What’s New on the Horizon in Pharmacology for Stroke Prevention?

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March 4, 2013

Objectives

- Review recommendations regarding use of anticoagulation in patients with atrial fibrillation
- Explain pharmacologic properties and other characteristics for novel anticoagulants
- Summarize clinical trial data for novel anticoagulants
- Considerations in selecting anticoagulant therapy for stroke prevention
Atrial Fibrillation

- Overall Prevalence of 5.5%
  - 17.8% in individuals ≥ 85 years old
- Major risk factor for stroke
- The rate of ischemic stroke among patients with nonvalvular atrial fibrillation averages 5% per year


Risk score for Stroke

\[ \text{CHADS}_2 \rightarrow \text{CHA}_2 \text{DS}_2 \text{VASc} \]

<table>
<thead>
<tr>
<th>CHADS2 Risk</th>
<th>Score</th>
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<tbody>
<tr>
<td>CHF</td>
<td>1</td>
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<tr>
<td>Hypertension</td>
<td>1</td>
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<tr>
<td>Age &gt; 75</td>
<td>1</td>
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<tr>
<td>Diabetes</td>
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<tr>
<td>Stroke or TIA</td>
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<tr>
<th>CHA2DS2-VASc Risk</th>
<th>Score</th>
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<tbody>
<tr>
<td>CHF or LVEF ≤ 40%</td>
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<tr>
<td>Hypertension</td>
<td>1</td>
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<tr>
<td>Age ≥ 75</td>
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<tr>
<td>Diabetes</td>
<td>1</td>
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<tr>
<td>Stroke/TIA/Thromboembolism</td>
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<tr>
<td>Vascular Disease</td>
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<td>Age 65 - 74</td>
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<tr>
<td>Female</td>
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From ESC AF Guidelines
CHEST Guidelines 9th ed. Updates

- CHADS2 = 0 – ASA 75mg-325mg (Grade 2B)
- CHADS2 = 1 – Oral Anticoagulation rather than ASA or combination therapy of clopidogrel/ASA (Grade 2B)
- CHADS2 ≥2 – Oral Anticoagulation (Grade 1B)

- If recommendations in favor of oral anticoagulation (intermediate and high risk groups w/ NVAF), suggest dabigatran 150 mg twice daily rather than adjusted-dose VKA therapy (target INR range, 2-3) (Grade 2B).

CHEST 2012; 141(2)(Suppl):e531S–e575S

Anticoagulants

Old
- Vitamin K Antagonist
  - Warfarin

Novel
- Direct Thrombin Inhibitor
  - Dabigatran (Pradaxa®)

- Factor Xa Inhibitors
  - Rivaroxaban (Xarelto®)
  - Apixaban (Eliquis®)
Vitamin K Antagonist (VKA)

- Warfarin
- 64% risk reduction for stroke vs. placebo
- 37% risk reduction for stroke vs. antiplatelet therapy

Limitations of VKA

- Time
- Monitoring
- Drug-Drug and Food-Drug interactions
- Patient Convenience and Resources (take time off work or activities; transportation)

Novel Anticoagulants
Mechanism of Novel Anticoagulants

Dabigatran (Pradaxa®)

- Gained FDA approval October 2010
- Indication: reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation
- Mechanism of Action: Direct Thrombin Inhibitor

Product Information: PRADAXA(R) oral capsules, dabigatran etexilate mesylate oral capsules. Boehringer Ingelheim Pharmaceuticals, Inc. (per FDA), Ridgefield, CT, 2012.
Dabigatran (Pradaxa®)

• Dosing:
  – CrCl > 30 mL/min: 150mg po bid
  – CrCl 15-30 mL/min: 75 mg po BID

• Monitoring:
  – No routine monitoring
  – Do not check protime/INR
  – ECT and TT may be monitored
  – Periodically check CBC, BMP

Product Information: PRADAXA(R) oral capsules, dabigatran etexilate mesylate oral capsules. Boehringer Ingelheim Pharmaceuticals, Inc. (per FDA), Ridgefield, CT, 2012.

