What's New in Anticoagulation?

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The speaker has no conflict to disclose.

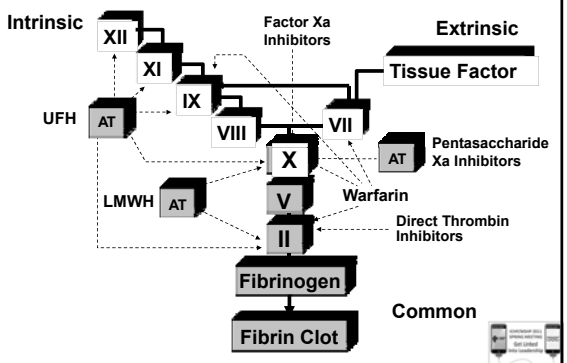
Objectives

- Describe the pharmacology and pharmacokinetics of dabigatran
- Review clinical studies and indications for dabigatran
- Describe other anticoagulation therapies in the pipeline
- Review the generic approval data for enoxaparin

Problems With Current Oral Anticoagulation Therapy

- Increased risk of
  - Major and minor bleeding (supratherapeutic INR)
  - Embolism (subtherapeutic INR)
- Need for routine anticoagulation monitoring
- Dosing variability
- Need for lots of patient education
- Drug/drug and food/drug interactions
- Slow onset/offset of action

Antithrombotic Drugs



A Few of the New and Emerging Antithrombotic Drugs

- Direct Thrombin Inhibitors
  - Dabigatran
  - AZD0837
- Direct Factor Xa inhibitors
  - Rivaroxaban
  - Apixaban
  - Betrixaban
  - Edoxaban
  - Otamixaban
  - Eribaxaban
- Indirect Factor Xa inhibitors
  - Idraparinux
  - Idrabiotaparinux

Phase III Clinical Trials

	Dabigatran	Rivaroxaban	Apixaban
THA	**RE-NOVATE**	**RECORD I** **RECORD II**	**ADVANCE-3**
TKA	**RE-MOBILIZE** **RE-MODEL**	**RECORD III** **RECORD IV**	**ADVANCE-1** **ADVANCE-2**
Medically Ill		MAGELLAN	**ADOPT**
VTE Tx	**RE-COVER** RE-MEDY RE-SONATE	**EINSTEIN-DVT** EINSTEIN-PE **EINSTEIN-EXT**	AMPLIFY AMPLIFY-EXT
AF	**RE-LY**	**ROCKET-AF**	ARISTOTLE **AVERROES**
ACS	**RE-DEEM**	ATLAS	APPRAISE-2 halted early

Comparison of New/Emerging Antithrombotic Agents

	Dabigatran	Rivaroxaban	Apixaban
Manufacturer	**Boehringer-Ingleheim**	**Bayer via Ortho McNeil**	**Pfizer with BMS**
Mechanism of Action	**Direct IIa inhibitor**	**Direct Xa inhibitor**	**Direct Xa inhibitor**
Approval Status	**2008: Approved in Europe/Canada (VTE prophylaxis in ortho pts)** **9/14/10: Recommended for approval by FDA advisory panel** **10/19/10: Approved by FDA for stroke prevention in AF**	**2008: Approved in Europe/Canada (VTE prophylaxis in ortho pts)** **3/09: FDA advisory panel approval (VTE prophylaxis in ortho pts)** **5/09: Additional info requested by FDA** **1/11: NDA submitted to FDA for stroke prevention in AF**	**6/2010: Submitted for European approval for VTE prophylaxis in ortho pts**

Comparative Properties

	Dabigatran	Rivaroxaban	Apixaban
Dialyzable	Yes	"not expected"	unlikely
Molecular weight	628 daltons	436 daltons	460 daltons
Binding to catalytic site	Reversible	Reversible	Reversible
Antidote	No	No	No

Erikkson BI et al. Clin Pharmacokinet 2009;48:1-22. Xarelto [Summary of Product Characteristics--EU]. Berlin, Germany: Bayer Schering Pharma AG; 2009. Pradaxa [Summary of Product Characteristics--EU]. Rhein, Germany: Boerhinger Ingelheim GmbH; 2009.

Comparative Pharmacokinetics

	Dabigatran etexilate	Rivaroxaban	Apixaban
Bioavailability	6.5%	90%	66%
Tmax	1.25 – 3 hr	2-4 hr	1-3 hr
T ½	7 - 17 hr	3-9 hr (12 hr in elderly)	8-15 hr
Protein Binding	35%	>90%	87%
Volume of distribution	60-70 liters	50 liters	Reported as low
Activation	Prodrug dabigatran etexilate is rapidly converted to active drug dabigatran via hydrolysis	None	none

Ufer M. Thromb Haemost 2010; 103: 572–585.

Comparative Pharmacokinetics

	Dabigatran etexilate	Rivaroxaban	Apixaban
Elimination pathway	100% unchanged drug & active metabolites	50% unchanged drug; 50% inactive metabolites	70% unchanged drug; 30% inactive metabolites
Route of elimination	Urine: 90-95% Feces: 5-10%	Urine: 70% Feces: 30%	Urine: 30% Feces: 70%
Metabolism	Conjugation, no CYP involvement	Oxidation (via CYP3A4, CYP2J2) and hydrolysis	Oxidation (via CYP3A4, minor CYP1A2 and CYP2J2) and conjugation
P-glycoprotein substrate?	yes	yes	yes

Ufer M. Thromb Haemost 2010; 103: 572–585.

