

Update on Novel Agents in Anticoagulation
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DISCLOSURES: NONE

Novel Anticoagulants: Case of Mr. T

Your Orthopedic surgeon calls you from the operating room requesting advice on VTE prevention for a 45yo male with congenital hip dysplasia and a remote history of DVT, now status post THA, who has an extreme phobia of needles and who refuses all injections and laboratory draws. What is an FDA approved option you could recommend?

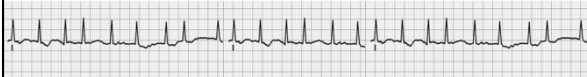
- A. Dabigatran Etexilate
- B. Apixaban
- C. Rivaroxaban
- D. All of the above

Novel Anticoagulants: Case of Mrs. H

A 76yo female with a history of HTN and CHF (EF 45%) presents to the Emergency Department with intermittent palpitations for 6 weeks and near syncope.

Exam reveals BP of 110/55 HR 140. CV with irregularly irregular rhythm.

ECG with atrial fibrillation with RVR.



Mrs. H: Question #1

Mrs. H has an increased risk of stroke and systemic embolism (CHADS2 score of 3 = 6%/year risk without anticoagulation). Which of the following is an established or emerging anticoagulant option to prevent stroke and systemic embolism in this patient?

- A. Direct thrombin inhibitor: Dabigatran etexilate
- B. Factor Xa inhibitors: Apixaban/Rivaroxaban
- C. Warfarin
- D. All of the above

Anticoagulants (AC): background

- ▶ Warfarin has been only oral AC in U.S. for past 50+ years
- ▶ Approximately 1% of U.S. population takes warfarin
 - Atrial fibrillation, DVT/PE, mechanical valves common indications
 - Afib incidence expected to increase to 16 million by 2050
- ▶ Major bleeding occurs in approximately 1-2% / year on warfarin
 - 3,500 attributable ICH per year
- ▶ Warfarin #1 in adverse drug-related deaths in the U.S.

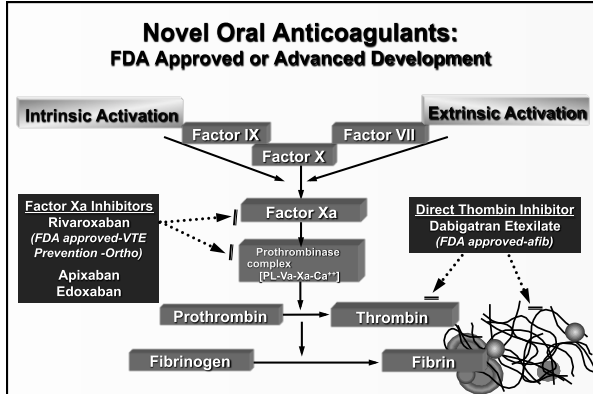
Arch Int Med 2004; 164:880, Drug Information Service, University of Utah.

Novel Oral ACs: Potential Advantages

Advantage	Potential Clinical Implication
Rapid onset of action	No need for routine bridging
Predictable anticoagulant effect	No need for routine coagulation monitoring
Specific coagulation enzyme targets	Low risk of off-target adverse effects
Low potential for food interactions	Few to no dietary precautions
Lower potential for drug interactions	Fewer drug restrictions

Although novel oral anticoagulants may be easier to use than warfarin, a risk of bleeding remains and new challenges emerge.

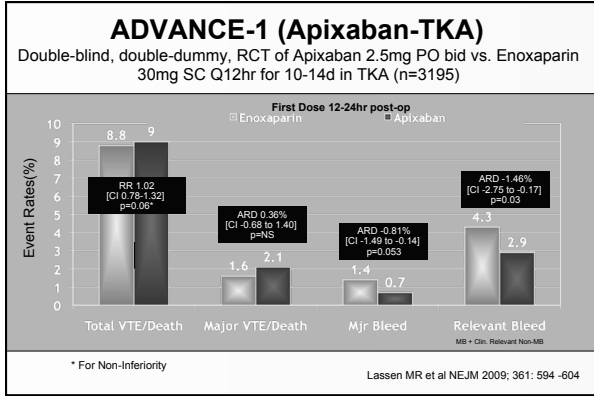
Adapted from Eriksson et al. Ann Rev Med 2011;62:41-57

