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

Dr. Michael Brenner, Pharm.D., BCPS (AQ Cardiology)

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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

Heeringa J et al. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. *Eur Heart J.* 2006;27:949-953.

2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 Guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in partnership with the European Society of Cardiology and in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. J Am Coll Cardiol 2011;57(11):e101-e198.

Risk score for Stroke

$CHADS_2$ -> CHA_2DS_2VASc

CHADS2 Risk	Score
CHF	1
Hypertension	1
Age > 75	1
Diabetes	1
Stroke or TIA	2

CHA2DS2-VASc Risk	Score
CHF or LVEF ≤ 40%	1
Hypertension	1
Age ≥ 75	2
Diabetes	1
Stroke/TIA/ Thromboembolism	2
Vascular Disease	1
Age 65 - 74	1
Female	1

From ESC AF Guidelines http://escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-afib-FT.pdf

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)

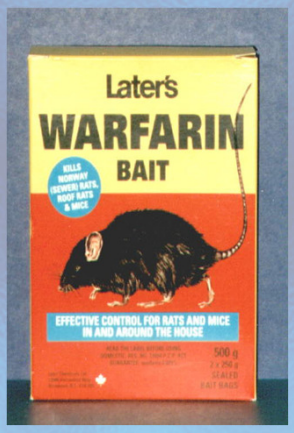
- If recommendations in favor of oral anticoagulation (intermediate and high risk groups w/ NVAF), suggest dabigatran 150 mg twice daily rather than adjusted-dose VKA therapy (target INR range, 2-3) (Grade 2B) .

CHEST 2012; 141(2)(Suppl):e531S–e575S

Anticoagulants

Old	Novel
Vitamin K Antagonist Warfarin	Direct Thrombin Inhibitor Dabigatran (Pradaxa®) Factor Xa Inhibitors Rivaroxaban (Xarelto®) Apixaban (Eliquis®)

Vitamin K Antagonist (VKA)



VKA

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

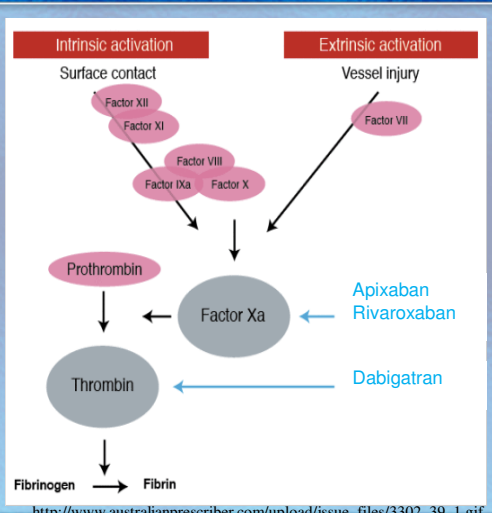
Hart RG, Pearce LA, Aguilar MI. Meta-Analysis: antithrombotic therapy to prevent stroke in patients
who have nonvalvular atrial fibrillation. *Ann Intern Med.* 2007;146:857-867.

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



http://www.australianprescriber.com/upload/issue_files/3302_39_1.gif

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; $CHADS_2$ 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

Connolly SJ, et al. Dabigatran versus Warfarin in Atrial Fibrillation. *N Engl J Med* 2009; 361:1139-1151

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

Product Information: XARELTO(R) oral tablets, rivaroxaban oral tablets. Janssen Pharmaceuticals, Inc. (per manufacturer), Titusville, NJ, 2012.

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

Product Information: XARELTO(R) oral tablets, rivaroxaban oral tablets. Janssen Pharmaceuticals, Inc. (per manufacturer), Titusville, NJ, 2012.

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

Product Information: XARELTO(R) oral tablets, rivaroxaban oral tablets. Janssen Pharmaceuticals, Inc. (per manufacturer), Titusville, NJ, 2012.

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

Kreutz R. Pharmacodynamic and pharmacokinetic basics of rivaroxaban. *Fundam Clin Pharmacol.* 2012 Feb;26(1):27-32.

Product Information: XARELTO(R) oral tablets, rivaroxaban oral tablets. Janssen Pharmaceuticals, Inc. (per manufacturer), Titusville, NJ, 2012.

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

Product Information: XARELTO(R) oral tablets, rivaroxaban oral tablets. Janssen Pharmaceuticals, Inc. (per manufacturer), Titusville, NJ, 2012.

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

Product Information: XARELTO(R) oral tablets, rivaroxaban oral tablets. Janssen Pharmaceuticals, Inc. (per manufacturer), Titusville, NJ, 2012.

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

Product Information: XARELTO(R) oral tablets, rivaroxaban oral tablets. Janssen Pharmaceuticals, Inc. (per manufacturer), Titusville, NJ, 2012.

ROCKET AF trial

- Non-inferiority, double-blind, RCT comparing rivaroxaban and dose adjusted warfarin; $CHADS_2$ 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)

Patel MR, et al. Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation. *N Engl J Med* 2011; 365:883-891

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

Product Information: ELIQUIS(R) oral tablets, apixaban oral tablets. Bristol-Myers Squibb (per manufacturer), Princeton, NJ, 2012.

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

Product Information: ELIQUIS(R) oral tablets, apixaban oral tablets. Bristol-Myers Squibb (per manufacturer), Princeton, NJ, 2012.

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

Product Information: ELIQUIS(R) oral tablets, apixaban oral tablets. Bristol-Myers Squibb (per manufacturer),
Princeton, NJ, 2012.

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

Product Information: ELIQUIS(R) oral tablets, apixaban oral tablets. Bristol-Myers Squibb (per manufacturer), Princeton, NJ, 2012.

Apixaban: Adverse Effects

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

Product Information: ELIQUIS(R) oral tablets, apixaban oral tablets. Bristol-Myers Squibb (per manufacturer), Princeton, NJ, 2012.

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

Product Information: ELIQUIS(R) oral tablets, apixaban oral tablets. Bristol-Myers Squibb (per manufacturer), Princeton, NJ, 2012.

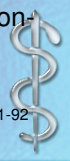
Apixaban: Counseling Tips

- 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!

Product Information: ELIQUIS(R) oral tablets, apixaban oral tablets. Bristol-Myers Squibb (per manufacturer), Princeton, NJ, 2012.

ARISTOTLE trial

- Non-inferiority, double-blind RCT comparing apixaban and dose adjusted warfarin. $CHADS_2$ 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



Granger CB, et al. Apixaban versus Warfarin in Patients with Atrial Fibrillation. *N Engl J Med* 2011;365:981-92

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