Dabigatran: Pharmacokinetics (PK)

• Dabigatran is a prodrug and converted to active form during metabolism primarily by esterase-catalyzed hydrolysis and conjugation to a lesser degree.
• Absorption: 3-7% bioavailability
• Distribution: 35% plasma protein bound and large volume of distribution
• Metabolism: Not a CYP P450 substrate, inhibitor, or inducer
• Elimination: 80% renal clearance
• Half-life: 12-17 hours in healthy subjects; 14-17 elderly

Product Information: PRADAXA(R) oral capsules, dabigatran etexilate mesylate oral capsules. Boehringer Ingelheim Pharmaceuticals, Inc. (per FDA), Ridgefield, CT, 2012.
Dabigatran: Warnings

- **Contraindications:** Active pathological bleeding, mechanical prosthetic heart valve and history of severe hypersensitivity reaction
- **Warnings/Precautions:** Risk for bleeding; increased risk for stroke with temporary discontinuation of dabigatran; thromboembolic and bleeding events in prosthetic heart valves; use of p-glycoprotein inhibitors/inducers
- **Pregnancy Category C**

Product Information: PRADAXA(R) oral capsules, dabigatran etexilate mesylate oral capsules. Boehringer Ingelheim Pharmaceuticals, Inc. (per FDA), Ridgefield, CT, 2012.

Dabigatran: Adverse Effects

- **Bleeding**
  - Increased bleeding with age
  - Higher incidence of GI bleeding than warfarin
  - Less ICH than warfarin
  - No reversal agent
- **GI:** Dyspepsia, Gastritis-like Symptoms

Product Information: PRADAXA(R) oral capsules, dabigatran etexilate mesylate oral capsules. Boehringer Ingelheim Pharmaceuticals, Inc. (per FDA), Ridgefield, CT, 2012.
Dabigatran: Drug interactions

- No CYP450 interactions
- Interacts with p-glycoprotein inhibitors/inducers
- Inducers: rifampin, carbamazepine, phenytoin – AVOID!
- Inhibitors consist of Amiodarone, Dronedarone, Verapamil, Ketoconazole, Clarithromycin
- Amiodarone: May increase exposure; no dose adjustments
- Dronedarone: CrCl 30-50 mL/min (use 75mg BID); if CrCl < 30 mL/min avoid dabigatran
- Verapamil: Take dabigatran 2 hours prior
- Ketoconazole: Reduce dose of dabigatran if CrCl 30-50 mL/min or avoid if CrCl < 30 mL/min
- Clarithromycin: Avoid using together if CrCl < 30 mL/min
- Anticoagulants/Antiplatelets/NSAIDs – increased risk for bleeding

Product Information: PRADAXA(R) oral capsules, dabigatran etexilate mesylate oral capsules. Boehringer Ingelheim Pharmaceuticals, Inc. (per FDA), Ridgefield, CT, 2012.

Dabigatran: Counseling Tips

- May be taken with or without food
- Instruct patient to swallow capsule whole
- Do not chew, break, or open capsules before swallowing
- If a dose is missed, then take ASAP. If cannot be taken at least 6 hours prior to next dose, then DO NOT DOUBLE!
- Store in original package and keep tightly closed
- Do not discontinue without talking to provider

Product Information: PRADAXA(R) oral capsules, dabigatran etexilate mesylate oral capsules. Boehringer Ingelheim Pharmaceuticals, Inc. (per FDA), Ridgefield, CT, 2012.
RE-LY trial

- Non-inferiority, open-label trial comparing dabigatran 110mg twice daily, 150mg twice daily, and dose-adjusted warfarin; CHADS\textsubscript{2} avg = 2.1
- Primary outcome: composite of stroke or systemic embolism
  - 150mg BID superior to warfarin
- Primary safety outcome: major hemorrhage
  - Less hemorrhagic stroke, life threatening and ICH in dabigatran group
  - GI bleed more common in dabigatran group
  - Less minor bleeding for dabigatran


Rivaroxaban (Xarelto®)

