

Effects of New Oral Anticoagulants on Measures of Anticoagulation

Douglas C. Anderson, Jr., Pharm.D.,
D.Ph., C.A.C.P.
Professor and Chair of Pharmacy
Practice

1

Objectives

1. Describe the mechanisms of action of the new anticoagulants and their effects on the clotting cascade.
2. Discuss the parts of the clotting cascade that are measured in standard laboratory tests used to assess anticoagulation.
3. Interpret effects of the new anticoagulants on laboratory test and used to assess anticoagulation.

2

New Oral Anticoagulants

- Dabigatran, and Rivaroxaban both recently on the market
- Apixaban NDA application (FDA review June 2012)
- Rates of major hemorrhage and intracranial hemorrhage are similar to or superior to warfarin
- Lack of specific reversal agents and monitoring parameters is a concern in the milieu of hemorrhagic emergency

3

Factor Xa and IIa Inhibitors

- Two classes of Factor IIa and Xa inhibitors
 - Indirect, Anti-thrombin-III (ATIII) dependent
 - Catalytic
 - Irreversible ATIII-mediated inhibition of factors IIa and Xa
 - Inhibits only free factor
 - Direct (Non-ATIII-dependent)
 - Stoichiometric
 - Specific and reversible inhibition of a single factor
 - Inhibit both free factor and bound factor

4

Factor Xa Inhibitors

Indirect ATIII-dependent inhibitors

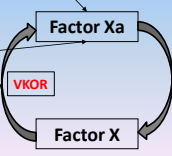
- Unfractionated Heparin
- LMWHs
 - Enoxaparin
 - Dalteparin
 - Tinzaparin
- Pentasaccharides
 - Fondaparinux

Direct Xa Inhibitors

- Apixaban (Eliquis®)
- Rivaroxaban (Xarelto®)
- DU176b Edoxaban

Vitamin K Antagonists (VKAs)

Warfarin



5

Factor IIa Inhibitors

Indirect ATIII-dependent inhibitors

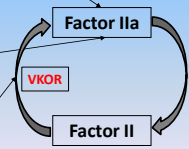
- Unfractionated Heparin
- LMWHs
 - Enoxaparin
 - Dalteparin
 - Tinzaparin

Direct IIa Inhibitors

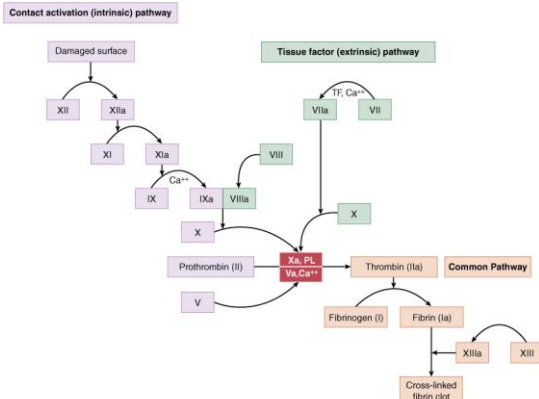
- Lepirudin
- Bivalirudin
- Argatroban
- Dabigatran (Pradaxa®)
- Ximelagatran

Vitamin K Antagonists (VKAs)

