Direct Oral Anticoagulants:
*Pearls & Pitfalls*

South Carolina ACP Chapter Meeting
Oct 26, 2019

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DISCLOSURES

- Desai Pharmaceuticals – research funding
- Pfizer / BMS – research funding
- BMS – funding for Afib educational module
GOALS

• Review data for novel anticoagulants
• Identify ideal patients for whom the newer agents may be appropriate
• Understand the contraindications and limitations of new anticoagulants
• Identify patients who may benefit from a reversal agent

DOACs vs NOACs

Recommendation on the nomenclature for oral anticoagulants: communication from the SSC of the ISTH

Scope and methodology

Oral anticoagulants are used to prevent and treat a wide range of thromboembolic diseases. Currently available oral anticoagulants include the vitamin K antagonists (VKAs), such as warfarin. VKAs reduce the synthesis of functional vitamin K-dependent factors (Factor II, FV, FVII, FIX, FX, as well as protein C and protein S) by interfering with the vitamin K cycle. The newer oral anticoagulant (DOACs) have advantages over VKAs (i.e., no need for regular monitoring, less risk of major bleeding, and shorter time to achieve steady-state levels). DOACs have been shown to be effective in reducing the risk of stroke and systematic thromboembolic events compared to VKAs. However, unlike VKAs, DOACs are not metabolized by the cytochrome P450 enzyme system and are not affected by cytochrome P450-inducing drugs. DOACs should be used with caution in patients with severe renal impairment or severe liver disease.
Who Am I?

- I am a 37 year old athlete.
- I am an American female.
- I have won 23 major championships in my sport.
- My sister is pretty good too.

Morbidity/Mortality

- Morbidity of untreated VTE
  - Pulmonary embolism/death
  - Recurrent DVT/PE
  - Post-thrombotic syndrome

- Thromboembolic CVA
Warfarin

![Diagram of Warfarin mechanism](image)

- **Warfarin**
- Prothrombin Precursor
- Glutamic Acid
- Prothrombin
- y-Carboxy-Glutamic Acid
- Reduced Vitamin K
- Oxidized Vitamin K
- Vitamin K Epoxide Reductase
- VKORC1 A*A*
- Cytochrome P2C9 (CYP2C9)
- Cytochrome P1A2
- Cytochrome P3A4
- Cytochrome P2C19

**Diagram Description**

1. **Prothrombin Precursor** (Glutamic Acid)
2. **Prothrombin**
3. **y-Carboxy-Glutamic Acid**
4. **Reduced Vitamin K**
5. **Oxidized Vitamin K**
6. **Vitamin K Epoxide Reductase**
7. **VKORC1 A*A**
8. **Cytochrome P2C9 (CYP2C9)**
9. **Cytochrome P1A2**
10. **Cytochrome P3A4**
11. **Cytochrome P2C19**
**Warfarin - Pharmacogenomic Dosing**

A Pharmacogenetic versus a Clinical Algorithm for Warfarin Dosing - NEJM 2013

- Dosing based on genotyping plus clinical variables vs clinical variables only
- Primary outcome – Time in the therapeutic INR range from day 5 through day 28
- Randomized 1015 patients at 18 U.S. centers


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**Warfarin - Pharmacogenomic Dosing**

**Pharmacogenetic dose-initiation algorithm**

Estimated daily dose, mg/day:

\[
\exp[0.9751 - (0.2066 \times \text{CYP2C9*2})
- (0.4008 \times \text{CYP2C9*3})
- (0.3238 \times \text{VKORC1})
- (0.00745 \times \text{age in years})
- (0.0901 \times \text{black race})
+ (0.0922 \times \text{smokes})
+ (0.4317 \times \text{body surface area})
- (0.2538 \times \text{amiodarone use})
+ (0.2029 \times \text{target INR})
+ (0.0664 \times \text{DVT/PE indication})]
\]

**Clinical dose-initiation algorithm**

Estimated daily dose, mg/day:

\[
\exp[0.613 - (0.0075 \times \text{age in years})
+ (0.156 \times \text{black race})
+ (0.108 \times \text{smokes})
+ (0.425 \times \text{body surface area})
- (0.257 \times \text{amiodarone use})
+ (0.216 \times \text{target INR})
+ (0.0784 \times \text{DVT/PE indication})]
\]

### Table 1. Percentage of Time in the Therapeutic INR Range through Week 4 of Therapy, According to Subgroup.7

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Patients</th>
<th>Genotype-Guided Group</th>
<th>Clinically-Guided Group</th>
<th>Mean Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>955</td>
<td>45.2±20.6</td>
<td>45.4±25.8</td>
<td>-0.2 (-3.4 to 3.1)</td>
<td>0.915</td>
</tr>
</tbody>
</table>

*Patient reported pain intensity between algorithms in predicted dose:

- ≥1.0 mg/dy: 392 45.1±25.5 46.5±27.1 -1.4 (-6.2 to 4.0) 0.67
- <1.0 mg/dy: 563 45.2±27.4 44.7±24.8 0.5 (-3.7 to 4.8) 0.81

