs are renally cleared
  2. Morbid obesity (weight > 120 kg) b/c…… Little data for wgt > 120 kg and no assay yet available
  3. Active bleeding b/c….. No definite antidote
     But, Kcentra may work with Rivaroxabn

- Dabigatran? Yes……but same contraindications and higher GI bleed risk, greater prolonged half-life in renal failure, Kcentra antidote may not “work as well” as with Rivaroxabn

- Switching to rivaroxaban from warfarin-
  - If time out of therapeutic range (TTR) with warfarin documented to be > 30-35% of the time
# NEW ORAL ANTICOAGULANTS VS WARFARIN: VTE

<table>
<thead>
<tr>
<th>Study</th>
<th>Events/total</th>
<th>Risk ratio (95% CI)</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Novel oral anticoagulants</td>
<td>Vitamin K antagonists</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EINSTEIN-DVT</td>
<td>36/1731</td>
<td>51/1718</td>
<td>0.70 (0.46 to 1.07)</td>
</tr>
<tr>
<td>EINSTEIN-PE</td>
<td>50/2419</td>
<td>44/2413</td>
<td>1.13 (0.76 to 1.69)</td>
</tr>
<tr>
<td>EINSTEIN-DOSE</td>
<td>3/115</td>
<td>7/101</td>
<td>0.38 (0.10 to 1.42)</td>
</tr>
<tr>
<td>OXIDa</td>
<td>2/100</td>
<td>1/112</td>
<td>2.24 (0.21 to 24.33)</td>
</tr>
<tr>
<td>Random effects model</td>
<td>91/4365</td>
<td>103/4344</td>
<td>0.85 (0.55 to 1.31)</td>
</tr>
<tr>
<td>Heterogeneity</td>
<td>$I^2=38%$, $P=0.185$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Botticelli-DVT</td>
<td>3/130</td>
<td>3/128</td>
<td>0.98 (0.20 to 4.79)</td>
</tr>
<tr>
<td>Random effects model</td>
<td>3/130</td>
<td>3/128</td>
<td>0.98 (0.20 to 4.79)</td>
</tr>
<tr>
<td>Heterogeneity</td>
<td>$I^2=NA$, $P=1$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dabigatran</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RECOVER I</td>
<td>30/1274</td>
<td>27/1265</td>
<td>1.10 (0.66 to 1.84)</td>
</tr>
<tr>
<td>RECOVER II</td>
<td>30/1279</td>
<td>28/1289</td>
<td>1.08 (0.65 to 1.80)</td>
</tr>
<tr>
<td>Random effects model</td>
<td>60/2553</td>
<td>55/2554</td>
<td>1.09 (0.76 to 1.57)</td>
</tr>
<tr>
<td>Heterogeneity</td>
<td>$I^2=0%$, $P=0.954$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ximelagatran</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>THRIVE II/V</td>
<td>26/1240</td>
<td>24/1249</td>
<td>1.09 (0.63 to 1.89)</td>
</tr>
<tr>
<td>THRIVE I</td>
<td>1/65</td>
<td>2/73</td>
<td>0.56 (0.05 to 6.05)</td>
</tr>
<tr>
<td>Random effects model</td>
<td>27/1305</td>
<td>26/1322</td>
<td>1.06 (0.62 to 1.80)</td>
</tr>
<tr>
<td>Heterogeneity</td>
<td>$I^2=0%$, $P=0.594$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fox BD: BMJ 2012;345:e74
### New Oral Anticoagulants vs Warfarin: Bleeding Risk in VTE