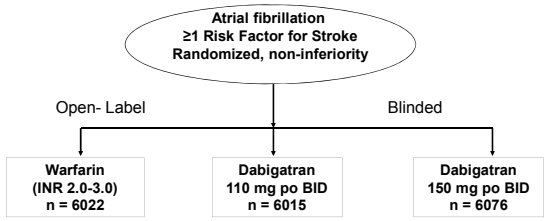
Comparative Drug Interactions

	Dabigatran	Rivaroxaban	Apixaban
CYP3A4 & P-gp inhibitors reported	n/a	Ketoconazole AUC/Cmax↑100% Ritonavir AUC/Cmax ↑ 100% Clarithromycin AUC/Cmax ↑50% Erythromycin AUC/Cmax ↑ 50%	Ketoconazole AUC ↑100%
CYP3A4 & P-gp inducers	n/a	Rifampin AUC ↓50%, St. John's wort, CBZ, Phenytoin	Rifampin AUC ↓50%
P-gp Inhib /inducers	Ketoconazole AUC ↑ 153% Verapamil: effect dependent on timing and formulation Amiodarone AUC ↑ 58%, clearance ↑ 65% to compensate Quinidine AUC ↑ 53% Rifampin AUC ↓ 66% avoid combo		

*All have increased risk of bleeding with antithrombotic and antiplatelet agents.

Nutescu EA et al. J Thromb Thrombolysis 2011 Feb. 27 published online ahead of print

RE-LY: Study Design



Patients were eligible if they had AF documented on ECG performed at screening or within 6 months beforehand and ≥1 of the following characteristics:

- **Previous stroke or TIA**
- **LVEF <40%**
- **NYHA class II-IV HF symptoms within 6 months before screening**
- **Age ≥ 75 years or age 65 to 74 years plus DM, HTN, or CAD.**

Exclusion: severe heart-valve disorder, stroke < 14 days or severe stroke <6 months before screening, increased risk of hemorrhage, CrCl <30 mL/min, active liver disease, pregnancy
Primary Efficacy Outcome: stroke or systemic embolism. Safety: major bleeding

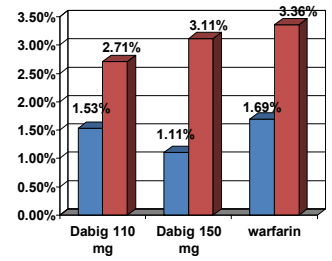
Connolly SJ, et al. *N Engl J Med*. 2009;361:1139-51.

RE-LY: Baseline Characteristics

	Dabigatran 110 mg (n = 6015)	Dabigatran 150 mg (n = 6076)	Warfarin (n = 6022)
Mean age (years)	71.4	71.5	71.6
Male (%)	64.3	63.2	63.3
$CHADS_2$ score (mean)	2.1	2.2	2.1
0-1 (%)	32.6	32.2	30.9
2 (%)	34.7	35.2	37.0
3+ (%)	32.7	32.6	32.1
Prior Stroke/TIA (%)	19.9	20.3	19.8
Prior MI (%)	16.8	16.9	16.1
CHF (%)	32.2	31.8	31.9
Baseline ASA (%)	40.0	38.7	40.6
Warfarin Naïve (%)	49.9	49.8	51.4

Connolly SJ, et al. *N Engl J Med*. 2009;361:1139-51.

RE-LY
Dabigatran etexilate vs. warfarin in AF



Stroke: D 150 mg vs. warfarin p<0.001 superiority

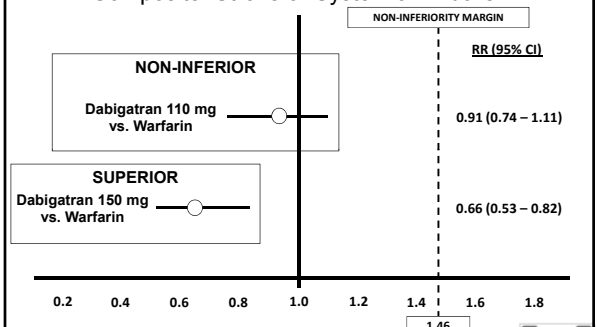
Major bleed: D 110 mg p=0.003 vs. warfarin

D 150 mg p = 0.31 vs. warfarin

N = 18,113 pts (mean CHADS2 score = 2.1). Non-inferiority design.
Primary outcome stroke or systemic embolism
Blinded dabigatran vs. unblinded warfarin 64% TTR for warfarin
Median follow up= 2 yrs

Connolly SJ et al. New Engl J Med 2009;361:1139-51.

