New Oral Anticoagulants and Other Updates

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Case

65 yo man with HTN & CHF is found on routine exam to be in AFIB. His meds include ASA, metoprolol, statin and ACE. He has normal renal function. What regimen will you suggest for stroke prevention?

1. ASA alone
2. ASA plus clopidigrel
3. Warfarin
4. Dabigatran
5. Rivaroxaban
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
## New Oral Anticoagulants

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran (Pradaxa)</th>
<th>Rivaroxaban (Xarelto)</th>
<th>Apixaban (Eliquis)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Approval status</strong></td>
<td>Nonvalvular AFIB</td>
<td>Nonvalvular AFIB/DVT prevention</td>
<td>2012?</td>
</tr>
<tr>
<td><strong>MOA</strong></td>
<td>DTI</td>
<td>antiXa</td>
<td>antiXa</td>
</tr>
<tr>
<td><strong>Renal metabolism</strong></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>
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</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>
RE-LY- DABIGATRAN v WARFARIN FOR STROKE PREVENTION IN AFIB

Connolly SJ et al. NEJM 2009

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Months</th>
<th>Warfarin</th>
<th>Dabigatran, 110 mg</th>
<th>Dabigatran, 150 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>6022</td>
<td>5862</td>
<td>5718</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>5862</td>
<td>5710</td>
<td>4593</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>5718</td>
<td>4593</td>
<td>2945</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>5718</td>
<td>4593</td>
<td>2945</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>5710</td>
<td>4593</td>
<td>2945</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>5779</td>
<td>4682</td>
<td>3044</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1429</td>
</tr>
<tr>
<td>Outcome</td>
<td>DABI 150 % per yr</td>
<td>WARR % per yr</td>
<td>RR (95% CI)</td>
<td>NNT or NNH</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>------------------</td>
<td>---------------</td>
<td>-------------</td>
<td>------------</td>
</tr>
<tr>
<td>Stroke/SEE (1° 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>NNT=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>

*Statistically significant.
ANALYSIS OF RELY TRIAL - TTR

Wallentin, Lancet 2010

TTR <57%

TTR 57-65%

TTR 65-72%

TTR >72%
Dabigatran : Drug Interactions

- A substrate of p-glycoprotein
  - Inducers may decrease dabigatran levels (rifampin), St John's wort AVOID
  - Inhibitors could theoretically increase dabigatran (amio, dronedarone, ketoconazole, quinidine) USE CAUTION

- dronedarone / ketoconazole & CrCl 30-50 –use 75 mg twice daily
Rising Concerns....

Stop The Bleeding: FDA Probes Pradaxa Deaths

By Ed Silverman // December 7th, 2011 // 3:26 pm

Less than a month after European regulators asked doctors to exercise caution about using the Pradaxa blood thinner, the FDA has decided to investigate post-marketing reports of serious bleeding patients. As of November 6, the European Medicines Agency was aware of 256 cases of serious bleeding that results in patient deaths associated with the Boehringer Ingelheim blood thinner (see this).

In announcing its review, the FDA notes that the Pradaxa labeling already contains a warning about significant and sometimes fatal bleeds. And a large clinical trial of roughly 18,000 patients that compared Pradaxa and warfarin, which has been the standard therapy for decades, major bleeding events occurred at similar rates.

Nonetheless, the reports of deaths have been causing concern for months. A recent report by the Institute for Safe Medicine Practices found that Pradaxa generated a large number of adverse event reports to the FDA (read this). And a flap erupted in New Zealand, where the government has been criticized for agreeing to provide reimbursement too quickly (read here).

Pradaxa, which was approved for preventing stroke in patients with atrial fibrillation, is...
MI/ACS with Dabigatran

