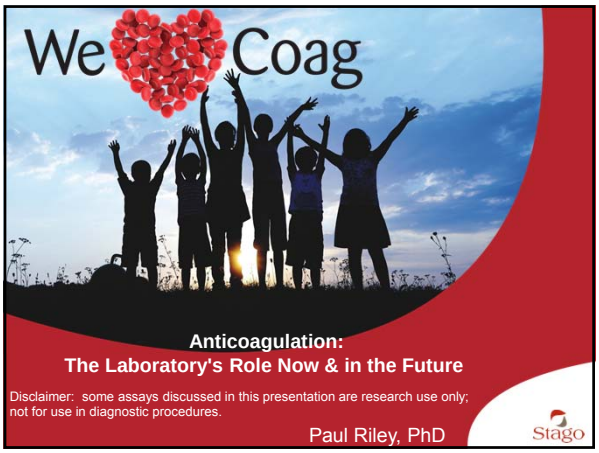

Anticoagulation:
The Laboratory's Role Now & in the Future

Disclaimer: some assays discussed in this presentation are research use only; not for use in diagnostic procedures.

Paul Riley, PhD

Stago

Outline

- Discuss current methods for monitoring traditional anticoagulants.
- Demonstrate the impact of new oral anticoagulants on routine and specialized coagulation assays
- Understand case studies highlighting the role of the laboratory for this testing regimen.

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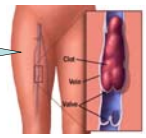
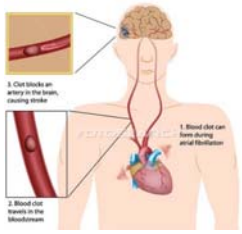
Indications for Anticoagulation

- Venous thrombosis
  - Treatment
  - Prophylaxis
- Atrial fibrillation
- Mechanical heart valve
- Arterial thrombosis
  - Acute heart attack
  - Cardiac surgery





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Heparin

- Widely used antithrombotic
- Naturally occurring glycosaminoglycan produced by mast cells
  - Drug isolated from the mucosa (porcine intestine / bovine lung)
  - Potentiates activity of *Antithrombin*
- Indications for use
  - Prevention & treatment of thrombosis
  - Drug of choice when rapid anticoagulant effect required

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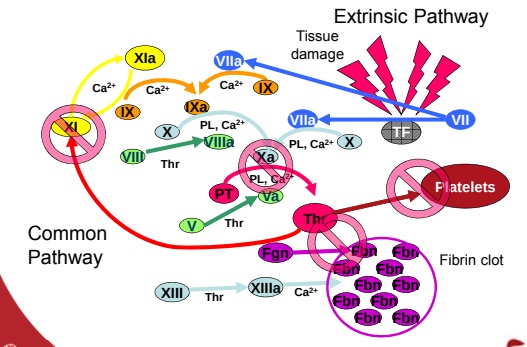
Heparin Effect on Coagulation Cascade



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High Alert Medications

- Drugs that bear risk of causing significant patient harm when used incorrectly
- Antithrombotic agents categorized as **"High-Alert Medications"** by the Institute for Safe Medication Practices (ISMP)

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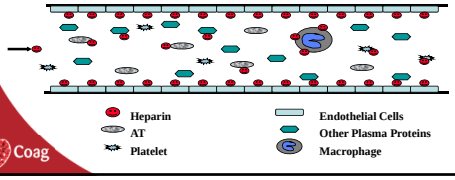
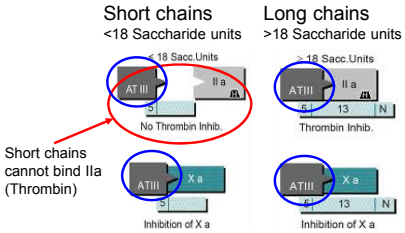
Unfractionated Heparin

- Heterogeneous structure
  - Varied molecular weights
- Negatively charged
  - Non-selective binding to plasma proteins and endothelial cells
- Variability of anticoagulant effect



Unfractionated Heparin



**Requires Antithrombin*

Methods for Heparin Monitoring

Methods for Heparin Monitoring

APTT

Heparin Assay

ACT: *Percutaneous coronary interventions & CPB*

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How did the APTT Become the Standard?

- A 1972 landmark study concluded that a range APTT of 1.5 - 2.5 x the baseline value is required (Basu D, Gallus A, Hirsh J, Cade J. A prospective study of the value of monitoring heparin treatment with the activated partial thromboplastin time. N Engl J Med 1972; 287: 324-327.)
  - This range was determined in animal studies and had not been tested clinically in humans
  - There was a question of whether you needed to monitor heparin or just use a standard dose
  - They were prospectively looking for a relationship between the APTT and recurrent venous thromboembolism (VTE) or bleeding
- 5 patients being treated for VTE developed a new thrombosis and all 5 had lower APTT than patients without new thrombus development
- Later, it was determined that the 1.5 - 2.5 x the baseline corresponded to 0.2 - 0.4 U/mL Heparin by protamine sulfate titration

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American College of Chest Physicians (ACCP) Guidelines for UFH Monitoring

- "…determine the appropriate therapeutic range based on the local laboratory reagent & adapt dosage adjustments accordingly…..the targeted APTT should be equivalent to a heparin level of 0.3-0.7 IU/mL by anti-factor Xa heparin levels."

Hirsh J, Warkentin TE, Shaughnessy SG, Anand SS, Halperin JL, Raschke R, et al. Heparin and Low-Molecular-Weight Heparin; Mechanisms of Action, Pharmacokinetics, Dosing, Monitoring, Efficacy, and Safety. Chest 2001; 119: 64S–94S

Since 2001, ACCP has recommended calibrating aPTT reagents used for UFH therapy against an anti-Xa range of 0.3 – 0.7 IU/mL

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CAP Guidelines for UFH Monitoring

- Adjusted dose & therapeutic UFH requires monitoring using method with a defined range
- Test at 6 hour intervals until a stable response achieved, then daily, at same time of day, preferably prior to 10 am
- Specimens should be collected from different extremity
- Clinicians should be informed of method & its therapeutic range
- aPTT reagents for UFH therapy should be calibrated against an anti-Xa reagent corresponding to 0.3 - 0.7 IU/mL
- Anti-Xa method is the preferred alternative method to the aPTT for monitoring UFH

Since 1998, CAP has recommended calibrating aPTT reagents used for UFH therapy against an anti-Xa range of 0.3 – 0.7 IU/mL

We Coag

Olson JD, Arkin CF, Brandt JT, Cunningham MT, Giles A, Koepke JA, Witte DL. College of American Pathologists Conference XXXI on laboratory monitoring of anticoagulant therapy: laboratory monitoring of unfractionated heparin therapy. Arch Pathol Lab Med 1998; 122: 782-798.

