

# **The New Oral Anticoagulants: Cause for Celebration or Concern?**

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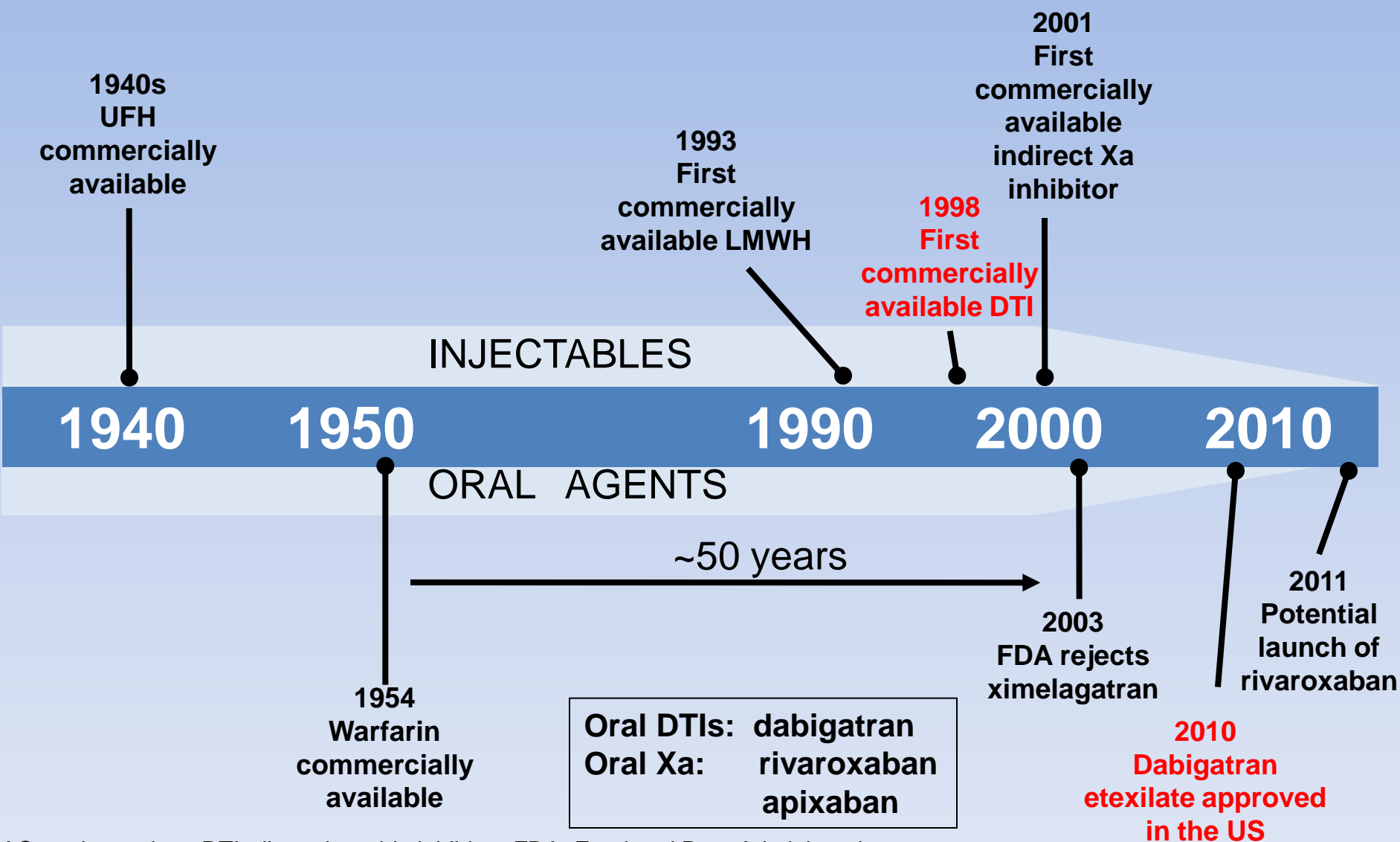
# Objectives

- Compare and contrast the pharmacology and pharmacokinetics of the new oral anticoagulants dabigatran etexilate and rivaroxaban
- Identify key clinical trials that have been or are being used to seek approval of dabigatran etexilate and rivaroxaban for key indications
- When new oral agents are approved by the FDA, identify key steps that should be taken to assure safe and effective use of the anticoagulant

# The “Ideal” Anticoagulant

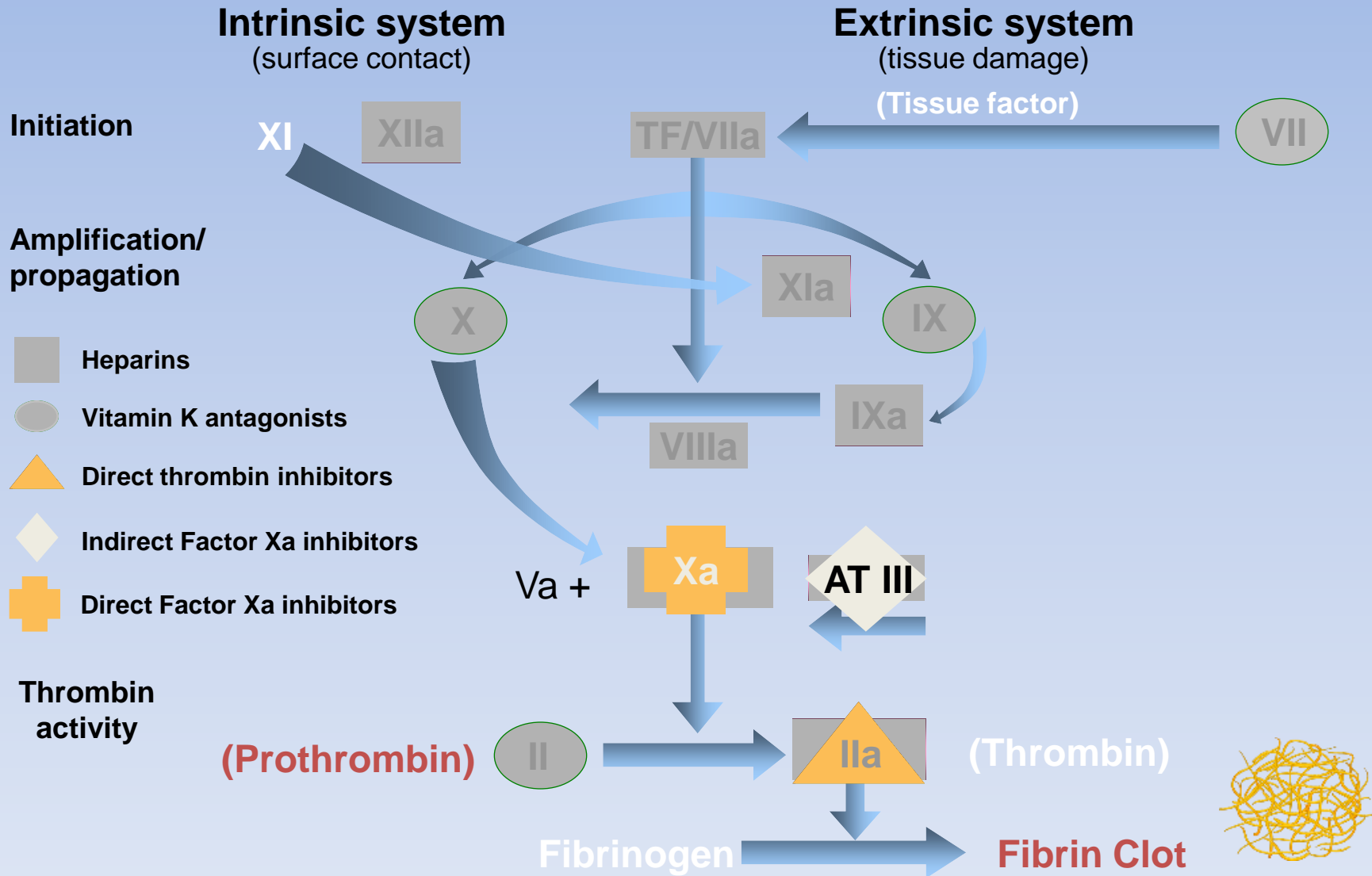
- Oral, fixed dosage (preferably once daily)
- Rapid onset
- Rapid offset of action
  - Perhaps not in valves?
- No need for renal or hepatic adjustment
- Predictable pharmacokinetics/dynamics
- No need to ever “switch” therapies
- Wide therapeutic window
- No need for routine anticoagulation effect monitoring
- Low propensity for food/drug interactions
- Available antidote
- Reasonable cost