<table>
<thead>
<tr>
<th>Study</th>
<th>Novel oral anticoagulants</th>
<th>Vitamin K antagonists</th>
<th>Risk ratio (95% CI)</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rivaroxaban</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EINSTEIN-DVT</td>
<td>14/1718</td>
<td>20/1711</td>
<td>0.70 (0.35 to 1.38)</td>
<td>0.50 (0.31 to 0.80)</td>
</tr>
<tr>
<td>EINSTEIN-PE</td>
<td>26/2412</td>
<td>52/2405</td>
<td>0.51 (0.05 to 5.53)</td>
<td>5.38 (0.26 to 110.96)</td>
</tr>
<tr>
<td>EINSTEIN-DOSÉ</td>
<td>1/135</td>
<td>2/137</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OXIDa</td>
<td>2/117</td>
<td>0/126</td>
<td></td>
<td>0.57 (0.39 to 0.84)</td>
</tr>
<tr>
<td>Random effects model</td>
<td>43/4382</td>
<td>74/4379</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity I²</td>
<td>0%, P=0.426</td>
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<td></td>
<td></td>
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<tr>
<td><strong>Apixaban</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Botticelli-DVT</td>
<td>1/128</td>
<td>0/126</td>
<td>2.95 (0.12 to 71.82)</td>
<td>2.95 (0.12 to 71.82)</td>
</tr>
<tr>
<td>Random effects model</td>
<td>1/128</td>
<td>0/126</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity I²</td>
<td>NA, P=1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dabigatran</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RECOVER I</td>
<td>20/1274</td>
<td>24/1265</td>
<td>0.83 (0.46 to 1.49)</td>
<td></td>
</tr>
<tr>
<td>RECOVER II</td>
<td>15/1279</td>
<td>22/1289</td>
<td>0.69 (0.36 to 1.32)</td>
<td></td>
</tr>
<tr>
<td>Random effects model</td>
<td>35/2553</td>
<td>46/2554</td>
<td>0.76 (0.49 to 1.18)</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity I²</td>
<td>0%, P=0.678</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Ximelagatran</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>THRIVE II/V</td>
<td>14/1240</td>
<td>26/1249</td>
<td>0.54 (0.28 to 1.03)</td>
<td></td>
</tr>
<tr>
<td>THRIVE I</td>
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<td>0/73</td>
<td></td>
<td></td>
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<td>26/1322</td>
<td>0.54 (0.28 to 1.03)</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity I²</td>
<td>NA, P=1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fox BD: BMJ 2012;345:e74
Acute Treatment of Pulmonary Embolism with Rivaroxaban—Real Life Data from the Prospective Dresden Noac (novel oral anticoagulant) Registry (NCT01588119)

- Prospective data from a regional registry of patients treated with novel anticoagulants
  - Saxony, Germany
  - Aim to study an unselected group of patients
  - Evaluated rates of recurrent VTE, CV complications, and bleeding
  - 69 patients received treatment with rivaroxaban for acute PE

“Real life use“ of Rivaroxaban

- So far, 69 patients treated with rivaroxaban for acute PE:
  - mean age 67.7 years (EINSTEIN PE: 58 years)
  - median time between PE diagnosis and start rivaroxaban: 4 days
  - 3 recurrent VTE events (3.4/100 patient years, no fatal events)
    - 1 DVT after discontinuation of riva (3 months after end of treatment)
    - 1 DVT during temporary interruption
    - 1 superficial phlebitis during rivaroxaban in pancreatic cancer
  - 5 major bleedings (5.6/100 patient years), but no fatal events
  - 2 deaths (both worsening of chronic heart failure)
- preliminary data of a small cohort, but reassuring for a cohort of daily care patients 10 years older than phase III trial patients

Koehler et al, Abstract 2380,
https://ash.confex.com/ash/2013/webprogram/Paper58333.html
Kaplan-Meier estimation for first major bleeding (intention-to-treat [ITT] analysis set)
Patient G.S.

History of multiple DVTs in setting of Factor V Leiden, post thrombotic syndrome and poor control of INRs on warfarin-
Patient R.O.

• 19 y/o with history of superior sagittal vein thrombosis 2 yrs. ago in setting of ATIII deficiency

• Has had 35 INRs since 2/2011 and was only in range therapeutic between 2-3 just 11/35 i.e. 31% and importantly 24/35 times she was subtherapeutic 51% of the time
The “skinny” on the NOACs

- Here to stay as unlike warfarin no effect by diet and very little if any effect with concurrent medications and hence require no monitoring
- End result is that the time in therapeutic range is much greater
- FDA approved already for:
  a) Stroke prevention in AF (dabigatran, rivaroxaban, apixiban)
  b) VTE prophylaxis for orthopedic surgery (rivaroxaban)
  c) VTE treatment and secondary prevention (rivaroxaban, dabigatran and eventually apixiban which is least bleeding risk of all but is bid drug)