<table>
<thead>
<tr>
<th>Study, y</th>
<th>Dabigatran, No.</th>
<th></th>
<th>Control, No.</th>
<th></th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ACEv No Event</td>
<td>ACEv No Event</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RE-NOVATE,⁹ 2007</td>
<td>13 2296</td>
<td>9 1133</td>
<td></td>
<td></td>
<td>0.71 (0.30-1.67)</td>
</tr>
<tr>
<td>RE-MODEL,¹¹ 2007</td>
<td>10 1372</td>
<td>4 690</td>
<td></td>
<td></td>
<td>1.26 (0.39-4.02)</td>
</tr>
<tr>
<td>PETRO,¹² 2007</td>
<td>2 443</td>
<td>0 70</td>
<td></td>
<td></td>
<td>0.79 (0.04-16.73)</td>
</tr>
<tr>
<td>RE-LY original,²³ 2009</td>
<td>175 11916</td>
<td>63 5959</td>
<td></td>
<td></td>
<td>1.39 (1.04-1.86)</td>
</tr>
<tr>
<td>RE-COVER,¹³ 2009</td>
<td>4 1269</td>
<td>2 1264</td>
<td></td>
<td></td>
<td>1.99 (0.36-10.90)</td>
</tr>
<tr>
<td>RE-DEEM,¹⁴ 2011</td>
<td>32 1458</td>
<td>4 313</td>
<td></td>
<td></td>
<td>1.72 (0.60-4.89)</td>
</tr>
<tr>
<td>RE-NOVATE II,¹⁵ 2011</td>
<td>1 1009</td>
<td>1 1002</td>
<td></td>
<td></td>
<td>0.99 (0.06-15.90)</td>
</tr>
<tr>
<td>FE model</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.33 (1.03-1.71)</td>
</tr>
</tbody>
</table>

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

Patient Selection—Cautions

Dabigatran
- History of GI bleeding-unclear source
- Age > 80
- Concomitant therapy with P-gp inhibitors
- At risk for ↓renal function

Rivaroxaban
- History of GI bleeding-unclear source
- Concomitant therapy with P-gp inhibitors/CYP3A4 inhibitors
- At risk for ↓renal function
- Problems with BID dosing
Case

You decide to start your patient with new AFIB on dabigatran or rivaroxaban because he will be unable to get INR draws regularly due to his work/travel schedule.
Starting Dabigatran/Rivaroxaban

- Baseline labs - CBC, Cr, PTT/PT, LFTS
- Patient education - med guide
- Monitoring
  - Adherence
  - Adverse effects - GI
  - Bleeding/Stroke
  - +/- Labs

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

“Pradaxa is eliminated by the kidneys; therefore, renal function should be assessed prior to treatment with Pradaxa to determine the appropriate dose. Also, renal function should be reassessed during treatment with Pradaxa if clinically indicated by fluctuating renal function, diuretic use, or hypovolemia and the dose should be adjusted following recommendations in the label.”
Dabigatran : Prescribing Info

- Indicated for stroke prevention in non-valvular AFIB
- 150 mg po twice daily; 75 mg po twice daily if CrCl 15-30 ml/min or on dronaderone and CrCL< 50 ml/min.
- Not recommended if CrCl< 15ml/min
- Capsule cannot be broken or chewed
- When converting patients from warfarin therapy, discontinue warfarin and start dabigatran when the INR is below 2.0
Rivaroxaban - Prescribing Info

- Dose 20 mg q.h.s @ meal if CrCl > 50 ml/min
- Dose 15 mg q.h.s @ meal if CrCl 15-50 ml/min
  - (beware CYP 3a4-dilt, amio verapamil, dronaderone)
- When Δ from warfarin start rivaroxaban when INR is 3.0
- When Δ from rivaroxaban to warfarin consider stopping rivaroxaban, starting parenteral agent and warfarin together
Case

Which is a good candidate for dabigatran

- a) 66 yo w/ AFIB, ESRD, poorly controlled INR admitted with TIA
- b) 66 you with AFIB & MVR
- c) 83 yo 50 kg woman with CRI (Cr Cl 30 ml/min) with new AFIB
- d) none of the above
ARISTOTLE
Apixaban versus Warfarin in Patients with Atrial Fibrillation

Christopher B. Granger, M.D., John H. Alexander, M.D., M.H.S., John J.V. McMurray, M.D., Renato D. Lopes, M.D., Ph.D., Elaine M. Hylek, M.D., M.P.H., Michael Hanna, M.D., Hussein R. Al-Khalidi, Ph.D., Jack Ansell, M.D., Dan Atar, M.D., Alvaro Avezum, M.D., Ph.D., M. Cecilia Bahit, M.D., Rafael Diaz, M.D., J. Donald Easton, M.D., Justin A. Ezekowitz, M.B., B.Ch., Greg Flaker, M.D., David Garcia, M.D., Margarida Geraldes, Ph.D., Bernard J. Gersh, M.D., Sergey Golitsyn, M.D., Ph.D., Shinya Goto, M.D., Antonio G. Hermosillo, M.D., Stefan H. Hohnloser, M.D., John Horowitz, M.D., Puneet Mohan, M.D., Ph.D., Petr Jansky, M.D., Basil S. Lewis, M.D., Jose Luis Lopez-Sendon, M.D., Prem Pais, M.D., Alexander Parkhomenko, M.D., Freek W.A. Verheugt, M.D., Ph.D., Jun Zhu, M.D., Lars Wallentin, M.D., Ph.D., for the ARISTOTLE Committees and Investigators

