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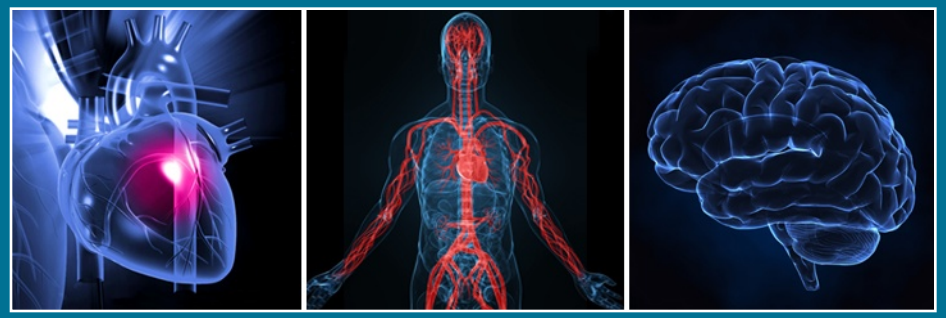

# New Anticoagulants Therapies

*Rachel P. Rosovsky, MD, MPH*
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MASSACHUSETTS
GENERAL HOSPITAL

**Department of
Hematology/Oncology**

# Conflicts of Interest

No disclosures

# Agenda

- Historical perspective
- Novel oral anticoagulants
  - Stats
  - Trials
  - Approval
  - Concerns/Limitations
  - Advantages/Disadvantages
  - How to treat bleeding

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# Novel Oral Anticoagulants

- Until recently, vitamin K antagonist was the only available orally active anticoagulant.
- The novel oral anticoagulants:
  - can be given in fixed doses
  - do not require routine monitoring
  - have fewer food or drug interactions
  - are more predictable.

# Novel Oral Anticoagulants

- Xarelto: Rivaroxaban
- Pradaxa: Dabigatran
- Eliquis: Apixaban
- Savaysa: Edoxaban

# Rivaroxaban

- ***Stats***
  - Oral direct factor Xa inhibitor
  - Rapid onset: 2.5-4 hours
  - T1/2 life: 11-13 hours
  - Excretion: renal.
  - Dosing:
    - For post operative thromboprophylaxis in orthopedic surgery
      - 10 mg/day
    - For non valvular Afib (to prevent strokes and systemic embolism)
      - 20 mg/day
    - For VTE
      - 15 mg/bid x 3 weeks and then 20 mg/day.

NVAF = non valvular atrial fibrillation
VTE = venous thromboembolism



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# Rivaroxaban

- ***Trials***
  - ROCKET
    - Prevention of stroke/VTE in atrial fibrillation
  - RECORD 1-4
    - Prevention of VTE after orthopedic procedures
  - EINSTEIN
    - Treatment of VTE
  - MAGELLAN
    - Extended Duration
- ***Approval***
  - VTE prevention after hip or knee arthroplasty
  - VTE treatment and for stroke prevention in non valvular atrial fibrillation.
  - VTE treatment and reduction in risk of recurrent VTE.

# EINSTEIN: Acute DVT Study

| Outcome | Rivaroxaban | LMWH/VKA or placebo | 95% CI; p value |
|---|---|---|---|
| Recurrent VTE (initial) | 2.1% | 3.0% | HR 0.68;<br>95% CI, 0.44 to 1.04;<br>P<0.001 (non inferior) |
| Recurrent VTE (continued) | 1.3% | 7.1% | HR 0.18;<br>95% CI, 0.09 to 0.39;<br>P<0.001 |
| Major Bleeding (initial) | 8.1% | 8.1% | NS |
| Non fatal Bleed (continued) | 0.7% | NA | P=0.11 |

Einstein Investigators. NEJM 2010;363:2499-2510

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# Rivaroxaban

- ***Renal and hepatic issues:***
  - Not recommended for creatinine clearance <30 mL/min.
  - Contraindicated for creatinine clearance <15 mL/min or significant hepatic impairment (Child-Pugh Class B and C).
  - Must take with food.
- ***Drug Interactions***
  - Potent inhibitors of CYP-3A4 & P-glycoprotein efflux transporter (ketoconazole, ritonavir, clarithromycin) - use contraindicated.
  - Potent inducers of CYP-3A4 (eg, rifampin, carbamazepine, St. John's wort) may reduce rivaroxaban's effects.
- ***Hemorrhage:*** there is no specific antidote.
  - Drug discontinuation since short half-life.
  - Over 90% protein bound - cannot be dialyzed
  - Charcoal hemofiltration has been suggested.
  - Life-threatening bleeding: options?