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Determining the Heparin Therapeutic Range using the APTT

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Establishing a Heparin Therapeutic Range

- Run PT, APTT and anti-Xa assays on samples from patients receiving UFH (no spiking samples!)
  - Plot values:
    - Heparin (IU/mL) on X-axis
    - APTT (seconds) on Y-axis
- Calculate statistical “best fit” using regression analysis
- Determine APTT range that correlates to 0.3 - 0.7 IU/mL heparin concentration

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Brill-Edwards P, Ginsberg JS, Johnston M, Hirsch J. Establishing a therapeutic range for heparin therapy. Ann Intern Med. 1993;119:104–109.

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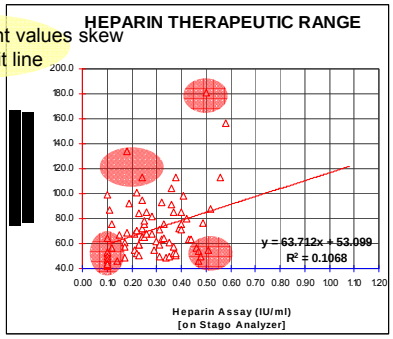
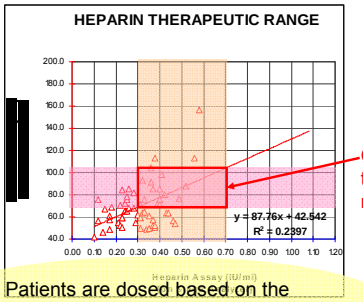
Heparin Therapeutic Range Graph

Discordant values skew the best fit line



n=80

Final Heparin Therapeutic Range Graph



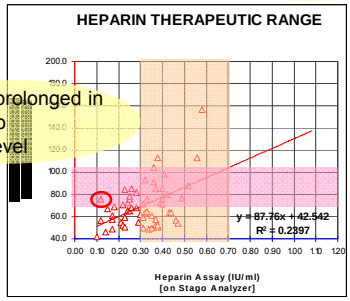
Concordant therapeutic results

Patients are dosed based on the graph constructed from these samples

n = 60

- Case #1:
  - APTT: 75.4 seconds
  - Anti-Xa: 0.12 IU/mL

APTT=Therapeutic
Anti-Xa=Sub therapeutic

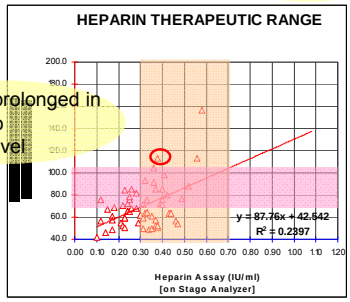


APTT is prolonged in relation to anti-Xa level

- Case #2:
  - APTT: 113.3 seconds
  - Anti-Xa: 0.38 IU/mL

APTT=Super therapeutic
Anti-Xa=Therapeutic

APTT is prolonged in relation to anti-Xa level



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Outcomes

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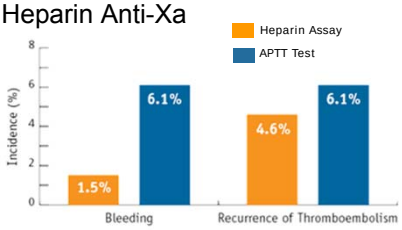
Bleeding or Thrombotic Outcomes: APTT vs. Heparin Anti-Xa



- The bleeding incidence was four times higher in the APTT-monitored group possibly because they were given an average of 4000 units/day more heparin than those monitored by the anti Xa assay

Levine MN, Hirsh J, Gent M, Turpie AG, Cruikshank M, Weitz J, Anderson D, Johnson M. A randomized trial comparing activated thromboplastin time with heparin assay in patients with acute venous thromboembolism requiring large daily doses of heparin. Arch Intern Med 1994; 154: 46-56

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APTT vs. Heparin Assay

- Evidence to suggest ***persistent subtherapeutic*** APTT associated with increased rate of recurrent VTE:
  - Anand S, Ginsberg JS, Hirsh J. Is There a Relationship Between the Intensity of Heparin Treatment and Recurrent Thomboembolism? Clin Appl Thromb Hemost 1997; 3: S64-S67
- Achieving target therapeutic range w/in 24 hours:
  - 87% of patients using ***Anti-Xa***
    - Rosborough TK, Shepherd MF. Achieving target antifactor Xa activity with a heparin protocol based on sex, age, height, and weight. Pharmacotherapy 2004; 24: 713-719.
  - 57% of patients using ***APTT calibrated to Anti-Xa***
    - Raschke RA, Reilly BM, Guidry JR, Fontana JR, Srinivas S. The weight-based heparin dosing nomogram compared with a "standard care" nomogram. A randomized controlled trial. Ann Intern Med 1993; 119: 874-881.

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Anti-Xa Levels as the Standard of Care - 1

- Several important studies show anti-Xa levels are well defined and safe at both ends of therapeutic range
- One study by Turpie et al. examined prevention of mural thrombosis (clot on vessel wall)
  - Mean APTT and anti-Xa levels were independently associated with thrombosis risk
  - For thrombosis-positive patients, mean APTT was 40.9 sec and mean anti-Xa was 0.1 U/mL
  - For thrombosis-negative patients, mean APTT was 48.6 sec and mean anti-Xa was 0.19 U/mL
  - This study supports the lower level of the heparin range of 0.2 U/mL for anti-Xa

Turpie AG, Robinson JG, Doyle DJ, Mulji AS, Mishkel GJ, Sealey BJ et al. Comparison of high-dose with low-dose subcutaneous heparin to prevent left ventricular mural thrombosis in patients with acute transmural anterior myocardial infarction. N Engl J Med 1989; 320: 352-357

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Anti-Xa Levels as the Standard of Care - 2