# Evolution of Anticoagulant Therapy



AC=anticoagulant; DTI=direct thrombin inhibitor; FDA=Food and Drug Administration; LMWH =low-molecular-weight heparin; UFH = unfractionated heparin.

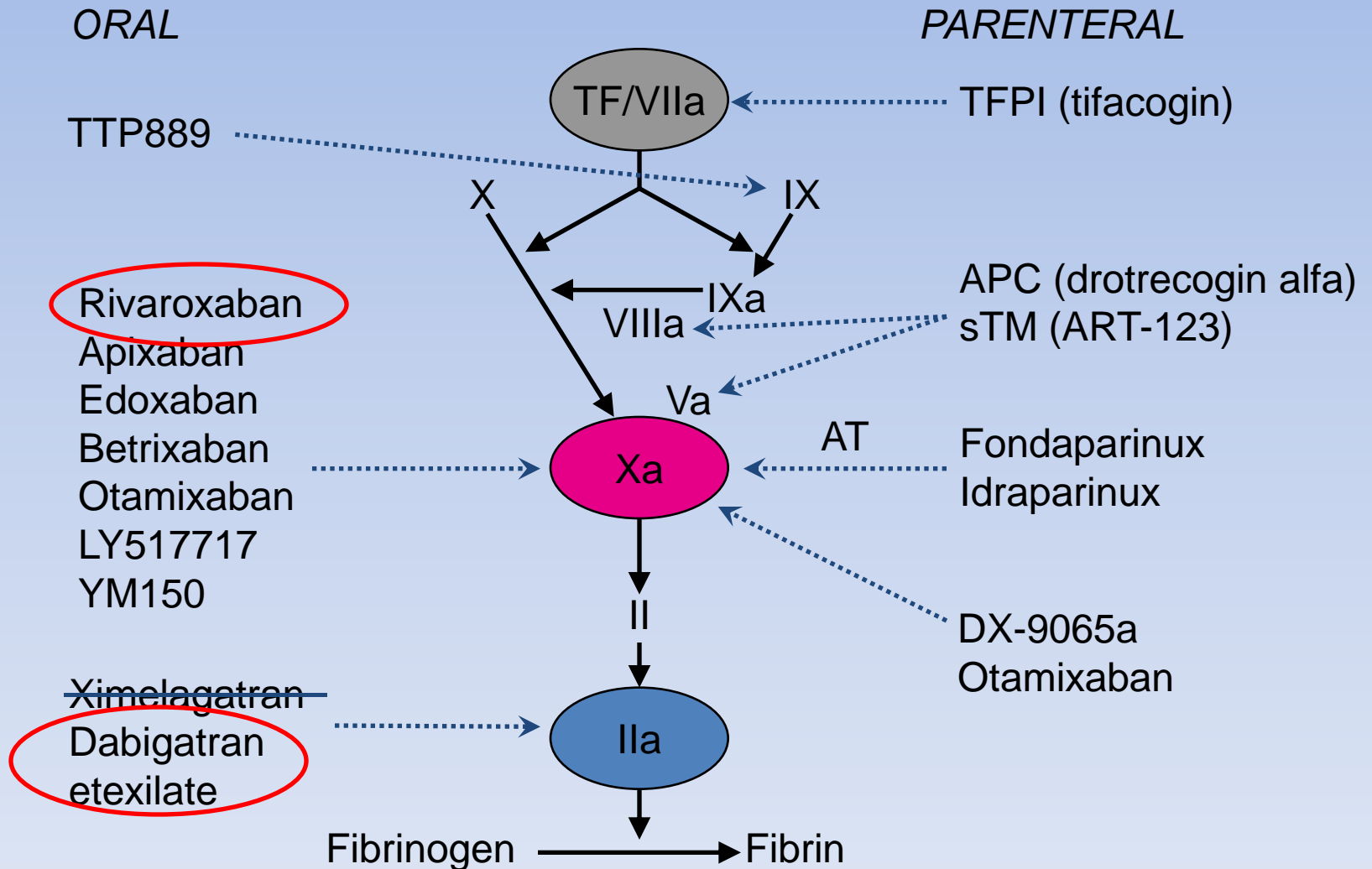
# Anticoagulants: Mechanism of Action



Adapted from Kubitzka et al. *Clin Pharmacol Ther.* 2005;78:412.

Weitz and Bates. *J Thromb Haemost.* 2005;3:1843.

# New anticoagulants



Adapted from Weitz & Bates, *J Thromb Haemost* 2005

# Comparison of Investigational Oral Agents

	DABIGATRAN	RIVAROXABAN
<i>Manufacturer</i>	BI	Bayer/J & J
<i>Brand Name</i>	Pradaxa	Xarelto
<i>Approval Status</i>	Approved in Eur/Can 2008 Approved in US Oct 2010 for a. fib.	Approved in Eur/Can 2008 1/11: Application submitted for a. fib. and response to FDA questions on VTE prevention
<i>Mechanism of Action</i>	Direct IIa inhibitor	Direct Xa inhibitor

## Comparative Pharmacokinetics

	DABIGATRAN	RIVAROXABAN
<i>Dialyzable</i>	yes	“not expected”
<i>Molecular weight</i>	628 daltons	436 daltons
<i>Protein binding</i>	35%	>90%
<i>Volume of distribution</i>	60-70 L	50 L
<i>Binding to catalytic site</i>	reversible	reversible
<i>Antidote</i>	NO	NO
T max	1-2 hours	2-4 hours
T 1/2	12-17 hours	5-9 hours
Activation	Prodrug rapidly converted to active drug via hydrolysis	none
Metabolism	Conjugation (no CYP involvement)	Oxidation (via CYP3A4 and CYP2J2) and hydrolysis
<i>Renal excretion of unchanged drug</i>	80%	36%

# Pharmacokinetics-Absorption Issues

	DABIGATRAN	RIVAROXABAN
Effect of food	Delayed Tmax	Delayed Tmax Higher Cmax Higher AUC Less Variability
Effect of gastric pH	none	none
Effect of antacids	none	none
Effect of H <sub>2</sub> blockers	none	none
Effect of PPIs	Exposure decreased 15% in Re-Ly	none
Recommended	Take with or without food	Take with food or within 2 hours of eating

# Other Clinical Issues

	DABIGATRAN	RIVAROXABAN
<b>Use in moderate hepatic failure (Child Pugh B)</b>	<b>No change in clearance</b>	<b>Reduction in clearance</b>
<b>Use in severe hepatic failure (Child Pugh C)</b>	<b>Excluded from clinical trials</b>	<b>Excluded from clinical trials</b>
<b>Effect on AST/ALT</b>	<b>Similar to enoxaparin in clinical trials</b>	<b>Similar to enoxaparin in clinical trials</b>
<b>Use in underweight patients</b>	<b>Dosing adjustment not recommended</b>	<b>Dosing adjustment not recommended</b>
<b>Use in obesity</b>	<b>Dosing adjustment not recommended</b>	<b>Dosing adjustment not recommended</b>

