New Anticoagulants: Pros and Cons
New Anticoagulants

**Oral Anti-Xa**
- Rivaroxaban
- Apixaban
- Betrixaban
- Edoxaban
- Eribaxaban
- YM150
- Many others

**Oral Anti-thrombin**
- Dabigatran
- AZD0837
- Others

**Oral Anti-IX**
- TTP889
- RB006

**Parenteral Anti-Xa**
- Idraparinux
- Idrabiotaparinux

**Parenteral Antithrombin**
- Desirudin
- Others
Targets of New Oral Anticoagulant Drugs

- Apixaban
- Rivaroxaban
- Edoxaban
- Dabigatran
# Atrial Fibrillation / VTE Trials for Oral DTIs/Factor Xa Inhibitors*

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<th>Drug</th>
<th>AF trials</th>
<th>VTE Treatment</th>
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<td>Dabigatran</td>
<td>RE-LY</td>
<td>RECORD</td>
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<tr>
<td>Rivaroxaban</td>
<td>ROCKET</td>
<td>EINSTEIN</td>
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<tr>
<td>Apixaban</td>
<td>ARISTOTLE</td>
<td>AMPLIFY</td>
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<td>Edoxaban</td>
<td>ENGAGE-AF TIMI 48</td>
<td>HOKUSAI</td>
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*VTE prophylaxis trials also underway / completed
Dabigatran exetilrate

- Approved by FDA for prevention of stroke and systemic embolism in patients with atrial fibrillation (AF) in October, 2010.
- Approved in 75 countries
Dabigatran etexilate – Oral DTI

- Oral direct inhibitor of thrombin.
- Rapidly converted by ubiquitous esterases to active drug
- Administered in fixed doses – no coagulation monitoring
- Excreted by the kidney, half-life of 12 to 17 h.
- Similar efficacy and safety to enoxaparin for the prevention of VTE in patients s/p THR or TKR\(^1,2\)
- Superior safety to warfarin with equivalent efficacy (110 mg q12h) (stroke prevention in AF)\(^3\)
- Superior efficacy to warfarin with similar safety (150 mg q12h) (stroke prevention in AF)\(^3\)

Cumulative Risk of Recurrent VTE or Related Death during 6 Months of Treatment among Patients Randomly Assigned to Dabigatran or Warfarin

- Recurrent VTE:
  - Dabigatran: 30/1274 (2.4%)
  - Warfarin: 27/1265 (2.1%)
  - P < 0.001 for prespecified noninferiority margin

- Major Bleeding:
  - Dabigatran: 20/1274 (1.6%)
  - Warfarin: 24/1265 (1.9%)
  - P < 0.001 (for noninferiority)

Dabigatran etexilate
Prescription Information

- **Dosing**
  - Oral: 150mg twice daily

- **Renal impairment:**
  - Clcr 15-30 mL/min: 75mg twice daily
  - Clcr <15 mL/min: no recommendation

- **Hepatic impairment:** No adjustment required

Accessed on 10/29/2010
Dabigatran: Use in 30 days!

- Dabigatran in bottle should be used within 30d of opening.
- This will only affect those whose dabigatran is dispensed in a bottle (customary method in retail pharmacies).
- In all other markets, dabigatran is only in blister packs.
- Dispensed in bottles of 60 capsules (1 mo. supply)
- If you capsules not used within 30 days, patient must dispose of remaining capsules and start new bottle.
- Tell your patient!
RIVAROXABAN
Rivaroxaban – THA / TKA: The RECORD Trials

- **RECORD 1:** Rivaroxaban 10 mg qd was significantly more effective for extended prophylaxis than 40 mg of enoxaparin in THA. The two drugs had similar safety profiles (4541 patients randomized).

- **RECORD 2:** Rivaroxaban was significantly more effective for extended prophylaxis than short-term enoxaparin for the prevention of VTE, including symptomatic events, in patients undergoing THA.

- **RECORD 3:** Rivaroxaban was superior to enoxaparin 40 mg qd for prophylaxis in TKA with similar rates of bleeding.

- **RECORD 4:** Rivaroxaban 10 mg qd for 10 to 14 days was significantly superior to SC enoxaparin 30 mg q12h for prevention of VTE after TKA.


Conclusions:

For symptomatic DVT, rivaroxaban is as effective as enox / VKA in the short-term and more effective than VKA for continued therapy. The bleeding risk was low in the trial.

The Einstein Investigators. NEJM Dec 23, 2010
Magellan: Prevention of VTE with Extended Prophylaxis in Medically Ill with Rivaroxaban

- The primary efficacy end point is a composite of asymptomatic proximal DVT detected by bilateral ultrasound, symptomatic DVT, non-fatal PE and VTE-related death
- The safety end points are major bleeding and clinically relevant non major bleeding
Magellan: Prevention of VTE with Extended Prophylaxis in Medically Ill with Rivaroxaban

- 8,101 patients randomized to either oral rivaroxaban (10 mg qd) x 35 d or SC enoxaparin (40 mg qd) for 10 d followed by placebo.
- Primary efficacy measure = composite of asymptomatic proximal DVT, symptomatic DVT, symptomatic non-fatal PE, and VTE-related death.

- At 10d, rivaroxaban noninferior to enoxaparin
  - Outcome reached by 2.7% of patients in both groups (RR = 0.968; p=0.0025).