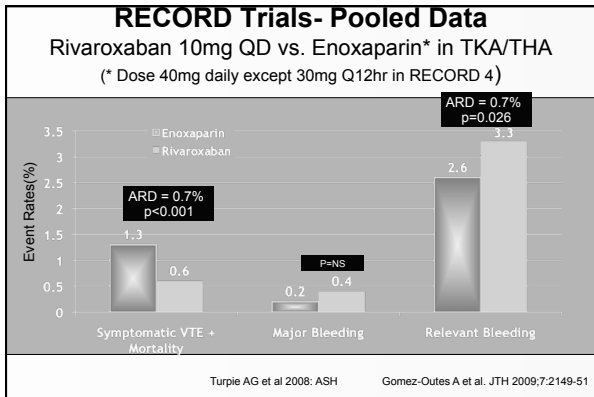


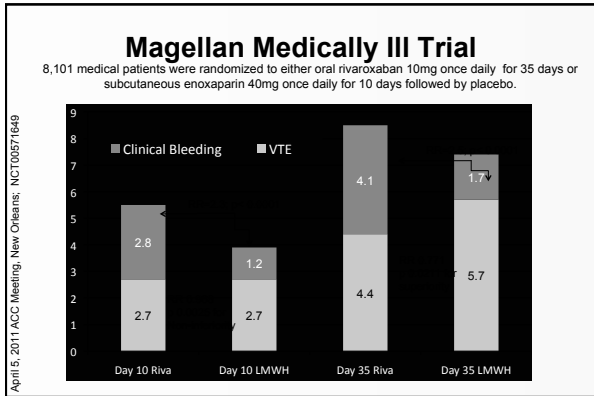
Pharmacology of Novel Oral Anticoagulants

	Dabigatran (Pradaxa®)	Rivaroxaban (Xarelto®)	Apixaban (Eliquis®)
Target	Factor IIa (reversibly binds to site)	Factor Xa (reversibly binds to site)	Factor Xa (reversibly binds to site)
US regulatory Status	Oct 2010 Approved non-valvular atrial fibrillation	Jul 2011 Approved – DVT/PE prevention joint replacement	Advanced clinical trials
Dosage Form	capsule	tablet	tablet
Bioavailability	6%	60-80%	50-85%
Time to Peak	1-2 hours	2-4 hours	1-3 hours
Metabolism	Conjugation; NO CYP involvement	Oxidation (via CYP3A4 & CYP2J2) + hydrolysis	Oxidation (via CYP3A4) + conjugation
Renal Excretion	80%	66%	25%
Half-life	14-17 hours	9-13 hours	9-14 hours
Dosing frequency, major trials	BID	QD	BID

Novel Oral Anticoagulants: Selected Clinical Trial Results







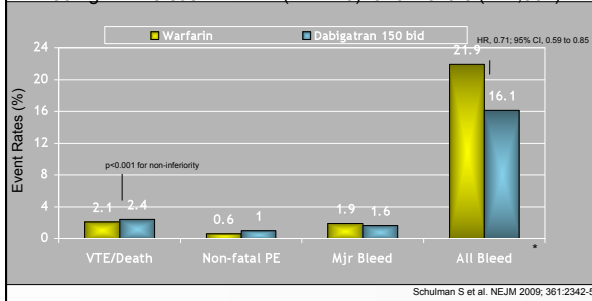
VTE Prevention Summary

- ▶ Novel anticoagulants may greatly simplify VTE prevention and obviate the need for both parenteral administration and monitoring
- ▶ Overall risk: benefit comparable to standard therapy, but interpretation is in the eye of the beholder
- ▶ Dosing/use in special populations will need to be elucidated

July 2011: FDA approved Rivaroxaban for DVT/PE prevention after major joint replacement surgery

RE-COVER: Dabigatran in Acute VTE

Open label, randomized non-inferiority trial of AT +Dabigatran 150mg BID versus AT+VKA (INR 2-3) for 6 months (n=2,564)