- But there are enough downsides/caveats to preclude “wholesale” conversion of patients already on warfarin-
  ① No reliable monitoring assays (though we expect eventually for rivaroxaban there will be a New York state approved Xa assay)
  ② No reliable antidote (though the new antidote FDA approved for warfarin, “Kcentra” may reverse rivaroxaban-induced bleeding)
  ③ NOACs are renally cleared
  ④ Not much safety and efficacy data in patients > 100-150 kg
Hi Peter,

Just checking in to see if our practice has changed regarding rivaroxaban use in obese patients. We had a 70 year old obese patient (~130 kg) who was newly diagnosed with a subacute subsegmental PE. She was started on rivaroxaban 15 mg twice daily for treatment of the PE. The pharmacist approached me about the patient and I expressed my concerns about her weight with rivaroxaban due to the limited number of patients included in the VTE trials that were > 100 kg. As you know, we have also included the potential weight issue in our anticoagulation guidelines - that it is not advised in patients who are >120 kg until further data is available.

The pharmacist discussed this with the team who then conferred with hematology which recommended continuing therapy since weight is not an issue per Up To Date (says up to 190 kg). I just wanted to check with you if we are becoming more comfortable with its use in this patient population so that I may educate the pharmacists that this is no longer a concern and will update it with the next edition of the anticoagulation guidelines.

Thanks for your help, Maura; Maura Wychowski, PharmD,BCPS Clinical Pharmacy Specialist Rochester General Hospital
48-year-old man with a BMI of 44.7 and a weight of 153 kg admitted to the hospital after he had a right hemispheric stroke. His medical history included long-standing hypertension, hypertrophic cardiomyopathy, congestive heart failure, and paroxysmal atrial fibrillation on dabigatran 150 mg po bid. He had also been a smoker.
Probability of Clinical Outcomes versus dabigatran levels

Reilly PA: J Am Coll Cardiol. 2014;63(4):321-328
Probability of Major Bleeding event and Ischemic Stroke

Reilly PA: J Am Coll Cardiol. 2014;63(4):321-328
Pradaxa® Alert

The FDA issued a drug safety communication regarding serious bleeding events linked to the blood thinner Pradaxa® that in the worst cases may result in death.

Serious side effects include:
• Coughing Up Blood Clots
• Severe Bleeding
• Vomiting Blood

If you or a loved one developed serious complications after taking Pradaxa®, call the law firm of Janet, Jenner & Suggs toll free at 1-800-556-4032.

YOU MAY BE ENTITLED TO
JUST COMPENSATION

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Employees also continued to question the merits of allowing a research paper to be published showing that some patients could benefit from monitoring of their blood. The paper was published on Tuesday but with some details removed.

“This publication will more harm than be useful for us, neither in the market but be especially harmful in the discussions with regulatory bodies,” one email read. “Can’t this be avoided?”

David K. Herndon, of the United States District Court in East St. Louis, who is overseeing thousands of lawsuits filed by patients and their families, who say that Boehringer Ingelheim failed to properly warn them about the risks of taking Pradaxa.
# Cost Comparison Of Oral Anticoagulants

<table>
<thead>
<tr>
<th>Usage</th>
<th>Dosage in Milligrams (No. of Capsules)</th>
<th>Price ($)</th>
<th>Monthly Cost ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>4 mg/day</td>
<td>172.34</td>
<td>51.70</td>
</tr>
<tr>
<td>Coumadin oral</td>
<td>4 (100)</td>
<td>52.81</td>
<td>15.84</td>
</tr>
<tr>
<td>Jantoven oral</td>
<td>5 (100)</td>
<td>63.25</td>
<td>18.98</td>
</tr>
<tr>
<td>Warfarin sodium oral</td>
<td>6 (100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dabigatran</td>
<td>150 mg/BD</td>
<td>300.44</td>
<td>600.88</td>
</tr>
<tr>
<td>Pradaxa</td>
<td>75 (60)</td>
<td>901.26</td>
<td>400.56</td>
</tr>
<tr>
<td>Pradaxa</td>
<td>150 (60)</td>
<td>300.44</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>20 mg/day</td>
<td>300.44</td>
<td></td>
</tr>
<tr>
<td>Xarelto</td>
<td>10 (30)</td>
<td>300.42</td>
<td>600.84</td>
</tr>
<tr>
<td>Xarelto</td>
<td>15 (90)</td>
<td>901.26</td>
<td>400.56</td>
</tr>
<tr>
<td>Xarelto</td>
<td>20 (90)</td>
<td>901.26</td>
<td>300.42</td>
</tr>
<tr>
<td>Apixaban</td>
<td>5 mg/BD(^a)</td>
<td>300.44</td>
<td>600.88</td>
</tr>
<tr>
<td>Eliquis</td>
<td>2.5 (60)</td>
<td>300.44</td>
<td></td>
</tr>
<tr>
<td>Eliquis</td>
<td>5 (60)</td>
<td>300.44</td>
<td></td>
</tr>
</tbody>
</table>