# Effect of Renal Function on Dabigatran Pharmacokinetics

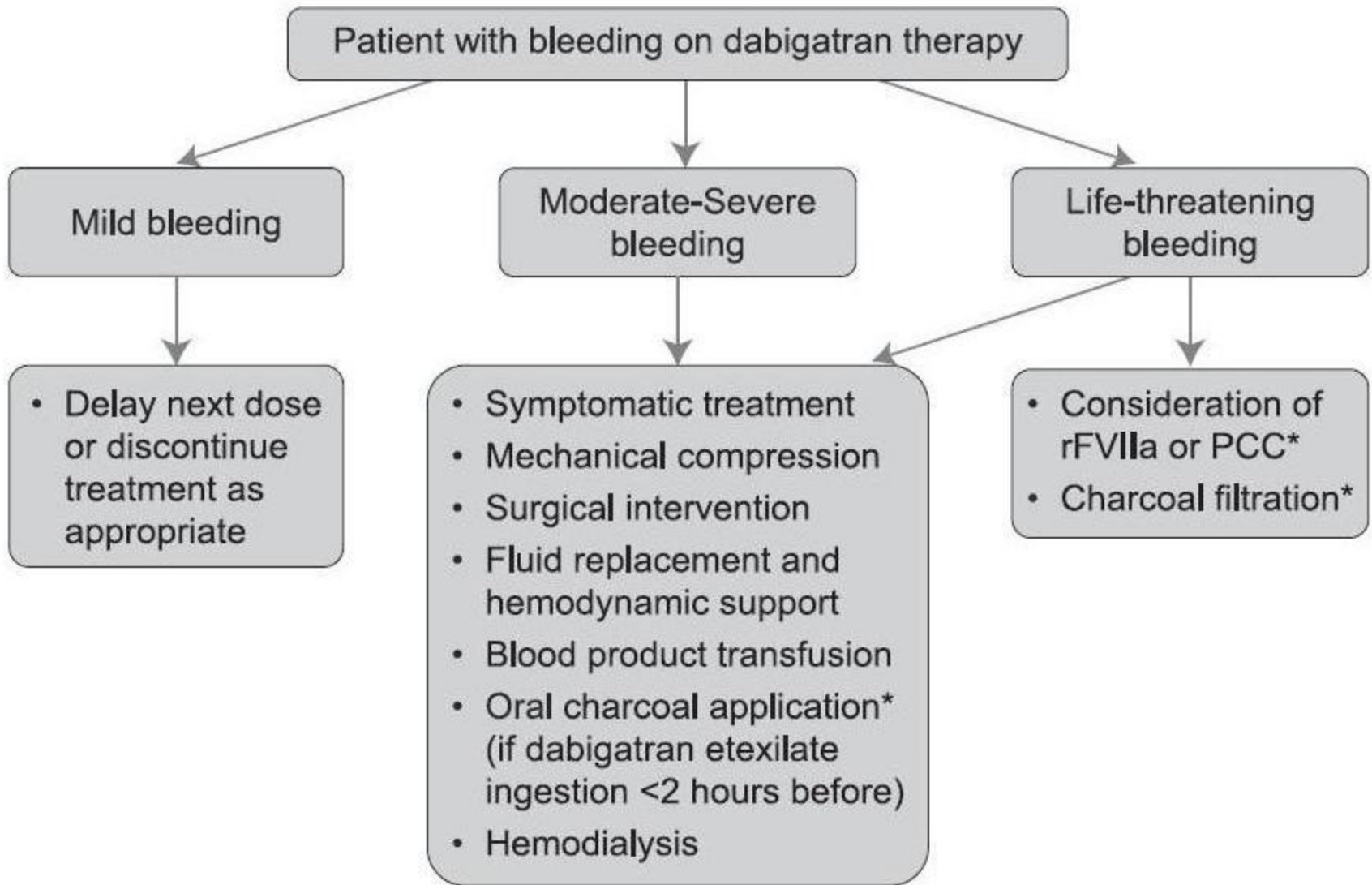
<b>Renal Function</b>	<b>CrCl (mL/min)</b>	<b>Increase in AUC</b>	<b>Increase in Cmax</b>	<b>t<sub>1/2</sub> (h)</b>
<b>Normal</b>	80	1x	1x	13
<b>Mild</b>	50	1.5x	1.1x	15
<b>Moderate</b>	30	3.2x	1.7x	18

# Drug Interactions

	DABIGATRAN	RIVAROXABAN
<b>Antithrombotic Agents</b>	<b>Increased bleeding</b>	<b>Increased bleeding</b>
<b>CYP3A4 inhibitors reported</b>	<b>N/A</b>	<b>Ketoconazole (100% inc AUC/Cmax) Ritonavir (100% inc AUC/Cmax) Clarithromycin (50% inc AUC/Cmax) Erythromycin (30% inc AUC/Cmax)</b>
<b>CYP3A4 inducers reported</b>	<b>N/A</b>	<b>Rifampin (50% dec AUC)</b>

# Drug Interactions

	DABIGATRAN	RIVAROXABAN	APIXABAN
p-GP inhibitors reported	<p>Amiodarone (12% inc exposure in Re-Ly)</p> <p>Quinidine (53% inc AUC)</p> <p>Verapamil (23% inc exposure in Re-Ly; needs to be in gut)</p> <p>Ketoconazole (150% inc AUC/Cmax)</p>	<p>Ketoconazole (100% inc AUC/Cmax)</p> <p>Ritonavir (100% inc AUC/Cmax)</p> <p>Clarithromycin (50% inc AUC/Cmax)</p> <p>Erythromycin (30% inc AUC/Cmax)</p>	Not yet reported
p-GP inducers reported	<p>Rifampin (67% dec AUC)</p>	<p>Rifampin (50% dec AUC)</p>	Not yet reported
p-GP substrates	<p>Digoxin (no interaction)</p>	<p>Digoxin (no interaction)</p>	Not yet reported



\*Recommendation based only on limited non-clinical data, there is no experience in volunteers or patients

# DIRECT THROMBIN INHIBITORS

Natural Product:	<i>hirudin</i>
Recombinant Derivatives:	<i>lepirudin</i> desirudin
Synthetic Derivatives:	<i>bivalirudin</i>
Related Small Molecules:	<i>argatroban</i> <i>ximelagatran</i> ; AZD0837 <i>dabigatran</i>

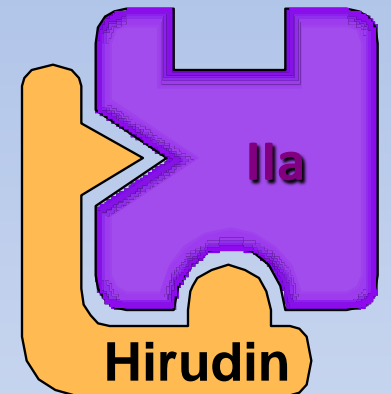
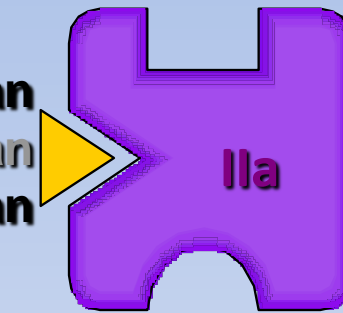
# Direct Thrombin Inhibitors: Mechanism of Action

