Anticoagulation in 2014: Using the New Agents Safely

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University of California, San Francisco
Chief, SF VA Anticoagulation & Thrombosis Service

Disclosures

I have nothing to disclose
Objectives

- Review of available agents
- Patient selection, monitoring and follow up
- Perioperative management
- Management of bleeding complications
New Oral Anticoagulants

Warfarin
- Need for frequent monitoring
- Myriad of drug interactions
- Interaction with alcohol
- Requirement for dietary stasis
- Fluctuating INR is the norm

New Agents
- No lab testing required
- Few drug interactions
- Activity independent of vitamin K — no food drug interactions
- More predictable dose effect

New Oral Anticoagulants

Ansell, J. Hematology
Update in Nomenclature

NOACS → TSOACS

New Oral Anticoagulants → Target specific oral anticoagulants

Target Specific Oral 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>Nonvalvular AFIB VTE tx &amp; prevention</td>
<td>Nonvalvular AFIB/VTE tx &amp; prevention</td>
<td>Nonvalvular AFIB VTE tx &amp; prevention</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MOA</th>
<th>DTI</th>
<th>antiXa</th>
<th>antiXa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal metabolism</td>
<td>80%</td>
<td>30-60%</td>
<td>25%</td>
</tr>
</tbody>
</table>
New Oral Antithrombotics

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran (Pradaxa)</th>
<th>Rivaroxaban (Xarelto)</th>
<th>Apixaban (n/a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1/2 hours</td>
<td>12-17</td>
<td>5-9</td>
<td>8-15</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>--</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>pGP</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

Mr K has a provoked DVT. He asks, 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
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.

The oral anticoagulant is already approved for DVT and PE after hip and knee surgery in people with atrial fibrillation, the FDA's priority review program.

EINSTEIN-Rivaroxaban in Symptomatic DVT

Vte rates
2.1% rivaroxan
3% warfarin

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

Connolly SJ et al NEJM 2011
APIXABAN FOR VTE TREATMENT

35% had PE-40% extensive
85% CrCl > 50

69% ↓ major bleeding

<table>
<thead>
<tr>
<th></th>
<th>apix</th>
<th>lmwh/warf</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE</td>
<td>2.3%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Major bleed</td>
<td>0.6%</td>
<td>1.8%</td>
</tr>
</tbody>
</table>


Apixaban for Secondary Prevention of VTE

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

# 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>dabi</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>dabi</td>
<td>2011</td>
<td>Yes</td>
<td>1.08 (0.64-1.80)</td>
<td>0.67 (0.56-0.81)</td>
</tr>
<tr>
<td>EINSTEIN DVT</td>
<td>riva</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>riva</td>
<td>2012</td>
<td>No</td>
<td>1.12 (0.75 – 1.68)</td>
<td>0.49 (0.31–0.79)</td>
</tr>
<tr>
<td>AMPLIFY</td>
<td>apix</td>
<td>2013</td>
<td>No</td>
<td>0.84 (0.60–1.18)</td>
<td>0.31 (0.17–0.55)</td>
</tr>
</tbody>
</table>

(Revised from: Schulman, S. NEJM 2009; Einstein Investigators: NEJM 2010 & NEJM 2012)

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# VTE Treatment Regimens—How Do They Compare?

- UFH/warfarin associated with ↑ recurrence rate. Rest similar.
- Apixaban and rivaroxaban had lower bleeding rate. HR 0.28/0.48
- NNT riva 258
- NNT apix 165

(Updated from: Castelucci et al JAMA 2014)
### Acute VTE Treatment with TSOACS - Key Differences

<table>
<thead>
<tr>
<th></th>
<th>dabigatran</th>
<th>rivaroxaban</th>
<th>apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>monotherapy</td>
<td>No, use 5-10 days heparin initially</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Dosing regimen</td>
<td>BID</td>
<td>BID for 1st 21 days then QD</td>
<td>BID</td>
</tr>
<tr>
<td>Bleeding risk v warfarin</td>
<td>Same</td>
<td>Lower</td>
<td>lower</td>
</tr>
</tbody>
</table>