- Gained FDA approval November 2011
- Indication: reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation
- Also indicated for treatment of DVT/PE, reduction of recurrence of DVT/PE, and prophylaxis of DVT after Hip/Knee replacement
- Mechanism of Action: Factor Xa Inhibitor

Rivaroxaban

• Dosing:
  – CrCl > 50 mL/min: 20mg po daily
  – CrCl 20-50 mL/min: 15mg po daily
• Monitoring:
  – No routine monitoring
  – Do not check protime/INR
  – Periodically check CBC, BMP, LFTs


Rivaroxaban: PK

• Absorption: 66% bioavailability in fasting state, but increases with food
• Distribution: highly plasma protein bound (92-95%)
• Metabolism: substrate for CYP 3A4/5 and 2J2
• Elimination: 36% renal elimination
• Half-life 5-9 hours in younger patients, 11-13 hours in elderly patients

Rivaroxaban: Warnings

- Contraindications: Active pathological bleeding or severe hypersensitivity reaction
- Warnings/Precautions: Risk for bleeding, Spinal/Epidural Anesthesia or Puncture, Discontinuing agent, renal and hepatic impairment, use of strong 3A4 inducers/inhibitors and p-glycoprotein, Risk of Pregnancy Related Hemorrhage
- Pregnancy Category C


Rivaroxaban: Adverse Effects

- Bleeding
  - Increased bleeding with age
  - Higher incidence of GI Bleeding than warfarin
  - Less incidence of ICH than warfarin
  - No reversal agent
- No difference in dyspepsia vs. warfarin

Rivaroxaban: Drug Interactions

- Substrate of CYP 3A4/5 and 2J2, and p-glycoprotein
- Avoid use with drugs that are combined strong 3A4 inhibitors/inducers and p-glycoprotein
- Inducers – Avoid use with rifampin, carbamazepine, phenytoin
- Inhibitors – Avoid use with ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, clarithromycin
- Amiodarone, dronedarone, diltiazem, ranolazine, azithromycin, felodipine – use with caution when CrCl < 50mL/min
- Anticoagulants/Antiplatelets/NSAIDs - increased risk for bleeding


Rivaroxaban: Counseling Tips

- Take once daily with evening meal
- May use pill box to store medication
- If a dose is missed, may take on the same day, but DO NOT DOUBLE!
- Do not use with feeding tube
- Advise patients to NOT discontinue without talking to provider

ROCKET AF trial

- Non-inferiority, double-blind, RCT comparing rivaroxaban and dose adjusted warfarin; CHADS2 avg = 3.5

- Primary outcome: composite of ischemic and hemorrhagic stroke and systemic embolism
  - Rivaroxaban non-inferior to warfarin

- Primary safety outcome: Composite of major and non-major clinically relevant bleeding.
  - Incidence of major bleeding and non-clinically relevant bleeding similar
  - More drops in hemoglobin and transfusions needed with rivaroxaban
  - Less hemorrhagic stroke, ICH, and fatal bleeding in rivaroxaban group
  - GI bleed more common in rivaroxaban group
  - Sub analysis showed similar efficacy and bleeding rates between rivaroxaban and warfarin in older patients with moderate renal impairment: (CrCl 30-49 mL/min)


Apixaban (Eliquis®)

- Gained FDA approval December 2012
- Indication: reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation
- Mechanism of Action: Factor Xa Inhibitor

Apixaban: Dosing

- Dosing: 5mg po bid
- 2.5mg po bid if patient has any 2 of the following:
  - Age > 80 y/o
  - Body weight < 60kg
  - SCr ≥ 1.5 mg/dL
- 2.5mg po bid when co-administered with strong dual inhibitors of CYP 3A4 and p-glycoprotein
- Monitoring:
  - No routine monitoring
  - Do not check protime/INR
  - Consider CBC, BMP, LFTs at baseline and periodically


Apixaban: PK

- Absorption: ~50% bioavailability
- Distribution: plasma protein binding 87%
- Metabolism: substrate for CYP 3A4; minor substrate for CYP1A2, 2C8, 2C9, 2C19, and 2J2
- Elimination: 27% renal clearance
- Half-life 12 hrs in healthy subjects