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# Dabigatran

- ***Stats***
  - Oral direct thrombin inhibitor (DTI)
  - Rapid onset: 2 hours
  - T1/2 life: 12-17 hours
  - Clearance: renal
  - Dosing: 150 mg bid (adjust if renal failure)
- ***Monitoring***: no need because of predictable PK
- ***Trials***
  - RE-LY
    - Prevention of stroke/VTE in atrial fibrillation
  - RE-MODEL, RE-NOVATE, RE-MOBILIZE
    - Prevention of VTE after orthopedic procedures
  - RE-COVER, RE-MEDY and RE-SONATE
    - Treatment of VTE

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# Dabigatran

- ***Approval***
  - To prevent stroke and systemic embolism in patients with nonvalvular atrial fibrillation.
  - To treat deep vein thrombosis and pulmonary embolism in patients who have been treated with a parenteral anticoagulant for 5-10 days
  - To reduce the risk of recurrence of deep vein thrombosis and pulmonary embolism in patients who have been previously treated.

# Dabigatran: RE-COVER

| Outcome | Dabigatran | Warfarin | 95% CI; p value |
|---|---|---|---|
| **Recurrent VTE** | 2.4% | 2.1% | -0.8 to 1.5; P<0.001 for prespecified noninferiority margin |
| **Major Bleed** | 1.6% | 1.9% | 0.45 to 1.48; P = 0.38 |
| **Any Bleed** | 16.1% | 21.9% | 0.59 to 0.85; P<0.001 |
| **Adverse event lead stopping** | 9.0% | 6.8% | P=0.05 |

**Schulman et al. NEJM 2009;361:2342-2352**

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# Dabigatran

- ***Limitations***
  - The first dose of dabigatran was given only after initial parenteral anticoagulation therapy had been administered for a median of 9 days.
  - FDA approval is for its use only after parenteral anticoagulation and not as monotherapy.

# Dabigatran

- ***Hemorrhage***
  - Stop drug.
    - Half life:
      - 13 hours (11-22)  if creatinine clearance > 80 mL/min
      - 18 hours (13-23) if creatinine clearance 30-50 mL/min
  - For patients with normal renal function, you can expect effects to be gone in 72-96 hours.
  - Obtain stat aPTT and PT-INR.
    - If normal, suggests Dabigatran effect gone.
  - Identify cause of bleeding
  - Be wary of giving procoagulant drugs as patients on DTI have underlying procoagulant condition.
  - Treat supportively with RBC.
  - Other options

# Dabigatran

- Patients on DTI are not deficient in coagulation factors.
- DTI unrelated to fibrinolytic or Vitamin K dependent pathways.
- Inhibits last enzymatic step in coag cascade. Agents that stimulate cascade or replace coag factors proximal to thrombin won't compensate for profound terminal defect in hemostasis.

# Dabigatran: Concerns

- Unclear how to use in individuals with low body weight or those who are morbidly obese.
- Drug interactions: p-glycoprotein
  - Inhibit (increases drug effect):
    - ketoconazole, quinidine, amiodarone, verapamil
  - Induce (decreases drug effect):
    - rifampin, St.John's wart

***These drugs may also interact with warfarin but you can monitor that with INR***

# Apixaban

- ***Stats***
  - Oral direct factor Xa inhibitor
  - Rapid onset: 3-4 hours
  - T1/2 life: 8-15
  - Excretion: 25% renal and feces
  - 87% protein bound so no role for hemodialysis
  - Dosing:
    - For post operative thromboprophlylaxis in orthopedic surgery.
      - 2.5 mg bid
    - For prevention of stroke in NVAF:
      - 5 mg bid
      - Patients with 2 following factors: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL, dose is 2.5 mg bid.
    - For treatment of VTE:
      - 10 mg bid for 7 days followed by 5 mg bid.
    - For reducing risk of recurrent VTE following initial therapy:
      - 2.5 mg bid

# Apixaban Trials

- ***Trials***
  - ARISTOTLE and AVERROES
  - ADVANCE 1,2, and 3
  - AMPLIFY
  - Extended VTE treatment: ADOPT trial
- ***Approval:***
  - To reduce the risk of stroke and systemic embolism in patients with nonvavular atrial fibrillation.
  - To treat VTE and to reduce risk of recurrent VTE following initial therapy.