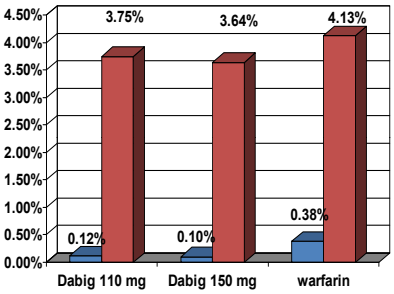
RE-LY: Primary Outcome
Composite: Stroke or Systemic Embolism



Dabigatran 150 mg results driven by reduction in stroke

Connolly SJ et al. *N Engl J Med*. 2009;361:1139-51.

RE-LY
Dabigatran etexilate vs. warfarin in AF



ICH: D 110 mg P<0.001 vs. warfarin

D 150 mg p<0.001 vs. warfarin

Mortality: NS for mortality

Connolly SJ et al. New Engl J Med 2009;361:1139-51.

RE-LY: Bleeding Rates

	D 110mg	D 150mg	Warfarin	D 110mg vs. Warfarin		D 150mg vs. Warfarin	
	Annual rate	Annual rate	Annual rate	RR (95% CI)	p-value	RR (95% CI)	p-value
Total	14.6%	16.4%	18.2%	0.78 (0.74-0.83)	<0.001	0.91 (0.86-0.97)	0.002
Major	2.7%	3.1%	3.4%	0.80 (0.69-0.93)	0.003	0.93 (0.81-1.07)	0.31
Life-threatening Major	1.2%	1.5%	1.8%	0.68 (0.55-0.83)	<0.001	0.81 (0.66-0.99)	0.04
Gastrointestinal Major	1.1%	1.5%	1.0%	1.10 (0.86-1.41)	0.43	1.50 (1.19-1.89)	<0.001

Connolly SJ et al. *New Engl J Med*. 2009; 361:1139-51.

RE-LY: Adverse Events

Adverse event	D 110 mg (%)	D 150 mg (%)	Warfarin (%)
Dyspepsia *	11.8	11.3	5.8
Dyspnea	9.3	9.5	9.7
Dizziness	8.1	8.3	9.4
Peripheral edema	7.9	7.9	7.8
Fatigue	6.6	6.6	6.2
Cough	5.7	5.7	6.0
Chest pain	5.2	6.2	5.9
Arthralgia	4.5	5.5	5.7
Back pain	5.3	5.2	5.6
Nasopharyngitis	5.6	5.4	5.6
Diarrhea	6.3	6.5	5.7
Atrial fibrillation	5.5	5.9	5.8
Urinary tract infection	4.5	4.8	5.6
Upper respiratory tract infection	4.8	4.7	5.2

*Occurred more commonly with dabigatran (p<0.001)

Connolly SJ et al. *New Engl J Med*. 2009; 361:1139-51.

RE-LY: Effect of TTR on Primary Outcome

Stroke and Systemic Embolism

	D 110mg	D 150mg	Warfarin	D 110mg vs. Warfarin		D 150mg vs. Warfarin	
cTTR	Rate*	Rate*	Rate*	RR (95% CI)	p-value	RR (95% CI)	p-value
<57.1%	1.91	1.10	1.92	1.00 (0.68-1.45)		0.57 (0.37-0.88)	
57.1-65.5%	1.67	1.04	2.06	0.81 (0.56-1.17)		0.50 (0.33-0.77)	
65.5-72.6%	1.34	1.04	1.51	0.89 (0.58-1.36)		0.69 (0.44-1.09)	
>72.6%	1.23	1.27	1.34	0.92 (0.59-1.45)	0.89	0.95 (0.61-1.48)	0.20

*** Rate per 100 person-years**
cTTR = Centre's mean time in therapeutic range

Wallentin L et al. *Lancet.* 2010; 376:975-83.

RE-LY: Effect of TTR on Safety Outcome

Major Bleeding

	D 110mg	D 150mg	Warfarin	D 110mg vs. Warfarin		D 150mg vs. Warfarin	
cTTR	Rate*	Rate*	Rate*	RR (95% CI)	p-value	RR (95% CI)	p-value
<57.1%	2.36	2.54	3.59	0.65 (0.48-0.89)		0.71 (0.52-0.96)	
57.1-65.5%	3.38	3.33	4.13	0.82 (0.63-1.06)		0.81 (0.62-1.05)	
65.5-72.6%	2.82	3.80	3.40	0.83 (0.62-1.11)		1.13 (0.87-1.48)	
>72.6%	2.81	3.60	3.11	0.90 (0.67-1.21)	0.50	1.16 (0.88-1.54)	0.03

*** Rate per 100 person-years**
cTTR = Centre's mean time in therapeutic range

Wallentin L et al. *Lancet.* 2010; 376:975-83.

CHA_2DS_2-VASc Score for Estimating Stroke Risk in AF

		Score	TE Rate at 1 Year	
C: CHF/LV dysfunction	1 point	0 points:	0%	**LOW**
H: HTN	1 point	1 point:	0.6%	**INTER**
A: Age ≥75 years	2 points	2 points:	1.6%	**HIGH**
D: Diabetes	1 point	3 points:	3.9%	
S: Stroke/TIA	2 points	4 points:	1.9%	
V: Vascular disease†	1 point	5 points:	3.2%	
A: Age 65-74 years	1 point	6 points:	3.6%	
S: Sex (female)	1 point	7 points:	8.0%	
	TOTAL	8 points:	11.1%	
		9 points:	100%	

† Prior MI, PAD, or aortic plaque

Lip GYH, et al. *Chest* 2010; 137: 263-72.