<table>
<thead>
<tr>
<th>Prespecified subgroup analyses</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race</td>
<td>0.00♂</td>
</tr>
<tr>
<td>Black</td>
<td>0.01♀</td>
</tr>
<tr>
<td>Nonblack</td>
<td>0.13♀</td>
</tr>
<tr>
<td>Sex</td>
<td>0.1♀</td>
</tr>
<tr>
<td>Male</td>
<td>0.3♀</td>
</tr>
<tr>
<td>Female</td>
<td>0.00♀</td>
</tr>
<tr>
<td>Total no. of genetic variants</td>
<td>0.01♀</td>
</tr>
<tr>
<td>1</td>
<td>0.1♀</td>
</tr>
<tr>
<td>0 or &gt;1 variant</td>
<td>0.4♀</td>
</tr>
</tbody>
</table>

* N=1650
* Patients ≥65 years undergoing TKA/THA
* Randomized to clinical or pharmacogenomic dosing

Genetic and clinical dosing algorithms programmed into WarfarinDosing.org

**Polymorphisms:**

- *VKORC1* **-1639 G>A, dbSNP rs9923231**
- *CYP2C9* **430C>T, dbSNP rs1799853**
- *CYP2C9* **1075A>C, dbSNP rs1057910**
- *CYP4F2* **V433M, 1297G>A, dbSNP rs2108622**

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**GIFT - Results**

Table 1. Components of the Composite Primary End Point

<table>
<thead>
<tr>
<th>Component</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
<th>Absolute Difference</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding on days 1-30</td>
<td>2 (0.2)</td>
<td>5 (1.3)</td>
<td>0.8 (0.2 to 1.8)</td>
<td>0.25 (0.03 to 1.15)</td>
</tr>
<tr>
<td>Death or MI at 30 days</td>
<td>1 (0.1)</td>
<td>2 (0.5)</td>
<td>1.0 (0.3 to 2.1)</td>
<td>0.17 (0.01 to 2.7)</td>
</tr>
</tbody>
</table>


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LMWH vs Heparin
*Meta-analyses of DVT Treatment*

- Decreased recurrences for LMWH  RRR 31% (P<.05)
- Less major bleeding for LMWH  RRR 42% (P<.05)
- Decreased mortality for LMWH  RRR 23% (P<.05)

*Van Dongen CJ. The Cochrane Collaboration. 2004.*

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**Dabigatran versus Warfarin - Acute VTE**

**RECOVER**

- DVT or PE, N = 2539
- 228 hospitals in 29 countries
- All patients receive LMWH or IV heparin
- Randomized to warfarin vs dabigatran 150mg BID

Dabigatran versus Warfarin in the Treatment of Acute Venous Thromboembolism


Rivaroxaban

DVT TREATMENT - EINSTEIN

- Oral direct factor Xa inhibitor, no monitoring
- Rivaroxaban 15mg twice daily x 3 weeks then 20mg daily
- Compared with LMWH/warfarin
- N = 3,449

VTE
Enox/warb  3.0%  p=NS
Riva       2.1%

VTE
Placebo  7.0%  p<.01
Riva      1.3%

Major / Clin relevant bleeding
Placebo  1.2%  p<.01
Riva      6.0%

EINSTEIN PE TRIAL
Apixaban
VTE TREATMENT - AMPLIFY

- N= 5400 (65% DVT, 35% PE)
- Apixaban 10mg bid x 7 days followed by 5mg BID x 6 months
- Compared with SC LMWH / warfarin
- Primary endpoint: Recurrent sx VTE or VTE related death

Agnelli G. NEJM. 2013;369:1799-808.

Table 2. Clinical Outcomes during the Intended Treatment Period.4

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Apixaban (N=2690)</th>
<th>Conventional Therapy (N=2700)</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy 1st recurrent VTE or VTE-related death</td>
<td>10 (0.4)</td>
<td>20 (0.8)</td>
<td>0.51 (0.37-0.70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Type of first recurrent VTE — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fetal PE</td>
<td>2 (0.1)</td>
<td>3 (0.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>death for which PE could not be ruled out</td>
<td>11 (0.4)</td>
<td>13 (0.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>death from PE with or without DVT</td>
<td>27 (1.0)</td>
<td>23 (0.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DVT only</td>
<td>14 (0.5)</td>
<td>13 (0.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safety</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding — no. (%)</td>
<td>13 (0.5)</td>
<td>48 (1.8)</td>
<td>0.31 (0.17-0.50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Type of major bleeding — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fetal PE</td>
<td>7 (0.3)</td>
<td>2 (0.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>death for which PE could not be ruled out</td>
<td>3 (0.1)</td>
<td>6 (0.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>intracranial</td>
<td>3 (0.1)</td>
<td>9 (0.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>retroperitoneal</td>
<td>1 (0.1)</td>
<td>3 (0.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>intrarachisitic</td>
<td>0</td>
<td>1 (0.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>intravascular</td>
<td>0</td>
<td>2 (0.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>intramuscular</td>
<td>0</td>
<td>2 (0.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other (subcutaneous/soft tissue)</td>
<td>12 (0.6)</td>
<td>33 (1.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular bleeding</td>
<td>7 (0.3)</td>
<td>18 (0.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurological deficit</td>
<td>1 (0.1)</td>
<td>2 (0.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epistaxis</td>
<td>1 (0.1)</td>
<td>1 (0.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urogenital bleeding</td>
<td>3 (0.2)</td>
<td>3 (0.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subcutaneous hematoma</td>
<td>1 (0.05)</td>
<td>2 (0.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinically relevant nonmajor bleeding — no. (%)</td>
<td>30 (1.2)</td>
<td>215 (8.0)</td>
<td>0.41 (0.20-0.86)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Major bleeding or clinically relevant nonmajor bleeding — no. (%)</td>
<td>313 (12.3)</td>
<td>261 (9.7)</td>
<td>0.44 (0.36-0.55)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death during intended treatment period</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients/misc. no. (%)</td>
<td>41 (0.76%)</td>
<td>52 (0.96%)</td>
<td>0.79 (0.55-1.13)</td>
<td></td>
</tr>
<tr>
<td>Cause of death — no. total no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT or PE not ruled out</td>
<td>12 (0.67%)</td>
<td>16 (0.61%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular cause</td>
<td>36 (0.97%)</td>
<td>7 (0.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding</td>
<td>2 (0.67%)</td>
<td>3 (0.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>14 (0.67%)</td>
<td>16 (0.61%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infectious disease</td>
<td>5 (0.67%)</td>
<td>7 (0.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Clinical and Safety Outcomes Associated With Treatment of Acute Venous Thromboembolism: A Systematic Review and Meta-analysis