# Apixaban: AMPLIFY

| Outcome | Apixaban (n=2691) | VKA (n=2704) | RR (95% CI); p value |
|---|---|---|---|
| **Primary (1st recurrent VTE or VTE-related death)** | 59 (2.3%) | 71 (2.7%) | 0.84 (0.60 to 1.18); P<0.001 for noninferiority. |
| **Safety Outcome** | 115 (4.3%) | 261 (9.7%) | 0.44; (0.36 to 0.55); P<0.001 for superiority. |
| **Major Bleeding** | 15 (0.6%) | 49 (1.8%) | 0.31; (0.17–0.55); P<0.001 for superiority |

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Agnelli et al. N Engl J Med 2013;369:799-808.

# Edoxaban

- ***Stats***
  - Oral direct factor Xa inhibitor
  - Rapid onset: 1-2 hours
  - T1/2 life: 10-14 hours
  - Excretion: renal.
  - Dosing:
    - For treatment of NVAF:
      - 60 mg daily if CrCL >50 to ≤ 95 mL/min.
      - 30 mg daily if creatinine clearance 15 to 50 mL/min.
      - **Do not use in patients with CrCL > 95 mL/min**.
    - For treatment of DVT and PE: after initial parenteral agent
      - 60 mg once daily.
      - 30 mg daily if CrCL 15 to 50 mL/min or weight < 60 kg.

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# Edoxaban

- ***Trials***
  - ENGAGE AF-TIMI 48
    - Prevention of stroke/VTE in atrial fibrillation
  - Hokusai VTE
    - Treatment of VTE
- ***Approval***
  - To reduce risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF).
  - For the treatment of deep vein thrombosis and pulmonary embolism following 5 to 10 days of initial therapy with parenteral anticoagulant.

# Edoxaban: Hokusai VTE Study

| Outcome | Edoxaban (n=4118) | VKA (n=4122) | 95% CI; p value |
|---|---|---|---|
| **Primary (1st recurrent VTE or VTE-related death)** | 130 (3.2%) | 146 (3.5%) | 0.70 to 1.13; P<0.001 for noninferiority. |
| **Safety Outcome** | 349 (8.5%) | 423 (10.3%) | 0.71 to 0.94; P = 0.004 for superiority. |
| **Major Bleeding** | 56 (1.4%) | 66 (1.6%) | 0.84 (0.59–1.21) P = 0.35 for superiority |

**Hokusai-VTE Investigators. N Engl J Med. 2013;369:1406-15.**

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# Edoxaban

- ***Concerns***
  - Should not be used in patients with CrCL > 95 mL/min because of an increased risk of ischemic stroke compared to warfarin.
  - Should not be used in patients with moderate or severe hepatic impairment (Child-Pugh B and C) as these patients may have intrinsic coagulation abnormalities. No dose reduction is required in patients with mild hepatic impairment.

**Hokusai-VTE Investigators. N Engl J Med. 2013;369:1406-15.**

# Edoxaban

- ***Limitations***
  - Need for heparin lead-in BUT it may have encouraged investigators to enroll a higher proportion of patients with severe grades of VTE.
- ***Potential Advantage***
  - Approximately one third patients had right ventricular dysfunction. There was reduction in recurrences among patients with elevated NT-proBNP levels in edoxaban group.
    - Rate of recurrent VTE in this subgroup was 3.3% in the edoxaban group and 6.2% in the warfarin group (HR, 0.52; 95% CI, 0.28 to 0.98).

# Cautions with Novel Oral Anticoagulants

- No reversal agent (but currently in trials)
- No monitoring for effect
- Adherence
- Compliance
- Renal and hepatic failure
- Reimbursement issues
- Post marketing bleeding rates
- Long term safety data
- Clinician familiarity
- Lack of guidelines
  - procedures or bleeding complications

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# Advantages with Novel Oral Anticoagulants

- Oral
- No need for monitoring
- No need for titration or dose adjustments
- Short onset
- Short half life
- Predictable absorption and metabolism
- Fewer drug-drug interactions
- Fewer dietary restrictions

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# Novel oral anticoagulants: Important questions

- How to treat patients on new oral anticoagulants who develop hemorrhage.
- How does one decide which novel oral anticoagulant to use?
  - Depends on patient factors

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