New Oral Anticoagulants  
Management of the Hospitalized Patient  
San Francisco, CA 2014

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Update in Nomenclature

NOACs—new oral anticoagulants are now TSOACs (target specific oral anticoagulants—they won’t be new forever)

Target Specific Anticoagulants

<table>
<thead>
<tr>
<th>Warfarin</th>
<th>Newer Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Need for frequent monitoring</td>
<td>No lab testing required</td>
</tr>
<tr>
<td>Myriad of drug interactions</td>
<td>Few drug interactions</td>
</tr>
<tr>
<td>Interaction with alcohol</td>
<td>Activity independent of vitamin K—no food drug interactions</td>
</tr>
<tr>
<td>Requirement for dietary stasis</td>
<td>More predictable dose effect</td>
</tr>
<tr>
<td>Fluctuating INR is the norm</td>
<td></td>
</tr>
</tbody>
</table>

remain blank
**Target Specific Anticoagulants**

<table>
<thead>
<tr>
<th>Approval status</th>
<th>Dabigatran (Pradaxa)</th>
<th>Rivaroxaban (Xarelto)</th>
<th>Apixaban (Eliquis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOMD AFIB</td>
<td>NO</td>
<td>NO</td>
<td>NOMD AFIB</td>
</tr>
<tr>
<td>DTI</td>
<td>antiXa</td>
<td>antiXa</td>
<td>antiXa</td>
</tr>
</tbody>
</table>

| Renal metabolism | 80%                  | 30-60%                | 25%               |

**Target Specific Anticoagulants**

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran (Pradaxa)</th>
<th>Rivaroxaban (Xarelto)</th>
<th>Apixaban (n/a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TT/2 hours</td>
<td>12-17</td>
<td>S-9</td>
<td>S-15</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>--</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>t1/2</td>
<td>Yes</td>
<td>Yes</td>
<td>--</td>
</tr>
<tr>
<td>Antidote</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Monitoring</td>
<td>ECT, TT, PTT</td>
<td>PT</td>
<td>Anti Xa</td>
</tr>
</tbody>
</table>
Case
70 yo man is admitted with new onset AFIB. His PMHx is significant only for hypertension. He is on ASA for primary CAD prophylaxis. He has normal renal function. What regimen will you suggest for stroke prevention?
1. Continue ASA alone
2. ASA plus clopidigrel
3. Warfarin
4. Dabigatran
5. Rivaroxaban

NEW CHEST GUIDELINES
AFIB CHADS2=0 no therapy (2B); CHADS ≥1 anticoagulant (1B); if unsuitable for AC use asa+clopidigrel rather than asa (1B)

RE-LEY- DABIGATRAN v WARFARIN FOR STROKE PREVENTION IN AFIB

Connolly SJ et al. NEJM 2009
RE-LY Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>DABI</th>
<th>WARF</th>
<th>RR (95% CI)</th>
<th>NNT or NNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/SEE (1st Endpt)</td>
<td>1.11</td>
<td>1.69</td>
<td>0.66* (0.53-0.82)</td>
<td>NNT=172</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>3.11</td>
<td>3.36</td>
<td>0.93 (0.81-1.07)</td>
<td>N/A</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>1.51</td>
<td>1.02</td>
<td>1.5* (1.19-1.89)</td>
<td>NNH=204</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>0.3</td>
<td>0.74</td>
<td>0.4* (0.27-0.6)</td>
<td>NNH=227</td>
</tr>
<tr>
<td>Myocardial infarction (MI)</td>
<td>0.81</td>
<td>0.64</td>
<td>1.27 (0.94-1.71)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

MI/ACS with Dabigatran

ANALYSIS OF RELY TRIAL-TTR

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ROCKET AF- Rivaroxaban v Warfarin in AFIB

- 20mg QD
- Non Inferior to warfarin
- Major bleeding same
- ↑ risk fatal & intracranial bleed
- ↑ risk GI bleed
- CHADS2 score - 3-3.5
- TTR 55%
- No effect of TTR on efficacy
- ↑ CVA when Δ back to warfarin


