Novel Anticoagulants: Case of Mr. T

Your Orthopedic surgeon calls you from the operating room requesting advice on VTE prevention for a 45yo male with congenital hip dysplasia and a remote history of DVT, now status post THA, who has an extreme phobia of needles and who refuses all injections and laboratory draws. What is an FDA approved option you could recommend?

A. Dabigatran Etexilate
B. Apixaban
C. Rivaroxaban
D. All of the above

Novel Anticoagulants: Case of Mrs. H

A 76yo female with a history of HTN and CHF (EF 45%) presents to the Emergency Department with intermittent palpitations for 6 weeks and near syncope.

Exam reveals BP of 110/55 HR 140. CV with irregularly irregular rhythm.

ECG with atrial fibrillation with RVR.
Mrs. H: Question #1

Mrs. H has an increased risk of stroke and systemic embolism (CHADS2 score of 3 = 6%/year risk without anticoagulation). Which of the following is an established or emerging anticoagulant option to prevent stroke and systemic embolism in this patient?

A. Direct thrombin inhibitor: Dabigatran etexilate
B. Factor Xa inhibitors: Apixaban/Rivaroxaban
C. Warfarin
D. All of the above

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Anticoagulants (AC): background

- Warfarin has been the only oral AC in U.S. for past 50+ years.
- Approximately 1% of U.S. population takes warfarin:
  - Atrial fibrillation, DVT/PE, mechanical valves common indications
  - AFib incidence expected to increase to 16 million by 2050
- Major bleeding occurs in approximately 1-2% / year on warfarin
  - 3,500 attributable ICH per year
- Warfarin #1 in adverse drug-related deaths in the U.S.

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Novel Oral ACs: Potential Advantages

<table>
<thead>
<tr>
<th>Advantage</th>
<th>Potential Clinical Implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid onset of action</td>
<td>No need for routine bridging</td>
</tr>
<tr>
<td>Predictable anticoagulant effect</td>
<td>No need for routine coagulation monitoring</td>
</tr>
<tr>
<td>Specific coagulation enzyme targets</td>
<td>Low risk of off-target adverse effects</td>
</tr>
<tr>
<td>Low potential for food interactions</td>
<td>Few to no dietary precautions</td>
</tr>
<tr>
<td>Lower potential for drug interactions</td>
<td>Fewer drug restrictions</td>
</tr>
</tbody>
</table>

Although novel oral anticoagulants may be easier to use than warfarin, a risk of bleeding remains and new challenges emerge.
Pharmacology of Novel Oral Anticoagulants

<table>
<thead>
<tr>
<th>Target</th>
<th>Dabigatran (Pradaxa®)</th>
<th>Rivaroxaban (Xarelto®)</th>
<th>Apixaban (Eliquis®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor IIa</td>
<td>(reversibly binds to site)</td>
<td>(reversibly binds to site)</td>
<td>(reversibly binds to site)</td>
</tr>
<tr>
<td>Factor Xa</td>
<td>(reversibly binds to site)</td>
<td>(reversibly binds to site)</td>
<td>(reversibly binds to site)</td>
</tr>
<tr>
<td>Dosage Form</td>
<td>capsule</td>
<td>tablet</td>
<td>tablet</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>5%</td>
<td>65-80%</td>
<td>55-85%</td>
</tr>
<tr>
<td>Time to Peak</td>
<td>1-2 hours</td>
<td>2-4 hours</td>
<td>1-3 hours</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Conjugation; NO CYP involvement</td>
<td>Oxidation (via CYP3A4 &amp; CYP2J2) + hydrolysis</td>
<td>Oxidation (via CYP3A4) + conjugation</td>
</tr>
<tr>
<td>Renal Excretion</td>
<td>80%</td>
<td>66%</td>
<td>25%</td>
</tr>
<tr>
<td>Half-life</td>
<td>14-17 hours</td>
<td>9-13 hours</td>
<td>9-14 hours</td>
</tr>
<tr>
<td>Dosing frequency, major trials</td>
<td>BID</td>
<td>QD</td>
<td>BID</td>
</tr>
</tbody>
</table>
ADVANCE-1 (Apixaban-TKA)
Double-blind, double-dummy, RCT of Apixaban 2.5mg PO bid vs. Enoxaparin 30mg SC Q12hr for 10-14d in TKA (n=3195)
Lassen MR et al NEJM 2009; 361: 594 -604
**First Dose 12-24hr post-op**