Note: Information based on Lexicomp database updated on May 7, 2013. All prices are median AWP and/or AWP price for the brand and/or generic product, respectively.

\(^a\)Assume patient does not have any 2 of the following: age \(\geq 80\) years, body weight \(\leq 60\) kilograms, or serum creatinine \(\geq 1.5\) mg/dL.

AWP = average wholesale price; BD = twice a day; mg/dL = milligram per deciliter.
<table>
<thead>
<tr>
<th>Plan</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Insurance: Patient Assistance Foundation</td>
<td>Free</td>
</tr>
<tr>
<td>Commercial Insurance With Discount Card</td>
<td>$10/Month</td>
</tr>
<tr>
<td>Commercial Insurance Without Discount Card</td>
<td>$20-150/mo. Co-pay</td>
</tr>
<tr>
<td>Medicare</td>
<td>$40/Month*</td>
</tr>
<tr>
<td>Medicaid</td>
<td>Free</td>
</tr>
</tbody>
</table>
Existing & Projected Future Anticoagulant Market

**2008**

- **U.S. Sales and %**
  - Low Molecular Weight Heparins: 69%
  - Other: 18%
  - Warfarin: 8%
  - Unfractionated Heparin: 5%

**2014**

- **U.S. Sales and %**
  - Novel Orals: 51%
  - LMWHs: 29%
  - Warfarin: 2%
  - UFH: 1%
  - Other: 17%

Anticoagulant Use by Indication*

<table>
<thead>
<tr>
<th>ORTH VTE Prevention</th>
<th>DVT/PE Treatment</th>
<th>Stroke Prevention in Afib</th>
<th>Acute Cardiac Syndrome</th>
<th>Medically Ill</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>7%</td>
<td>21%</td>
<td>31%</td>
<td>2%</td>
<td>17%</td>
<td>18%</td>
</tr>
</tbody>
</table>

Most frequently asked questions I get about the NOACs

1. Can we use it in HIT(T)?
2. Can we use it in cancer-related VTE or other very prothrombotic conditions like APAS?
3. Can we use it in valvular AF?
4. Can we use it for PE from ED to home without admission?
5. Can we use it for thromboprophylaxis in medical inpatients?
6. Is there a rebound effect?
7. How do I bridge for procedures?
8. How do I reverse a bleed?
Patient H.C.-
PE in setting of cancer and HIT

- 66 year old wm first presented in November with hemoptysis and was subsequently diagnosed with non-small cell lung cancer. At that time, they also noted incidentally pulmonary embolus.
- He was started appropriately on 1 mg/kg bid enoxaparin
- But, he developed HIT with a positive ELISA of 2.8 (control 0.4)
- Switched to Fondaparinux
- 6 wks later (2/2013), presents SOB with a new pulmonary embolus; ELISA still positive
- After initial in-patient treatment with bivalirudin, at time of discharge, by exclusion we prescribed dabigatran
Why be Cautious in the Use of NOACs in Cancer related VTE

1. **Efficacy concerns**
   - *Post hoc* data from trials comparing fondaparinux or rivaroxaban with enoxaparin suggest that specific FXa inhibition might be less efficacious than LMWH inhibition in cancer patients

2. **GI issues**
   - may not be ideal in patients with nausea, vomiting, and diarrhea
   - GI absorption and bioavailability may be altered in patients with mucositis or diarrhea