**Heparin-Binding Site  
(Exosite 2)**  
(Linked to fibrin-binding site)

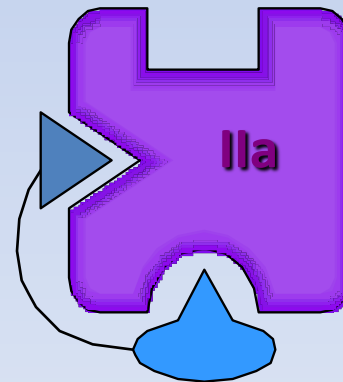
**Catalytic Site  
(Active Site)**  
(Enzymatic actions of thrombin)

**Substrate Recognition Site  
(Exosite 1)**  
(Binds to fibrinogen)

**Argatroban  
(Xi)melagatran  
Dabigatran**



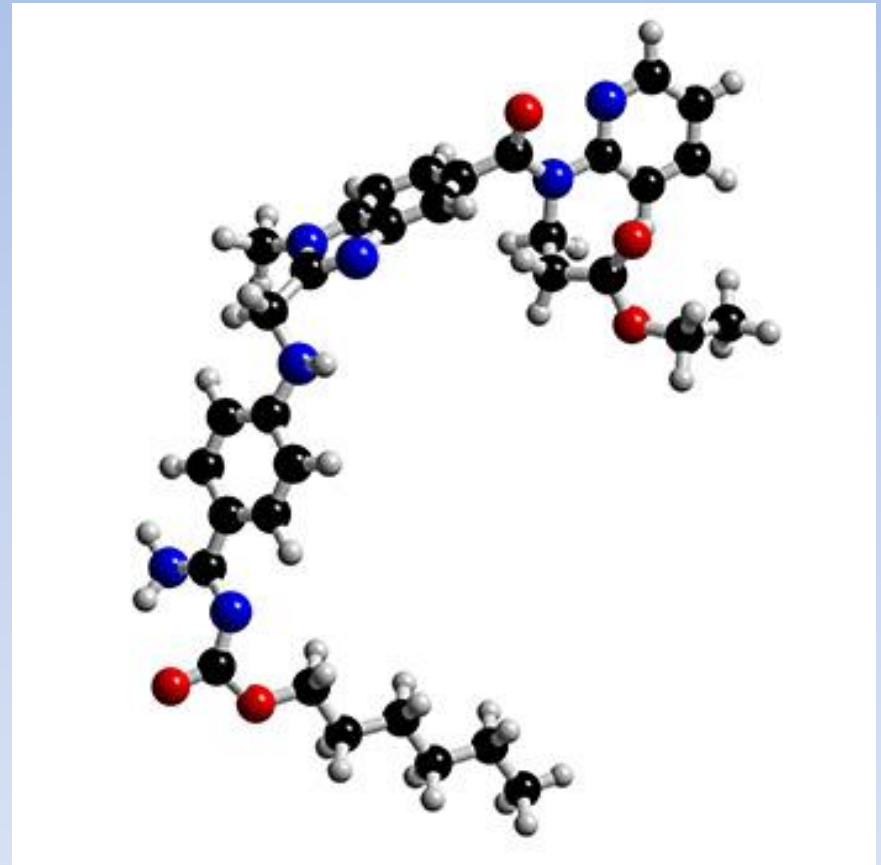
**Hirudin  
and  
Derivatives**



**Bivalirudin**

# Dabigatran Etexilate

- **Double pro-drug; MW 628**
- **Low bioavailability**
  - Requires high doses
- **Absorption is dependent on an acid environment**
  - Tartaric-acid containing capsules
- **Effect on coagulation markers**
  - Minimal effect on INR
  - aPTT prolonged but curve flattens at higher concentrations
  - ACT prolonged, but curve flattens at higher concentrations
  - Thrombin clotting times and ecarin clotting times are linear with dabigatran concentrations



# Dabigatran Etexilate

Features	Dabigatran Etexilate
Bioavailability (%)	3-7
Formulation	Capsule
CYP450 metabolism	No
Time to Peak (h)	1-3
T1/2 (h)	12-17
Renal Excretion (%)	80
Liver Toxicity	No effects seen in trials

# Dabigatran etexilate Clinical Program Overview

## Primary DVT prevention

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## VTE secondary prevention

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## VTE treatment

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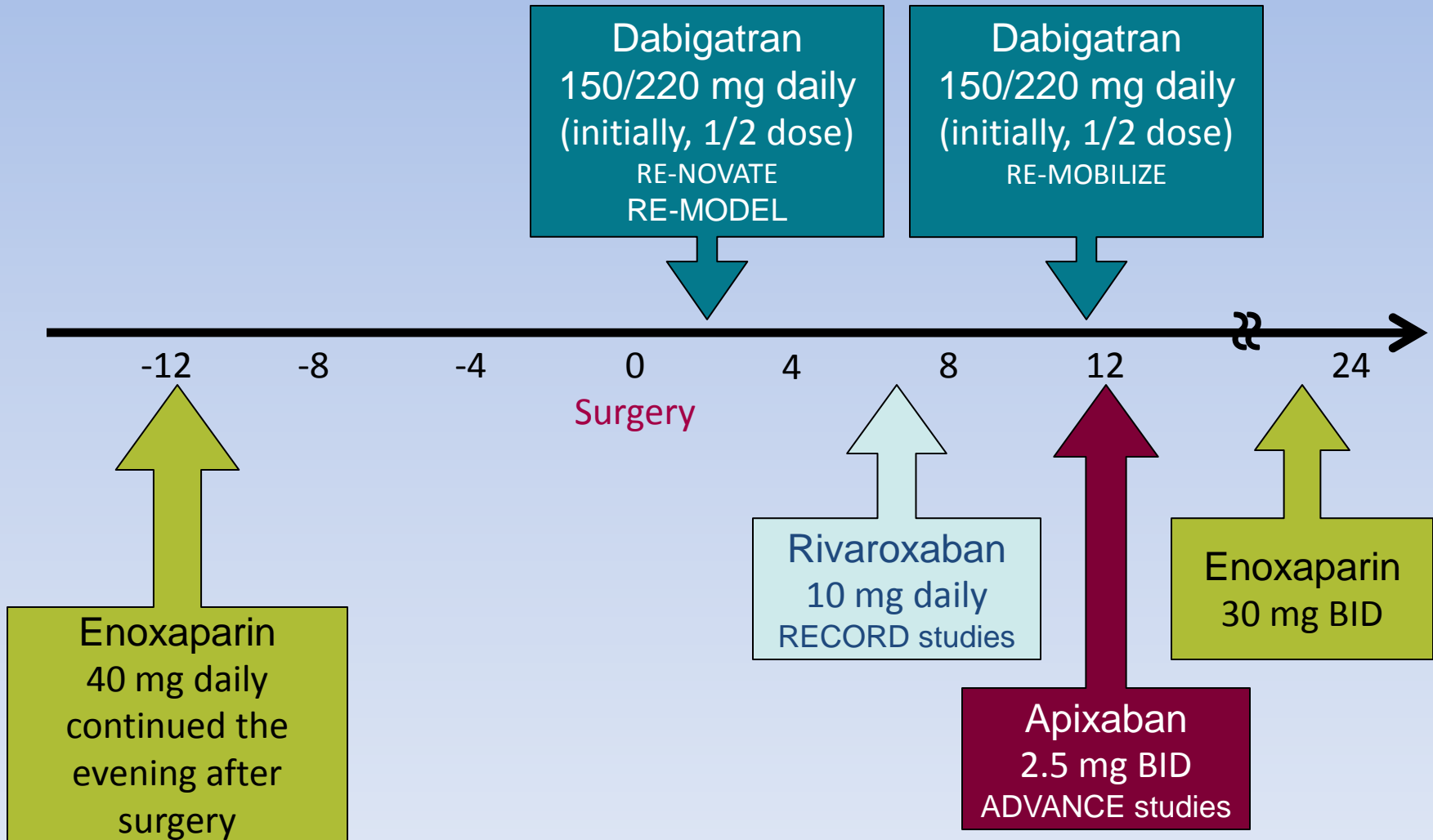