ARISTOTLE: APIXABAN V WARFARIN in AFIB

- ↓ stroke 21%
- ↓ major bleed 13%
- 5mg BID
- 20% prior CVA
- ↓ death 11%*
- ↑ CVA when Δ back to warfarin


Then There Were Three…
New Comers v Warfarin - Stroke

<table>
<thead>
<tr>
<th>DABIGATRAN</th>
<th>RIVAROXABAN</th>
<th>APIXABAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ stroke</td>
<td>X (34%)</td>
<td>noninferior</td>
</tr>
<tr>
<td>↓ INTRACRANIAL BLEED</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>↓ MORTALITY</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>BLEEDING</td>
<td>↓ GI bleeding</td>
<td>↓ GI bleeding</td>
</tr>
<tr>
<td>DRUG INTERACTIONS</td>
<td>pGP &amp; CYP3A4</td>
<td>pGP &amp; CYP3A4</td>
</tr>
<tr>
<td>NUISANCE Side effects</td>
<td>10-20% dyspepsia</td>
<td>-----</td>
</tr>
<tr>
<td>DOSING</td>
<td>BID</td>
<td>QD</td>
</tr>
<tr>
<td>METABOLISM</td>
<td>80% RENAL</td>
<td>60% RENAL</td>
</tr>
</tbody>
</table>
Case

70 yo man is admitted with new onset AFIB. His PMHx is significant only for hypertension. He is on ASA for primary CAD prophylaxis. He has normal renal function. What regimen will you suggest for stroke prevention?

1. Continue ASA alone
2. ASA plus clopidigrel
3. Warfarin
4. Dabigatran
5. Rivaroxaban
**Patient Selection—Contraindications**

- Mechanical valve
- Low CrCl (< 15-30 ml/min-agent dependent)

**Patient Selection—Cautions**

<table>
<thead>
<tr>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of GI bleeding-unclear source</td>
<td>History of GI bleeding-unclear source</td>
<td>Concomitant therapy with P-gp inhibitors &amp; strong CYP3A4 inhibitors/inducers</td>
</tr>
<tr>
<td>Age &gt; 80</td>
<td>Concomitant therapy with P-gp inhibitors</td>
<td>At risk for ↓ renal function</td>
</tr>
<tr>
<td>Concomitant therapy with P-gp inhibitors</td>
<td>At risk for ↓ renal function</td>
<td>Problems with BID dosing CAD/MI?</td>
</tr>
<tr>
<td>GI bleeding-unclear source</td>
<td>GI bleeding-unclear source</td>
<td></td>
</tr>
<tr>
<td>Problems with BID dosing CAD/MI?</td>
<td>Problems with BID dosing</td>
<td></td>
</tr>
</tbody>
</table>

**Drug Interactions**

(Rudd et al. Thrombosis 2013)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Interaction</th>
<th>Dose adjustment necessary</th>
<th>Dose adjustment not recommended</th>
<th>Dose adjustment not recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>clopidogrel</td>
<td>P-gp inhibitors and strong CYP3A4 inhibitors</td>
<td>Increase dose to 2x or discontinue</td>
<td>Increase dose to 2x or discontinue</td>
<td>Reduce dose to 1x or discontinue</td>
</tr>
<tr>
<td>aspirin</td>
<td>P-gp inhibitors and strong CYP3A4 inhibitors</td>
<td>Increase dose to 2x or discontinue</td>
<td>Increase dose to 2x or discontinue</td>
<td>Reduce dose to 1x or discontinue</td>
</tr>
<tr>
<td>warfarin</td>
<td>P-gp inhibitors and strong CYP3A4 inhibitors</td>
<td>Increase dose to 2x or discontinue</td>
<td>Increase dose to 2x or discontinue</td>
<td>Reduce dose to 1x or discontinue</td>
</tr>
<tr>
<td>abciximab</td>
<td>P-gp inhibitors and strong CYP3A4 inhibitors</td>
<td>Increase dose to 2x or discontinue</td>
<td>Increase dose to 2x or discontinue</td>
<td>Reduce dose to 1x or discontinue</td>
</tr>
<tr>
<td>clopidogrel</td>
<td>P-gp inhibitors and strong CYP3A4 inhibitors</td>
<td>Increase dose to 2x or discontinue</td>
<td>Increase dose to 2x or discontinue</td>
<td>Reduce dose to 1x or discontinue</td>
</tr>
</tbody>
</table>