<table>
<thead>
<tr>
<th>Event Rates(%)</th>
<th>RR 1.02</th>
<th>[CI 0.78-1.32]</th>
<th>p=0.06*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total VTE/Death</td>
<td>3.8</td>
<td>3.4</td>
<td>1.06</td>
</tr>
<tr>
<td>Major VTE/Death</td>
<td>2.1</td>
<td>1.6</td>
<td>1.26</td>
</tr>
<tr>
<td>All-Bleed</td>
<td>2.4</td>
<td>2.1</td>
<td>1.11</td>
</tr>
<tr>
<td>Serious VTE/Death</td>
<td>2.5</td>
<td>2.4</td>
<td>1.05</td>
</tr>
</tbody>
</table>

* For Non-Inferiority

RECORD Trials- Pooled Data
Rivaroxaban 10mg QD vs. Enoxaparin* in TKA/THA
(* Dose 40mg daily except 30mg Q12hr in RECORD 4)
Turpie AG et al 2008: ASH
Gomez-Outes A et al. JTH 2009;7:2149-51

<table>
<thead>
<tr>
<th>Event Rates(%)</th>
<th>RR</th>
<th>[CI]</th>
<th>p=</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event Rates(%)</td>
<td>0.7%</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Magellan Medically Ill Trial
8,101 medical patients were randomized to either oral rivaroxaban 10mg once daily for 35 days or subcutaneous enoxaparin 40mg once daily for 10 days followed by placebo.
April 5, 2011 ACC Meeting, New Orleans; NCT00571649

<table>
<thead>
<tr>
<th>Clinical Bleeding</th>
<th>VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 30 Riva</td>
<td>2.8</td>
</tr>
<tr>
<td>Day 30 LMWH</td>
<td>2.7</td>
</tr>
<tr>
<td>Day 35 Riva</td>
<td>4.1</td>
</tr>
<tr>
<td>Day 35 LMWH</td>
<td>5.7</td>
</tr>
</tbody>
</table>
**VTE Prevention Summary**

- Novel anticoagulants may greatly simplify VTE prevention and obviate the need for both parenteral administration and monitoring.
- Overall risk: benefit comparable to standard therapy, but interpretation is in the eye of the beholder.
- Dosing/use in special populations will need to be elucidated.

*July 2011: FDA approved Rivaroxaban for DVT/PE prevention after major joint replacement surgery.*

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**RE-COVER: Dabigatran in Acute VTE**

Open label, randomized non-inferiority trial of AT + Dabigatran 150mg BID versus AT + VKA (INR 2-3) for 6 months (n=2,564).

<table>
<thead>
<tr>
<th>Event Rate (%)</th>
<th>Warfarin</th>
<th>Dabigatran 150 (q.d.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE/Death</td>
<td>2.1</td>
<td>1.1</td>
</tr>
<tr>
<td>Non-fatal PE</td>
<td>0.4</td>
<td>0.1</td>
</tr>
<tr>
<td>Mjor Bleed</td>
<td>4.3</td>
<td>1.8</td>
</tr>
<tr>
<td>All Bleed</td>
<td>6.1</td>
<td>4.1</td>
</tr>
</tbody>
</table>

*Event Rates (%)*

$p<0.001$ for non-inferiority

*Schulman S et al. NEJM 2009; 361:2342-52*

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**EINSTEIN: Rivaroxaban in Acute VTE**

Open label, randomized non-inferiority trial of Rivaroxaban* versus Enoxaparin + VKA (INR 2-3) for 6 months in 3,449 DVT/PE patients.