## SPAF

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# Orthopedic Surgery | Time of Doses



# Dabigatran

## Phase III Trials-VTE Prevention

Study	Patients	Comparison: dabigatran 150/220 mg PO daily (initially, ½ dose) versus	Treatment Duration
RE-NOVATE (n=3493)	THR	Enoxaparin 40 mg SC daily	28-35 days (venography)
RE-MODEL (n=2076)	TKR	Enoxaparin 40 mg SC daily	6-10 days (venography)
RE-MOBILIZE (n=1896)	TKR	Enoxaparin 30 mg SC twice daily	12-15 days (venography)

PO, oral; SC, subcutaneous; THR, total hip replacement; TKR, total knee replacement ; VTE, venous thromboembolism

Eriksson BI, et al. Lancet 2007;370:949-56 (NCT00168818).

Eriksson BI, et al. J Thromb Haemost 2007;5:2178-85 (NCT00168805).

Ginsberg JS, et al. J Arthroplasty 2009;24:1-9 (NCT00152971).

# Dabigatran | Phase III Trials

Enoxaparin

Dabigatran (150)

Dabigatran (220)

## DVT, PE, & mortality

**RE-NOVATE**

6.7%

8.6%  
*p*<0.0001\*

6.0%  
*p*<0.0001\*

**RE-MODEL**

37.7%

40.5%  
*p*=0.017\*

36.4%  
*p*=0.0003\*

**RE-MOBILIZE**

25.3%

33.7%  
*p*<0.001†

31.1%  
*p*=0.02†

## Major bleeding

**RE-NOVATE**

1.6%

1.3%

2.0%

**RE-MODEL**

1.3%

1.3%

1.5%

**RE-MOBILIZE**

1.4%

0.6%

0.6%

\* P value for non-inferiority ; † P value for superiority

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# Dabigatran | RE-COVER

- **Population:** Acute DVT and/or PE patients
- **Methods:** Randomized, double-blind non-inferiority design
- **Treatment:** Dabigatran (150 mg twice daily vs. adjusted dose warfarin)-both groups received parenteral anticoagulation therapy
  - » Dabigatran started when parenteral therapy stopped (median of 9 days), warfarin was started early
- **Follow-up:** 6 months
- **Outcome:** Symptomatic, objectively confirmed recurrent VTE and related death

# Dabigatran | RE-COVER

	Warfarin (n=1265)	Dabigatran (n=1274)
Event	%	%
VTE/related death	2.1	2.4†
All Cause Mortality	1.7	1.6
Major Bleeding	1.9	1.6
Major and Clinically Relevant Non-Major Bleeding	5.6	8.8¶

† P < 0.001 for non-inferiority criteria; ¶ P = 0.002

Warfarin time in therapeutic range was 60%

Dyspepsia occurred in 3.1% of the dabigatran patients compared to 0.7% of warfarin patients (p<0.001)

No difference regarding elevations of serum transaminase levels

# Dabigatran | RE-LY

- **Population:** Atrial fibrillation and stroke risk
- **Methods:** Randomized, non-inferiority design
- **Treatment:** Dabigatran (110 or 150 mg twice daily [blinded] vs. adjusted dose warfarin)
- **Follow-up:** 2 years (median)
- **Outcome:** Stroke or systemic embolism

# Dabigatran | RE-LY

	Warfarin (n=6022)	Dabigatran (110 mg; n=6015)	Dabigatran (150 mg; n=6076)
Event	% per year	% per year	% per year
<b>Stroke or systemic embolism</b>	1.69	1.53*	1.11†
<b>Stroke</b>	1.57	1.44	1.01†
<b>Hemorrhagic</b>	0.38	0.12†	0.10†
<b>Ischemic (NS)</b>	1.20	1.34	0.92‡
<b>Mortality</b>	4.13	3.75	3.64¶
<b>Major Bleeding</b>	3.36	2.71#	3.11

\* P<0.001 (non-inferiority); † P<0.001; ‡ P≤0.03; ¶ P=0.051; # P=0.003

MI rate: Warfarin 0.64% per yr

Dabigatran 110 mg 0.82% per yr (RR, 1.29; 95% CI, 0.96 to 1.75; P = 0.09)

Dabigatran 150 mg 0.81% per yr (RR, 1.27, 95% CI, 0.94 to 1.71; P = 0.12)

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

Connolly SJ, et. al. *N Engl J Med*. 2010;363:1875-1876.

# Dabigatran | RE-LY

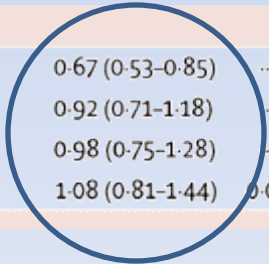
- **Dyspepsia:**
  - Warfarin 5.8%
  - Dabigatran 110 mg 11.8% (p<0.001 vs. warfarin)
  - Dabigatran 150 mg 11.3% (p<0.001 vs. warfarin)
- **Major GI Bleeding:**
  - Warfarin 1.02%/yr
  - Dabigatran 110 mg 1.10%/yr (p=0.42 vs. warfarin)
  - Dabigatran 150 mg 1.5%/yr (p<0.001 vs. warfarin)
- **No difference regarding elevations of serum transaminase levels**
- **Mean time in therapeutic range was 64%**

# The Importance of INR Control

	110 mg dabigatran			150 mg dabigatran			Warfarin			110 mg dabigatran vs warfarin		150 mg dabigatran vs warfarin	
	Patients (n)	Events	Rate per 100 person-years	Patients (n)	Events	Rate per 100 person-years	Patients (n)	Events	Rate per 100 person-years	HR (95% CI)	p (interaction)	HR (95% CI)	p (interaction)
<b>Stroke and systemic embolism</b>													
<57.1%	1497	55	1.91	1509	32	1.10	1504	54	1.92	1.00 (0.68-1.45)	..	0.57 (0.37-0.88)	..
57.1-65.5%	1524	51	1.67	1526	32	1.04	1514	62	2.06	0.81 (0.56-1.17)	..	0.50 (0.33-0.77)	..
65.5-72.6%	1474	40	1.34	1484	31	1.04	1487	45	1.51	0.89 (0.58-1.36)	..	0.69 (0.44-1.09)	..
>72.6%	1482	36	1.23	1514	38	1.27	1509	40	1.34	0.92 (0.59-1.45)	0.89	0.95 (0.61-1.48)	0.20
<b>Non-haemorrhagic stroke and systemic embolism</b>													
<57.1%	1497	51	1.77	1509	26	0.89	1504	46	1.63	1.09 (0.73-1.62)	..	0.54 (0.34-0.88)	..
57.1-65.5%	1524	46	1.51	1526	30	0.98	1514	49	1.63	0.92 (0.62-1.38)	..	0.59 (0.38-0.94)	..
65.5-72.6%	1474	39	1.31	1484	30	1.01	1487	33	1.11	1.19 (0.75-1.89)	..	0.91 (0.56-1.50)	..
>72.6%	1482	32	1.10	1514	35	1.17	1509	29	0.97	1.13 (0.69-1.87)	0.86	1.21 (0.74-1.98)	0.076
<b>Intracranial bleeding</b>													
<57.1%	1497	8	0.28	1509	10	0.34	1504	18	0.64	0.43 (0.19-1.00)	..	0.53 (0.25-1.15)	..
57.1-65.5%	1524	9	0.30	1526	13	0.42	1514	28	0.93	0.31 (0.15-0.66)	..	0.45 (0.24-0.88)	..
65.5-72.6%	1474	4	0.13	1484	7	0.24	1487	20	0.67	0.20 (0.07-0.58)	..	0.35 (0.15-0.82)	..
>72.6%	1482	6	0.21	1514	9	0.30	1509	23	0.77	0.27 (0.11-0.66)	0.71	0.39 (0.18-0.84)	0.89