### Note Different Dosing for Each Indication with TSOACS

<table>
<thead>
<tr>
<th></th>
<th>VTE prophylaxis</th>
<th>VTE treatment</th>
<th>VTE secondary prevention</th>
<th>AFIB</th>
</tr>
</thead>
<tbody>
<tr>
<td>apixaban</td>
<td>2.5 mg BID</td>
<td>10 mg BID x7 days then 5 mg BID</td>
<td>2.5 mg BID after 6-12 months of full dose</td>
<td>5 mg BID 2.5 mg BID renal/age/kg</td>
</tr>
<tr>
<td>rivaroxaban</td>
<td>10 mg qd</td>
<td>15 mg BID x 21 days then 20 mg QHS With food</td>
<td>Same as tx</td>
<td>20 mg QHS 15 mg QHS renal With food</td>
</tr>
<tr>
<td>dabigatran</td>
<td>****</td>
<td>150 mg BID</td>
<td>Same as tx</td>
<td>150 mg BID 75 mg BID renal</td>
</tr>
</tbody>
</table>
**Rivaroxaban Dosing**

### Dosage and Administration

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction in Risk of Stroke and</td>
<td></td>
</tr>
<tr>
<td>Systemic Embolism in Non-valvular</td>
<td></td>
</tr>
<tr>
<td>AF</td>
<td></td>
</tr>
<tr>
<td>DVT (2.4)</td>
<td>CrCl &gt;50 mL/min: 20 mg once daily with the</td>
</tr>
<tr>
<td></td>
<td>evening meal</td>
</tr>
<tr>
<td>DVT (2.4)</td>
<td>CrCl 15 to 30 mL/min: 15 mg once daily with</td>
</tr>
<tr>
<td></td>
<td>the evening meal</td>
</tr>
<tr>
<td>Treatment of DVT (2.4)</td>
<td>15 mg twice daily with food, for first 21</td>
</tr>
<tr>
<td></td>
<td>days ▼</td>
</tr>
<tr>
<td>Treatment of PE (2.4)</td>
<td>20 mg once daily with food, for remaining</td>
</tr>
<tr>
<td></td>
<td>treatment</td>
</tr>
<tr>
<td>Reducing the Risk of Recurrence of</td>
<td>20 mg once daily with food</td>
</tr>
<tr>
<td>DVT and PE (2.4)</td>
<td></td>
</tr>
<tr>
<td>Prophylaxis of DVT</td>
<td>Hip replacement: 10 mg once daily for 26</td>
</tr>
<tr>
<td>Following Hip or Knee replacement</td>
<td>days</td>
</tr>
<tr>
<td>Surgery (2.5)</td>
<td>Knee replacement: 10 mg once daily for 12</td>
</tr>
<tr>
<td></td>
<td>days</td>
</tr>
</tbody>
</table>

**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

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**Dabigatran Dosing**

### Indication  | Dosage
---|---
Reduction in Risk of Stroke and Systemic Embolism in Non-valvular AF  | 150 mg twice daily
CrCl >30 mL/min: 150 mg twice daily
CrCl 15 to 30 mL/min: 75 mg twice daily
CrCl <15 mL/min or on dialysis: Dosing recommendations cannot be provided
Consider reducing dose to 75 mg twice daily if given with P-gp inhibitors, dexamethasone or ketoconazole. Dose adjustment is not necessary when co-administered with other P-gp inhibitors
CrCl <30 mL/min with concomitant use of P-gp inhibitors: Avoid co-administration
Treatment of DVT and PE | 150 mg twice daily
Reduction in the Risk of Recurrence of DVT and PE | 150 mg twice daily
CrCl >30 mL/min: 150 mg twice daily
CrCl <30 mL/min or on dialysis: Dosing recommendations cannot be provided
Avoid co-administration
CrCl <30 mL/min with concomitant use of P-gp inhibitors: Avoid co-administration
AIXABAN DOSING

--- DOSAGE AND ADMINISTRATION ---

- Reduction of risk of stroke and systemic embolism in nonvalvular atrial fibrillation:
  - The recommended dose is 5 mg orally twice daily. (2.1)
  - In patients with at least 2 of the following characteristics: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL, the recommended dose is 2.5 mg orally twice daily. (2.2)
- Prophylaxis of DVT following hip or knee replacement surgery:
  - The recommended dose is 2.5 mg orally twice daily. (2.1)
- Treatment of DVT and PE:
  - The recommended dose is 10 mg taken orally twice daily for 7 days, followed by 5 mg taken orally twice daily. (2.1)
- Reduction in the risk of recurrent DVT and PE following initial therapy:
  - The recommended dose is 2.5 mg taken orally twice daily. (2.1)

TSOAC Metabolism

Dabigatran
- Parent drug: Metabolized by CYP2C19
- Bio-availability: 3–7%
- T1/2: 12-12h