Lana A. Cassilett, MD, Chris Cameron, MSc, Grégory Le Gall, MD, PhD, Marc A. Rodger, MD, MSc, Douglas Cleeland, PhD, Philip S. Wells, MD, MSc, Tammy Clifford, PhD, Christine Cormier, MD, MSc, George Wells, PhD, Marc Carrier, MD, MSc

**Importance:** Many anticoagulant strategies are available for the treatment of acute venous thromboembolism, yet little guidance exists regarding which drug is most effective and safe.

**Objective:** To summarize and compare the efficacy and safety outcomes associated with 8 anticoagulation options (unfractionated heparin [UFH], low-molecular-weight heparin [LMWH], or fondaparinux in combination with vitamin K antagonists), LMWH with dabigatran or edoxaban, rivaroxaban, apixaban, and LMWH alone) for treatment of venous thromboembolism.

**Data Sources:** A systematic literature search was conducted using MEDLINE, EMBASE, and the evidence-based medicine reviews from inception through February 28, 2014.

**Study Selection:** Eligible studies were randomized trials reporting rates of recurrent venous thromboembolism and major bleeding in patients with acute venous thromboembolism. Of the 197 studies identified, 43 studies including 64,989 patients were included in the analyses.

**Data Extraction and Synthesis:** Two reviewers independently extracted trial-level data including number of patients, duration of follow-up, and outcomes. The data were pooled using network meta-analysis.

**Main Outcomes and Measures:** The primary clinical and safety outcomes were recurrent venous thromboembolism and major bleeding, respectively.

**Results:** Compared with the LMWH-vitamin K antagonist combination, a treatment strategy...

### Recurrent venous thromboembolism and major bleeding

<table>
<thead>
<tr>
<th>Comparator Treatment</th>
<th>Hazard Ratio (95% Credible Interval)</th>
<th>Favors Comparator Treatment</th>
<th>Favors Low-Molecular Weight Heparin + Vitamin K Antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unfractionated heparin + vitamin K antagonist</td>
<td>1.42 (1.15-1.80)</td>
<td>Prioritize</td>
<td></td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fondaparinux + vitamin K antagonist</td>
<td>1.19 (0.90-1.58)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-molecular-weight heparin + dabigatran</td>
<td>1.01 (0.65-1.62)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-molecular-weight heparin + edoxaban</td>
<td>1.07 (0.65-1.70)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>0.83 (0.46-1.49)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>0.84 (0.51-1.39)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Recurrent venous thromboembolism by index event

<table>
<thead>
<tr>
<th>Comparator Treatment</th>
<th>Hazard Ratio (95% Credible Interval)</th>
<th>Favors Comparator Treatment</th>
<th>Favors Low-Molecular Weight Heparin + Vitamin K Antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unfractionated heparin + vitamin K antagonist</td>
<td>1.74 (1.27-2.45)</td>
<td>Prioritize</td>
<td></td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Additional context

[Supplemental context at jama.com]
In patients with VTE and no cancer, for the first 3 months of anticoagulant therapy we suggest dabigatran, rivaroxaban, apixaban, or edoxaban over vitamin K antagonist (VKA) therapy (Grade 2B)