- Two additional studies by Holm et al. and Niewenhuis et al. supported not exceeding 0.7 – 0.8 U/mL at the upper range of the anti-Xa range
  - Holm HA, Abildgaard U, Kalvenes S. Heparin assays and bleeding complications in treatment of deep venous thrombosis with particular reference to retroperitoneal bleeding. Thromb Haemost 1985; 53: 278–281.
    - Patients at 0.24-0.36 U/mL did not have bleeding complications but 11% of patients had bleeding at levels 0.74-0.83 U/mL
  - Niewenhuis HK, Albada J, Banga JD, Sixma JJ. Identification of risk factors for bleeding during treatment of acute venous thromboembolism with heparin or low molecular heparin. Blood 1991; 78: 2337–43.
    - Bleeding risk greatly increased at >0.8 (30%) vs. <0.8 U/mL (10%)
- Anti-Xa levels are well defined and safe at both ends of the therapeutic range

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Anti-Xa Methodology

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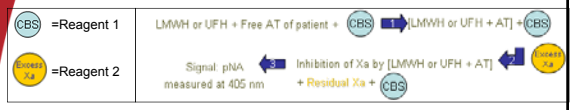
Heparin Anti-Xa Assay Methodology



One-step test with two simultaneous reactions:

1. Inhibition of factor Xa by the UFH/AT complex
2. Hydrolysis of the chromogenic substrate by factor Xa

UFH concentration ↑ | Inhibition of FXa ↑ = Hydrolysis of chromogenic substrate ↓ | Color development ↓

There is an inverse relationship between chromogenic readout and drug levels

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Heparin Anti-Xa Assays With/Without AT/DS

Test Description	Possible benefits	Possible drawbacks
No exogenous AT or DS	In vitro effect closely emulates in vivo	May underestimate anticoagulation
Exogenous AT only	Identifies scenarios in which UFH effect is limited by AT availability	May overestimate in vivo anticoagulation status
Exogenous DS only	Identifies scenarios where binding proteins are competing extensively with AT for UFH	May overestimate in vivo anticoagulation status

Anti-Xa reagents without AT and DS are preferred for the reasons above, but please refer to your Stago Positioning System for more details

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Gehrie E, Laposata M. Test of the Month: The chromogenic antifactor Xa assay. Am J Hematol 2012; 87: 194-197

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Moving from the APTT to the Anti-Xa Assay: Experience at Exempla St. Joseph's

- The author's institution and their experience
- Switching to anti-Xa requires lab and pharmacy to work together to improve patient care while accepting higher reagent costs
- Electronic Medical Record (EMR) conversion is critical; as is healthcare provider education
- They still collect baseline APTT values to screen for coagulopathies
- They discourage practitioners from requesting both an APTT and anti-Xa due to lack of correlation

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Vandiver JW, Vondracek TG. Antifactor Xa levels versus activated partial thromboplastin time for monitoring unfractionated heparin. Pharmacotherapy 2012; 32: 546-558

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Economic Implications of Switching

	Anti-Xa	APTT
Mean # tests/patient/day	2.08	2.73
Mean # of UFH dosage adjustments/patient/day	0.62	1.47
Reagent cost (Stago)	$2.55/test $5.30/patient/day	$0.65/test $1.77/pt/day
Lab tech and phlebotomy labor	$3.08/test $6.40/patient/day	$3.08/test $8.41/patient/day
Nurse lab	$2.58/dosage adj $1.60/patient/day	$2.58/dosage adj $2.58/patient/day
Total cost/pt/day	$13.30	$13.97

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Vandiver JW, Vondracek TG. Antifactor Xa levels versus activated partial thromboplastin time for monitoring unfractionated heparin. Pharmacotherapy 2012; 32: 546-558

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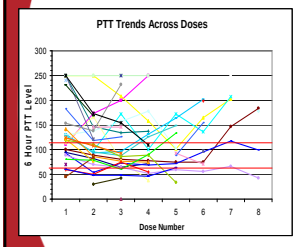
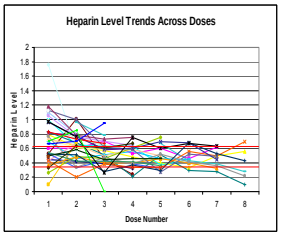
Dosing Efficacy: APTT vs. Anti-Xa





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Courtesy of Boulder Community Hospital Dept of Pharmacy (personal communication)

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APTT to Anti-Xa Comparison (pkg ins)

Interference	PTT-Automate	STA Liquid Anti-Xa
Lupus Anticoagulant	Yes - prolonged	No effect
AT Deficiency	Not affected	Yes*
Triglycerides	Not affected	Levels > 6.9 g/L
Bilirubin (conjugated)	Not affected	Levels > 288 mg/L
Bilibrubin (unconjugated)	Not affected	Levels > 138 mg/L
Hemoglobin	Not affected	Levels > 1.5 g/L
High or Low FVIII levels	Shortened with high levels; prolonged with low levels	No effect
Low Fibrinogen levels	Yes - prolonged	Not affected
Coumadin	Yes, but unpredictable	Not affected
Direct Thrombin Inhibitors	Yes - prolonged	Not affected
Synthetic anti-Xa drugs	Yes, but unpredictable	Yes – can be used as an assay for drug effect
Therapeutic Range	May change from lot to lot	Does not change with lot changes

*STA Liquid Anti-Xa is affected by antithrombin (AT) because the assay is dependent on the patient's AT, and thus measures the effective active heparin concentration

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Case Study - Heparin

- Presentation:
  - 41-yr old patient, 25 weeks gestation, twin pregnancy
  - Left lower extremity pain & swelling
  - Ultrasound showed occlusive clots
- Treatment:
  - UFH bolus 6300 units & infusion of 1400 u/hr (wt based nomogram)
  - APTT therapeutic range determined by correlation to Heparin assay

Raschke RA, Guidry JR, Foley MR. Apparent heparin resistance from elevated factor VIII during pregnancy. Obstet Gynecol 2000; 96: 804-806.

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Case Study Continued

- Patient required 48,000 units UFH/day to achieve therapeutic APTT levels
- Patient developed persistent hematuria, hemoglobin dropped from 10.4-7.9 g/dL
  - (bladder trauma caused by catherization)
  - Catheter removed & 2 units of RBCs transfused
  - Heparin continued & hematuria persisted
    - o 4 additional units required

Raschke RA, Guidry JR, Foley MR. Apparent heparin resistance from elevated factor VIII during pregnancy. Obstet Gynecol 2000; 96: 804-806.

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Case Study Laboratory Results

- Anti-Xa levels performed in addition to APTT
  - APTT results significantly depressed (68.4 sec, HTR 68-100 sec) compared to anti-Xa (0.68 IU/mL, HTR 0.3 – 0.7 IU/mL)
- FVIII level 566%
- Heparin therapy monitored with anti-Xa, dose reduced to 1500 units/hr
  - Next week: all anti-Xa therapeutic, 10/11 APTT subtherapeutic
- Leg swelling & hematuria resolved
  - Twin delivery at 32 weeks

Raschke RA, Guidry JR, Foley MR. Apparent heparin resistance from elevated factor VIII during pregnancy. Obstet Gynecol 2000; 96: 804-806.