Rivaroxaban
- Parent drug: Metabolized by CYP3A4 and CYP2C19
- Bio-availability: 60% (without food)
- T1/2: 11-12h (elderly)

Apixaban
- Parent drug: Metabolized by CYP3A4
- Bio-availability: 30%
- T1/2: 12h

Edoxaban
- Parent drug: Metabolized by CYP3A4
- Bio-availability: 62%
- T1/2: 11h
### Drug Interactions

**Table 2:** Selected P-glycoprotein and Cytochrome P450 34A4 drug interactions with NOAC based on current FDA-approved indications [19, 21, 31, 35]

<table>
<thead>
<tr>
<th>Medications</th>
<th>Mechanism of Interaction</th>
<th>Delisalone&lt;sup&gt;®&lt;/sup&gt; (Palexis)</th>
<th>Kassavetis&lt;sup&gt;®&lt;/sup&gt; (Xarelto)</th>
<th>Apixaban (Eliquis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampin</td>
<td>P-glycoprotein inducer</td>
<td>Avoid combination</td>
<td>Avoid</td>
<td>Avoid</td>
</tr>
<tr>
<td>Cimetidine, phenytoin, St. John’s wort</td>
<td>P-glycoprotein inducers and Strong CYP 34A4 inducers</td>
<td>Avoid</td>
<td>Avoid</td>
<td>Avoid</td>
</tr>
<tr>
<td>Digoxin</td>
<td>P-glycoprotein inhibitors</td>
<td>When CIC 30mg/Leq, dose reduction suggested in dosing for Atrial Fibrillation For CIC 1.25 mg/Leq, Avoid</td>
<td>Not addressed in Package Insert</td>
<td>Not addressed</td>
</tr>
<tr>
<td>Systemic ketoconazole, itraconazole</td>
<td>P-glycoprotein-inducers and Strong CYP 34A4 inducers</td>
<td>For CIC 30mg/Leq, dose reduction suggested in dosing for Atrial Fibrillation</td>
<td>Avoid</td>
<td>Reduce dose in 1/2 for those starting on the full dose of 3mg BD&lt;sup&gt;®&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fluoxetine, paroxetine, mirtazapine, clomipramine</td>
<td>P-glycoprotein-inducers and Strong CYP 34A4 inducers</td>
<td>Not addressed in Package Insert</td>
<td>Avoid</td>
<td>Reduce dose in 1/2 for those starting on the full dose of 5mg BD&lt;sup&gt;®&lt;/sup&gt;</td>
</tr>
<tr>
<td>Venlafaxine, amitriptyline, doxepin</td>
<td>P-glycoprotein inhibitors</td>
<td>For CIC 30mg/Leq, No dose adjustment needed, monitor clinical course For CIC 1.25 mg/Leq, Avoid</td>
<td>Not addressed in Package Insert</td>
<td>Reduce dose in 1/2 for those starting on the full dose of 3mg BD&lt;sup&gt;®&lt;/sup&gt;</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>P-glycoprotein-inducers and strong CYP 34A4 inducers</td>
<td>For CIC 30mg/Leq, Avoid</td>
<td>For CIC 30mg/Leq, No dose adjustment needed, monitor clinical course</td>
<td>Under refer to package insert</td>
</tr>
</tbody>
</table>

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**www.NOACforAF.eu**

- [European Heart Rhythm Association Recommendations for the management of atrial fibrillation](http://depts.washington.edu/anticoag/home/)
- [NOAC for AF Website](http://depts.washington.edu/anticoag/home/)

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**SCHOOL OF MEDICINE * UNIVERSITY OF CALIFORNIA, SAN FRANCISCO**
**Case**

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

**Starting TSOACs**

- Baseline labs-CBC, Cr, PTT/PT, LFTS
- Patient education-med guide
- Refer to provider for follow up
- Monitoring
  - Adherence
  - Adverse effects-GI
  - Bleeding/TE
  - +/-Labs

**Follow up**
- 2 weeks
- 1 month
- 3 months
- *continue q 4-8 wk check in*
Which of the patients below with AFIB would be a good candidate for a TSOAC?