Apixaban: Warnings

- **Contraindications:** Active pathological bleeding or severe hypersensitivity reaction
- **Warnings:** Increased risk for stroke with discontinuation of apixaban, risk for bleeding, prosthetic heart valves
- **Pregnancy Category B** (Not recommended in pregnant patients)
- **Not recommended for severe liver impairment**


Apixaban: Adverse Effects

- **Bleeding**
  - Less ICH compared to warfarin
  - GI bleeding rate is similar to warfarin
  - No reversal agent

Apixaban: Drug Interactions

- Substrate of both CYP3A4 and P-glycoprotein
- Inducers – Avoid use with rifampin, carbamazepine, phenytoin
- Inhibitors – 2.5mg po BID with ketoconazole, itraconazole, ritonavir, or clarithromycin
- Anticoagulants/Antiplatelets/NSAIDs – increased risk for bleeding


Apixaban: Counseling Tips

- May be taken with or without food
- Advise patients to NOT discontinue without talking to provider
- If a dose is missed, take ASAP on same day and resume twice daily. DO NOT DOUBLE THE DOSE!

ARISTOTLE trial

- Non-inferiority, double-blind RCT comparing apixaban and dose adjusted warfarin. CHADS₂ avg = 2.1
- Primary outcome: composite of stroke or systemic embolism
  - Apixaban superior to warfarin
- Bleeding
  - Less major bleeding or non-clinically relevant bleeding than warfarin
  - Less hemorrhagic stroke and ICH in apixaban group
  - GI bleed incidence similar in both groups
  - Sub analysis showed less major bleeding with apixaban in patients with moderate or severe renal impairment and non-diabetes


Controversies With New Agents

- Clinical trial data can be different than real world data
  - Post marketing reports of serious bleeding events with dabigatran
- No head to head trials between new agents
- Warfarin management in some of the trials not as good as that achieved in many dedicated anticoagulation clinics.
- Unable to monitor for compliance
- How is CrCl being calculated prior to initiation and/or renewal?
Factors to consider choosing therapy

- Dabigatran: some evidence for cardioversion
- Rivaroxaban: once daily, can use in pill box, better for patients with history of gastritis
- Apixaban: less risk for GI bleeding, can use in pill box
- Warfarin: stable INRs, could consider for renal impairment, history of GI bleeding, and noncompliance

Patient Case#1

AC is a 60 YO male with history of diabetes mellitus, and hypertension and a new diagnosis of atrial fibrillation.

Current medications consist of Aspirin 81mg/day, amlodipine, lisinopril, and metformin. No known allergies

Labs: SCr 1.1, BUN 19, K+ 4.5, LFTs and CBC within acceptable limits; CrCl 76.1 mL/min

Weight: 85 kg; Height: 71 in

Factors to consider in choosing therapy?
Questions to ask patients?
Patient Case#2

WB is a 84 YO male with history of atrial fibrillation, CKD, heart failure (EF < 30%), hypertension, epilepsy, and memory impairment. Uses a pillbox to manage medications.

Current medications: carvedilol, furosemide, lisinopril, spironolactone, atorvastatin, carbamazepine, levetiracetam, and donepezil. No known allergies.

Labs: SCr 2.0, BUN 42, K+ 4.7, LFTs and CBC acceptable; CrCl 26mL/min

Weight: 74 kg, Height: 68 in

Factors to consider in choosing therapy?
Questions to ask patient?

Patient case#3

CV is 58 YO female with history of atrial fibrillation, hypertension, GERD.

Current meds: warfarin, metoprolol tartrate, omeprazole.

Labs: SCr 1.2, BUN 18, LFTs and CBC within acceptable limits

Weight: 80 kg, Height: 64 in

Factors to consider in choosing therapy?
Questions to ask patient?
Conclusion

- Novel anticoagulants are as safe and effective as warfarin
- Assess each patient individually and medication compliance before starting therapy
- Watch out for antidotes