Outpatient PE Treatment - HESTIA

LMWH/VKA
N = 297

<table>
<thead>
<tr>
<th>Hestia Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>In the patient hemodynamically unstable?</td>
</tr>
<tr>
<td>Is thrombolytic or embolotherapy necessary?</td>
</tr>
<tr>
<td>Active bleeding or high risk for bleeding?</td>
</tr>
<tr>
<td>More than 24 hours of oxygen supply to maintain oxygen saturation &gt;90%?</td>
</tr>
<tr>
<td>Is pulmonary embolism diagnosed during anticoagulant treatment?</td>
</tr>
<tr>
<td>Severe pain needing intravenous pain medication for more than 24 hours?</td>
</tr>
<tr>
<td>Medical or social reason for treatment in the hospital for more than 24 hours? (infection, malignancy, no support system)</td>
</tr>
<tr>
<td>Does the patient have a creatinine clearance of less than 30 mL/min?</td>
</tr>
<tr>
<td>Does the patient have severe liver impairment?</td>
</tr>
<tr>
<td>Is the patient pregnant?</td>
</tr>
<tr>
<td>Does the patient have a documented history of hepatic induced thrombocytopenia?</td>
</tr>
<tr>
<td>If one or the questions is answered with YES, the patient can not be treated as usual in the Hestia study</td>
</tr>
</tbody>
</table>

**Table 3 Adverse clinical outcome during 3 months of follow-up (n = 297)**

<table>
<thead>
<tr>
<th>Clinical outcome</th>
<th>No.</th>
<th>Percentage (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total recurrences</td>
<td>6</td>
<td>2.0 (0.75-4.3)</td>
</tr>
<tr>
<td>Fatal recurrent PE</td>
<td>0</td>
<td>0 (0-1.2)</td>
</tr>
<tr>
<td>Non-fatal recurrent PE</td>
<td>5</td>
<td>1.7 (0.55-3.9)</td>
</tr>
<tr>
<td>Non-fatal recurrent DVT</td>
<td>1</td>
<td>0.34 (0.008-2.19)</td>
</tr>
<tr>
<td>Major bleeding complications</td>
<td>2</td>
<td>0.67 (0.082-2.4)</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>1</td>
<td>0.34 (0.008-2.19)</td>
</tr>
<tr>
<td>Non-fatal major bleeding</td>
<td>1</td>
<td>0.34 (0.008-2.19)</td>
</tr>
<tr>
<td>Clinically relevant non-major bleeding</td>
<td>15</td>
<td>5.1 (2.9-8.2)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>3</td>
<td>1.0 (0.21-2.9)</td>
</tr>
</tbody>
</table>

Outpatient PE Treatment

- Acute PE with low PE Risk Score
- RCT - 19 hospitals in Europe and US, N = 344
- Randomized to home vs hospital-based acute care
- Received LMWH plus VKA
- Primary outcome: Recurrence at 90 days


Pulmonary Embolism Severity Index

<table>
<thead>
<tr>
<th>Condition</th>
<th>Score Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age +1 per year</td>
<td>+1 per year</td>
</tr>
<tr>
<td>Male sex</td>
<td>+10</td>
</tr>
<tr>
<td>Cancer</td>
<td>+30</td>
</tr>
<tr>
<td>CHF</td>
<td>+10</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>+10</td>
</tr>
<tr>
<td>Pulse ≥110</td>
<td>+20</td>
</tr>
<tr>
<td>SBP &lt;100</td>
<td>+30</td>
</tr>
<tr>
<td>RR ≥30</td>
<td>+20</td>
</tr>
<tr>
<td>Temperature &lt;36°C</td>
<td>+20</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>+60</td>
</tr>
<tr>
<td>O2 saturation &lt;90%</td>
<td>+20</td>
</tr>
</tbody>
</table>

**SCORE**

- <66 I
- 66–85 II
- 86–105 III
- 106–125 IV
- >125 V

### Outpatient PE Treatment - Rivaroxaban

**PE patients - Premier Database**  
**Primary dx code 415.1x**  
**11/2012 - 9/2015**

Rivaroxaban (allowed ≤2 days of parenteral therapy) 1:1 propensity score matched to patients parenterally bridged to warfarin

#### Outcomes:
- LOS, total cost, readmission for VTE or major bleeding w/in 2 months
Outpatient PE Treatment - Rivaroxaban

PE patients - Premier Database
2012 – 2015
N = 8800

RESULTS

- Rivaroxaban 1.4-day shorter LOS and $2322 less cost compared to parenterally bridged warfarin
- No difference in readmission for VTE (1.5 versus 1.7 %) or major bleeding (0.3 versus 0.2 %)


Outpatient PE Treatment

Retrospective review
N = 1081

Outpatient PE Treatment

*Chest - Patient Selection*

In patients with low-risk PE and whose home circumstances are adequate, we suggest treatment at home or early discharge over standard discharge (Grade 2B)

✓ Clinically stable, good cardiopulmonary reserve
✓ No contraindications - recent bleeding, severe renal/liver disease, severe thrombocytopenia
✓ Expected to be compliant
✓ Feels well enough to be treated at home


---

Outpatient PE Treatment

- PESI <85 or simplified PESI 0 can help identify low-risk patients
- Do not require patients to have a predefined score
- Routine RV or biomarker testing is not indicated
- If identified, RV dysfunction or increased biomarker levels suggest poorer prognosis
Acute PE

Systemic Anticoagulation

Are any of the following PRESENT?
- SBP <100 mm Hg
- O2 Sat <90%
- Altered mental status
- Syncope

NO

YES

Massive PE
STAT Pulmonary Consult

NO

Obtain TTE and Troponin OR BNP
High-risk features present?***

YES

Submassive PE
Consider Specialty Consult

NO

PESI Score

Low risk PE
PESI CLASS I-II

GFR ≥30 ml/min

NO

YES

Discharge Home* Riva/Apixaban OR enoxaparin/warfarin

Admit for Bridging UFH with warfarin (start day 0)

SBP <90 mmHg for 15 minutes OR on vasopressors?