1) 55 yo man with AFIB, CAD, DM, HTN, normal renal function
2) 55 year old man with AFIB
3) 89 year old man with AFIB CKD and CHF, CrCl ranging from 20-30 ml/min.
4) 1 and 2
5) all of the above

Then There Were Three... New Comers v Warfarin - Stroke

<table>
<thead>
<tr>
<th></th>
<th>DABIGATRAN</th>
<th>RIVAROXABAN</th>
<th>APIXABAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ stroke</td>
<td>X</td>
<td>→</td>
<td>X</td>
</tr>
<tr>
<td>↓ INTRACRANIAL BLEED</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>↓ MORTALITY</td>
<td>X</td>
<td>X</td>
<td>X**</td>
</tr>
<tr>
<td>BLEEDING</td>
<td>↓ GI bleeding</td>
<td>↑ GI bleeding</td>
<td>↓ any cause</td>
</tr>
<tr>
<td>DRUG INTERACTIONS</td>
<td>Least-pGP</td>
<td>pGp &amp; CYP3A4</td>
<td>CYP 3A4</td>
</tr>
<tr>
<td>NUISANCE Side effects</td>
<td>10-20% dyspepsia</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>DOSING</td>
<td>BID</td>
<td>QD</td>
<td>BID</td>
</tr>
<tr>
<td>METABOLISM</td>
<td>80% RENAL</td>
<td>60% RENAL</td>
<td>25% RENAL</td>
</tr>
</tbody>
</table>
RE-LY- DABIGATRAN v WARFARIN FOR STROKE PREVENTION IN AFIB

Connolly SJ et al. NEJM 2009
SCHOOL OF MEDICINE * UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

The Trouble with Dabigatran

New Emails in Pradaxa Case Show Concern Over Profit

Feature
Anticoagulants
Dabigatran: how the drug company withheld important analyses
BMJ 2014; 349: doi: http://dx.doi.org/10.1136/bmj.g6570 (Published 20 July 2014)
Cite this as: BMJ 2014;349:g6570

In an investigation by The BMJ Deborah Cohen finds that recommendations for use of new generation oral anticoagulants may be flawed because regulators did not see evidence showing that monitoring drug plasma levels could improve safety.
ROCKET AF- Rivaroxaban v Warfarin in AFIB

• 20mg QD
• Non-Inferior to warfarin
• Major bleeding same
• ↓ risk fatal & intracranial bleed

• ↑ risk GI bleed
• trend ↑ bleed > 75

• 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

5mg BID
20% prior CV

↓ stroke 21%
↓ major bleed 13%
↓ death 11%
↑ CVA when Δ back to warfarin

The effect of apixaban vs. warfarin on stroke or systemic embolism and major bleeding in patients ≥75 years in relation to apixaban dose.

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Apixaban</th>
<th>Warfarin</th>
<th>Hazard ratio (95% CI)</th>
<th>Interaction P-value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or systemic embolism (n=5678)</td>
<td>790</td>
<td>11 (1.65)</td>
<td>20 (3.13)</td>
<td>0.52 (0.25, 1.08)</td>
</tr>
<tr>
<td>5 mg bid</td>
<td>4888</td>
<td>68 (1.54)</td>
<td>89 (2.05)</td>
<td>0.75 (0.55, 1.03)</td>
</tr>
<tr>
<td>Major bleeding (n=5655)</td>
<td>786</td>
<td>20 (3.29)</td>
<td>35 (6.54)</td>
<td>0.55 (0.31, 0.94)</td>
</tr>
<tr>
<td>5 mg bid</td>
<td>4869</td>
<td>131 (3.21)</td>
<td>189 (5.00)</td>
<td>0.66 (0.53, 0.83)</td>
</tr>
</tbody>
</table>

A reduced dose of 2.5 mg twice daily or placebo were administered to a total of 831 patients; 790 of these patients were ≥75 years.

** Interaction among treatment, age and dose based on randomized or treated population

Halvorsen S et al. Eur Heart J 2014
What do the Published Recommendations Say About Warfarin vs TSOACS for AFIB?

**ACCP 2012**
we suggest dabigatran 150 mg bid rather than adjusted-dose vitamin K antagonist therapy

**Canada 2012**
We suggest, that when OAC therapy is indicated, most patients should receive dabigatran, rivaroxaban, or apixaban in preference to warfarin

**ESC**
Where OAC is recommended, one of the NOACs, (dabigatran, rivaroxaban, or apixaban) should be considered rather than adjusted-dose VKA (INR 2-3) for most patients with non-valvular AF, based on their net clinical benefit.

**AHA 2014**
For patients with nonvalvular AF with prior stroke, transient ischemic attack (TIA), or a CHA2DS2-VASc score of 2 or greater, oral anticoagulants are recommended. Options include: warfarin (INR 2.0 to 3.0) (Level of Evidence: A), dabigatran (Level of Evidence: B), rivaroxaban (Level of Evidence: B), or apixaban (Level of Evidence: B).