HAS-BLED Score for Estimating Bleeding Risk in AF

n = 3665 patients taking warfarin from SPORTIF cohort

Events		Score	Major Bleeding
H: HTN	1 point	0 points:	0.9%
A: Abnormal renal/liver function	1 point each	1 point:	3.4%
S: Stroke	1 point	2 points:	4.1%
B: Bleeding history/predisposition	1 point	3 points:	5.8%
L: Labile INR (TTR <60%)	1 point	4 points:	8.9%
E: Elderly (>65 yr)	1 point	5 points:	9.1%
D: Drugs†/alcohol	1 point each		
	TOTAL		

† Antiplatelets, NSAIDS, or steroids

Lip GYH, et al. *J Am Coll Cardiol* 2011; 57: 173-80.

Role of Dabigatran for Stroke Prevention in AF

- 2011 ACCF/AHA/HRS Guidelines
  - Dabigatran given a Class I (LOE B) recommendation
    - Dabigatran is useful as an alternative to warfarin for prevention of stroke and systemic thromboembolism in patients with paroxysmal to permanent AF and risk factors for stroke or systemic embolization who do not have the following:
      - Prosthetic heart valve or hemodynamically significant valve disease
      - CrCl <15 mL/min
      - Advanced liver disease

Wann S, et al. J Am Coll Cardiol 2011 Mar 15;57(11):1330-7. Epub 2011 Feb 14.

Role of Dabigatran for Stroke Prevention in AF

- 2011 ACCF/AHA/HRS guidelines also state the following:
  - Patients already taking warfarin with excellent INR control may have little to gain by switching to dabigatran because of dabigatran's:
    - Twice-daily dosing
    - Greater risk of nonhemorrhagic side effects
  - Selection of patients with AF and ≥1 additional risk factor for stroke who could benefit from treatment with dabigatran as opposed to warfarin should consider individual factors, including:
    - Ability to comply with twice-daily dosing
    - Availability of an anticoagulation management program to sustain routine monitoring of INR
    - Patient preferences
    - Cost
    - Other factors

Wann S, et al. J Am Coll Cardiol 2011 Mar 15;57(11):1330-7. Epub 2011 Feb 14.

ROCKET-AF Study Design

Atrial Fibrillation
≥2 Risk Factors for Stroke
Randomized, Double-Blind,
Double Dummy, Non-inferiority
90% have a CHADS2 score of 3 or higher

Rivaroxaban
20 mg daily
(15 mg for CrCl 30-49 mL/min)
n = 7081

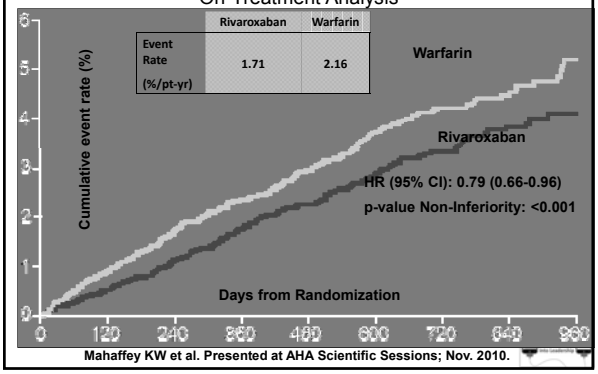
Warfarin
INR = 2-3
n = 7090

Primary Efficacy Endpoint: Stroke or Systemic Embolism
Primary Safety Endpoint: Major Bleeding

ROCKET AF Study Investigators. *Am Heart J.* 2010;159:340-7.

ROCKET AF: Primary Endpoint

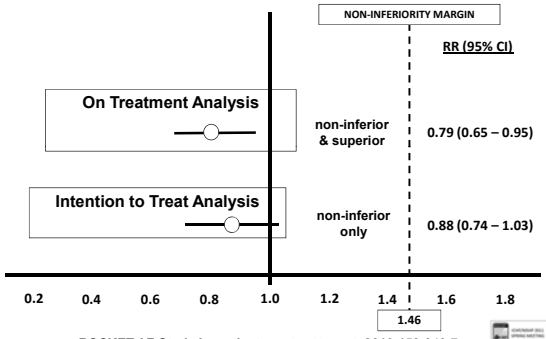
Composite: Stroke or Systemic Embolism
On-Treatment Analysis



Mahaffey KW et al. Presented at AHA Scientific Sessions; Nov. 2010.

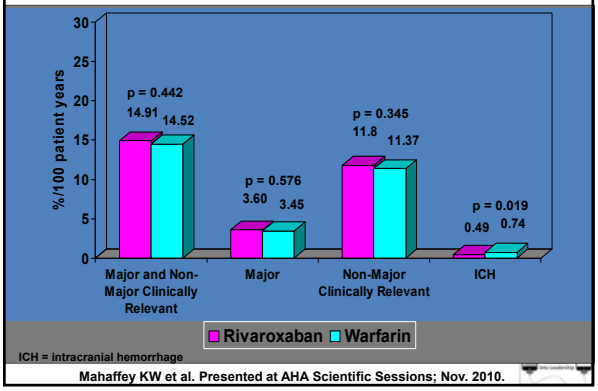
ROCKET AF: Primary Endpoint Results

Composite: Stroke or Systemic Embolism



ROCKET AF Study Investigators. *Am Heart J.* 2010;159:340-7.
Mahaffey KW et al. Presented at AHA Scientific Sessions; Nov. 2010.