Case Study Conclusions

- "Apparent" heparin resistance due to elevated FVIII
  - APTT subtherapeutic: led to increasing UFH dosing
  - Testing w/ anti-Xa levels
    - o ***Allowed for reduction in dose & good clinical outcome***
- "..anti-Xa monitoring should be considered in pregnant women who need more than 35,000 U/day…"

Raschke RA, Guidry JR, Foley MR. Apparent heparin resistance from elevated factor VIII during pregnancy. Obstet Gynecol 2000; 96: 804-806.

New Oral Anticoagulant (NOAC) Overview

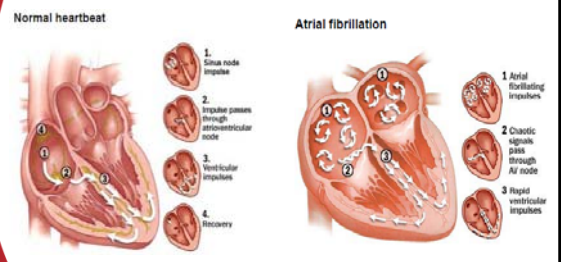
DVT/VTE Prevention

- > 2 million people acquire VTE per year; 50% acquire it as inpatients or 30 days post hospitalization, and PE is the most common cause of preventable death
- 23 million people have surgery per year; up to 20% of high risk surgical patients acquire DVT, and only 5% are at low risk of VTE
- In one year, a single 400 bed hospital will have 200 hospital acquired VTEs with 50% of those having been preventable
- Anticoagulant drug prophylaxis reduces all DVT/PE incidence by 50-65%

➔ Traditional anticoagulants and NOACs will play large roles in effective prevention and treatment of DVT, VTE, and PE, with a need for more clinical guidelines

US Department of Health and Human Services Agency for Healthcare Research and Quality
http://www.ahrq.gov/qual/vtguide/vtguideapa.htm accessed July 5th 2012

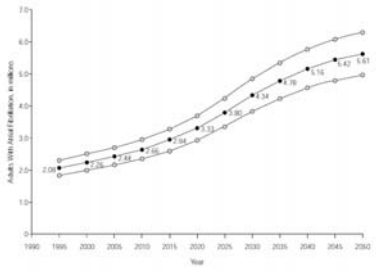
Atrial Fibrillation Basics



➔ Atrial fibrillation is a serious cardiac disease that can cause stroke

http://www.mayoclinic.org/atrial-fibrillation/treatment.html accessed July 5th 2012

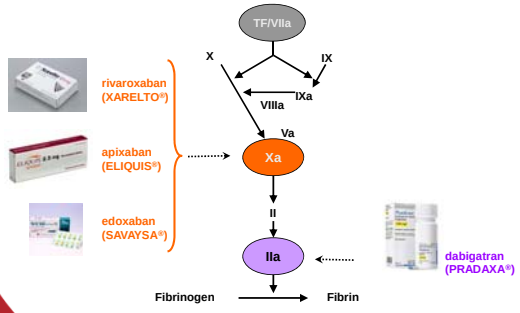
Projections for Atrial Fibrillation Incidence



➔ **The incidence of atrial fibrillation will continue to increase**

Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA 2001; 285: 2370-2375.

NOACs Target a Single Coagulation Factor



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NOAC Approvals - US

	Hip/Knee surgery	Atrial Fibrillation (AF)	Long term anticoagulation
Dabigatran etexilate (Pradaxa®)		√	
Rivaroxaban (Xarelto®)	√	√	√
Apixaban (Eliquis®)		√	
Edoxaban (Savaysa®)	Filed with FDA Jan 2014	Filed with FDA Jan 2014	

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Results of Clinical Trials - AF

- Primary objective has been to study effectiveness of NOACs vs. warfarin
- Proven non-inferiority - and probably superiority - in preventing stroke and systemic embolism
- Major bleeding events similar to or less frequent
- Fewer intracranial bleeding complications
- Easier to use, no monitoring, fewer interactions

W. Hacke. Optimizing SPAF management in AF patients with history of stroke or TIA. ESC August 2013 - Amsterdam

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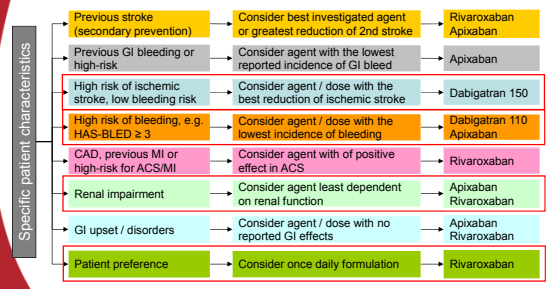
How to Choose a NOAC ?



J. Camm. Optimizing stroke prevention in nonvalvular atrial fibrillation
ESC August 2013 - Amsterdam

Warfarin Comparison Trials (theheart.org)

Trial	RE-LY	ROCKET-AF	ARISTOTLE
Patients enrolled in trial	18,113 (3 arms)	14,264	18,201
Drug (Brand name) Frequency of dosing	Dabigatran (Pradaxa®) 150 mg twice daily	Rivaroxaban (Xarelto®) 20 mg once daily	Apixiban (Eliquis®) 5 mg twice daily
Trial design, randomized	Open label	Double blind, double dummy	Double blind, double dummy
Mean Age (yrs)	71.5	73	70
Male ratio	63.6%	60.1%	65.3%
Previous stroke	20%	54.7%	18.9%
Efficacy % vs.warfarin (stroke or systemic embolism)	1.71 vs. 1.11 p < .001 (statistically significant difference = more effective than warfarin)	2.42 vs. 2.12 p = 0.12 (NO statistically significant difference = no difference in effectiveness vs. warfarin)	1.60 vs. 1.27 p < .001 (statistically significant difference = more effective than warfarin)
Major Bleeding % Intracranial hemorrhage %	3.57 vs. 3.32 p = 0.31 0.74 vs. 0.3 p< .001	3.45 vs. 3.6 p = 0.58 0.74 vs. 0.49 p = 0.019	3.09 vs. 2.13 p < 0.001 0.47 vs. 0.24 p < 0.001
Conclusion vs. warfarin	Superior efficacy, similar bleeding, less ICH	Non-inferior on efficacy and safety measures	Superior efficacy, less major and ICH, lower mortality