3. **Bleeding issues**
   - Lack of antidote
   - Lack of experience in managing these agents in the perioperative/procedural period and in patients with thrombocytopenia

4. **Drug interactions**
   - Agents may induce (e.g. dexamethasone, doxorubicin, and vinblastine) or inhibit (e.g. tamoxifen, cyclosporine, sunitinib, and other TKIs) P-glycoprotein transport and CYP3A4 metabolic pathways

5. **Disadvantage of lack of monitoring**
   - in the management of recurrent VTE or with major bleeding
Most frequently asked questions I get about the NOACs

1. Can we use it in HIT(T)?
   - For now till more data, only in very select cases

2. Can we use it in cancer-related VTE or other very prothrombotic conditions like APAS
   - 3 cases of APAS related thrombosis on NOAC- 
   - For now till more data, only in very select cases

3. Can we use it in valvular AF?
   - Definitely not Dabigatran-5% stroke rate vs 0% with warfarin -Eikelboom JW N Engl J Med 2013; 369:1206-1214
   - Theoretically Fxa inhibitors may have a role

4. Can we use it for PE from ED to home without admission?
   - Growing Canadian and German experience of safety, consider it for low risk stable patients per PESI score?
Outpatient Rx of PE with Rivaroxaban

- EINSTEIN PE study reported that only 10% were not hospitalized, or observed for <24 h.
- Several clinical prognostic scores for PE have been validated to identify low-risk patients with a PE who are potential candidates for outpatient care, e.g. (simplified) Pulmonary Embolism Severity Index (PESI).
  - Six variables: age > 80 years, history of cancer, chronic cardiopulmonary disease, pulsations ≥ 110 beats per min, systolic blood pressure < 100 mmHg and arterial oxyhemoglobin saturation < 90% of equal weight (1 point per variable).
  - The score corresponds to the following classes: 0 point, low risk; 1 or more points, high risk. - Righini et al JTH 9(10) 2115-2117
  - Fatal PE 1/165 (0.6%) in low risk vs. 9/165 (3.1%) in high risk.
- Unfortunately, these scores were not determined in the EINSTEIN PE study but the simplified PESI may be a useful tool in deciding on outpatient rx of PE with a NOAC.
Patient R.F.

- 54-year-old wm referred regarding duration of anti-coagulation having developed a DVT/PE May 2014 presenting with a ten-day history of left lower extremity pain
- CT done apparently because MD thought he was winded-

After these tests were completed, he returned to the office and was promptly started on Xarelto 15 mg twice a day. He was not admitted for initial observation.
- Since then he has been doing quite well
Most frequently asked questions I get about the NOACs

1. Can we use it in HIT(T)?
   - For now till more data, in very select cases

2. Can we use it in cancer-related VTE or other very prothrombotic conditions like APAS?
   - For now till more data, in very select cases

3. Can we use it in valvular AF?
   - Definitely not
   - Dabigatran-5% stroke rate vs 0% with warfarin
   - Theoretically Fxa inhibitors may have a role

4. Can we use it for PE from ED to home without admission?
   - Growing Canadian and German experience of safety, possibly consider it for low risk stable patients per simplified PESI score

5. Can we use it for thromboprophylaxis in medical in-patients?
   - ADOPT and MAGELLAN trials- more bleeding with apixiban, rivaroxaban then enoxaparin

6. Is there a rebound effect?
   - AF- Probably not unless switching from NOAC to warfarin without overlap; VTE-No

7. How do I bridge for procedures?

8. How do I reverse a bleed?
What to do before and after dental work or other invasive procedures if patient is on a NOAC

• Routine dental cleaning
  – Continue same dose

• Dental extraction or similarly invasive procedure like skin biopsy
  – Skip dose evening before if Xarelto (Rivaroxaban), both doses if Pradaxa (Dabigatran)
  – Resume 24 hrs if no excessive bleeding

• Extensive dental surgery or major surgery
  – Hold two days of drug
  – Resume 48 hrs if no excessive bleeding

• In each scenario, add 1-2 days if renal insufficiency for Xarelto, 2-3 days for Pradaxa