(Rudd et al. Thrombosis 2013)
AFIB-WHICH AGENT

- Non-valvular AFIB
- Cost prohibitive
- AF < 15-30
cost prohibitive
- ASA for 3 problems
- BID dosing
- GI bleed, MI,
high bleed risk,
yes or no
- Rivaroxaban
- Apixaban
- No warfarin
with poor TTR
or monitoring issues
- Rivaroxaban
- Apixaban
- Dabigatran
- Warfarin

**AFib.ca**

Clinical Decision Tool

**HTTP://WWW.AFIB.CA**
AFIB TREATMENT COST

<table>
<thead>
<tr>
<th></th>
<th>day</th>
<th>month</th>
<th>annual</th>
</tr>
</thead>
<tbody>
<tr>
<td>warfarin</td>
<td>&lt; 20 cents</td>
<td>$80*</td>
<td>$960</td>
</tr>
<tr>
<td>apixaban</td>
<td>??</td>
<td>~$300</td>
<td>~$3600</td>
</tr>
<tr>
<td>dabigatran</td>
<td>$6.75-8.00</td>
<td>$260</td>
<td>~$3000</td>
</tr>
<tr>
<td>rivaroxaban</td>
<td>$8.00</td>
<td>$260</td>
<td>~$3000</td>
</tr>
</tbody>
</table>

Case
Which is a good candidate for dabigatran/rivaroxaban/apixaban
a) 66 yo w/ AFIB, ESRD, poorly controlled INR admitted with TIA
b) 66 yo with AFIB & prosthetic mitral valve
c) 83 yo 50 kg woman with CKD (Cr Cl 30 ml/min) with new AFIB
d) none of the above
Case

The patient strongly prefers a TSOAC due to barriers to frequent clinic visits and general distrust of “rat poison”.

Starting TSOAC

- Review for drug-drug interactions
- Baseline labs-CBC, Cr, PTT/PT, LFTS
- Patient education-med guide
- Monitoring
  - Adherence
  - Adverse effects-GI
  - Bleeding/Stroke
  - +/- Labs
  - www.NOACforAF.eu.

Follow up
- 1 weeks
- 2 weeks
- 1 month
- 3 months
- *continue monthly check-in

Case

Six months later he admitted for total hip arthroplasty. Anesthesia calls you from the pre op area and asks “when was he supposed to stop his dabigatran?”
### Case

The patient is in the pre-op area and surgeon calls you to say the patient cannot remember if he held his dose yesterday. He asks if he should get an INR to be sure the drug has cleared. What do you recommend?

a) Yes send stat INR  

b) No send PTT  

c) No send thrombin time

### Monitoring TSOACS

<table>
<thead>
<tr>
<th>Drug Specific</th>
<th>dabigatran</th>
<th>rivaroxaban</th>
<th>apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>aPTT</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
</tr>
<tr>
<td>PT/INR</td>
<td>↑ (or →)</td>
<td>↑ (or →)</td>
<td>↑ (or →)</td>
</tr>
<tr>
<td>TT</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>Drug Specific Anti xa</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>In development</td>
<td>NOT urine</td>
<td>Prothrombinase induced clotting assay</td>
<td></td>
</tr>
</tbody>
</table>
**Case**

One year later the patient presents to the ED with syncope. He is found be lethargic, hypotensive with BP in the 80s, HCT of 24 (baseline 38) with melanotic stool. His creatinine is 3.5 (baseline 0.9). His wife reports that he dutifully took his dabigatran this morning at 8 am. It is now 9:15 am. How will you manage his anticoagulation?

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**Management of NOAC Bleeding**

- **THERE IS NO ANTIDOTE**
- Discontinue drug
- Administer charcoal if recent ingestion
- Maintain adequate diuresis
- Check PTT/ TT(dabigatran) or PT(riva)
- Dabigtran is dialyzable. 60% of drug may be removed over 2-3 hours
- 4 component PCC has been shown to reverse anticoagulant effect of rivaroxaban but not dabigatran
- Platelet transfusion if on antiplatelet drug

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Case

Mr K has a provoked DVT. Does he have to take the same "rat poison" his Dad takes, or can he take one of the newer medications he’s heard about in the news "to prevent clots?"