YES

PESI at 48hrs
PESI I&II => Follow Low Risk PE   PESI III => Cont. Current Mmg.
PESI ≥4 => Follow Submassive PE

NO

PESI Score

Low risk PE
PESI CLASS I-II

GFR ≥30 ml/min

YES

Admit for Bridging UFH with warfarin (start day 0)

NO

PESI at 48hrs
PESI I&II => Follow Low Risk PE   PESI III => Cont. Current Mmg.
PESI ≥4 => Follow Submassive PE

Low Risk PE
PESI CLASS I-III

PESI at 48hrs
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Discharge Home* Riva/Apixaban OR enoxaparin/warfarin
Outpatient Treatment of VTE

Non-clinical considerations

- Patient compliance, health literacy
- Home situation - domiciled, clean, close
- Ability to administer the medication
- Insurance status
  - ✓ pay for med
  - ✓ co-pay - short or long-term therapy
- Outpatient follow-up

Now what?

Duration of Treatment, 1st unprovoked VTE

Key Considerations:

- Risk of recurrence
- Risk of major bleeding
- Risk of waiting for the next recurrence
- Guidelines
- Well, what do you want to do?
- I’m just the hospitalist, go ask your PCP
**Apixaban**
- Reduced VTE
- No increase in bleeding

**Rivaroxaban**
- Reduced VTE
- No increase in bleeding
- LMWH x 5 days then randomized
- Edoxaban 60mg daily vs Dalteparin x 6-12 months
- Primary outcome: Recurrent VTE or major bleeding, 12 months


VTE Treatment – Cancer Patients

Table 3: Clinical Outcomes during the Overall Trial Period

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Edoxaban (N=122)</th>
<th>Dalteparin (N=126)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent venous thromboembolism or major bleeding — no. (%)</td>
<td>47 (38.3)</td>
<td>73 (58.5)</td>
<td>0.47 (0.27-0.82)</td>
<td>0.014</td>
</tr>
<tr>
<td>Recurrent venous thromboembolism — no. (%)</td>
<td>41 (7.0)</td>
<td>39 (2.3)</td>
<td>0.46 (0.26-0.80)</td>
<td>0.009</td>
</tr>
<tr>
<td>Major bleeding — no. (%)</td>
<td>36 (3.9)</td>
<td>21 (4.9)</td>
<td>0.77 (0.40-1.50)</td>
<td>0.526</td>
</tr>
</tbody>
</table>

An Ounce of Prevention?

Betrixaban for Extended Prophylaxis for Medical Patients - APEX

- Enoxaparin 40mg daily x 10 days vs Betrixaban 80mg daily x 35-42 days
- Inclusion criteria narrowed mid-trial
- 3 cohorts: elevated d-dimer, d-dimer or age >75, or total population
- Primary outcome: Asymptomatic prox VTE or sx VTE

**Primary Outcome:** 6.9% vs 8.5%, p=.054

**Major or CRNMB:** 3.1% vs 1.9%, p<.001

Rivaroxaban for Extended Prophylaxis for Medical Patients - MARINER

- Increased risk (IMPROVE score ≥4 or 2-3 with elevated d-dimer)
- Rivaroxaban 10mg vs placebo for 45 days
- Primary outcome: Symptomatic VTE or fatal VTE


Afib - Who Am I?

- I am an American singer and bass player.
- I am male and was born in 1949.
- Jewish but never called a “nice Jewish boy.”
- Recently inducted in the Rock and Roll Hall of Fame with friends Ace, Peter, and Paul.
- Considers “Rock City” to be Detroit.
in major hemorrhage attributed to antithrombotic therapy (Tables 6 and 8). We were unable to define the relative value of aspirin compared with warfarin because too few events occurred in the warfarin and aspirin arms of group 1 to allow meaningful direct comparison. Indirect comparison of the magnitude of reduction in primary events in those assigned to warfarin (67%) versus all patients (groups 1 and 2 a perceived requirement for antithrombotic therapy (i.e., placebo treatment unacceptable) such as recent myocardial infarction, stroke, unstable angina, prosthetic cardiac valves, and so on. We believe that our results are generalizable to the substantial proportion of excluded patients who were eligible but refused entry, because their clinical features were similar to those of patients who entered the trial.

**RELY**

*Randomized Evaluation of Long-term Anticoagulation*

Dabigatran vs warfarin in afib

Dabigatran 110mg BID, 150mg BID, warfarin 2.0-3.0

N = 18,113. 950 sites in 44 countries.

**INCLUSION**

- Afib on ecg or within 6 months
- ≥1 CVA RF (age >75, prior TIA/CVA, EF <40% or CHF sx)


Table 3. Safety Outcomes, According to Treatment Group.