ACCP 2012 guidelines; Canadian Cardiovascular Society Atrial Fibrillation Guidelines Committee 2012* AHA 2014 guidelines

### 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</td>
</tr>
<tr>
<td>Age &gt; 75</td>
<td>Age &gt; 75</td>
<td>Concomitant therapy with P-gp inhibitors &amp; strong CYP3A4 inhibitors/inducers</td>
</tr>
<tr>
<td>Concomitant therapy with P-gp inhibitors</td>
<td>Concomitant therapy with P-gp inhibitors &amp; strong CYP3A4 inhibitors/inducers</td>
<td>At risk for ↓ renal function</td>
</tr>
<tr>
<td>At risk for ↓ renal function</td>
<td>At risk for ↓ renal function</td>
<td>Problems with BID dosing</td>
</tr>
<tr>
<td>Problems with BID dosing CAD/MI?</td>
<td></td>
<td>Problems with BID dosing</td>
</tr>
</tbody>
</table>

*School of Medicine * University of California, San Francisco
# Note Different Dosing for Each Indication with TSOACS

<table>
<thead>
<tr>
<th></th>
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<th>VTE treatment</th>
<th>VTE secondary prevention</th>
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<tr>
<td>apixaban</td>
<td>2.5 mg BID</td>
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<td>rivaroxaban</td>
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</tr>
<tr>
<td>dabigatran</td>
<td>**** 150 mg BID</td>
<td>Same as tx</td>
<td>Same as tx</td>
<td>150 mg BID 75 mg BID renal</td>
</tr>
</tbody>
</table>

## TSOAC DOSING FOR AFIB CKD

<table>
<thead>
<tr>
<th>TSOAC</th>
<th>Dosing if CKD</th>
</tr>
</thead>
</table>
| dabigatran  | When CCI > 49 ml/min, 150 mg bid is possible (SmPC) but 110 mg bid if high risk of bleeding (SmPC) or recommended (GL update) Note: 75 mg bid approved in US only.  
- If CCI 15–30 ml/min  
- If CCI 30–49 ml/min and other factors from Table 5 (e.g. versaptin). |
| apixaban    | CCI 15–29 ml/min: 15 mg bid Serum creatinine > 1.5 mg/dl in combination with age > 80 years or weight < 60 kg/m² or with other 'yellow' factor (Table 5): 3.5 mg bid |
| rivaroxaban | Not available                  |

Heidbuchel H et al. EHRA Practical Guide EUROPACE 2013
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>$6-7</td>
<td>~$180-210</td>
<td>~$2700</td>
</tr>
<tr>
<td>dabigatran</td>
<td>$6.75-8.00</td>
<td>$250-260</td>
<td>~$3000</td>
</tr>
<tr>
<td>rivaroxaban</td>
<td>$6-8.00</td>
<td>$180-240</td>
<td>~$3000</td>
</tr>
</tbody>
</table>

AFIB-WHICH AGENT

- **Non-valvular AFIB**
  - Cost prohibitive
  - eGFR <15-30, ASA needed?
  - Contraindicated medication
  - Low compliance suspected

- **Warfarin**
  - BID dosing not possible
  - GI bleed, (MI) high bleed risk, >80
  - Dyspepsia
  - On warfarin with poor TTR or monitoring issues

- **Rivaroxaban**
- **Apixaban**
- **Dabigatran**
- **Rivaroxaban or Apixaban**

- **Apixaban**
- **Dabigatran**

- **Dabigatran**
Which of the patients below with AFIB would be a good candidate for a TSOAC?

- 1) 55 yo man with AFIB, CAD, DM, HTN, normal renal function
- 2) 55 year old man with AFIB
- 3) 89 year old man with AFIB CKD and CHF, CrCl ranging from 20-30 ml/min.
- 4) 1 and 2
- 5) all of the above

Case

Six months later he is admitted with acute cholecystitis. He is seen in consultation by surgery and they schedule him for open chole in 3 weeks. The patient wants to know when he should stop his dabigatran prior to the operation.