Granger CB, N Engl J Med
September 15, 2011
ARISTOTLE: APIXABAN V WARFARIN in AFIB

5mg BID
20% prior CV


↓ stroke 21%
↓ major bleed 13%
↓ death 11%*

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A Primary Outcome: Stroke or Systemic Embolism

B Major Bleeding

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AVERROES - Apixaban v ASA in AFIB


Cumulative stroke risk
3.7% v 1.6%
If hx stroke
8.3% v 2.5%

Major bleeding
1.2% v 1.4%
More minor bleeding with apixaban
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>

SCHOOL OF MEDICINE * UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
# AFIB Treatment Cost

<table>
<thead>
<tr>
<th>Medication</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>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>
## 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: <strong>Recurrent VTE</strong> vs. warfarin (95% CI)</th>
<th>HR: <strong>Major Bleeding</strong> 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>ONGOING</td>
<td></td>
<td></td>
<td></td>
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<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>
</tbody>
</table>

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

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

Six months later your patient on dabigatran informs you that he is having a laproscopic cholecystectomy for recurrent cholecystitis. His procedure is next week. He wants to know when he should stop his dabigatran.
## Dabigatran Perioperative Management

<table>
<thead>
<tr>
<th>Renal Function †</th>
<th>t1/2</th>
<th>Procedure associated with <strong>standard</strong> risk of bleeding (mild-to-moderate residual anticoagulant effect present at surgery)</th>
<th>Procedure associated with <strong>high</strong>* risk of bleeding (no or minimal residual anticoagulant effect is present at surgery)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-op</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CrCl &gt;50 ml/min</td>
<td>13-15</td>
<td>Stop dabigatran 1 day before procedure (Take last dose 2 days before procedure)</td>
<td>Stop dabigatran 2 – 4 days before procedure (Take last dose 3 – 5 days before procedure)</td>
</tr>
<tr>
<td>CrCl 30-50 ml/min</td>
<td>15-18</td>
<td>Stop dabigatran at least 2 days before procedure (Take last dose at least 3 days before procedure)</td>
<td>Stop dabigatran 3 – 4 days before procedure (Take last dose 4 – 5 days before procedure)</td>
</tr>
<tr>
<td><strong>Post-op</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(all patients)</td>
<td>n/a</td>
<td>Consider resuming therapy 24 – 72 hrs or longer postoperatively and when hemostasis has been achieved, depending on bleeding risk of procedure and the patient’s thromboembolic risk‡</td>
<td></td>
</tr>
</tbody>
</table>
### Rivaroxaban Perioperative Management

<table>
<thead>
<tr>
<th>Renal Function</th>
<th>Half-Life (hours)</th>
<th>Any procedure requiring interruption of anticoagulation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-op</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal or mild renal impairment (CrCl &gt; 50 ml/min)</td>
<td>5-9</td>
<td>Stop rivaroxaban 1 day before procedure (Take last dose 2 days before procedure)</td>
</tr>
<tr>
<td>Moderate renal impairment (CrCl 30-50 ml/min)</td>
<td>11-13 noted in elderly</td>
<td>Stop rivaroxaban at least 2 days before procedure (Take last dose at least 3 days before procedure)</td>
</tr>
<tr>
<td><strong>Post-op</strong></td>
<td>(all patients)</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consider resuming therapy 24 – 72 hrs or longer post-operatively and when hemostasis has been achieved, depending on bleeding risk of procedure and the patient’s thromboembolic risk‡</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?
Management of NOAC Bleeding

- Discontinue drug
- Consider activated charcoal orally
- Maintain adequate diuresis
- Check PTT/ TT(dabigatran) or PT(riva)
- Dabigatran 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
Spontaneous Intraparenchymal Hemorrhage

- STAT bloods: Emergency Hemorrhage Panel (PT/INR, fibrinogen, platelets, hematocrit), as well as PTT, TT, anti-Xa level and plasma-diluted thrombin time/DTI assay
- Type and Screen – EMERGENCY
- If crash craniotomy considered, request 2 Units emergent uncrossmatched Group O (universal donor) packed red blood cells.