<table>
<thead>
<tr>
<th>Event</th>
<th>Displegase, 110 mg</th>
<th>Displegase, 150 mg</th>
<th>Warfarin</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>322</td>
<td>271</td>
<td>375</td>
<td>357</td>
<td>3.39</td>
<td>0.40 (0.49-0.99)</td>
<td>0.035</td>
<td>0.53 (0.43-0.67)</td>
<td>0.51</td>
</tr>
<tr>
<td>Life-threatening</td>
<td>345</td>
<td>175</td>
<td>143</td>
<td>222</td>
<td>1.80</td>
<td>0.08 (0.53-0.93)</td>
<td>&lt;0.001</td>
<td>0.82 (0.66-0.97)</td>
<td>0.04</td>
</tr>
<tr>
<td>Non-life-threatening</td>
<td>198</td>
<td>1.66</td>
<td>216</td>
<td>208</td>
<td>1.76</td>
<td>0.34 (0.78-0.78)</td>
<td>0.56</td>
<td>1.67 (0.89-2.20)</td>
<td>0.47</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>222</td>
<td>1.13</td>
<td>152</td>
<td>129</td>
<td>0.82</td>
<td>1.00 (0.86-1.14)</td>
<td>0.98</td>
<td>1.30 (0.94-1.80)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Major or minor bleeding</td>
<td>1340</td>
<td>14.62</td>
<td>1917</td>
<td>15.84</td>
<td>10.37</td>
<td>0.70 (0.74-0.86)</td>
<td>&lt;0.001</td>
<td>0.51 (0.43-0.61)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>27</td>
<td>0.24</td>
<td>36</td>
<td>0.50</td>
<td>0.74</td>
<td>0.51 (0.20-0.91)</td>
<td>&lt;0.001</td>
<td>0.40 (0.27-0.60)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>269</td>
<td>2.51</td>
<td>340</td>
<td>2.84</td>
<td>1.95</td>
<td>0.94 (0.83-1.00)</td>
<td>0.45</td>
<td>1.07 (0.92-1.23)</td>
<td>0.48</td>
</tr>
<tr>
<td>Net clinical benefit-outcome</td>
<td>851</td>
<td>7.09</td>
<td>852</td>
<td>6.91</td>
<td>0.91</td>
<td>0.92 (0.84-1.00)</td>
<td>0.15</td>
<td>0.53 (0.42-0.68)</td>
<td>0.024</td>
</tr>
</tbody>
</table>

1 Data are shown for all patients who had at least one event. All analyses were based on the time to the first event. Hemorrhagic stroke was a subcategory of stroke in the efficacy analysis and in the safety analysis is also counted as major, life-threatening bleeding and as part of gastrointestinal bleeding.
2 The net clinical benefit outcome was the composite of stroke, systemic embolism, pulmonary embolism, myocardial infarction, death, major bleeding.
Rivaroxaban - ROCKET

- Rivaroxaban 20mg daily vs Warfarin
- N = 14,264
- Afib and ≥2 stroke risk factors
- Primary Outcome: Stroke (ischemic or hemorrhagic) or systemic TE
- Median Follow-up 1.9 years
- INR therapeutic 55% TTR


Rivaroxaban - ROCKET

- No difference in CVA or systemic embolism
- No difference in major bleeding (3.6% vs 3.4%)
- Increased GI bleeding (3.2% vs 2.2%)
- Decreased intracranial hemorrhage (0.5% vs 0.7%)

Apixaban - ARISTOTLE

- Compared apixaban 5mg BID vs Warfarin INR 2.0-3.0
- N = 18,201
- Patients with afib and $\geq 1$ stroke risk factor
- Primary Outcome: Stroke (ischemic or hemorrhagic) or systemic embolism
- Median Follow-up: 1.8 years


Apixaban - ARISTOTLE

- Decreased stroke
- Decreased major bleeding
- Decreased mortality
- Decreased ICH

CASE - A Fib

The patient is a 78 year-old man with a history of htn, DM, CAD, CHF, OA. He is admitted for cellulitis and noted to be in Afib. Afib persists throughout a prolonged hospitalization.

He has been noncompliant with his DM medications. Hb A1c is 10.4.

CHADS-VASC
1 - CHF
1 – htn
2 – Age ≥75
1 – DM
2 – Stroke/TIA
1 – Vascular disease
1 - Age 65-75
1 - Sex Category F

What treatment strategy would you choose?

- Aspirin
- Warfarin
- DOAC
- Referral to Cardiology, Hematology, Neurology, and Cardothoracic Surgery

Apixaban - AVERROES

Patients “unsuitable” for VKA

Compared apixaban 5mg BID vs ASA
N = 5599

UNSUITABLE - REASONS
Prior or presumed difficulty with INR
- diff maintaining therapeutic range 17%
- unable to measure INR adequately 43%
- uncertain adherence 16%
- patient refusal 38%
CHADS = 1 (only reason) 11%
Multiple 51%

Apixaban vs Asa

1.6% 3.7%
P<.05

No. at Risk
Aspirin
Apixaban
2791
2758
2716
2546
1932
3543
3512
2125
2155
528
615

A Stroke or Systemic Embolism
Hazard ratio with apixaban, 0.45
(95% CI, 0.32-0.66)
Apixaban
Aspirin