# The Importance of INR Control

	110 mg dabigatran			150 mg dabigatran			Warfarin			110 mg dabigatran vs warfarin		150 mg dabigatran vs warfarin	
	Patients (n)	Events	Rate per 100 person-years	Patients (n)	Events	Rate per 100 person-years	Patients (n)	Events	Rate per 100 person-years	HR (95% CI)	p (interaction)	HR (95% CI)	p (interaction)
<b>Stroke, systemic embolism, pulmonary embolism, myocardial infarction, death, and major bleeding</b>													
<57.1%	1497	220	7.65	1509	199	6.83	1504	285	10.13	0.74 (0.62-0.89)	..	0.67 (0.56-0.80)	..
57.1-65.5%	1524	239	7.84	1526	217	7.09	1514	241	8.03	0.97 (0.81-1.16)	..	0.87 (0.73-1.05)	..
65.5-72.6%	1474	205	6.88	1484	220	7.41	1487	212	7.13	0.97 (0.80-1.17)	..	1.05 (0.87-1.27)	..
>72.6%	1482	200	6.85	1514	212	7.07	1509	192	6.42	1.07 (0.87-1.30)	0.036	1.11 (0.91-1.35)	0.0006
<b>Stroke, systemic embolism, pulmonary embolism, myocardial infarction, and cardiovascular death</b>													
< 57.1%	1497	150	5.21	1509	115	3.95	1504	175	6.22	0.83 (0.67-1.04)	..	0.64 (0.50-0.80)	..
57.1-65.5%	1524	131	4.30	1526	107	3.50	1514	130	4.33	0.99 (0.78-1.27)	..	0.80 (0.62-1.04)	..
65.5-72.6%	1474	111	3.72	1484	108	3.64	1487	115	3.87	0.97 (0.74-1.25)	..	0.94 (0.72-1.22)	..
>72.6%	1482	112	3.84	1514	108	3.60	1509	91	3.04	1.27 (0.97-1.67)	0.14	1.19 (0.90-1.57)	0.006
<b>Non-haemorrhagic stroke, systemic embolism, pulmonary embolism, myocardial infarction, and cardiovascular death</b>													
<57.1%	1497	170	5.91	1509	147	5.05	1504	210	7.46	0.79 (0.64-0.97)	..	0.67 (0.55-0.83)	..
57.1-65.5%	1524	170	5.58	1526	148	4.84	1514	153	5.10	1.09 (0.88-1.36)	..	0.94 (0.75-1.18)	..
65.5-72.6%	1474	147	4.93	1484	144	4.85	1487	138	4.74	1.04 (0.88-1.32)	..	1.03 (0.81-1.29)	..
>72.6%	1482	146	5.00	1514	137	4.57	1509	115	3.91	1.29 (1.01-1.64)	0.017	1.17 (0.91-1.50)	0.0046
<b>Total death</b>													
<57.1%	1497	120	4.17	1509	112	3.85	1504	161	5.72	0.73 (0.58-0.92)	..	0.67 (0.53-0.85)	..
57.1-65.5%	1524	121	3.97	1526	115	3.75	1514	123	4.09	0.97 (0.75-1.24)	..	0.92 (0.71-1.18)	..
65.5-72.6%	1474	95	3.19	1484	108	3.64	1487	110	3.70	0.86 (0.65-1.13)	..	0.98 (0.75-1.28)	..
>72.6%	1482	105	3.60	1514	99	3.30	1509	91	3.04	1.18 (0.89-1.57)	0.066	1.08 (0.81-1.44)	0.052



Wallentin, LW, et al. *The Lancet* 2010; 375: 975-983.

# Rivaroxaban: Clinical Trial Program Overview

	Phase II	Phase III
VTE prevention	<ul style="list-style-type: none"> <li>▪ ODIXa-HIP1</li> <li>▪ ODIXa-HIP2</li> <li>▪ ODIXa-KNEE</li> <li>▪ ODIXa-OD-HIP</li> </ul>	 <ul style="list-style-type: none"> <li>▪ RECORD1</li> <li>▪ RECORD2</li> <li>▪ RECORD3</li> <li>▪ RECORD4</li> </ul>
VTE treatment	<ul style="list-style-type: none"> <li>▪ ODIXa-DVT</li> <li>▪ EINSTEIN DVT</li> </ul>	 <ul style="list-style-type: none"> <li>▪ EINSTEIN DVT</li> <li>▪ EINSTEIN PE</li> <li>▪ EINSTEIN EXT</li> </ul>
Stroke prevention in atrial fibrillation		
Secondary prevention of acute coronary syndromes	<ul style="list-style-type: none"> <li>▪ Dose finding</li> <li>▪ Dose confirmation</li> </ul>	

# Rivaroxaban | Phase III Trials

Study	Patients	Comparison: rivaroxaban 10 mg PO daily versus	Treatment Duration
RECORD 1 (n=4541)	THR	Enoxaparin 40 mg SC daily	36 days (venography)
RECORD 2 (n=2509)	THR	Enoxaparin 40 mg SC daily	31-39d (R) 10-14d (E) (venography)
RECORD 3 (n=2531)	TKR	Enoxaparin 40 mg SC daily	10-14 days (venography)
RECORD 4 (n=3148)	TKR	Enoxaparin 30 mg twice daily	10-14 days (venography)

PO, oral; SC, subcutaneous, THR, total hip replacement; TKR, total knee replacement

Eriksson BI, et al. N Engl J Med 2008;358:2765-75 (NCT00329628).

Kakkar AK, et al. Lancet 2008;372:31-9 (NCT00332020).

Lassen MR, et al. N Engl J Med 2008;358:2776-86 (NCT00361894).

Turpie AG, et al. Lancet 2009;373:1673-80 (NCT00362232).

# Rivaroxaban | Phase III Trials

	Rivaroxaban	Enoxaparin	P-value
<b>DVT, non-fatal PE &amp; death</b>			
<b>RECORD 1</b>	1.1%	3.7%	<0.001
<b>RECORD 2</b>	2.0%	9.3%	<0.0001
<b>RECORD 3</b>	9.6%	18.9%	<0.001
<b>RECORD 4</b>	6.9%	10.1%	0.0118
<b>Major bleeding</b>			
<b>RECORD 1</b>	0.3%	0.1%	0.18
<b>RECORD 2</b>	<0.1%	<0.1%	--
<b>RECORD 3</b>	0.6%	0.5%	--
<b>RECORD 4</b>	0.7%	0.3%	0.1096

Eriksson BI, et al. N Engl J Med 2008;358:2765-75 (NCT00329628).  
Kakkar AK, et al. Lancet 2008;372:31-9 (NCT00332020).  
Lassen MR, et al. N Engl J Med 2008;358:2776-86 (NCT00361894).  
Turpie AG, et al. Lancet 2009;373:1673-80 (NCT00362232).