**IF ON DABIGATRAN** (direct thrombin inhibitor)
and TT and/or DTI assay prolonged

**IF ON RIVAROXABAN or ARIXABAN** (factor Xa inhibitor)
and PT/INR is prolonged or anti-Xa level elevated

IF ingestion within 2 hrs, give one dose activated charcoal orally

• infuse 25 units/kg* body weight** PCC*** over 10 minutes, not to exceed 2 ml/min
• (at the same time) order “2 units thawed plasma (FFP) STAT” and transfuse 2 units universal-donor (AB) thawed plasma (FFP). At HMC, call Transfusion Services (4-3088) and request 2 units emergency release thawed AB plasma

Check the following labs at 1 hour and 24 hours after completion of above PCC infusion:
PT/INR, TT, EKG and Cardiac enzymes, Fibrinogen, D-dimer, DTI assay and anti-Xa level

(TT, DTI, PT/INR and anti-Xa levels alone should not guide decisions on repeating a Bebulin dose, which should only be done in extreme circumstances.)

Emergent dialysis may be considered in certain circumstances (renal failure, overdose): ^ 65% removed by hemodialysis
Dabigatran t ½ = 14 hrs (up to 34 hrs in severe renal impairment)

Rivaroxaban and Apixaban are NOT dialyzable
Rivaroxaban t 1/2 = 9 hrs (longer in renal impairment)
Apixaban t 1/2 = 12 hrs (longer in renal impairment)

* rounded to nearest vial size
** in obese patients (BMI>30), use maximum weight of ideal body weight + 20%
*** PCC = Prothrombin Complex Concentrate; preferred agent is Bebulin
Case

- A 65 obese man with OA, COPD is POD #4 s/p total hip arthroplasty and is ready to go home. For DVT prophylaxis you prescribe:
  a) LMWH for 10-14 days
  b) LMWH for at least one month
  c) Rivaroxaban for 10-14 days
  d) Rivaroxaban for at least one month
  e) Warfarin for 2-4 weeks
NEW CHEST GUIDELINES

“We recommend the use of LMWH, fondaparinux, dabigatran, apixaban, rivaroxaban (THA TKA only), UFH, warfarin for a minimum of 10 to 14 days.”

Yngve FY et al. CHEST 2012 141(2)( Suppl)
<table>
<thead>
<tr>
<th>Trial</th>
<th>Setting</th>
<th>Enoxaparin regimen</th>
<th>Rivaroxaban regimen</th>
<th>DVT/PE/death (%)</th>
<th>RRR (%)</th>
<th>Symptomatic VTE (%)</th>
<th>ARR(%) /NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>RECORD1, n=4541</td>
<td>Hip arthroplasty</td>
<td>40 mg od, 35 d</td>
<td>10 mg od, 35 d</td>
<td>3.7 vs 1.1</td>
<td>70</td>
<td>—</td>
<td>2.6%/38</td>
</tr>
<tr>
<td>RECORD2, n=2509</td>
<td>Hip arthroplasty</td>
<td>40 mg od, 10-14 d</td>
<td>10 mg od, 31-39 d</td>
<td>9.3 vs 2.0</td>
<td>79</td>
<td>1.2 vs 0.2</td>
<td>7.3%/14</td>
</tr>
<tr>
<td>RECORD3, n=2531</td>
<td>Knee arthroplasty</td>
<td>40 mg od, 10-14 d</td>
<td>10 mg od, 10-14 d</td>
<td>18.9 vs 9.6</td>
<td>49</td>
<td>2.0 vs 0.7</td>
<td>9.2%/11</td>
</tr>
<tr>
<td>RECORD4, n=3148</td>
<td>Knee arthroplasty</td>
<td>30 mg bid, 10-14 d</td>
<td>10 mg od, 10-14 d</td>
<td>10.1 vs 6.9</td>
<td>31</td>
<td>—</td>
<td>3.2%/31</td>
</tr>
</tbody>
</table>
Rivaroxaban for DVT prevention

- RECORD trials
  - Superior to enoxaparin 40 mg daily and 30 mg BID for DVT prevention
- Approved for THA (35d) & TKA (12d)
- 10 mg po daily
- No coagulation laboratory monitoring
- Avoid if CrCL < 30, monitor for bleeding if CrCL 30-<50, stop if acute renal failure
NEW CHEST GUIDELINES

“We suggest the use of low-molecular-weight heparin in preference to the other agents we have recommended as alternatives (Grade 2C/2B).