- At 35d rivaroxaban significantly better than enoxaparin and placebo, as the composite endpoint reached by 4.4% of patients in rivaroxaban group compared to 5.7% in enoxaparin and placebo group (RR 0.771, p=0.0211).

Cohen AT, et al. ACC April 5, 2011
However, there was a significantly increased risk of bleeding in the rivaroxaban group at both 10 d and 35 d.

At 10 d, clinically relevant bleeding occurred in 2.8% of rivaroxaban patients versus 1.2% of patients in the enoxaparin group (RR=2.3; p< 0.0001).

At 35 days, clinically relevant bleeding occurred in 4.1% of patients in the rivaroxaban group versus 1.7% of patients in the enoxaparin group (RR=2.5; p<0.0001).

Cohen AT, et al. ACC April 5, 2011
ADVANCE-3: Apixaban Versus Enoxaparin for Thromboprophylaxis after THR

- Major VTE occurred in 0.5% of patients prophylaxed with apixaban and 1.1% of patients prophylaxed with enoxaparin (for ≥ 32 days).

- During f/u prophylaxis (60 days after the last dose of study drug was given):
  - Symptomatic VTE/death in none of apixaban patients
  - Symptomatic VTE/death in six patients prophylaxed with enoxaparin.

- Rates of clinically adjudicated major bleeding were similar in both treatment arms:
  - 0.8% of patients treated with apixaban
  - 0.7% of patients treated with enoxaparin

- Composite of major and clinically relevant nonmajor bleeding occurred in:
  - 4.8% of the apixaban patients
  - 5.0% of the enoxaparin patients (NS).

Lassen, et al. NEJM Dec 23, 2010
Edoxaban

- Early phase for AF in U.S. and Japan are completed (approx 2,000 patients)
- **Two Phase III** studies for prevention of VTE were initiated in March 2009, both in Japan. About 600 THR and 520 TKR patients were recruited for the two randomised, D-B studies.
- Daiichi Sankyo filed the NDA for edoxaban in Japan following completion of these two trials.
- ENGAGE AF-TIMI 48, begun late 2009 (1400 centers, 46 countries).
  - It compared edoxaban 30 mg or 60 mg QD with warfarin in approx 20,000 patients with AF and has completed recruitment.
- The second trial, called Hokusai, announced in Feb 2010, will include 7,500 patients at 450 centers across 40 countries.
  - It will test the drug's safety and efficacy in reducing recurrent VTE in DVT and PE.
Betrixaban

- Merck has returned rights to Portola (3/24/11)
- Beginning Phase III trials
- “Working on a factor Xa inhibitor antidote.”
New Parenteral Anticoagulants:
Desirudin (Ipravask)
New Direct Thrombin Inhibitor Becomes Available

- Desirudin (a DTI) was FDA-approved in 2003 but not immediately launched, became available in March 2010.
- Similar in structure to hirudin and selectively inhibits free circulating and clot-bound thrombin.
- FDA-approved for prevention of DVT in elective THR.
- Dose = 15 mg SC q12h (first dose given up to 15 min before surgery but after induction of regional anesthesia).
- With moderate renal insufficiency, start with 5 mg q12 h.
- With severe renal insufficiency, start with 1.7 mg q12 h.
- aPTT and serum creatinine should be monitored at least qd and used as basis for dose adjustments.
Aptamers

- Pegnivacogin is an aptamer.

- Aptamers are single stranded oligonucleotides that adopt a specific conformation enabling direct, specific inhibition of a targeted protein.

- A key unique feature of aptamers derives from the fact that they are formed from nucleic acids.

- Their pharmacologic activity can be controlled by a matched, complementary oligonucleotide active control agent which binds to the aptamer, removing it from its target and reversing its biologic effects; i.e., antidote.

- Anivamersen is the complementary active control agent of pegnivacogin.
Reg 1 and Reg 2
(Pegnivacogin paired with IV anivamersen)

- **REG1**: (Intravenous)
  - Intended for application in arterial thrombosis indications, such as ACS patients undergoing PCI.
  - ACS data presented at ACC 2011 (Povsic, et al)

- **REG2** (Subcutaneous depot formulation).
  - Plan is for use in VTE prophylaxis in abdominal surgery patients.
<table>
<thead>
<tr>
<th>Advantage</th>
<th>Clinical Implications</th>
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<tr>
<td>Rapid onset of action</td>
<td>No need for bridging</td>
</tr>
<tr>
<td>Predictable anticoagulant effect</td>
<td>No need for routine coagulation monitoring</td>
</tr>
<tr>
<td>Specific coag enzyme target</td>
<td>Low risk of off-target adverse effects</td>
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<tr>
<td>Minimal food interactions</td>
<td>No dietary precautions</td>
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<tr>
<td>Minimal drug interactions</td>
<td>Fewer drug restrictions</td>
</tr>
<tr>
<td>Low potential for HIT</td>
<td>Clinical very important! Safer!</td>
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Conclusions:

- Heparin and warfarin have served us well.
- Newer oral anticoagulants have better bioavailability and do not require monitoring.
- Dabigatran has been approved for anticoagulation in setting of atrial fibrillation.
- Cost may be a problem
- Renal insufficiency must be considered
- Rivaroxaban and apixaban are coming soon.
- Newer parenteral anticoagulants (desirudin) are available.
- Aptamers appear promising, particularly with regard to reversing anticoagulant effects.