B Major Bleeding
Hazard ratio with apixaban, 1.13
(95% CI, 0.74-1.75)
Apixaban
Aspirin

P<.05

15,526 patients with ACS

- All patients receive asa ± thienopyridine
- Rivaroxaban 2.5mg or 5mg BID vs placebo for 13-31 months
- Primary end point - Composite of CV death, MI, CVA

Stable CAD

27,395 patients

Randomized to:
- asa 100mg
- riva 5mg BID
- asa 100mg + riva 2.5mg BID

Primary outcome: Death, CVA, or MI

Stable CAD - COMPASS


<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rivaroxaban plus Aspirin (N=9152)</th>
<th>Rivaroxaban Alone (N=9128)</th>
<th>Aspirin Alone (N=9128)</th>
<th>Rivaroxaban plus Aspirin vs Aspirin Alone</th>
<th>Rivaroxaban Alone vs Aspirin Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome: CV death, stroke, or myocardial infarction</td>
<td>375 (4.1)</td>
<td>418 (4.5)</td>
<td>496 (5.4)</td>
<td>0.74 (0.56-1.00)</td>
<td>0.06</td>
</tr>
<tr>
<td>Ischemic stroke, myocardial infarction, or death from CHF</td>
<td>826 (9.1)</td>
<td>932 (9.4)</td>
<td>1029 (11.3)</td>
<td>0.72 (0.53-0.98)</td>
<td>0.06</td>
</tr>
<tr>
<td>Ischemic stroke, myocardial infarction</td>
<td>480 (5.3)</td>
<td>513 (5.6)</td>
<td>614 (7.0)</td>
<td>0.74 (0.54-1.00)</td>
<td>0.06</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>313 (4.4)</td>
<td>544 (6.0)</td>
<td>137 (4.8)</td>
<td>0.82 (0.71-0.96)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

MAJOR BLEEDING
Asa 1.9%
Riva+Asa 3.1%
P<.01

Breaking news from The Journal of Glass Half-Full Medicine

Rivaroxaban bonus: Early unmasking of occult GI cancers

Publish date: September 22, 2018
By Bruce Jancin, Internal Medicine News

MUNICH – The increased risk of major GI bleeding documented with dual-antiplatelet therapy using rivaroxaban and aspirin when compared with aspirin alone for vascular protection in the previously reported massive COMPASS trial may turn out to be a blessing in disguise.

That’s because a new secondary analysis of COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies), a randomized trial...
The Afib with PCI Conundrum

PIioneer AF PCI Trial

- Warfarin + DAPT
- Low dose rivaroxaban (15mg daily) + Thienopyridine
- “Too low dose” rivaroxaban (2.5mg BID) + DAPT

Primary endpoint: Clinically significant bleeding (major bleeding, minor bleeding requiring medical attention)
N = 2124


Warfarin+DAPT (Group 3) increased bleeding

No difference in MACE

DOAC
CAUTIONS / LIMITATIONS

▪ Renal insufficiency

▪ Lack of reversibility

▪ Cost
**RENAL INSUFFICIENCY / ESRD**

Dabigatran - Usual Afib dose: 150mg BID
   - GFR 15-30: 75mg BID******
   - GFR <15: Not recommended

Rivaroxaban – *VTE Prophylaxis*
   - GFR <30: Not recommended

Rivaroxaban – Usual Afib dose 20mg daily
   - GFR 30-50 mL/min: 15mg daily
   - GFR <30: Not recommended

Apixaban – *Atrial fibrillation*
   - GFR <25: Excluded

**LIMITATIONS**

- Renal insufficiency
- **Lack of reversibility**
- Cost
**Implications of Irreversibility**

<table>
<thead>
<tr>
<th></th>
<th>ATRIAL FIBRILLATION</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VKA</td>
<td>DOAC</td>
<td>NNT</td>
</tr>
<tr>
<td>Fatal Bleeding</td>
<td>0.51%</td>
<td>0.27%</td>
<td>419</td>
</tr>
<tr>
<td>Case Fatality Rate</td>
<td>8.3%</td>
<td>5.8%</td>
<td>39</td>
</tr>
</tbody>
</table>

**VENOUS THROMBOEMBOLISM**

<table>
<thead>
<tr>
<th></th>
<th>VKA</th>
<th>DOAC</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal Bleeding</td>
<td>0.16%</td>
<td>0.06%</td>
<td>978</td>
</tr>
<tr>
<td>Case Fatality Rate</td>
<td>9.3%</td>
<td>5.2%</td>
<td>NS</td>
</tr>
</tbody>
</table>

11 trials
N = 100,324

---

**4-Factor PCC in Patients on VKA with Major Bleeding**

Randomized to 4F-PCC or FFP

Primary analyses:
- 24-hour hemostatic efficacy
- INR correction (≤1.3) at 30 minutes

N = 202 patients

Median INR 3.9 (1.8–20.0) PCC group and 3.6 (1.9–38.9) for FFP group
RESULTS

- Effective hemostasis achieved in 72% and 65% of patients, demonstrating noninferiority
- Rapid INR reduction was achieved in 62% of patients receiving 4F-PCC versus 9% receiving FFP (P<.05)
- Coagulation factors higher in the PCC group from 0.5 to 3 hours after infusion start (P<0.02)
- No diff - adverse events, TE, deaths
9.3. For patients with VKA-associated major bleeding, we suggest rapid reversal of anticoagulation with 4-factor prothrombin complex concentrate rather than with plasma (2C).