ROCKET AF: Bleeding Rates



ICH = intracranial hemorrhage

Mahaffey KW et al. Presented at AHA Scientific Sessions; Nov. 2010.

Apixaban Trials in AF

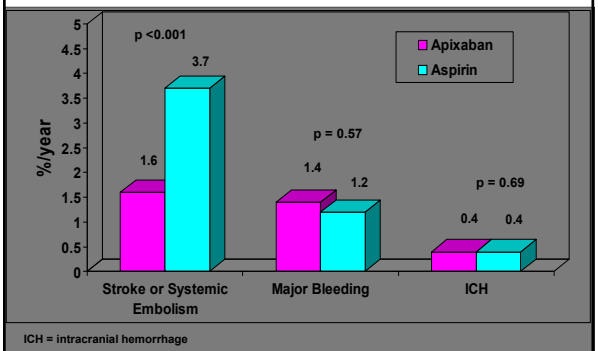
AVERROES
ASA 81-324 mg daily vs apixaban 5 mg BID ‡
Randomized, double blind, placebo controlled
Superiority design
CHADS2 score ≥1
Failed or unsuitable for warfarin therapy
n = 5599
Primary efficacy end point = Stroke or systemic embolism
Primary safety end point = Major bleeding

ARISTOTLE
Warfarin (INR 2-3) vs apixaban 5 mg BID ‡
Randomized, double-blind, placebo controlled
Noninferiority design
$CHADS_2$ score ≥1
n > 18,000
Primary efficacy end point = Stroke or systemic embolism
Primary safety end point = Major bleeding
Results expected in 2011

‡ Apixaban 2.5 mg BID used in patients with ≥2 of the following: ≥80 yrs, wt ≤60 kg, SCr ≥1.5 mg/dL

Lopes RD et al. *Am Heart J.* 2010;159:331-9
Connolly S, et al. *New Engl J Med* 2011;364: 806-17.

AVERROES: Results



ICH = intracranial hemorrhage

Connolly S, et al. *New Engl J Med* 2011;364:806-17.

Dosing in Renal dysfunction

	Dabigatran	Rivaroxaban*	Apixaban*
CrCL 80-100	150 mg BID for AF	20 mg daily for AF	5 mg BID for AF
CrCL 50 -80	No adjustment	No adjustment	No adjustment
CrCL 30 - 50	No adjustment	15 mg daily for AF	
CrCL 15 - 29	Reduced dose to 75 mg BID for AF based on PK modeling only	Excluded from ROCKET AF	AVERROES and ARISTOTLE Excluded: SCr >2.5 or CrCL < 25 ml/min
CrCL < 15	Contraindicated	Not recommended	

*Not FDA approved

Other Factor Xa Inhibitors in the Pipeline

Stroke Prevention in AF Clinical Trials

Edoxaban (Oral, daily)

- ENGAGE AF TIMI-48: Ongoing (estimated completion in 2/2012); target enrollment >20,000

Betrixaban (Oral, daily)

- EXPLORE Xa: Completed, dose ranging

Idraparinux (SC injection, weekly)

- AMADEUS: Stopped early, excessive bleeding risk

Idrabiotaparinux (SC injection, weekly)

- BOREALIS AF: Terminated by manufacturer

www.ClinicalTrials.gov
Ruff CT et al. *Am Heart J.* 2010;160:635-41.
Alexander W. *P & T.* 2010;35:291-4.
The AMADEUS Investigators. *Lancet.* 2008;371:315-21.

Re-COVER Study Design

Acute, symptomatic DVT
Randomized, double-blind, non-inferiority study
initially given tx with parenteral AC for 9 days

Dabigatran
150 mg BID
n = 1274

Warfarin INR 2-3
n = 1265

Primary Efficacy Endpoint: 6 month incidence of recurrent, symptomatic VTE and related deaths
Primary Safety Endpoint: Bleeding, ACS, ADE, LFT results

Schulman S et al. N Engl J Med 2009;361:2342-52.

RE-COVER Results

- Recurrent VTE: 2.4% dabigatran vs. 2.1% warfarin
  - the difference in risk was 0.4 % (95% CI, −0.8 to 1.5; P<0.001 for the prespecified noninferiority margin). The hazard ratio with dabigatran was 1.10 (95% CI, 0.65 to 1.84).
- Major bleeding: 1.6% dabigatran vs. 1.9% warfarin (HR dabigatran, 0.82; 95% CI, 0.45 to 1.48),
  - episodes of any bleeding: 16.1% dabigatran vs. 21.9% warfarin, (HR dabigatran, 0.71; 95% CI, 0.59 to 0.85).
- Deaths, acute coronary syndromes, and abnormal LFTs were similar in the two groups.
  - Adverse events leading to discontinuation of the study drug occurred in 9.0% of dabigatran pts and 6.8% of warfarin pts (P = 0.05)
- Fixed dose of dabigatran is as effective as warfarin with similar safety profile

Schulman S et al. N Engl J Med 2009;361:2342-52.