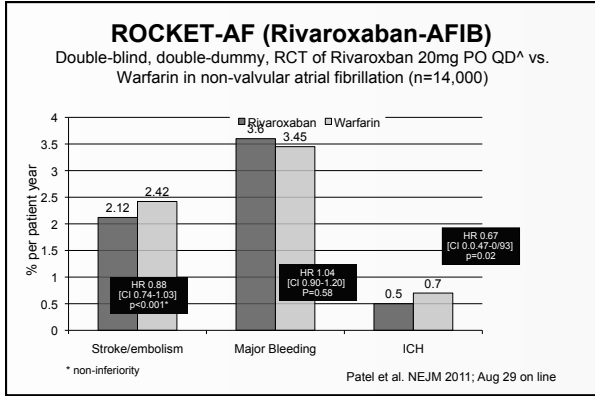
EINSTEIN: Rivaroxaban in Acute VTE

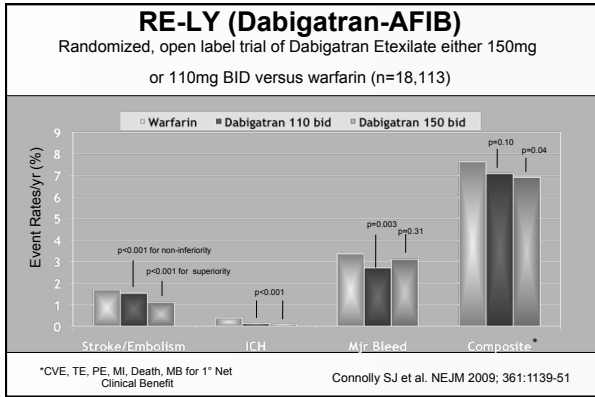
Open label, randomized non-inferiority trial of Rivaroxaban* versus Enoxaparin + VKA (INR 2-3) for 6 months in 3,449 DVT/PE patients



*15mg BID x 3 weeks then 20mg QDay

NEJM 2010;363:2499-510

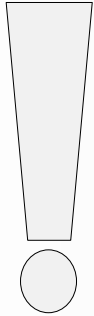




RE-LY: Impact of Warfarin Control

Composite: Stroke/systemic embolism/myocardial infarction/death/pulmonary embolism/major bleeding				
	Dabigatran	Warfarin		
	(Events per 100-person years)		Hazard Ratio	95% CI*
TTR:				
<57.1	6.83	10.13	0.67	0.56-0.80
57.1-65.5	7.09	8.03	0.87	0.73-1.05
65.5-72.6	7.41	7.13	1.05	0.87-1.27
>72.6	7.07	6.42	1.11	0.91-1.35

Wallentin et al Lancet (2010);376:975-83 *(p=0.0006 for interaction)



October 2010 FDA approves **dabigatran etexilate** (Pradaxa) for stroke prevention in non-valvular afib.

July 2011 FDA approves **Rivaroxaban (Xarelto)** for DVT/PE prevention after joint replacement

Sept 2011 FDA votes 9-2 to approve Rivaroxaban for stroke prevention in non-valvular afib



Novel Anticoagulants Clinical Implications

- Drug interactions
- Use in hepatic/renal
- Extreme weights
- Monitoring
- Peri-procedure Mgt
- Bleeding/reversibility
- Provider Knowledge

Without thought - efficacy & safety in practice will NOT mimic clinical trial results

Back to Mrs. H: Question #2

At the time of discharge, Mrs. H is taking fluoxetine, diltiazem and amiodarone. You note that she has a weight of 56kg and a creatinine clearance of 40ml/min. Which of the following anticoagulant options has a high potential for clinically important drug-drug interactions?

- A. Direct thrombin inhibitor: Dabigatran etexilate
- B. Factor Xa inhibitors: Apixaban/Rivaroxaban
- C. Warfarin
- D. All of the above

"If you look statistically at 'what are the drug interactions that kill people,' warfarin interactions are at the top of the list." - Dr. D.S. Paauw, Professor of Medicine, University of Washington

BUT

Warfarin drug-drug interactions can be effectively managed through frequent INR assessment and dose titration

Drug Interactions of Novel Anticoagulants

	Apixaban (Eliquis®)	Rivaroxaban (Xarelto®)	Dabigatran (Pradaxa®)
CYP3A4	Y	Y	N
p-glycoprotein	Y	Y	Y
Means to monitor interaction	No	No	No!