4-Factor PCC for DOAC Bleeding

4F-PCC vs placebo in volunteers given anti-FXa inhibitor

Edoxaban 60mg vs Placebo, N=93

Punch biopsy - Bleeding duration corrected with 4F-PCC (50 U/kg)

GROUP A: Serious bleeding (n=301)
GROUP B: Urgent procedure (n=202)


Median percentage reversal at 4 hours: 100%

Group A
Median time to bleeding cessation: 2.5 hours

Group B
Normal intra-operative hemostasis: 93%

Thrombotic events (90d): 7%
Reversal Agents

Factor Xa Inhibitors

Andexanet alfa: F-Xa Inhibitor Antidote

- Factor Xa decoy - Targets and sequesters Factor Xa inhibitors
- Factor Xa inhibitors unable to bind to native Factor Xa
- Demonstrated reversal of Factor Xa inhibitors by biomarkers

Original Article

Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors

Acute major bleeding
N = 67
Bolus plus 2 hour infusion

LIMITATIONS

- Renal insufficiency
- Lack of reversibility
- Cost

Cost-effectiveness of Dabigatran Compared with Warfarin

- Markov decision model
- Modeled patients >65 years without ac contraindications
- Modeled warfarin vs both doses of dabigatran
- Main outcomes: QALY, Cost and Incremental cost-effectiveness ratios

**Table 2. Projected Costs and QALYs for Patients With Nonvalvular Atrial Fibrillation, by Varying Risk for Stroke and ICH**

<table>
<thead>
<tr>
<th>Annual Stroke and ICH Rate With Warfarin, %</th>
<th>Therapy</th>
<th>Cost, $</th>
<th>QALYs</th>
<th>Marginal Cost per QALY, $</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke: 0.72 (CHADS2 score, 1); ICH: 0.74</td>
<td>Warfarin</td>
<td>129 749</td>
<td>10.72</td>
<td>Reference</td>
</tr>
<tr>
<td>Stroke: 1.2 (CHADS2 score, 1–2); ICH: 0.74</td>
<td>Warfarin</td>
<td>148 935</td>
<td>11.20</td>
<td>Reference</td>
</tr>
<tr>
<td>Stroke: 2.35 (CHADS2 score, 1–4); ICH: 0.74</td>
<td>Warfarin</td>
<td>164 576</td>
<td>10.70</td>
<td>Reference</td>
</tr>
<tr>
<td>Stroke: 1.2 (CHADS2 score, 1–2); ICH: 0.44</td>
<td>Warfarin</td>
<td>134 655</td>
<td>10.75</td>
<td>Reference</td>
</tr>
<tr>
<td>Stroke: 1.2 (CHADS2 score, 1–2); ICH: 1.48</td>
<td>Warfarin</td>
<td>158 912</td>
<td>9.39</td>
<td>Reference</td>
</tr>
<tr>
<td>Warfarin</td>
<td>169 482</td>
<td>10.05</td>
<td>16 147</td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>173 721</td>
<td>10.06</td>
<td>263 543</td>
<td></td>
</tr>
</tbody>
</table>

ICER = incremental cost-effectiveness ratio; ICH = intracranial hemorrhage; QALY = quality-adjusted life-year.
* Risk for stroke defined by CHADS2 score (range, 0 to 4). Costs are in 2008 U.S. dollars.
† Dabigatran, 110 mg, is dominated by extended dominance, meaning that it is less cost-effective than 150-mg dabigatran and the overall QALY results are lower than that of 150-mg dabigatran. For a stroke risk of 1.2%, the ICER of 110-mg dabigatran vs. warfarin was $82 746. For a stroke risk of 2.35%, the ICER of 110-mg dabigatran vs. warfarin was $82 746. For a stroke risk of 0.44%, the ICER of 110-mg dabigatran vs. warfarin was $82 746.
‡ Dabigatran, 110 mg, is dominated by extended dominance, meaning that its value in cost per QALY is less than that of 150-mg dabigatran and the overall QALY results are lower than that of 150-mg dabigatran. For an ICH risk of 0.44%, the ICER of 110-mg dabigatran vs. warfarin was $115 129. For an ICH risk of 0.74%, the ICER of 110-mg dabigatran vs. warfarin was $115 129.


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**Take Home Points**

- **ATRIAL FIBRILLATION**
  - Dabigatran decreases CVA
  - Apixaban decreases CVA, bleed, mort
  - Rivaroxaban decreases fatal/intracranial bleed

- **VTE**
  - Apixaban/rivaroxaban decrease bleeding
  - Consider indefinite low-dose apixaban/rivaroxaban

- **CAD** – Decreases cardiac events but increases bleeding

- Use antidote or 4-factor PCC for life-threatening bleeding

- Pay attention to cost and payer - society and patient
THANK YOU!

Questions?