<table>
<thead>
<tr>
<th>Event Rate (%)</th>
<th>Rivaroxaban*</th>
<th>Enoxaparin + VKA (INR 2-3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE/Death</td>
<td>2.0</td>
<td>2.4</td>
</tr>
<tr>
<td>Non-fatal PE</td>
<td>0.2</td>
<td>0.4</td>
</tr>
<tr>
<td>Mjor Bleed</td>
<td>3.8</td>
<td>4.2</td>
</tr>
<tr>
<td>All Bleed</td>
<td>7.3</td>
<td>5.9</td>
</tr>
</tbody>
</table>

*15mg BID x 3 weeks then 20mg QDay

*p<0.001 for NI*
Novel Oral Anticoagulant Atrial Fibrillation Clinical Trial Overview

<table>
<thead>
<tr>
<th>Drug &amp; Dose</th>
<th>Dabigatran Etexilate 150mg &amp; 110mg bid</th>
<th>Rivaroxaban 20mg QD*</th>
<th>Apixaban 5mg BID*</th>
<th>Apixaban 5mg BID*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted dose?</td>
<td>N</td>
<td>Y: 15mg QD if CrCl ≤50ml, Y: 110mg bid if CrCl ≤50ml, Y: 110mg bid if age &gt;80, ≤60kg, CrCl &gt;1.5</td>
<td>Y-2.5mg bid if 2 of: age &gt;80, weight &lt;60kg, CrCl &gt;1.5</td>
<td>Y-2.5mg bid if 2 of: age &gt;80, weight &lt;60kg, CrCl &gt;1.5</td>
</tr>
<tr>
<td>Design</td>
<td>Randomized open label (n=18,113)</td>
<td>Randomized double blind (n=14,000)</td>
<td>Randomized double blind (n=18,201)</td>
<td>Randomized double blind (n=5,599)</td>
</tr>
<tr>
<td>Mean age (yr)</td>
<td>71.5</td>
<td>73</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>Prior Stroke/TIA</td>
<td>20%</td>
<td>55%</td>
<td>19%</td>
<td>13.5%</td>
</tr>
<tr>
<td>Mean CHADS2</td>
<td>2.1</td>
<td>2.1</td>
<td>2.1</td>
<td>2.1</td>
</tr>
<tr>
<td>Warfarin Naive (%)</td>
<td>50.4</td>
<td>37.5</td>
<td>43</td>
<td>60.5</td>
</tr>
</tbody>
</table>

Comparator | Warfarin: INR 2-3 67% TTR | Warfarin: INR 2-3 57.8% TTR | Warfarin: INR 2-3 66% TTR | Aspirin 81-324mg |

**AVERROES (Apixaban-AFIB)**
Double-blind RCT of Apixaban 5mg PO bid* vs. aspirin (81-324mg) in non-valvular atrial fibrillation patients for whom warfarin was unsuitable (n=5599)

**ARISTOTLE (Apixaban-AFIB)**
Double-blind, double-dummy, RCT of Apixaban 5mg PO bid* vs. Warfarin in non-valvular atrial fibrillation (n=18,201)
ROCKET-AF (Rivaroxaban-AFIB)
Double-blind, double-dummy, RCT of Rivaroxaban 20mg PO QD vs. Warfarin in non-valvular atrial fibrillation (n=14,000)

<table>
<thead>
<tr>
<th>Event Rate/yr (%)</th>
<th>Rivaroxaban</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/embolism</td>
<td>0.5%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>2.4%</td>
<td>3.4%</td>
</tr>
<tr>
<td>ICH</td>
<td>2.1%</td>
<td>3.6%</td>
</tr>
</tbody>
</table>

HR 0.88 [CI 0.74-1.03] p<0.001*
HR 1.04 [CI 0.90-1.20] P=0.58
HR 0.67 [CI 0.47-0.93] p=0.02

Patel et al. NEJM 2011; Aug 29 on line

RE-LY (Dabigatran-AFIB)
Randomized, open label trial of Dabigatran Etexilate either 150mg or 110mg BID versus warfarin (n=18,113)