EINSTEIN-DVT Study Design

Acute, symptomatic DVT
Open label, non-inferiority study

Rivaroxaban
15 mg BID X 3 weeks, then
20 mg daily
n = 1731

Enoxaparin SC then VKA for
3, 6, or 12 months
n = 1718

Primary Efficacy Endpoint: Recurrent VTE
Primary Safety Endpoint: Major Bleeding
or clinically relevant nonmajor bleeding

EINSTEIN DVT And EINSTEIN EXT investigators. N Engl J Med 2010;363:2499-510.

EINSTEIN-EXT Study Design

Acute, symptomatic DVT
Double-blind, randomized,
event-driven superiority trial of pts who completed
6 – 12 months tx for VTE

Rivaroxaban 20 mg daily
n =602

Placebo
n = 594

Primary Efficacy Endpoint: Recurrent VTE
Primary Safety Endpoint: Major Bleeding

EINSTEIN DVT And EINSTEIN EXT investigators. N Engl J Med 2010;363:2499-510.

EINSTEIN-DVT and EINSTEIN –EXT Results

- EINSTEIN-DVT:
  - Rivaroxaban noninferior efficacy for primary outcome: 36 events (2.1%), vs. 51 events with enoxaparin–VKA (3.0%)
    - HR, 0.68; 95% CI, 0.44 to 1.04; P<0.001.
  - Principal safety outcome occurred in 8.1% of the pts in each group
- EINSTEIN-EXT:
  - Rivaroxaban had superior efficacy: 8 events (1.3%), vs. 42 with PBO (7.1%)
    - HR, 0.18; 95% CI, 0.09 to 0.39; P<0.001
  - Four patients in the rivaroxaban group had nonfatal major bleeding (0.7%), versus none in the placebo group (P = 0.11)

EINSTEIN DVT And EINSTEIN EXT investigators. N Engl J Med 2010;363:2499-510.

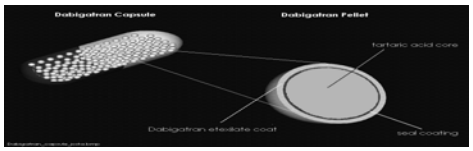
Apixaban DVT Trials

- AMPLIFY: Apixaban After the Initial Management of Pulmonary Embolism and Deep Vein Thrombosis with First-Line Therapy (AMPLIFY):
  - Ongoing, Phase III, evaluating apixaban 10 mg BID x 7 days for DVT tx followed by 5 mg twice daily for the remainder of the 6 months
- AMPLIFY-EXT: Apixaban After the Initial Management of Pulmonary Embolism and Deep Vein Thrombosis with First-Line Therapy – Extended Treatment (AMPLIFY-EXT):
  - efficacy and safety of an additional 12 months of apixaban 2.5 mg or 5 mg BID compared to PBO for prevention of recurrent DVT in pts who have already received 6 to 12 months of tx for DVT or PE

Efficacy and safety study of apixaban for the treatment of DVT or PE. http://clinicaltrials.gov/ct2/show/NCT00643201?term=apixaban&rank=6 (accessed 2011 February 11).

Dabigatran: Ensuring Appropriate Use
Capsule Stability

- Dabigatran exetilate requires an acid environment for absorption
- Capsules contain multiple drug pellets
- Each pellet has a tartaric acid core (coated with drug) that creates an acidic microenvironment to improve dissolution and absorption independent of gastric pH

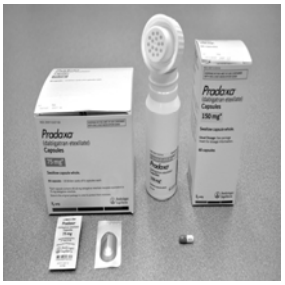


DO NOT CRUSH, CHEW OR BREAK CAPSULES

Stangier J. *Clin Pharmacokinetic* 2008; 47:285-95.

Dabigatran: Capsule Stability

- Available as 150 mg and 75 mg capsules
- Use contents within 30 days once bottle is opened
  - Cap on bottle contains dessicant to reduce moisture and avoid degradation
- Blister packs should be used in inpatient setting



Pradaxa prescribing information. Ridgefield, CT, BI Pharm, Inc. 2010.

Dabigatran: Lab Monitoring of Anticoagulant Effects

- At recommended therapeutic doses, dabigatran etexilate prolongs the aPTT, ECT, and TT.
  - With an oral dose of 150 mg twice daily the median peak aPTT is approximately 2x control.
  - 12 hr after the last dose the median aPTT is 1.5x control, with < 10% of pts exceeding 2x control.
  - In the RE-LY trial, the median (10th to 90th percentile) trough aPTT in pts receiving the 150 mg dose was 52 (40 to 76) sec. The median (10th to 90th percentile) trough ECT in pts receiving the 150 mg dose was 63 (44 to 103) sec.
- The INR test is relatively insensitive to the activity of dabigatran and may or may not be elevated in patients on dabigatran. When converting a patient from dabigatran to warfarin, the INR is unlikely to be useful until at least 2 days after d/c of dabigatran.
- There is limited data on the use of the ACT
- Currently no routine monitoring is recommended

Pradaxa prescribing information. Ridgefield, CT, BI Pharm, Inc. 2010.
van Ryn J et al. *Thromb Haemost* 2010; 103: 1116–27.