CYP3A4 Drug Interactions

Inducers

carbamazepine
efavirenz
glucocorticoids
nevitapine
phenobarbital
phenytoin
primidone
Rifampin
rifapentine
rintonavir
St John's Wort

Inhibitors

amiodarone
amprenavir
Aprepitant
atazanavir
cimetidine
clarithromycin
diltiazem
erythromycin
fluconazole
fluoxetine
flvoxamine
cyclosporin
quinidine

grapefruit juice
indinavir

itraconazole
ketoconazole
lopinavir
nefazodone
nelfinavir
nofluoxetine
ritonavir
saquinavir
synercid
verapamil
voriconazole

P-Glycoprotein Drug Interactions

Inducers

clotrimazole
St John's Wort
midazolam
nifedipine
phenobarbital
phenytoin
rifampin

Inhibitors

amiodarone
cefprozime
ceftriaxone
clarithromycin
cyclosporin
diltiazem
dipyridamole
erythromycin
hydrocortisone
verapamil

itraconazole
ketoconazole
nicardipine
nifedipine
propranolol
quinidine
quinine
tacrolimus
tamoxifen

FDA Product labeling

"P-gp inducers and inhibitors: Avoid co-administration of rifampin with **PRADAXA** because of effects on dabigatran exposure... P-gp inhibitors ketoconazole, verapamil, amiodarone, quinidine, and clarithromycin do not require dose adjustments. These results should not be extrapolated to other Pgp Inhibitors"

"Concomitant use of **XARELTO** with drugs that are combined P-gp and strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort) should be avoided.

Avoid concomitant administration of **XARELTO** with combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir/ritonavir, and conivaptan) which cause significant increases in rivaroxaban exposure that may increase bleeding risk."

Back to Mrs. H

At the time of discharge, Mrs. H is taking **fluoxetine, diltiazem and amiodarone**. You note that she has a weight of **56kg** and a creatinine clearance of **40ml/min**.

- A. Direct thrombin inhibitor: Dabigatran etexilate
- B. Factor Xa inhibitors: Apixaban/Rivaroxaban
- C. ~~Warfarin~~
- D. All of the above

Combination of low body weight, moderate renal impairment AND both P-GP and CYP3A4 inhibitors would likely lead to 50-200% increase in drug exposure with FDA approved doses & prolonged clearance

New Anticoagulants: Back to Mrs. H What is your management recommendation?

Presenting History: Mrs. H presents to the ED 2 months later, now after a ground level fall with neck pain and left hand numbness. CT imaging reveals C6 compression fracture with posterior subluxation. Neurosurgery wants to take the patient to the OR.

Medications: Dabigatran etexilate, lisinopril, diltiazem

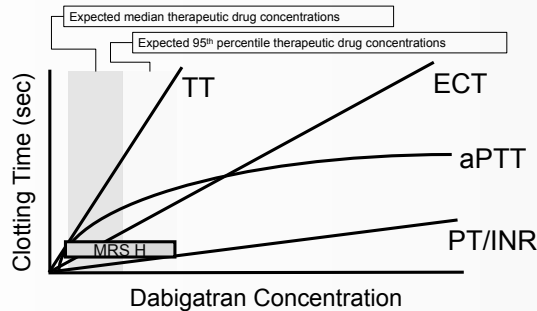
Physical

BP 124/84, P 89, RR 14, Weight 56kg
Lungs: Clear to A & P b/l
Heart: Irregular without murmur
Neuro: No focal weakness.
Decreased sensation Left C6/C7 dermatomes

Labs/Studies

Creatinine: 1.4 mg/dL
CBC: normal
INR = 1.4 aPTT = 40 seconds

Dabigatran: Clotting Assay Summary



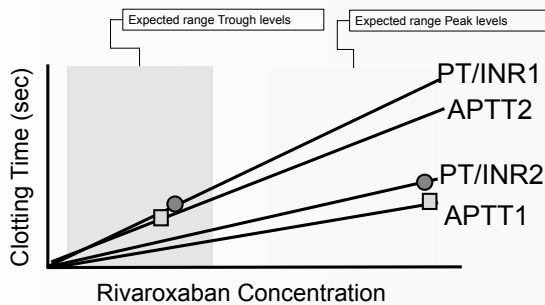
New Anticoagulants; Back to Mr. T

You prescribed Rivaroxaban for DVT/PE prevention after Mr. T's hip replacement surgery. The orthopedist calls again (2 weeks later) because patient had a fall and has a complex peri-prosthetic fracture requiring surgical intervention. He wants to know when he can take him to the OR – there needs to be NO residual anticoagulation as he is going to use spinal anesthesia.