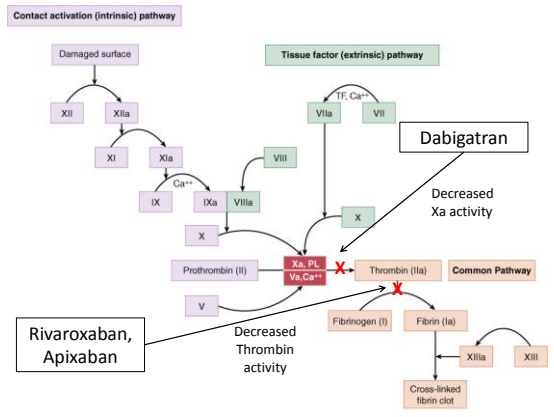
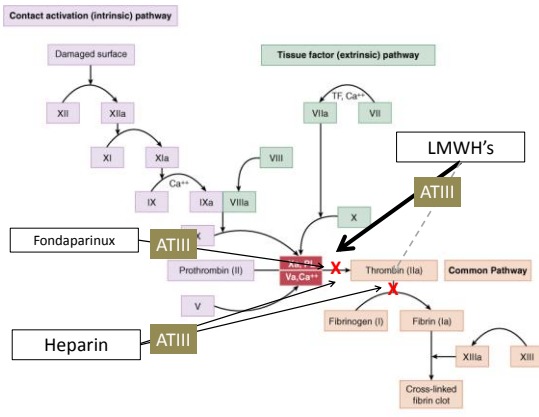
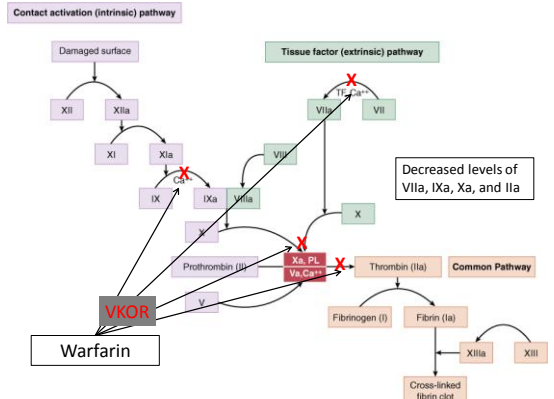
Warfarin



6



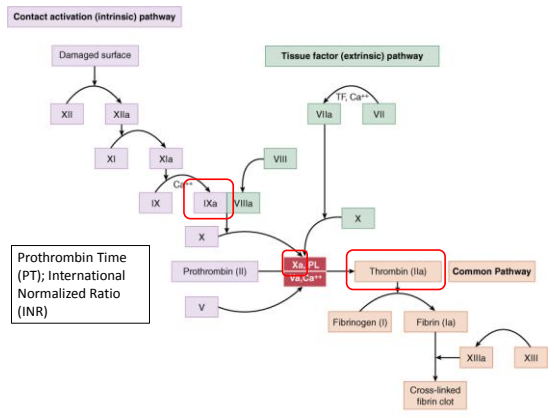
Secondary hemostasis. Ca^{2+} = calcium; fibrinogen is Factor I; PL = phospholipid surface (often platelets); prothrombin is Factor II.



Tests Used to Measure Anticoagulant

	PT/INR	dPT	TT	ECT	aPTT	HepTest	PiCT	Chromagenic Assay*
Factors	II, VII, X	II, VII, X	II	II	II, V, VIII, IX, X, XI, XII	X	X, V	X or II
Units	Seconds	Seconds	Seconds	Seconds	Seconds	Seconds	Seconds	Specific Activity
Uses	Warfarin	Lupus anti-coag.	UH	DTTs	UH, LMWH's, Fonda.,	UH, LMWH's, Fonda., DTTs	UH, LMWH's, Fonda., DTTs	UH, LMWH's, Fonda., DTTs

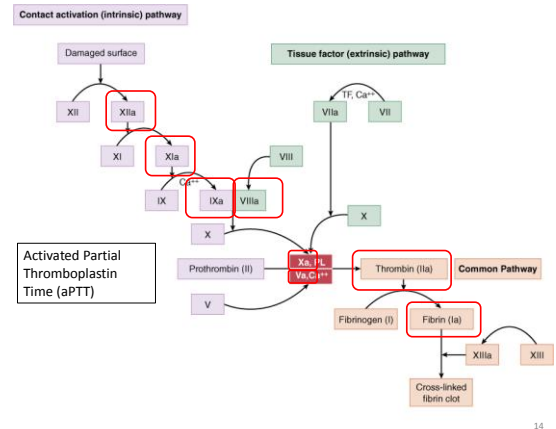
*Anti-Xa assay is commonly available, anti-IIa is not widely available
 PT=prothrombin time; dPT=dilute prothrombin time; TT=thrombin time; ECT=ecarin clotting time; aPTT=activated partial thromboplastin time; PiCT=Prothrombinase induced clotting time