Dabigatran: Converting from or to Warfarin

- From dabigatran to warfarin
  - CrCl >50 mL/min → Start warfarin 3 days before D/C dabigatran
  - CrCl 31-50 mL/min → Start warfarin 2 days before D/C dabigatran
  - CrCl 15-30 mL/min → Start warfarin 1 day before D/C dabigatran
  - CrCl <15 mL/min → No recommendations can be made
- From warfarin to dabigatran
  - When converting patients from warfarin therapy to dabigatran, discontinue warfarin and start dabigatran when the INR < 2

Pradaxa prescribing information. Ridgefield, CT, BI Pharm, Inc. 2010.

Dabigatran: Converting from or to Parenteral Anticoagulants

- Patient currently receiving a parenteral anticoagulant
  - Start dabigatran 0 to 2 hours before the time that the next dose of the parenteral drug was to have been administered or at the time of D/c of a continuously administered parenteral drug (e.g., IV unfractionated heparin)
- Patient currently taking dabigatran
  - Wait 12 hours (if CrCl ≥30 mL/min) or 24 hours (if CrCl <30 mL/min) after the last dose of dabigatran before initiating treatment with a parenteral anticoagulant

Pradaxa prescribing information. Ridgefield, CT, BI Pharm, Inc. 2010.

Dabigatran: Surgery and Interventions

- If possible, discontinue dabigatran 1 to 2 days (CrCl ≥50 mL/min) or 3 to 5 days (CrCl <50 mL/min) before invasive or surgical procedures because of the increased risk of bleeding.
- Consider longer times for patients undergoing major surgery, spinal puncture, or placement of a spinal or epidural catheter or port, in whom complete hemostasis may be required

Pradaxa prescribing information. Ridgefield, CT, BI Pharm, Inc. 2010.

Dabigatran: Perioperative Mgmt

- In patients with normal renal function and standard bleeding risk:
  - Discontinue 24 hours before surgery → ↓ 25% of steady-state
  - Discontinue 36 hours before surgery → ↓ 12-15% of steady-state
  - Discontinue 48 hours before surgery → ↓ 5-10% of steady-state

CrCL ml/min	T1/2 (hrs)	Timing of D/c of last dose of dabigatran before surgery	
		Std risk of bleeding	High risk of bleeding
>80	13 (11-22)	24 hr	2-4 days
>50- ≤80	15 (12-34)	24 hrs	2-4 days
>30 - ≤ 50	18 (13-23)	At least 48 hrs	4 days
≤30	27 (22-35)	2-5 days	>5 days

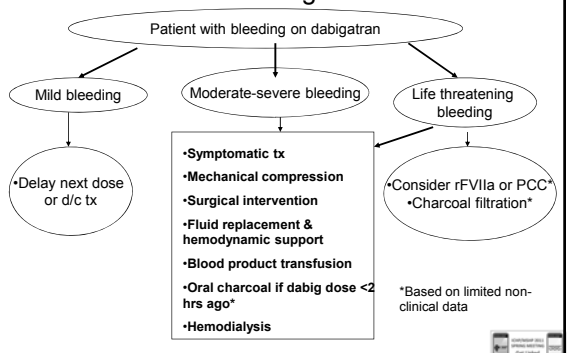
van Ryn J et al. *Thromb Haemost* 2010; 103: 1116–27.

Dabigatran: Managing Unique Situations Bleeding

- No antidote available
- In overdose setting
  - Activated charcoal has been demonstrated to work in vitro
- Local control measures should be employed
- Adequate diuresis should be maintained
- Administration of blood-products of FFP
- One study suggested dabigatran can be dialyzed
  - 62% removed at 2 hours
  - 68% removed at 4 hours
- Recombinant Factor VIIa has been shown to reverse effects of dabigatran ex vivo (rat model)

van Ryn J et al. *Thromb Haemost* 2010; 103: 1116–27.

Dabigatran: Managing Unique Situations Bleeding



van Ryn J et al. *Thromb Haemost* 2010; 103: 1116–27.

Generic Enoxaparin

- Manufacturer of Lovenox filed a Citizen Petition to the FDA in 2003 to refuse to approve generic enoxaparin unless the following conditions were met
  - Consider complex chemical structure of enoxaparin
  - Demonstrating "sameness" in ability to cause immunogenic reactions
  - Addressing the potential for contamination of heparin, from which LMWH is produced
- Through June of 2007, Aventis followed up its Citizen Petition with four different supplements containing additional arguments against generic approval
- Through April of 2009, Aventis also added eight sets of comments regarding the Citizen Petition.