• If also on ASA, your usual approach of holding or not

• Please feel free to call us (office 922-4020/my cell 766-3980) to double check
What to do if urgent procedure needed or life-threatening bleeding when patient therapeutic or supratherapeutic on warfarin?
Clinical Scenario Dictates Therapeutic Intervention

Nonemergency

High INR without active bleeding or with low risk of bleeding

Elective Surgery

Reduce / Withdraw Warfarin

Add Vitamin K

Major bleeding

High INR with risk of bleeding

Rapid Reversal Required

Infuse FFP or 4F-PCC
Four factor PCCs can replenish all factors

<table>
<thead>
<tr>
<th>Vitamin K-dependent coagulation Factors</th>
<th>rFVIIa</th>
<th>Plasma</th>
<th>3F-PCC*</th>
<th>4F-PCC*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ⅱ</td>
<td>✓</td>
<td>✓⁺</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Ⅶ</td>
<td>✓</td>
<td>✓⁺</td>
<td>Low levels²</td>
<td>✓</td>
</tr>
<tr>
<td>Ⅸ</td>
<td>✓⁺</td>
<td>✓⁺</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Ⅹ</td>
<td>✓⁺</td>
<td>✓⁺</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

*Factors in PCCs are ~25x more concentrated than the Factors in plasma.

†In plasma, total content of Factors relative to volume is low; large volumes are required for reversal.
New Option for Warfarin reversal of life-threatening coagulopathy

- Kcentra is a non-activated 4F-PCC containing Factors II, VII, IX and X, and the antithrombotic Proteins C and S
- Kcentra is a lyophilized powder for IV infusion packaged with the necessary components for easy reconstitution
- Kcentra is supplied as a single-use vial
Kcentra dosing and administration

Dosing should be individualized based on the patient’s baseline INR and body weight:

<table>
<thead>
<tr>
<th>Baseline INR</th>
<th>Kcentra Dose* (units of Factor IX/kg)</th>
<th>Maximum Dose† (units of Factor IX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 to &lt;4</td>
<td>25</td>
<td>Not to exceed 2,500</td>
</tr>
<tr>
<td>4 to 6</td>
<td>35</td>
<td>Not to exceed 3,500</td>
</tr>
<tr>
<td>&gt;6</td>
<td>50</td>
<td>Not to exceed 5,000</td>
</tr>
</tbody>
</table>

- Vitamin K should be administered to patients receiving Kcentra to maintain Factor levels once the effects of Kcentra have diminished
- Repeat dosing with Kcentra is not supported by clinical data and is not recommended
What to do if urgent procedure needed or life-threatening bleeding when patient therapeutic or supratherapeutic on a NOAC?
Patient R.P.

- 86 y/o wf on dabigatran for atrial fibrillation presented with acute renal failure and upper gastrointestinal bleeding.
- She had been taking dabigatran 150 mg twice daily for two months with a history of intermittent renal insufficiency during the previous 6 months.
- On admission, laboratory values included a serum creatinine 3.6 mg/dL, hematocrit 21%, and international normalized ratio greater than 10. She was treated with packed red blood cells, prothrombin complex concentrate, and multiple sessions of dialysis.
- There were no further bleeding events or additional transfusions for the remainder of the hospitalization. Her renal function never recovered and she remained hemodialysis-dependent.
- After a 47-day length of stay, she was transferred to a nursing home where she expired two months later.

Guidance on the emergent reversal of oral thrombin and factor Xa inhibitors

Scott Kaatz,¹ Peter A. Kouides,² David A. Garcia,³ Alex C. Spyropoulos,⁴ Mark Crowther,⁵ Jim D. Douketis,⁵ Anthony K. C. Chan,⁶ Andra James,⁷ Stephan Moll,⁸ Thomas L. Ortel,⁹ Elizabeth M. Van Cott,¹⁰ and Jack Ansell¹¹

The new oral anticoagulants dabigatran, rivaroxaban and apixaban have advantages over warfarin which include no need for laboratory monitoring, less drug–drug interactions and less food-drug interactions. However, there is no established antidote for patients who are bleeding or require emergent surgery and there is a paucity of evidence to guide the clinical care during these situations. Members of thrombosis and anticoagulation groups participating in the Thrombosis and Hemostasis Summit of North America formulated expert opinion guidance for reversing the anticoagulant effect of the new oral anticoagulants and suggest: routine supportive care, activated charcoal if drug ingestion was within a couple of hours, and hemodialysis if feasible for dabigatran. Also, the pros and cons of the possible use of four factor prothrombin complex concentrate are discussed. Am. J. Hematol. 00:000–000, 2012. © 2012 Wiley Periodicals, Inc.