➔ Major bleeding and intracranial hemorrhage rates are comparable for all 3 drugs vs. warfarin though apixaban had slightly better outcomes by both measures

www.theheart.org/documents/WarfarinComparisonTrials.ppt; accessed on July 5th, 2012

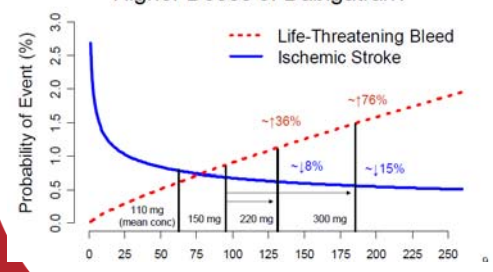
Dabigatran Pharmacokinetic Properties

- **Oral** administration
- ½ life: 14-17 h
- Limitations: renal failure
- No monitoring
- Approved in USA, Canada & Europe
  - Prevention of VTE after orthopedic surgery (Canada, Europe)
  - Atrial fibrillation (US, Canada)
- Other applications under investigation
  - Prevent recurrence of acute VTE

Boehringer Ingelheim

From Dabigatran® package insert (Oct 2010), Boehringer Ingelheim

Does Benefit/Risk Support Exploration of Higher Doses of Dabigatran?



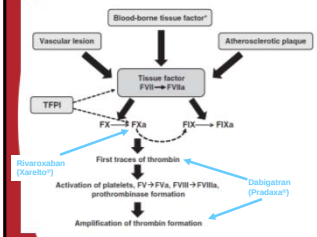
NDA 22-512 Dabigatran Efficacy Review http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM226704.pdf accessed Sep 14th 2012

What is Rivaroxaban?

- New oral anticoagulant drug
- Discovered by: Bayer HealthCare
- Jointly developed with Janssen Pharmaceuticals:
- Marketed by Janssen in US, Bayer in Canada
- Trade name: Xarelto rivaroxaban
- Direct factor Xa inhibitor[1]
- Not dependent on antithrombin[1]
- 10-15-20 mg film-coated tablets[1]

1. From Xarelto® package insert (Dec 2011), Janssen Pharmaceuticals

Rivaroxaban Mechanism of Action



- Highly selective direct Factor Xa inhibitor[1], no effect on thrombin or platelets[2]
- Low propensity for food-drug and drug-drug interactions[2]
- No cofactor (e.g. antithrombin) required[1]
- Oral bioavailability[1]
- Maximum concentration appears 2-4 hours after administration[1,2]
- Half life is 5-9 hours[1]
- Contraindicated in patients with compromised renal function[1]
- Inhibits both free and clot-bound factor Xa as well as prothrombinase activity[2]

Bullet point references:

1. Xarelto® package insert (Dec 2011), Janssen Pharmaceuticals
2. Samama MM. The mechanism of action of rivaroxaban – an oral, direct factor Xa inhibitor – compared with other anticoagulants, Thromb Res 2011; 127: 497-504; In addition, figure above is from reference #2

Dosing and Method of Administration

Indication	Dosage	Frequency daily	Therapy length
Venous thromboembolism (VTE) prophylaxis after hip/knee surgery	10 mg	Once; Initial dose taken 6 - 10 hrs after surgery	major hip surgery: 5 weeks major knee surgery: 2 weeks
Treatment of deep vein thrombosis (DVT) / Prevention of recurrent DVT and pulmonary embolism (PE)	15 mg for 3 weeks, 20 mg long term	15 mg 3 week course: twice 20 mg long term course: once	Individualized; careful assessment required of treatment risk vs. bleeding risk
Prevention of stroke and systemic embolism in atrial fibrillation (AF) patients	20 mg	Once	Long term

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From Xarelto® package insert (Dec 2011), Janssen Pharmaceuticals

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EINSTEIN Trial

- Acute DVT subtrial:
  Open label, randomized noninferiority study examining 15 mg of rivaroxaban daily 3 weeks, 20 mg daily thereafter vs. enoxaparin (Lovenox®) followed by warfarin for 3, 6, and 12 months in approximately 3400 symptomatic DVT patients
- Continued treatment subtrial:
  Double blind, randomized study of 20mg rivaroxaban vs. placebo for 6 or 12 months in patients receiving VTE treatment
- Outcome measured was recurrent DVT (event rate)

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EINSTEIN Investigators, Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, Gallus AS et al. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010; 363: 2499-510

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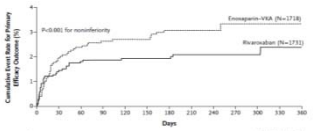
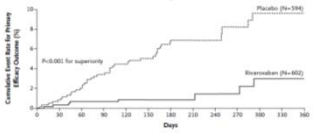
EINSTEIN Trial

Acute DVT



Continued Treatment



- As in the figures above, event rates in rivaroxaban treated patients were lower vs. the enoxaparin and placebo-treated patients
- NO statistically significant increase in bleeding risk in rivaroxaban-treated patients vs. enoxaparin

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EINSTEIN Investigators, Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, Gallus AS et al. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010; 363: 2499-510

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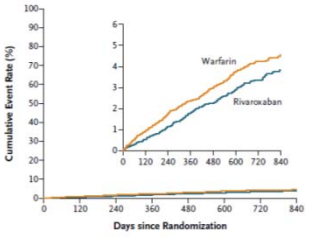
ROCKET-AF Trial

- A double blind noninferiority trial of approximately 14,000 patients with atrial fibrillation and increased stroke risk received either 20 mg daily rivaroxaban or dose-adjusted warfarin
- Outcome measured was stroke or systemic embolism

Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011; 365: 883-91

ROCKET-AF Trial

- As shown in the figure at right, event rates in rivaroxaban treated patients were numerically lower than in the warfarin treated patients
- **When the effectiveness of the two drugs were compared, there was no statistically significant difference**
- **Significant reductions in intracranial hemorrhage and fatal bleeding were also observed for rivaroxaban patients vs. warfarin**



Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011; 365: 883-91

Apixaban (Eliquis®)

- Developed by Bristol-Myers Squibb (BMS) and by Pfizer
- Highly selective active site inhibitor of factor Xa in both free, clot-bound, and prothrombinase-bound forms
- ~ 50% bioavailability after oral dosage
- Elimination
  - 27% renal
  - 25% transformed in metabolites → intestinal excretion
  - biliary and direct intestinal excretion
- No routine monitoring required

Dosage					
Drug Indication	Renal function				
	CrCl ≥ 90	CrCl 89 - 60	CrCl 30 - 59	CrCl 15 - 29	CrCl < 15
AF	**5 mg bid**	**5 mg bid**	**5 mg bid**	**Caution**	**CI**

Frost C, Wang J, Nepal S, Schuster A, Barrett YC, Mosqueda-Garcia R, et al. Apixaban, an oral, direct factor Xa inhibitor: single dose safety, pharmacokinetics, pharmacodynamics and food effect in healthy subjects. Br J Clin Pharmacol 2013; 75: 476-487.