You note on labs that patient has AKI with a creatinine of 2.5mg/dL (estimated CrCl of 40ml/min), a APTT of 42 seconds, and an INR of 1.5

What is your management recommendation?

Rivaroxaban: Clotting Assay Summary



Novel AC Agents- Peri-Procedural Management

PRE-PROCEDURE	Half-life (range) hrs	Low Bleeding Risk Procedures (Average of 2-3 Drug Half-Lives Separate Last Dose and Surgery)	Moderate to High Bleeding Risk * (Average of 5 Drug Half-Lives Separate Last Dose and Surgery)
DABIGATRAN: CrCl >50 CrCl 30-50 CrCl <30	14 (11-24) 18 (13-23) 27 (22-35)	Skip 2 doses (one day) Skip 4 doses (two days) Skip 4-10 doses (2-5d)	Skip 4 doses (2 days) Skip 6-8 doses (3-4 days) Skip >10 doses (>5days)
RIVAROXABAN CrCl>50 CrCl<50	8 hours 9-10 hours	Skip 1 dose (one day) Skip 2 doses (two days)	Skip 2 doses (2 days) Skip 3-4 doses (3-4 days)
APIXABAN	9 hours	Skip 1 dose (one day)	Skip 2 doses (2 days)

* For high risk surgeries consider most sensitive test pre-operatively

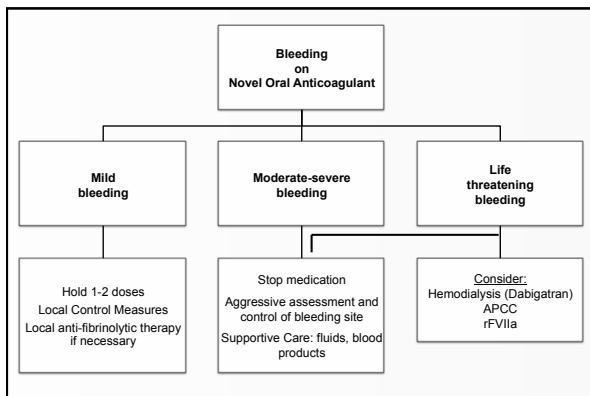
Post-Procedure: Delay re-initiation until hemostasis is certain(24-72 hours) and no epidural

Although novel anticoagulants offer great promise, they will cause bleeding, and lack effective antidotes. Managing bleeding is therefore challenging. Fundamentals of care include rapid clinical assessment of the source, cause, and severity of bleeding, and prompt appropriate action, both mechanical and systemic, to control the bleeding.

-Crowther & Warkentin

Bleeding Management Principles

- ▶ There is **NO reversal agent** for DTIs or Xa inhibitors
- ▶ Giving clotting factors (e.g. FFP) is **unlikely** to be beneficial – these drugs do not cause factor depletion
- ▶ **Cornerstones of treatment:**
 - Aggressively control bleeding site despite coagulopathy
 - Supportive treatment for as long anticoagulant effect persists
- ▶ rFVIIa or APCC are of uncertain/unproven benefit
- ▶ Hemodialysis is expected to remove 60% of dabigatran after 2 hours
- ▶ Activated charcoal is likely to be effective within 2 hr overdose



Conclusions

- ▶ Novel Oral anticoagulants have arrived! –
 - Dabigatran etexilate is approved for stroke prevention in afib
 - Rivaroxaban approved for VTE prevention in joint replacement
 - Additional indications/drugs are expected in 2011+
- ▶ Clinical trials demonstrate that in a RCT setting that these agents are effective and have a safety profile in general at least as good as comparator
- ▶ Safe implementation into routine clinical care settings will require: appropriate patient selection and knowledge about laboratory interpretation and management in urgent settings.