<table>
<thead>
<tr>
<th>Event Rate/yr (%)</th>
<th>Dabigatran 150 bid</th>
<th>Dabigatran 110 bid</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVE, TE, PE, MI, Death</td>
<td>6.83%</td>
<td>7.09%</td>
<td>8.03%</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>7.41%</td>
<td>7.07%</td>
<td>6.42%</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>6.83%</td>
<td>7.09%</td>
<td>8.03%</td>
</tr>
</tbody>
</table>

Connolly SJ et al. NEJM 2009; 361:1139-51

RE-LY: Impact of Warfarin Control

<table>
<thead>
<tr>
<th>Composite: Stroke/systemic embolism/myocardial infarction/death/pulmonary embolism/major bleeding</th>
<th>Dabigatran</th>
<th>Warfarin</th>
<th>Hazard Ratio</th>
<th>95% CI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTR: (&lt;57.1) (Events per 100-person years)</td>
<td>6.83</td>
<td>10.13</td>
<td>0.67</td>
<td>0.56-0.80</td>
</tr>
<tr>
<td>57.1-65.5</td>
<td>7.09</td>
<td>8.03</td>
<td>0.87</td>
<td>0.73-1.05</td>
</tr>
<tr>
<td>65.5-72.6</td>
<td>7.41</td>
<td>7.13</td>
<td>1.05</td>
<td>0.87-1.27</td>
</tr>
<tr>
<td>&gt;72.6</td>
<td>7.07</td>
<td>6.42</td>
<td>1.11</td>
<td>0.91-1.35</td>
</tr>
</tbody>
</table>

Wallentin et al Lancet (2010);376:879-83

*(p=0.0006 for interaction)
October 2010 FDA approves dabigatran etexilate (Pradaxa) for stroke prevention in non-valvular afib.

July 2011 FDA approves Rivaroxaban (Xarelto) for DVT/PE prevention after joint replacement

Sept 2011 FDA votes 9-2 to approve Rivaroxaban for stroke prevention in non-valvular afib

Novel Anticoagulants
Clinical Implications

- Drug interactions
- Use in hepatic/renal
- Extreme weights
- Monitoring
- Peri-procedure Mgt
- Bleeding/reversibility
- Provider Knowledge

Without thought - efficacy & safety in practice will NOT mimic clinical trial results
Back to Mrs. H: Question #2

At the time of discharge, Mrs. H is taking fluoxetine, diltiazem and amiodarone. You note that she has a weight of 56kg and a creatinine clearance of 40ml/min. Which of the following anticoagulant options has a high potential for clinically important drug-drug interactions?

A. Direct thrombin inhibitor: Dabigatran etexilate
B. Factor Xa inhibitors: Apixaban/Rivaroxaban
C. Warfarin
D. All of the above

"If you look statistically at 'what are the drug interactions that kill people,' warfarin interactions are at the top of the list." - Dr. D.S. Paauw, Professor of Medicine, University of Washington

BUT

Warfarin drug-drug interactions can be effectively managed through frequent INR assessment and dose titration

Drug Interactions of Novel Anticoagulants

<table>
<thead>
<tr>
<th></th>
<th>Apixaban (Eliquis®)</th>
<th>Rivaroxaban (Xarelto®)</th>
<th>Dabigatran (Pradaxa®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP3A4</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>p-glycoprotein</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Means to monitor interaction</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
CYP3A4 Drug Interactions

**Inducers**
carbamazepine
efavirenz
glucocorticoids
nevirapine
phenobarbital
phenytoin
primidone
Rifampin
rifapentine
ritonavir
St John's Wort

**Inhibitors**
amiodarone
amprenavir
Aprepitant
atazanavir
cimetidine
clarithromycin
diltiazem
erythromycin
fluconazole
fluoxetine
fluvoxamine
cyclosporin
quinidine

grapefruit juice
indinavir
itraconazole
ketoconazole
lopinavir
nefazodone
nelfinavir
nofluoxetine
ritonavir
saquinavir
synergavir
verapamil
voriconazole