Dosing On Indication and Renal Function

Drug Indication	Renal function				
	CrCl ≥ 90	CrCl 89 - 60	CrCl 30 - 59	CrCl 15 - 29	CrCl < 15
Dabigatran					
AF / FDA	150 mg bid	150 mg bid	75 mg bid	CI	CI
Rivaroxaban					
AF	20 mg od	20 mg od	15 mg od	15 mg od	CI
MOS VTE prophylaxis	10 mg od	10 mg od	10 mg od	Caution	CI
VTE/PE treatment	15 mg bid / 20 mg od	15 mg bid / 20 mg od	15 mg bid / 15 mg od	15 mg bid / 15 mg od	CI
Apixaban					
AF	5 mg bid	5 mg bid	5 mg bid	Caution	CI

➔ In case of decreased renal function, less risk of drug accumulation with apixaban

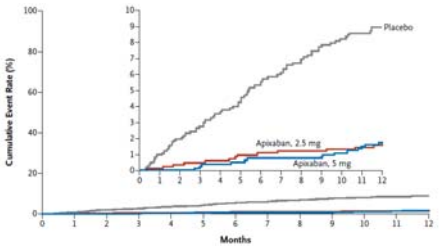
Poulsen BK, Grove EL, Husted SE. New oral anticoagulants: a review of the literature with particular emphasis on patients with impaired renal function. Drugs 2012; 72: 1739-1753

AMPLIFY Trial - Apixaban

- A double blind trial of approximately 2,500 patients with VTE received either a thromboprophylatic dose (2.5 mg twice daily) or a treatment dose (5 mg twice daily) apixaban or placebo
- Outcome measured was symptomatic recurrent VTE or death, along with major bleeding

Agnelli G, Buller HB, Cohen A, Curto M, Gallus AS, Johnson M, et al. Apixaban for Extended Treatment of Venous Thromboembolism. N Engl J Med 2013; 368: 699-708

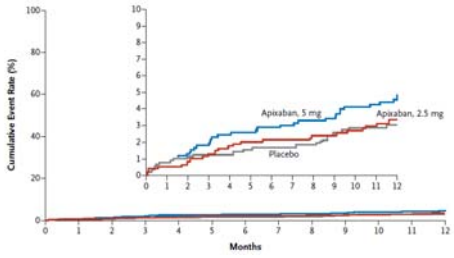
AMPLIFY Trial – Event Rates



➔ 8.8% of placebo patients had an event, which was reduced to 1.7% for 2.5 mg and 1.7% for 5 mg apixaban

Agnelli G, Buller HB, Cohen A, Curto M, Gallus AS, Johnson M, et al. Apixaban for Extended Treatment of Venous Thromboembolism. N Engl J Med 2013; 368: 699-708

AMPLIFY Trial – Bleeding Rates



➔ 0.5% of placebo patients had major bleeding, which was reduced to 0.2% for 2.5 mg and 0.1% for 5 mg apixaban

Agnelli G, Buller HB, Cohen A, Curto M, Gallus AS, Johnson M, et al. Apixaban for Extended Treatment of Venous Thromboembolism. N Engl J Med 2013; 368: 699-708

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NOAC Market Trends

- Dabigatran was first to market, but growth is slow (2.2M prescriptions in 2011 vs. 33M for warfarin)[1]
- Rivaroxaban has the most indications, with 3M prescriptions written as of Dec 2013[2]
- Apixaban shows best safety profile, less dependence on kidney function, expected to take major market share[1]
- US anticoagulant market expected to grow from $4.7B in 2010 to $11.8B in 2016[3]
- Higher prices of NOACs are inhibiting growth ($3K per year vs $200 for warfarin)[1]

1. http://www.reuters.com/article/2012/06/14/us-drugs-bloodthinners-idUSBRE85D06G20120614, accessed 1/30/14
2. http://www.investor.jnj.com/releasedetail.cfm?ReleaseID=811270, accessed 1/30/14
3. http://www.dicardiology.com/article/rollout-new-oral-anticoagulants-will-drastically-change-clinical-practice, accessed 1/30/14

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Clinical Perspectives from Prescribers

- **Dr. Alexander Turpie:**

"…is very positive about the new agents…major advantages over warfarin…used in preference to warfarin in most cases"

"…for patients who are compliant but cannot maintain a stable INR on warfarin…But if a patient is stable on warfarin…I don't think there is an overwhelming need to switch them"

- **Dr. Larry Goldstein:**

"…believes they should have a more restricted role, for the time being."

"…long-term use of these agents is still…unknown…we don't know if patients are actually taking their drugs… If they are on warfarin we can assess their blood coagulation levels with a simple blood test…while the monitoring of warfarin is a nuisance..contact with a medical professional…helps with adherence."

http://www.theheart.org/article/1497581.do?utm_medium=email&utm_source=20130123_heartwire&utm_campaign=newsletter accessed Feb 16, 2013

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What is the Future for Traditional ACs?

- Vitamin K antagonists will not completely go away and will be used in selected circumstances
  - Thrombosis in mechanical heart valve patients cannot be completely inhibited by NOACs
  - Patients who fail therapy on a NOAC will likely be switched to a VKA.
  - When there is a question of compliance, a physician will prefer a monitored drug with an antidote available
  - There may be some physician resistance to convert a stable patient to a NOAC
- High dose heparin is still the preferred drug for cardiac interventions, especially for patients with GI problems

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The Laboratory and NOACs

Situations Where Laboratory Testing Provides a Value Proposition

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Potential NOAC Laboratory Testing Situations

- Before **surgery** or invasive procedure
  - If the patient has taken the drug
    - o in previous 24 hrs (or longer if creatinine clearance is > 50 mL / min)
- Identification of **sub- and supratherapeutic levels**
  - taking other drugs known to significantly affect pharmacokinetic
  - at extremes of body weight
  - with deteriorating renal function
- **Reversal** of anticoagulation
- Suspicion of **overdose**
- Assessment of **compliance** (If thrombosis or bleeding occurs during therapy)

Baglin T, Hillarp A, Tripodi A, Elalamy I, Buller H, Ageno W. Measuring oral direct inhibitors of thrombin and factor Xa: a recommendation from the Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and HAemostasis. J Thromb Haemost 2013; 11: 756-60.

