UPDATE ON THE TARGET SPECIFIC ORAL ANTICOAGULANTS (TSOAC): WHERE ARE WE IN THE LABORATORY FOURYEARS LATER?

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THE FOLLOWING MEDICATION(s) MAY AFFECT THE COAGULATION OF YOUR BLOOD!!

- Vitamin E-, Ginseng, Garlic, Gingko Biloba, Feverfew, Fish Oil, Glucosamine.
- Celebrex, Vioxx, Aspirin (ASA, Baby ASA, CAMA, Ecotrin, Fiorinal)
- Percodan, Dislacid, ECASA, Zorprin
- Arthropan (Cholin salicylate); Voltaren (Diclofenac, Cataflam), Dolobid (Diflunisal); Lodine (Etodolac); Nalfon (Fenoprofen Calcium)
- Ibuprofen- Advil, Excedrin, Medipren, Menadol, Midol-200, Motrin, Motrin IB, Nuprin, Pamprin-IB, Rufen, Saleto (200,400, 600, 800), Trendar, Indocin, Orudis (ketoprofen); Toradol (Ketoralac), Doan's Pills, Magan, Modibin (Magnesium salicylate), Meclomen, Ponstel, Relafen, Alleve, Anaprox (Naproxen), Daypro, Feldene, Butazolidin, Amigenic,, Rexolate, Tusal, Tolmetin.
- MAO Inhibitor: Nardil and Parnate
- Plavix, Prasugrel, Cangrelor, Ticagrelor, Ticlopidine, Coumadin, Pradaxa (Dabigatran), Rivaroxaban (Xarelto), Apixaban (Eliquis), Edoxaban (Lixiana), Betrixaban (PRT054,021), Heparinoids, Argatroban, Bivalirudin, Lepirudin.
- Numerous antibotics, Dilantin, GRAPEFRUIT (Forbidden fruit?).

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Purpose of Anticoagulation: First do no harm?

- If a patient is at risk for a clot - prevent it
  - Genetic predisposition or acquired coagulopathy
  - Abdominal surgery
  - Orthopedic surgery
  - Atrial fibrillation

- Prevent propagation of a clot
  - Chris Ferrell Seattle 2012

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Ideal Anticoagulant

- Fixed oral dose
- No need for dose adjustment
- Wide therapeutic range
- Acceptable bleeding risks
- No need for monitoring

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Background (2)

- In the 1980's the onset of LMW heparins brought in the idea of not requiring monitoring.
- The need to monitor was dependent on having an effective assay and was limited to "special" populations: renal subjects, obese and underweight, pediatric and spontaneous abortion patients.
- The pharmaceutical industry has championed the need for no monitoring. (Good selling point).

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Background (3)

- Previously there were two coagulation assays used to monitor lab tests.
- PT initially as a ratio and then as INR to monitor Coumadin therapy.
- APTT to monitor UFH therapy.
- Anti-Xa assays were introduced later to monitor LMWH in "special" groups and recently for both UFH and LMWH. (hybrid curve)
- Chromogenic FX used to monitor DTI's conversion back to Coumadin and for monitoring LA's.

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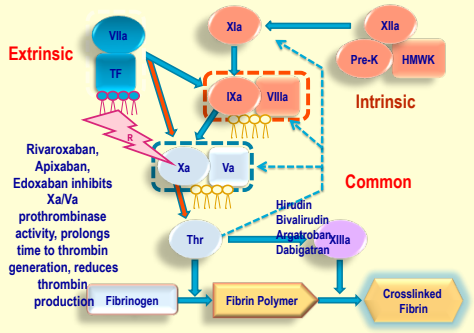

Figure courtesy of Margaret G. Fritsma

When to Use the TSOAC's? FDA Approvals: Clinical Development Programs

Condition	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Prophylaxis of VTE in orthopedic Surgery	Completed	Approved 2011	Approved 2014	Approved 2015
Stroke Prevention in Atrial Fibrillation	Approved 2010	Approved 2011	Approved 2014	Approved 2015 also for PE
Medically ill	_	Completed	Completed	_
VTE treatment Acute Chronic	Approved 2014	Approved 2012	Completed	Approved 2015
ACS	_	Completed	Completed	_

Dr. Ken Bauer MD, THSNA 2014 modified 2015

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Issues

- All anticoagulants have one major complication: bleeding
- Anticoagulant therapy is a constant challenge between efficacy and safety.
- The reference assay tests both PT/INR and APTT have major limitations when monitoring any anticoagulant.
- They became the standard by default. (no alternatives FDA-cleared to date with some anticoagulation Rx's).

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Issues (2)

- About 10% of patients who are treated with UFH have a prolonged APTT before starting therapy. How do you assess efficacy in this situation?
  - What happens if a lupus anticoagulant is present?
- People still quote the original 1.5–2.5 times "something" as acceptable UFH therapy. This was based on reagents used in the 1980's.
- I still get asked for control PT/INR and APTT results.