P-Glycoprotein Drug Interactions

**Inducers**
clofibrate
clofibrate
St John’s Wort
midazolam
nifedipine
phenobarbital
phenytoin
rifampin

**Inhibitors**
amiodarone
cefoprazone
ceftiraxone
clarithromycin
cyclosporin
diltiazem
dipyridamole
erythromycin
hydrocortisone
verapamil
itraconazole
ketoconazole
nicardipine
nifedipine
propranolol
quinidine
quinine
tacrolimus
tamoxifen

FDA Product labeling

“P-gp inducers and inhibitors: Avoid co-administration of rifampin with PRADAXA because of effects on dabigatran exposure… P-gp inhibitors ketoconazole, verapamil, amiodarone, quinidine, and clarithromycin do not require dose adjustments. These results should not be extrapolated to other P-gp Inhibitors”

“Concomitant use of XARELTO with drugs that are combined P-gp and strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, St. John’s wort) should be avoided.

Avoid concomitant administration of XARELTO with combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir/ritonavir, and conivaptan) which cause significant increases in rivaroxaban exposure that may increase bleeding risk.”
At the time of discharge, Mrs. H is taking fluoxetine, diltiazem and amiodarone. You note that she has a weight of 56 kg and a creatinine clearance of 40 ml/min.

A. Direct thrombin inhibitor: Dabigatran etexilate
B. Factor Xa inhibitors: Apixaban/Rivaroxaban
C. Warfarin
D. All of the above

Combination of low body weight, moderate renal impairment AND both P-GP and CYP3A4 inhibitors would likely lead to 50-200% increase in drug exposure with FDA approved doses & prolonged clearance

Presenting History:
Mrs. H presents to the ED 2 months later, now after a ground level fall with neck pain and left hand numbness. CT imaging reveals C6 compression fracture with posterior subluxation. Neurosurgery wants to take the patient to the OR.

Medications: Dabigatran etexilate, lisinopril, diltiazem

**Physical**
BP 124/84, P 89, RR 14, Weight 56 kg
Lungs: Clear to A & P bil
Heart: Irregular without murmur
Neuro: No focal weakness, Decreased sensation Left C6/C7 dermatomes

**Labs/Studies**
Creatinine: 1.4 mg/dL
INR = 1.4  aPTT = 40 seconds  
CWC: normal

What is your management recommendation?

Dabigatran: Clotting Assay Summary

Expected median therapeutic drug concentrations
Expected 95th percentile therapeutic drug concentrations

**Clotting Time (sec)**
- TT
- ECT
- aPTT
- PT/INR

Dabigatran Concentration
New Anticoagulants; Back to Mr. T

You prescribed Rivaroxaban for DVT/PE prevention after Mr. T’s hip replacement surgery. The orthopedist calls again (2 weeks later) because patient had a fall and has a complex peri-prosthetic fracture requiring surgical intervention. He wants to know when he can take him to the OR – there needs to be NO residual anticoagulation as he is going to use spinal anesthesia.

You note on labs that patient has AKI with a creatinine of 2.5mg/dL (estimated CrCl of 40ml/min), a APTT of 42 seconds, and an INR of 1.5

What is your management recommendation?