www.fda.gov news release July 23, 2010. Citizen Petition # 2003-P-0273

Generic Enoxaparin

- The crux of the petition and related supplements is that the FDA should not approve the ANDA for enoxaparin unless the ANDA applicant:
  - completely characterizes enoxaparin by isolating, purifying, and sequencing each of its unique polysaccharide chains and determining their relative abundance, which you state is curently impossible
  - uses Aventis's or the equivalent manufacturing process, or
  - conducts clinical trials to demonstrate the equivalent safety and effectiveness of the product
- The FDA did not find it necessary for an ANDA applicant seeking approval of generic enoxaparin to submit the information requested.

www.fda.gov news release July 23, 2010. Citizen Petition # 2003-P-0273

5 Criteria for meeting "sameness"

- Physical and chemical characteristics of enoxaparin
- Nature of the source material and method used to break up the polysaccharide chains
- Nature and arrangements of components that constitute enoxaparin
- Certain lab measurements of anticoagulant activity
- Certain aspects of the drug's effects on humans

- Approved by FDA July 23, 2010 to Sandoz, as the first generically approved LMWH

FDA Response to the Citizens Petition www.fda.gov news release July 23, 2010.

Role of the Pharmacist with the new anticoagulants

- Ensure appropriate use at the patient level
  - Renal/hepatic function
    - Selection of appropriate dosing regimen
  - Drug interactions
  - Compliance issues
  - Bleeding risk
  - Insurance coverage
  - Already well-maintained on warfarin?
    - Guidelines suggest that there may be little to gain by switching "just to switch"
- Formulary decisions
  - Limited to FDA-approved indications?
  - Prior authorization?
  - Restricted by specialty service?
  - Management when patients are already on a new agent when they come to your facility?
- Clinical decision support
  - Computerized rules alerts for appropriate dosage, duplication of therapy, lab monitoring
- Education
  - To physicians, nurses, pharmacists, patients

New Antithrombotic Agents: Remaining Questions

- Drug interactions
- Use in special populations:
  - Hepatic failure
  - Renal insufficiency
  - Obese/underweight patients
  - Pregnancy
  - Children
- Role of monitoring and appropriate tests
- Bridging prior to and following procedures
- Cardioversion/ablation
- Stroke protocols involving thrombolytic therapy

Conclusions

- Newer anticoagulants will offer ease of dosing and minimal lab monitoring
- Dabigatran is currently available and is a new alternative to warfarin for AF
- Several other antithrombotic agents are in the pipeline for AF, DVT prophylaxis, VTE treatment, and ACS
- Pharmacists may play a key role in selection, dosing, and monitoring of these new agents
- There are many unanswered questions remaining to be studied

Self-assessment Questions

PL is a 71 yo WM with $CHA_2DS_2VAS_C$ score of 4, AF, and CrCL 62 ml/min. Which of the following are reasonable options for anticoagulation for stroke prevention?

A. Warfarin therapy; titrate to goal INR 2-3
B. Dabigatran 75 mg po BID
C. Dabigatran 150 mg po BID
D. ASA 81 mg po daily

Which of the following may be effective for dabigatran reversal?

A. Administration of oral vitamin K
B. Hemodialysis
C. Administration of recombinant Factor VIIa
D. Charcoal filtration
E. B, C, and D are correct

Which of the following are oral direct Factor Xa inhibitors?

A. Warfarin
B. Dabigatran
C. Rivaroxaban
D. Apixaban
E. C and D are correct

Which of the following is an FDA-approved generic LMWH?

A. Enoxaparin
B. Dalteparin
C. Tinzaparin
E. None of the above

Computerized decision support for dabigatran at your institution could include which of the following?

A. Documentation of AF as a diagnosis
B. Renal alerts for reduced dose if CrCl < 30 mL/min and > 15 mL/min
C. Renal alerts to avoid use if CrCl < 15 ml/min
D. Warning of duplication of therapy if the patient has a current order for warfarin to be given on the same day
E. All of the above

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ICHP/MSHP 2011 Spring Meeting
Clinical Pearls – What's New in Anticoagulation?
Nancy Shapiro, PharmD, FCCP, BCPS
121-000-11-015-L01-P

Post Test Questions:

1. PL is a 71 yo WM with CHA2DS2VASC score of 4, AF, and CrCL 62 ml/min. Which of the following are reasonable options for anticoagulation for stroke prevention?
   A. Warfarin therapy; titrate to goal INR 2-3
   B. Dabigatran 75 mg po BID
   C. Dabigatran 150 mg po BID
   D. ASA 81 mg po daily

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   B. Hemodialysis
   C. Administration of recombinant Factor VIIa
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   C. Rivaroxaban
   D. Apixaban
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   B. Dalteparin
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5. Computerized decision support for dabigatran at your institution could include which of the following?
   A. Documentation of AF as a diagnosis
   B. Renal alerts for reduced dose if CrCl < 30 mL/min and > 15 mL/min
   C. Renal alerts to avoid use if CrCl < 15 ml/min
   D. Warning of duplication of therapy if the patient has a current order for warfarin to be given on the same day
   E. All of the above

6. The dose of rivaroxaban and dabigatran should be reduced in patients with renal impairment.
   A. True
   B. False

7. Which of the following is a potential advantage of rivaroxaban compared with warfarin?
   A. Lack of drug interactions
   B. Less expensive
   C. Lack of a need for routine laboratory monitoring
   D. Less major bleeding