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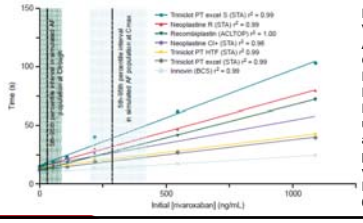
Limitations of Nonspecific NOAC tests (PT)

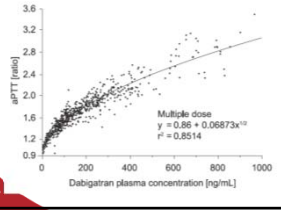
- PT is not specific
  - may be prolonged in case of factor deficiency or lupus anticoagulants
  - risk of drug concentration overestimation
- PT baseline not always available
- Apixaban induces little to no PT prolongation
- PT prolongation depends on reagent sensitivity



Heidbuchel H, Verhamme P, Alings M, Antz M, Hacke W, Oldgren J et al. European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. Europace 2013; 15: 625-651

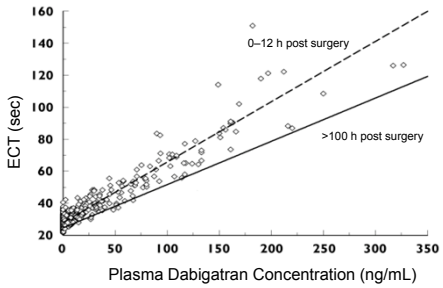
Limitations of Nonspecific NOAC tests (aPTT)

- APTT: measures activity of various factors
- Anti-IIa drug (dabigatran)
  - curvilinear dose-response, steep increase at low concentrations
  - normal aPTT cannot exclude degree of anticoagulation
- Anti-Xa drugs: APTT is not sensitive enough
  - Minimal to no prolongation



van Ryn J, Stangier J, Haertter S, Liesenfeld K-H, Wienan W, Feuring M, et al. Dabigatran etexilate – a novel, reversible, oral direct thrombin inhibitor: Interpretation of coagulation assays and reversal of anticoagulant activity. Thromb Haemost 2010; 103: 1116-1127

Ecarin Clotting Time (ECT) and Dabigatran



Liesenfeld KH, Schäfer HG, Trocóniz IF, Tillmann C, Eriksson BI, Stangier J. Effects of the direct thrombin inhibitor dabigatran on ex vivo coagulation time in orthopaedic surgery patients: a population model analysis. Br J Clin Pharmacol 2006; 62: 527-37.

NOAC Measurement Guidelines – ISTH SSC

- **Dabigatran**
  - APTT is acceptable in emergency situations to determine relative treatment intensity, but reagent response varies
  - Normal TT indicates low or undetectable dabigatran
  - Dilute TT in combination with dabigatran cals/QC can be used to determine a drug level
  - ECT recommended on drug package insert
- **Rivaroxaban**
  - PT is acceptable in emergency situations to determine relative treatment intensity
  - Each lab should be aware of differences between PT reagents
  - Anti-Xa in combination with rivaroxaban cals/QC can be used to determine a drug level

Baglin T, Hillarp A, Tripodi A, Elalamy I, Buller H, Ageno W. Measuring oral direct inhibitors of thrombin and factor Xa: a recommendation from the Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and HAemostasis. J Thromb Haemost 2013; 11: 756-60.

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Clinical Guidelines Studies on NOAC Reversal

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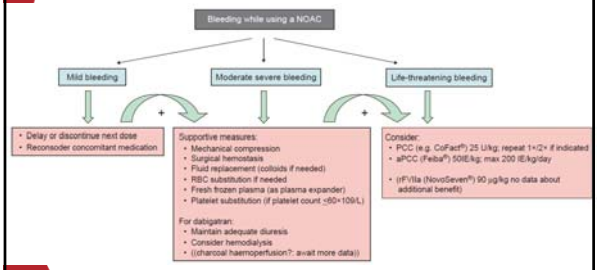
NOAC Treatment Guidelines for Bleeding - AF



Heidbuchel H, Verhamme P, Alings M, Antz M, Hacke W, Oldgren J et al. European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. Europace 2013; 15: 625-651

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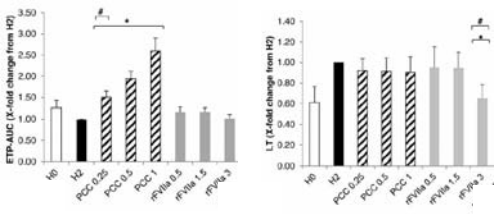
NOAC Treatment Reversal (Ex Vivo)

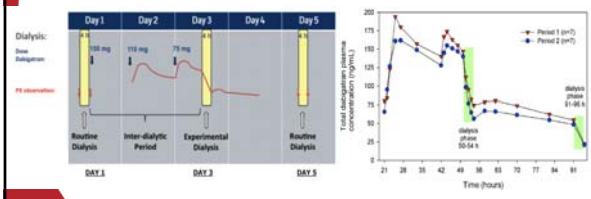
- 10 healthy volunteers randomized to dabigatran or rivaroxaban (not shown)
- Reversal of anticoagulation tested (ex vivo)
- 4 factor PCC and FEIBA (not shown) corrected all parameters, rFVIIa kinetic parameters only for both dabigatran and rivaroxaban reversal



Marlu R, Hodaj E, Paris A, Albaladejo P, Crackowski JL, Pernod G. Effect of non-specific reversal agents on anticoagulant activity of dabigatran and rivaroxaban. Thromb Haemost 2012; 108: 217-224

NOAC Treatment Reversal – Hemodialysis

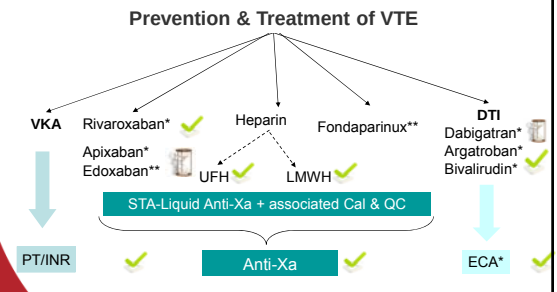
- 7 patients treated with dabigatran then reversed with hemodialysis
- Patients had ESRD without atrial fibrillation with up to 9 other drugs on board
- Hemodialysis used as per the protocol effective at reducing dabigatran levels
- Large scale trials difficult, but would be required to fully assess reversal