Revised slide

# Record 4 | Additional Endpoints

Outcome	Rivaroxaban (%)	Enoxaparin (%)	P-value
Major VTE	1.2	2.0	0.1237
Symptomatic VTE	0.7	1.2	0.1868
Major bleeding	0.7	0.3	0.1096
Clinically relevant non-major bleeding	2.6	2.0	--

No difference between rivaroxaban & enoxaparin regarding liver enzyme rises >3x upper limit of normal [ULN] (1.3% vs. 2.6%), >5x ULN (0.3% vs. 1.0%), >10x ULN (0.1% vs. 0.1%), respectively.

Rivaroxaban Once-daily oral direct factor Xa inhibition  
Compared with vitamin K antagonism for prevention of  
stroke and Embolism Trial in Atrial Fibrillation

ROCKET AF 

# Study Design

## Atrial Fibrillation

### Risk Factors

- CHF
- Hypertension
- Age  $\geq$  75
- Diabetes

At least 2 or 3 required\*

OR

- Stroke, TIA or Systemic embolus

Rivaroxaban

20 mg daily  
15 mg for CrCl 30-49 ml/min

Randomized  
Double Blind /  
Double Dummy  
(n ~ 14,000)

Warfarin

INR target - 2.5  
(2.0-3.0 inclusive)

Monthly Monitoring  
Adherence to standard of care guidelines

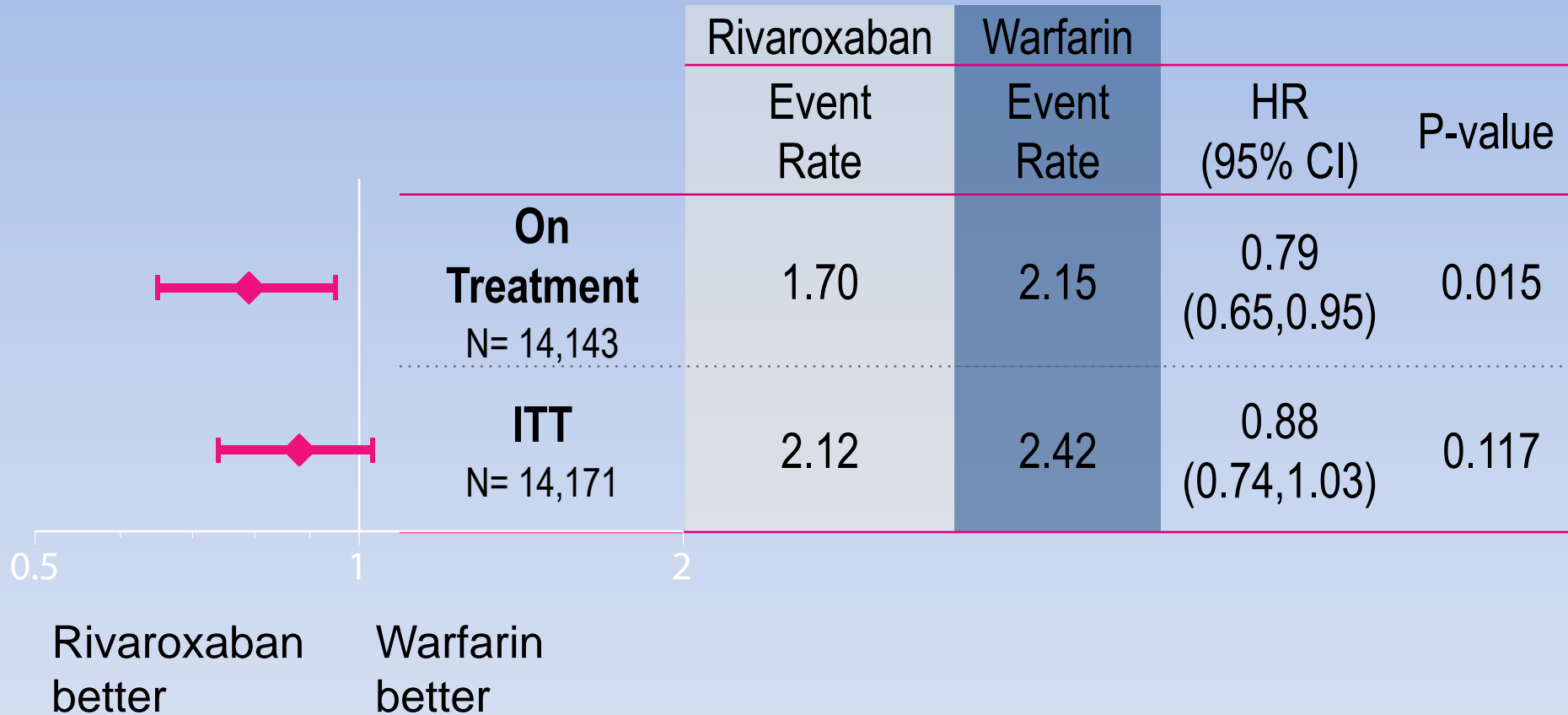
Primary Endpoint: Stroke or non-CNS Systemic Embolism

\* Enrollment of patients without prior Stroke, TIA or systemic embolism and only 2 factors capped at 10%

Califf R. LBCT I, Abstract 21839. Presented at: American Heart Association Scientific Sessions 2010; Nov. 13-17; Chicago.

# Primary Efficacy Outcome

## Stroke and non-CNS Embolism



Event Rates are per 100 patient-years

Based on Safety on Treatment or Intention-to-Treat thru Site Notification populations

Califf R. LBCT I, Abstract 21839. Presented at: American Heart Association Scientific Sessions 2010; Nov. 13-17; Chicago.

# Key Secondary Efficacy Outcomes

	Rivaroxaban	Warfarin		
	Event Rate	Event Rate	HR (95% CI)	P-value
Vascular Death, Stroke, Embolism	3.11	3.63	0.86 (0.74, 0.99)	0.034
Stroke Type				
Hemorrhagic	0.26	0.44	0.59 (0.37, 0.93)	0.024
Ischemic	1.34	1.42	0.94 (0.75, 1.17)	0.581
Unknown Type	0.06	0.10	0.65 (0.25, 1.67)	0.366
Non-CNS Embolism	0.04	0.19	0.23 (0.09, 0.61)	0.003
Myocardial Infarction	0.91	1.12	0.81 (0.63, 1.06)	0.121
All Cause Mortality	1.87	2.21	0.85 (0.70, 1.02)	0.073
Vascular	1.53	1.71	0.89 (0.73, 1.10)	0.289
Non-vascular	0.19	0.30	0.63 (0.36, 1.08)	0.094
Unknown Cause	0.15	0.20	0.75 (0.40, 1.41)	0.370

Event Rates are per 100 patient-years  
Based on Safety on Treatment Population

# Time in Therapeutic Range (TTR) INR Data

INR range	Warfarin
	Median (25 <sup>th</sup> , 75 <sup>th</sup> )
<1.5	2.7 (0.0 – 9.0)
1.5 to <1.8	7.9 (3.5 – 14.0)
1.8 to <2.0	9.1 (5.3 – 13.6)
2.0 to 3.0	57.8 (43.0 – 70.5)
>3.0 to 3.2	4.0 (1.9 – 6.5)
>3.2 to 5.0	7.9 (3.3 – 13.8)
>5.0	0.0 (0.0 – 0.5)

Based on Rosendaal method with all INR values included  
Based on Safety Population