We suggest extending thromboprophylaxis for up to 35 days (Grade 2B)”

Yngve FY et al. CHEST 2012 141(2)( Suppl)
OTHER HEADLINES

- ASA for secondary prevention of VTE
- DVT prophylaxis for high risk medical patients only
- Only select patients should continue ASA while on warfarin
Aspirin for Prevention of Recurrent VTE.

Recurrent VTE
• ASA 6.6%
• Placebo 11.2 %
• ↓ VTE 40%
• No difference in major bleeding

NEW CHEST GUIDELINES

For acutely ill hospitalized medical patients at low risk of thrombosis, we recommend against the use of pharmacologic prophylaxis or mechanical prophylaxis (Grade 1B)

Khan SR et al. CHEST 2012 141(2)( Suppl)
### Padua Risk Assessment Model*

RAM Score $\geq 4 = \text{high risk of VTE}$

<table>
<thead>
<tr>
<th>Points</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>CA, past VTE, mobility, thrombophillic condition</td>
</tr>
<tr>
<td>2</td>
<td>Trauma or surgery in past month</td>
</tr>
<tr>
<td>1</td>
<td>$\geq 70$, CHF, AMI, ischemic CVA, BMI $\geq 30$, hormones, other*</td>
</tr>
<tr>
<td></td>
<td>* acute infectious or rheumatologic disorder</td>
</tr>
</tbody>
</table>

### Prospective Cohort Study

<table>
<thead>
<tr>
<th>Patient Groups</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Padua Score</td>
<td>RAM $\geq 4$</td>
<td>RAM $\geq 4$</td>
<td>RAM $&lt; 4$</td>
</tr>
<tr>
<td>VTE Frequency</td>
<td>4/186 (2.2%)</td>
<td>31/283 (11.0%)</td>
<td>2/711 (0.3%)</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>0.13</td>
<td>32.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>95% CI, 0.04-0.40</td>
<td>95% CI, 4.1-251.0</td>
<td></td>
</tr>
<tr>
<td>Bleeding Risk</td>
<td>-</td>
<td>3/186 (1.6%)</td>
<td>-</td>
</tr>
</tbody>
</table>

Kahn SR. Chest. 2012; Barbar SJ Thromb Haemost 2010
VTE Prophylaxis in Medical Patients

HIGH RISK 11% 90-day risk
Padua score ≥ 4

LOW RISK 0.3% 90-day risk
Padua score <4

- NOT FOR CRITICALLY ILL-THEY ALL GET PROPHYLAXIS
- Previous VTE/active cancer only scores 3-? Should they also receive prophylaxis
Case

A 65 year old man with history of HTN and hyperlipidemia is admitted with a new PE. He is on ASA and statin. He is started on LMWH and bridged to warfarin. You

A) stop his aspirin now that he is on warfarin due to concerns of increased risk of bleeding

B) continue ASA for primary prophylaxis
Risk of Bleeding With Single, Dual, or Triple Therapy With Warfarin, Aspirin, and Clopidogrel in Patients With Atrial Fibrillation

warfarin + asa = 2x
warfarin + asa + clopidigrel = 3x

Hansen M et al. Arch Intern Med. 2010
NEW CHEST GUIDELINES

- “For patients taking warfarin we suggest AVOIDING concomitant antiplatelet therapy except where benefit is likely to be greater than harm: valves, ACS, stents, CABG” (2C)

Holbrook A et al. CHEST 2012 141(2)( Suppl)
New Oral Anticoagulants
Take Home Points

- No lab testing required
- Independent of vitamin K
- No need for frequent visits

- No way to test anticoagulant effect
- No way to reliably reverse anticoagulant effect
- Need to create structure to monitor patient
Take Home Points

- These agents DO need monitoring, just not by INR-transition time critical
- Proper patient selection critical to avoid potentially fatal complications
- Patient education perhaps even more important as they will probably not be plugged into an anticoagulation program
- No reversal agent for any of these. Know your options. Be sure your institution has reversal protocols.
THE WORKSHOP

- Duration of therapy for VTE
- Thrombophilia work up
- Periop management of anticoagulation
- Identifying candidates for outpatient PE treatment
- IVC filters
- Anticoagulation dosing pearls
- Treatment of distal DVT
- Management line associated DVT