Khadzhynov D, Wagner F, Formella S, Wiegert E, Moschetti V, Slowinski T, et al. Effective elimination of dabigatran by haemodialysis; A phase I single-centre study in patients with end-stage renal disease. Thromb Haemost 2013; 109: 596-605

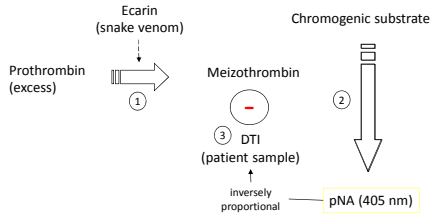
Anticoagulant Measurement Solutions

Anticoagulant Measurement Products



*Research use only; not for use in diagnostic procedures
**Not available currently or in development

Ecarin Chromogenic Assay (ECA)*



→**CHROMOGENIC** assay derived from the Ecarin Clotting Time (ECT)
→determines exact DTI concentration
→**NO INFLUENCE** of coagulation factors or inhibitors of the sample

*Research use only; not for use in diagnostic procedures

Ecarin Clotting Time (ECT) vs. Ecarin Chromogenic Assay (ECA)*

ECT	ECA
• Clotting test	• Chromogenic assay
• Sensitive to prothrombin and fibrinogen levels	• insensitive to factor levels
• Not standardized	• Standardized, fully automated
• No commercially available kits	• RUO
• Carry over artifacts	• No carry over artifacts

*Research use only; not for use in diagnostic procedures

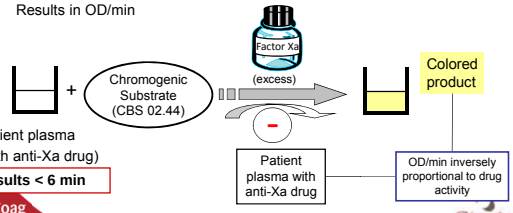
Anti-Xa protocol on the STA line

Test principle

One step chromogenic assay:

1. Addition of the patient sample and Chromogenic Substrate (CBS 02.44)
2. Addition of Factor Xa in excess
   - Competition occurs between:
     - Hydrolysis of CBS 02.44 and release of a colored product (para-nitroaniline)
     - Inhibition of Factor Xa

→ Results in OD/min



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Anti-Xa Products (Rivaroxaban, Apixaban)

- STA®-Liquid Anti-Xa (4 & 8 mL)
  - chromogenic assay
  - method of choice insensitive to
    - plasmatic coagulation factors variation
    - lupus anticoagulants
  - stability: 7 days on board / 3 months at 2-8° C

•barcoded reagents
•TAT< 6 min

- STA®-Rivaroxaban Calibrator*
  - 3 x 4 levels of calibrator
    - 0, 100, 250, and 500 ng/mL
  - stability: 8 hrs on board
- STA®-Rivaroxaban Control*
  - 3 x 2 levels of control
    - 100 and 300 ng/mL
  - stability: 8 hrs on board / 7 days at 2-8° C

- STA®-Apixaban Calibrator**
  - 3 x 4 levels of calibrator
    - 0, 100, 250, and 500 ng/mL
  - stability: 4 hrs on board
- STA®-Apixaban Control**
  - 3 x 2 levels of control
    - 100 and 300 ng/mL
  - stability: 8 hrs on board / 7 days at 2-8° C

Coming soon

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*Research use only; not for use in diagnostic procedures
**Not available currently or in development

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Case Study - NOACs

- Presentation:
  - 75-yr old patient, 65 kg
  - CrCl: 19 mL/min
  - Atrial fibrillation for 3 years
- Treatment:
  - Initially treated with warfarin after diagnosis, was stably anticoagulated, but patient complained about limitations of warfarin therapy (no leafy greens, too many trips to clinic to monitor)
  - Put on dabigatran after 2 years on warfarin
  - Treatment for 1 year with dabigatran, 75 mg/day
- Acute event:
  - Fell in home, cranial hemorrhage resulted, transported to hospital

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Case Study Laboratory Results

TEST	RESULT	REFERENCE RANGE
INR	2.8	0.9 – 1.1
APTT	55 sec	24 – 30 sec
TT	90 sec	< 18 sec
Fib (derived)	138 mg/dL	195 – 450 mg/dL
Fib (Clauss)	295 mg/dL	177 – 466 mg/dL
Anti-Xa	0.11 IU/mL	UFH: 0.3 – 0.7 IU/mL
ECA	270 ng/mL	60 – 160 ng/mL

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Case Study – Treatment (From Guidelines)

- Half life of dabigatran for patient with this CrCl is up to 28 hrs
- Estimate normalization of hemostasis in ≥ 48 hrs
- If non-life threatening
  - RBC/platelet infusion/fresh frozen plasma (if necessary)
  - Tranexamic acid/desmopression/dialysis could be considered
- If life threatening
  - All of the above
  - Prothrombin complex concentrate (PCC) 25 U/kg
  - Activated PCC 50 IE/kg, max 200 IE/kg/day
  - Activated rFVIIa, 90 µg/kg

Heidbuchel H, Verhamme P, Alings M, Antz M, Hacke W, Oldgren J et al. European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. Europace 2013; 15: 625-651

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Case Study Conclusions

- Specific tests for NOACs can be helpful in emergency situations
- Reference ranges for NOACs have to be validated in a clinical population
- Reversal agents can be used to assist in reversal of NOACs
- Use of NOAC specific tests can help to monitor effectiveness of reversal strategies

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Conclusions

- NOAC use can improve overall clinical outcomes
- NOACs should be measured in certain circumstances
- NOAC measurement solutions exist
- Reversal of NOACs currently requires haemodialysis or PCCs/rFVIIa
- **All methods for NOAC measurement are research Use Only for US & Canada; not for use in diagnostic procedures**

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Thank you! Questions?

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BCSLS Telehealth Feb 25th Survey
With Dr. Paul Riley

Enter to WIN $100 by doing our NEW SURVEY ONLINE!! It's quick!! It's anonymous.
Use the below QR code to take you directly to the survey or use the below web address.
https://www.surveymonkey.com/s/Feb2014Surveys

or use the QR code:

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