Rivaroxaban: Clotting Assay Summary

- Expected range Trough levels
- Expected range Peak levels

Rivaroxaban Concentration

Novel AC Agents - Peri-Procedural Management

<table>
<thead>
<tr>
<th>PRE-PROCEDURE</th>
<th>Half-life (range) hrs</th>
<th>Low Bleeding Risk Procedures</th>
<th>Moderate to High Bleeding Risk* Procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>DABIGATRAN*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CrCl &gt; 50</td>
<td>14 (11-24)</td>
<td>Skip 2 doses (one day)</td>
<td>Skip 4 doses (2 days)</td>
</tr>
<tr>
<td>CrCl 30-50</td>
<td>18 (13-23)</td>
<td>Skip 4 doses (two days)</td>
<td>Skip 6-8 doses (3-4 days)</td>
</tr>
<tr>
<td>CrCl &lt; 30</td>
<td>27 (22-35)</td>
<td>Skip 4-10 doses (2-5d)</td>
<td>Skip &gt;10 doses (&gt;5 days)</td>
</tr>
<tr>
<td>RIVAROXABAN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CrCl &gt; 60</td>
<td>8 hours</td>
<td>Skip 1 dose (one day)</td>
<td>Skip 2 doses (2 days)</td>
</tr>
<tr>
<td>CrCl &lt; 60</td>
<td>9-10 hours</td>
<td>Skip 2 doses (two days)</td>
<td>Skip 3-4 doses (3-4 days)</td>
</tr>
<tr>
<td>APIXABAN</td>
<td>CrCl &gt; 50</td>
<td>9 hours</td>
<td>Skip 1 dose (one day)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Skip 2 doses (2 days)</td>
</tr>
</tbody>
</table>

* For high risk surgeries consider most sensitive test pre-operatively

Post-Procedure: Delay re-initiation until hemostasis is certain (24-72 hours) and no epidural
Although novel anticoagulants offer great promise, they will cause bleeding, and lack effective antidotes. Managing bleeding is therefore challenging. Fundamentals of care include rapid clinical assessment of the source, cause, and severity of bleeding, and prompt appropriate action, both mechanical and systemic, to control the bleeding.

-Crowther & Warkentin

Bleeding Management Principles

- There is **NO reversal agent** for DTIs or Xa inhibitors
- Giving clotting factors (e.g. FFP) is **unlikely** to be beneficial – these drugs do not cause factor depletion
- **Cornerstones of treatment:**
  - Aggressively control bleeding site despite coagulopathy
  - Supportive treatment for as long anticoagulant effect persists
- If/VIIa or APCC are of uncertain/unproven benefit
- Hemodialysis is expected to remove 60% of dabigatran after 2 hours
- Activated charcoal is likely to be effective within 2 hr overdose

**Bleeding on Novel Oral Anticoagulant**

- **Mild bleeding**
  - Hold 1-2 doses
  - Local Control Measures
  - Local anti-fibrinolytic therapy if necessary

- **Moderate-severe bleeding**
  - Stop medication
  - Aggressive assessment and control of bleeding site
  - Supportive Care: fluids, blood products

- **Life threatening bleeding**
  - Consider:
    - Hemodialysis (Dabigatran)
    - APCC
    - rFVIIa
Thrombosis Service
New Anticoagulant Resource Room

http://www.healthcare.utah.edu/thrombosis/dabigatran.html

Medication Use Guideline
Clinical Screening Checklist
Bleeding Mgmt Guideline
Peri-procedural Mgmt Guideline
Lab use Guideline
Patient/Provider Education
Full Text Articles
Consult Request

Clinical Screening Worksheet

http://healthcare.utah.edu/thrombosis/newagents/TS_Dabi_ScreenChecklist.doc

Thrombosis Service – Retooling the “coumadin clinic”

Novel AC Consultation Program


Clinical Assessment
Patient Education
Financial/Insurance analysis & Prior-authorization
Individualized treatment recommendations
Follow-up with referring provider to finalize plan
Initiation of therapy if appropriate: provide RX

Clinical Assessment
Patient Education
Peri-procedural management

Initial Thrombosis Clinic Consultation
Follow-up phone call in 2 weeks to evaluate drug tolerance/ adverse effects
Follow-up phone call 1 month later
RX = refills
Quarterly phone follow-up
SCr and calculated CrCl as the clinical situation dictates
Conclusions

- Novel Oral anticoagulants have arrived! –
  - Dabigatran etexilate is approved for stroke prevention in afib
  - Rivaroxaban approved for VTE prevention in joint replacement
  - Additional indications/drugs are expected in 2011+

- Clinical trials demonstrate that in a RCT setting that these agents are effective and have a safety profile in general at least as good as comparator.

- Safe implementation into routine clinical care settings will require: appropriate patient selection and knowledge about laboratory interpretation and management in urgent settings.