1) Last dose 1 day prior
2) Last dose 2 days prior
3) Last dose 5 days prior
3) It depends on renal function
Perioperative Management of TSOACS

1) what is bleeding risk of procedure
- If high bleed risk want minimal anticoagulant effect - need 4-5 half lives to pass to get 3-6% AC effect
- If low bleed risk can tolerate some residual AC effect - after 2-3 half lives will have 12-25% AC effect

2) what is half life of anticoagulant?
- Depends on which agent and renal function of patient

---

Table 6. Interruption of Target-Specific Oral Anticoagulant Therapy for Invasive Procedures and Surgery

<table>
<thead>
<tr>
<th>Drug (Creatinine Clearance)</th>
<th>Time of Last Dose before Minor Procedure (days)</th>
<th>Time of Last Dose before Major Surgery (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran (&gt; 50 mL/min)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Dabigatran (31–50 mL/min)</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Dabigatran (&lt;30 mL/min)</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Rivaroxaban or apixaban (&gt;50 mL/min)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Rivaroxaban or apixaban (30–50 mL/min)</td>
<td>1–2</td>
<td>3–4</td>
</tr>
<tr>
<td>Rivaroxaban or apixaban (&lt;30 mL/min)</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

Nutescu et al AJHP 2013
Perioperative Management of TSOACS

Anderson et al. CCJM 2014

Perioperative Management of TSOACS
EHRA Recommendations

Heidbuchel H et al. EHRA Practical Guide EUROPACE 2013
Case

Six months later he is admitted with acute cholecystitis. He is seen in consultation by surgery and they schedule him for open chole in 3 weeks. The patient wants to know when he should stop his dabigatran prior to the operation.

1) Last dose 1 day prior
2) Last dose 2 days prior
3) Last dose 5 days prior
3) It depends on renal function
**Case**

The patient is in the pre op area and surgeon calls you to say the patient can’t remember if he held his dose yesterday. He asks if he should get an INR to be sure the drug has cleared. You recommend:

a) Stat INR  
b) Stat PTT  
c) Stat thrombin time  
d) Stat coffee for yourself. It is 7 am and way to early for this kind of question.

---

**Monitoring TSOACS**

<table>
<thead>
<tr>
<th>Monitoring</th>
<th>dabigatran</th>
<th>rivaroxaban</th>
<th>apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>aPTT</td>
<td>↑↑</td>
<td>↑ (less sensitive than aPT)</td>
<td>↑</td>
</tr>
<tr>
<td>PT</td>
<td>↑ (or →)</td>
<td>↑↑(or → at low concentrations)</td>
<td>↑(or →)</td>
</tr>
<tr>
<td>TT</td>
<td>↑↑↑</td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td>Drug specific anti xa</td>
<td></td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>In development</td>
<td>POC urine Prothrombinase induced clotting assay</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Hemming
- Urgent surgery
- Ac failure
- Drug interactions
Case

One year later the patient presents to the ED with syncope. He is found to be lethargic, hypotensive with BP in the 80s, HCT of 24 (baseline 38) with melanotic stool. His creatinine is 2.5 (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?

Management of Life Threatening Bleeding on TSOAC

- Discontinue drug
- Maintain adequate diuresis
- Charcoal if ingestion is recent
- Check PTT/ TT(dabigatran) or PT(riva)
- Dabigtran is dialyzable. 60% of drug may be removed over 2-3 hours
- “Consider PCC, aPCC, FFP, Factor VII in life threatening bleed”
- Platelet transfusion if on antiplatelet drug
Take Home Points

- Know who NOT to use new anticoagulants in
- Patients on these agents should be monitored routinely despite freedom from INR measurement
- Know your hospitals policy/guideline for management of bleeding on TSOACs
Take Home Points

- Be familiar with your institutions recommendations for perioperative management of TSOACs
- Consider bleeding risk of procedure and renal function of patient when determining perioperative management of TSOACs

WORKSHOP

- Catheter related thrombosis
- Calf vein thrombosis
- Duration of anticoagulation for VTE
- Management of recurrent VTE
- Management of subsegmental PE
- When to restart anticoagulation after warfarin associated GI bleed
- IVC filters
Practical Issues
EHRA Exec Summary: Heidbechel et al Eur Heart 2013

- Renal function should be assessed on a regular basis because all TSOACs require dose reductions depending on renal function.
- The aPTT provides a qualitative (but not quantitative) indicator of the presence of dabigatran
- The PT provides a qualitative indicator of the presence of rivaroxaban and apixaban

Practical Issues
EHRA Exec Summary: Heidbechel et al Eur Heart 2013

- Quantitative laboratory tests for determining the degree of anticoagulation in patients taking TSOACs are not readily available.
- Rivaroxaban should be taken with food while the other TSOACSs can be taken with or without food.
- Because the anticoagulant effects of TSOACs dissipate 12-24 hours after a dose, warfarin may be preferable to a TSOAC if low compliance suspected.