Effects on PT/INR

- Dabigatran
 - Causes PT/INR elevations
 - False elevations of INR have been reported
 - Relatively insensitive and variable
 - We do not yet know what INR elevations mean in relation to levels of anticoagulation with Dabigatran
 - Has not proven useful in hemorrhagic emergencies
- Rivaroxaban
 - Prolongs PT in a concentration dependent fashion
 - Only has a weak effect at therapeutic concentrations, more profound at higher concentrations
 - Converting to INR appears to *increase* variability of results
 - May be useful in hemorrhagic emergencies
- Apixaban
 - Prolongs PT in a concentration dependent fashion
 - Converting to INR appears to *increase* variability of results
 - May be useful in hemorrhagic emergencies

13



14

Effects on aPTT

- Dabigatran
 - aPTT more sensitive and less variable than PT
 - Supratherapeutic doses prolong aPTT in (curvi)linear fashion
 - Response curve may flatten at very high concentrations
 - No relationship established yet with outcomes
 - Could be useful in hemorrhagic emergency
- Rivaroxaban
 - Concentration dependent prolongation
 - Minimal variability between reagents
 - PT appears to be more sensitive compared to aPTT
 - Less useful than aPTT in hemorrhagic emergency
- Apixaban
 - Prolongs aPTT in dose dependent manner
 - High degree of variability between reagents
 - PT is much more sensitive than aPTT
 - Less useful than aPTT in hemorrhagic emergency

15

Other Tests

	PT	dPT	TT	ECT	aPTT	HepTest	PiCT	Chromagenic Assay
Dabigatran	+	++	+++	+++	++	N/A	N/A	N/A
	Insensitive	Not widely available	Too sensitive to be useful	Limited availability	Use is supported	Does not correlate	Not studied	Not currently available
Rivaroxaban	++	++	--	--	+	+++	+++	+++
	More sensitive at higher conc.	Highly variable	No effect	No effect	Less sensitive than PT	Sensitive at low and high conc.	Sensitive over wide range of conc.	Accurate and precise
Apixaban	++	+++	--	N/A	+	+++	N/A	+++
	More sensitive at higher conc.	More sensitive than PT	No effect	Unlikely to have an effect	Less sensitive than PT	More sensitive than PT	Not studied, but likely to have an effect	More sensitive than PT and aPTT

PT=prothrombin time; dPT=dilute prothrombin time; TT=thrombin time; ECT=ecarin clotting time; aPTT=activated partial thromboplastin time; PiCT=Prothrombinase induced clotting time

16

Summary

- Dabigatran
 - aPTT
 - Appears to be a useful measure in hemorrhagic emergency
 - Therapeutic ranges have not yet been established
 - Ecarin clotting time
 - Also useful in hemorrhagic emergency, but not widely available.
- Rivaroxaban and Apixaban
 - Prothrombin time, but not INR
 - Appears to be useful in hemorrhagic emergency
 - Therapeutic ranges have not yet been established
 - HepTest, PiCT, and chromagenic assay all appear to be useful, but not commonly available

17

References

1. Samama, M.M., Gerotziapas, G.T. Newer Anticoagulants in 2009. *J Thromb Thrombolysis* 2010 Jan;29(1):92-104.
2. Garcia, D, Libby, E, and Crowther, M. The new oral anticoagulants. *Blood* 2010;115(1):15-20.
3. Kakkar, A., Brenner, B, Dahl, O, et al. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double blind, randomised controlled trial. *Lancet* 372:31-39
4. Eriksson, B., Borris, L., Friedman, R., et al. Rivaroxaban versus Enoxaparin for Thromboprophylaxis after Hip Arthroplasty. *New Engl J Med* 2008;358(26):2765-2775.
5. Connelly, S., Ezekowitz, M., Yusuf, S., et al. Dabigatran versus warfarin in patients with atrial fibrillation. *New Engl J Med* 2009;361(12):1139-51.
6. Hardman, J., Limbird, L., and Gilman, A. *The Pharmacological Basis of Therapeutics* (11th edition) 2006.
7. Patel, MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *New Engl J Med* 2011;365:883-891.

18