### TABLE III. Suggestions for Reversal of New Oral Anticoagulants

<table>
<thead>
<tr>
<th></th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral activated charcoal</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Hemoperfusion with</td>
<td>Possible</td>
<td>Yes</td>
<td>Possible</td>
</tr>
<tr>
<td>activated charcoal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fresh frozen plasma</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Activated factor VIIa</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>3-factor PCC</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>4-factor PCC</td>
<td>Possible</td>
<td>Possible</td>
<td>Possible</td>
</tr>
</tbody>
</table>
Suggested strategy for management of TSOAC-associated bleeding

Risk stratification

Minor bleeding
- Local hemostatic measures
- Consider anticoagulant withdrawal (balance thrombotic and bleeding risks)

Moderate bleeding
- General measures
  - Anticoagulant withdrawal
  - Mechanical compression
  - Monitor hemodynamic status
  - Volume replacement
  - Definitive interventions
- Blood product transfusion
  - RBC transfusion for anemia
  - Plasma for coagulopathy (e.g., DIC, dilutional)
  - Consider platelets for patients on antiplatelet agents

Severe/life-threatening bleeding
- General measures and blood product transfusion as per moderate bleeding
  - Intensive care setting
  - Hemodynamic support
  - Consider:
    - 4-factor PCC (50 U/kg)*
    - Activated PCC (80 U/kg)**
- Adjunctive therapies
  - Oral charcoal for dabigatran ingestion within 2 hours
  - Hemodialysis for dabigatran removal
  - Desmopressin
  - Antifibrinolytic agents

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Siegal D M et al. Blood 2014;123:1152-1158
How would you manage this patient?

71 year old female on dabigatran for AF admitted for MI then develops cardiogenic shock/respiratory failure and acute renal failure (BUN/Cr 54/2.6) with marked bleeding at time of intubation with PT 40.6 sec and PTT 60 sec

1. Immediate dialysis
2. DDAVP
3. Kcentra 50 u/kg
The Future - Antibody reversal of the NOACs

Idarucizumab > dabigatran

- Phase III study assessing the direct reversal of dabigatran with the antibody idarucizumab in patients with severe bleeding or emergency surgery has just started recruitment
  - http://clinicaltrials.gov/show/NCT02104947?link_type=CLINITRIALGOV&access_num=NCT02104947

Abdexanet > riviroxaban

- Phase II study completed with the antibody PRT064445 against direct/indirect factor Xa inhibitors in healthy volunteers has been completed
  - Phase III planned - ClinicalTrials.gov identifier:NCT1758432
The Future-Monitoring

• tandem mass spectrometry
• functional coagulation assay-
  – dilute thrombin time
  • Anticipate a NYS approved test in the next 1-2 years
## New oral anticoagulant scorecard

<table>
<thead>
<tr>
<th><strong>Plus</strong></th>
<th><strong>Minus</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid onset of action – can use for initial Rx, no bridging</td>
<td>Risk of bleeding in patients with impaired kidney function</td>
</tr>
<tr>
<td>Short half-life- “can turn on and off”</td>
<td>Short half-life → greater risk of treatment failure with missed doses?</td>
</tr>
<tr>
<td>Fewer drug/No known food interactions</td>
<td>Cannot titrate dose</td>
</tr>
<tr>
<td>Less genetic variation in dose-response- predictable effect</td>
<td>Harder to determine compliance or overdose</td>
</tr>
<tr>
<td>No routine monitoring, fixed dose</td>
<td>Rebound effect</td>
</tr>
<tr>
<td>Patient/Doctor convenience</td>
<td>No specific antidote or reversing agent</td>
</tr>
<tr>
<td></td>
<td>Cost</td>
</tr>
</tbody>
</table>