- A. Yes-same old rat poison for him
- B. No-what the heck, let’s try something new

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Rivaroxaban Gains FDA Indications For The Treatment And Prevention Of DVT And PE

The FDA today expanded the indication for rivaroxaban (Xarelto, Johnson & Johnson) to include the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and to reduce the risk of recurrent DVT and PE.

This new indication is already approved to reduce the post-surgical risk of DVT and PE after hip and knee replacement surgery and to reduce the risk of stroke in people with atrial fibrillation. The new indication was granted under the FDA's priority review program.

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EINSTEIN-Rivaroxan in Symptomatic DVT

Vte rates
- 2.1% rivaroxan
- 3% warfarin

Vte rates
- 1.3% rivaroxan
- 7.1% placebo
- DVT by 82%
- Minor bleed by 5.4% v 1.2%

Connolly SJ et al NEJM 2011
## Acute VTE Treatment

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Drug</th>
<th>Year Published</th>
<th>Overlap with heparin/LMWH</th>
<th>HR: Recurrent VTE vs. warfarin (95% CI)</th>
<th>HR: Major Bleeding vs. warfarin (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-COVER (DVT and/or PE)</td>
<td>dabigatran</td>
<td>2009</td>
<td>Yes</td>
<td>1.10 (0.65 – 1.84)</td>
<td>0.82 (0.45 – 1.48)</td>
</tr>
<tr>
<td>RE-COVER II</td>
<td>dabigatran</td>
<td>ONGOING</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EINSTEIN DVT</td>
<td>rivaroxaban</td>
<td>2010</td>
<td>No</td>
<td>0.68 (0.44 – 1.04)</td>
<td>0.65 (0.33 – 1.30)</td>
</tr>
<tr>
<td>EINSTEIN PE</td>
<td>rivaroxaban</td>
<td>2012</td>
<td>No</td>
<td>1.12 (0.75 – 1.68)</td>
<td>0.49 (0.31 – 0.79)</td>
</tr>
</tbody>
</table>

Schulman S NEJM 2009; Einstein Investigators NEJM 2010 & NEJM 2012

## Key Differences

- **Dabigatran**
  - Direct thrombin inhibitor
  - Taken twice daily
  - 5 days of parenteral (e.g. LMWH) treatment needed

- **Rivaroxaban**
  - Direct FXa inhibitor
  - Taken twice daily for 3 weeks, then once daily
  - Can be used as monotherapy

## Rivaroxaban Dosing

### Renal Function

- **AFIB**
  - CrCl 15–30 not studied
- **DVT/PE**
  - Avoid if CrCl < 30
- **DVT prophylaxis**
  - Avoid if CrCl < 30. Observe closely if CrCl 30–50 ml/min
Apixaban for Secondary Prevention of VTE


Recurrent VTE
Placebo 8.8%
5 mg 1.7%
2.5 mg 1.7%

Starting Rivaroxaban

- Review for drug-drug interactions
- Baseline labs-CBC, Cr, PTT/PT, LFTS
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  - Adverse effects-GI
  - Bleeding/Stroke
  - +/-Labs
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Follow up
- 2 weeks
- 1 month
- 3 months
- *continue monthly check in

Case

Do you give Mr K rivaroxaban or "rat poison"?
Choose warfarin if on contraindicated med, renal insufficiency, cost, want INR to track adherence
Choose rivaroxaban if monitoring a big burden, refuse parenteral bridge, cost not an issue, low risk of missed doses, poor TTR in past
Take Home Points

- Know who NOT to use new anticoagulants in
- Patients on these agents should be monitored systematically despite freedom from INR measurement
- Know your hospital's policy/guideline for management of bleeding on new anticoagulants

THROMBOSIS WORKSHOP

- Duration of anticoagulation for VTE—who knows?
- IVC filters—should we?
- Management of catheter-associated thrombosis—how long?
- The thrombophilia work up—is it necessary?
- Help my patient is clotting ON anticoagulation!
- And more.....