# Primary Safety Outcomes

	Rivaroxaban	Warfarin		
	Event Rate or N (Rate)	Event Rate or N (Rate)	HR (95% CI)	P- value
Major	3.60	3.45	1.04 (0.90, 1.20)	0.576
≥2 g/dL Hgb drop	2.77	2.26	1.22 (1.03, 1.44)	0.019
Transfusion (> 2 units)	1.65	1.32	1.25 (1.01, 1.55)	0.044
Critical organ bleeding	0.82	1.18	0.69 (0.53, 0.91)	0.007
Bleeding causing death	0.24	0.48	0.50 (0.31, 0.79)	0.003
Intracranial Hemorrhage	55 (0.49)	84 (0.74)	0.67 (0.47, 0.94)	0.019
Intraparenchymal	37 (0.33)	56 (0.49)	0.67 (0.44, 1.02)	0.060
Intraventricular	2 (0.02)	4 (0.04)		
Subdural	14 (0.13)	27 (0.27)	0.53 (0.28, 1.00)	0.051
Subarachnoid	4 (0.04)	1 (0.01)		

Event Rates are per 100 patient-years  
Based on Safety on Treatment Population

# Rivaroxaban | Einstein DVT

- **Population:** Acute DVT patients
- **Methods:** Randomized, open label non-inferiority design
- **Treatment:** Rivaroxaban 15 mg po twice daily for three weeks, followed by 20 mg po daily  
Enoxaparin/warfarin titrated to an INR of 2-3
- **Follow-up:** 3, 6, or 12 months of therapy
- **Outcome:** Symptomatic, objectively confirmed recurrent VTE and related death

# Rivaroxaban | Einstein DVT

	Warfarin (n=1718)	Rivaroxaban (n=1731)
Event	%	%
VTE/related death	3	2.1†
All Cause Mortality	2.9	2.2
Major Bleeding	1.2	0.8
Major and Clinically Relevant Non-Major Bleeding	8.1	8.1

† P < 0.001 for non-inferiority criteria  
Warfarin time in therapeutic range was 57.7%

# Rivaroxaban | Einstein Extended

- **Population:** VTE patients who had completed 6-12 months of therapy
- **Methods:** Randomized, double-blind superiority design
- **Treatment:** Rivaroxaban 20 mg po daily  
Placebo
- **Follow-up:** 6 or 12 months of therapy
- **Outcome:** Symptomatic, objectively confirmed recurrent VTE and related death

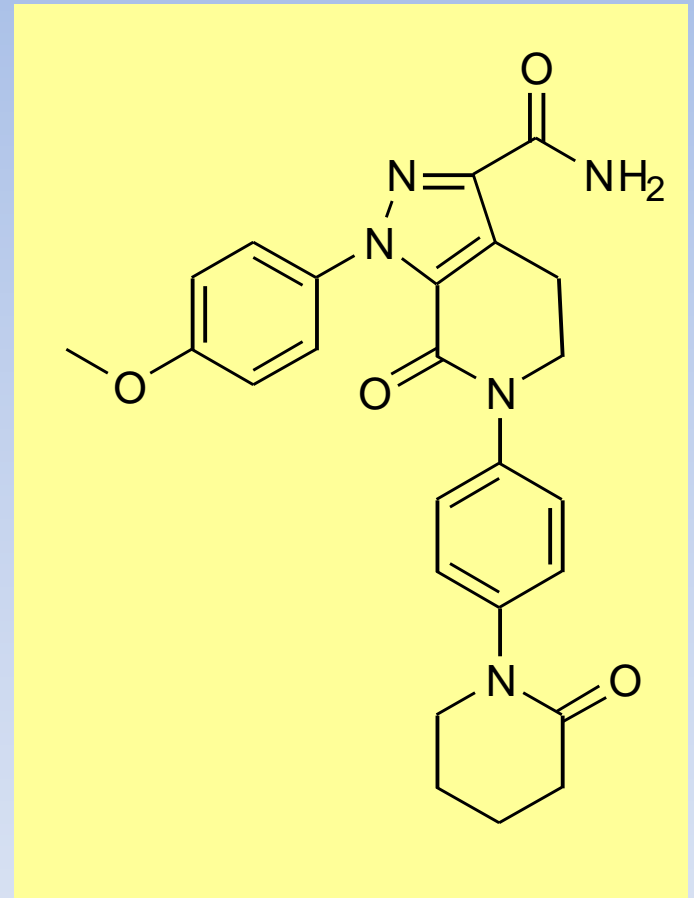
# Rivaroxaban | Einstein Extended

	Placebo (n=594)	Rivaroxaban (n=1274)
Event	%	%
VTE/related death	7.1	1.3†
All Cause Mortality	0.3	0.2
Major Bleeding	0	0.7
Major and Clinically Relevant Non-Major Bleeding	1.2	6†

† P < 0.001

# Direct Xa Inhibitor: Apixaban (BMS & Pfizer)

- Highly potent, oral, direct, reversible, selective factor Xa inhibitor
- High affinity and high degree of selectivity for factor Xa ( $K_i = 0.08$  nM)
- Produces concentration-dependent anticoagulation
- No formation of reactive intermediates
- No organ toxicity or LFT abnormalities in chronic toxicology studies
- Low likelihood of drug interactions or QTc prolongation
- Good oral bioavailability
- No food effect
- Balanced elimination (~25% renal)
- Half-life ~12 hrs



**New Slide**

# Apixaban Clinical Program

- **AMPLIFY** – DVT/PE treatment
- **AMPLIFY-EXT** – Extended prevention of VTE after initial therapy
- **ADVANCE 1, 2, and 3** – VTE prophylaxis in orthopedic surgery
- **ADOPT** –VTE prophylaxis in medically-ill patients
- **ARISTOTLE** – Stroke prophylaxis in atrial fibrillation
- **AVERROES** – Stroke prophylaxis in atrial fibrillation in patients with contraindications or intolerance to warfarin therapy
- **APPRAISE 1 and 2** – Treatment of ACS with antiplatelet therapy

# Now, some practical thoughts:

- Remember, systematic “airline cockpit” approaches are best to keep patients safe
- Address the renal issues:
  - Consider requiring baseline serum creatinine assessments and allowing pharmacists to order further labs as clinically needed
  - Consider developing order sets
- Assure your systems find duplicate anticoagulation therapy:
  - Education is critical
  - Analyze your alerts

# Now, some practical thoughts:

- Assure your systems identify critical drug interactions:
  - Can you make the more critical interactions look different?
  - Education is again critical
- Proactively address reversal:
  - Consider adding what may help to current reversal guidelines
  - Add them to any specific drug guidelines developed by your system

# Now, some practical thoughts:

- Assure that these new agents are specifically screened for when patients are scheduled for invasive procedures:
  - Can you standardize your screening process and have them use a checklist of drugs to look for?
  - Address how labs may be used as a backup
- Assure spinal and epidural anesthesia is handled safely:
  - Add these agents to any current guidelines
  - Consider building alerts to avoid use with indwelling catheters

# Now, some practical thoughts:

- Address who to handle dabigatran etexilate if a patient needs a tube:
  - Can you build alerts against a tube route of drug administration?
  - Education is again critical
- Analyze your stroke orders:
  - What will you do if the patient is on a new therapy?
  - Any new lab tests needed?

# Now, some practical thoughts:

- Address patient education issues for the new agents:
  - Compliance is key
  - Still need to assess for signs/symptoms of bleeding
- Address the 30 day stability issue with dabigatran etexilate:
  - Have the patient mark on their bottle how long the capsules are stable once it is opened
  - Educate patient not to open new bottles until needed or use unit dose packaging at home

# Conclusion

- Dabigatran etexilate and rivaroxaban have different pharmacology and pharmacokinetic profiles
- Dabigatran etexilate and rivaroxaban have had their efficacy studied in numerous phase three trials; pay attention to the critical trial differences
- Systematic approaches, much like have been utilized for warfarin, will be the key in assuring these agents are used safely
  - *Remember, there is no such thing as a safe anticoagulant, but pharmacists and other health care professionals, can play a key role in assuring they are used safely*