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Issues (3)

- For many years despite the improvement in the control of OACs using the INR method some patients still had bleeds and others had very variable INRs and were considered OAC "failures" or non compliant
- May be due to VKORC-1 gene mutations. But rarely ordered.
- Time in therapeutic range (TTRs) in some populations is less than half. Recent article by Dr. J Dlott in Circulation 2014: looked at real-world TTRs in 2.6 million INR values processed by Quest on subjects on warfarin with AF:
  - TTR in first 6 months was only 48%
  - The fewer the patients in a practice the lower the TTR.
  - The higher the patients >60-70 the TTR was closer to 60%
  - Some anticoagulation clinics have thousands in their population.

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The "Monitoring or not" Concept

- Drugs that have been used for 50+ years still have major issues for safe use.
- Pharmacogenomics have important roles in predicting or monitoring therapies for Coumadin/aspirin/Plavix/UFH/LMWH/DTI's. (Rarely ordered!!).
- The effectiveness of therapy for controlling glucose, cholesterol, and blood pressure is routinely monitored but the effectiveness of new "anticoagulant therapy is not suggested?"
- Are we naïve enough to think any anticoagulant drug is inherently safe?

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Safety versus Efficacy

- The PT/INR and APTT/anti Xa are used to quantify drug efficacy to make sure the therapy is working.
- Levels of any of these lab values if high or low usually lead to adjustments of doses and or complications of bleeding or clots.
- In modern medical practice safety considerations are important QC metrics.
- "Would you ever treat a ICH from a OAC "overdose" without an INR to help guide therapy?"
  - *Dr. Sandy Duncan M.D. GNOCC 2012*

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New Anticoagulants

- In the past 20 years the laboratory has scrambled to monitor new drugs.
- LMW heparins (4) [anti-Xa]: (enoxaparin, nadroparin, tinzaparin, dalteparin).
- Fondaparinux (Pentasaccharide) [anti-Xa]
- Bivalarudin [anti-IIa] Argatroban [anti-IIa]
- Dabigatran [oral anti-IIa], Pradaxa
- Rivaroxaban [oral anti-Xa], Xarelto
- Apixaban [oral anti-Xa], Eliquis
- Edoxaban [oral anti-Xa] Liliana
- Betrixiban [oral anti-Xa] not cleared

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Advantages of TSOACs vs. Warfarin

Feature	Warfarin	New OAC
Onset	Slow	Rapid
Dosing	Variable	Fixed
Food effect (Vitamin K)	Yes	No
Drug interactions	Many	Few
Monitoring	Yes	No?
Offset	Long	Shorter

Dr. Ken Bauer, MD THSNA 2014

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TSOAC anticoagulants: approved for prevention of systemic embolism or stroke in patients with AF

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Action	DTI	Activated FXa inhibitor	Activated FXa inhibitor	Activated Fxa inhibitor
Dose	150 mg bid 110 mg bid 75 mg one kidney?	20 mg qd 15 mg qd	5 mg bid 2.5 mg bid	60 mg qd 30 mg qd 15 mg qd
Phase 3 clinical trial	RE-LY	ROCKET-AF	ARISTOTLE AVERROES	ENGAGE-AF

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ABSORPTION AND METABOLISM OF THE DIFFERENCE TSOACs

	DABIGATRAN	APIXABAN	EDOXABAN	RIVAROXABAN
Elimination half-life	12-17 h	12 h	9-11 h	5-9 h young 11-13 h elderly
Prodrug	Yes	No	No	No
Clearance if normal renal function	80%	27%	50%	35%
Liver metabolism	No	Yes	Minimal	Yes
H2B/PPI absorption	-12-30% ?	No effect	No effect	No effect
Asian ethnicity	+25%	No problem	No problem	No problem
GI tolerance	Dyspepsia 5-10%	None	None	None

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Pharmacology

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	Thrombin	FXa	FXa	FXa
Bioavailabilty	6%	80%	60%	60%
Peak Activity (tmax)	1-3 hrs	1-3 hrs	1-3 hrs	1-2 hrs
Half-life	14-17 hrs	7-11 hrs	12 hrs	9-10 hrs
Protein binding	35%	92-95%	84%	50%
Renal clearance	80%/	25%		49%
Drug interactions	P-glycoprotein	CYP3A4 P-glycoprotein	CYP3A4	Combined P-gp inhibitor and *strong* inhibitor of CYP3A4

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INTERPRETATION OF COAGULATION ASSAYS WHEN USING TSOACs

	DABIGATRAN	APIXABAN	EDOXABAN	RIVAROXABAN
Plasma peak	2 hours	1-4 hours	1-2 hours	2-4 hours
Plasma trough	12-24 h	12-24 h	12-24 h	16-24 h
PT	Don't use	Don't use	Prolonged but meaningless	Elevated. Local calibration required
INR	Don't use	Don't use	Don't use	Don't use
aPTT	At trough>2 risk	Don't use	> ? Bleeding	Don't use
dTT	Trough >200 ng	Don't use	Don't use	Don't use
Anti-FXa	Don't use	Quantitative/No bleeding data	Quantitative/No bleeding data	Quantitative/No bleeding data
ECT	Trough>200ng	Not affected	Not affected	Not affected

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Dabigatran etexilate (Pradaxa) (DTI)

- Oral dosing
  - Dabigatran etexilate absorbed from GI tract
  - Pro drug: transforms to active dabigatran
- Future – replace warfarin
  - Wider therapeutic range
  - Acceptable bleeding risk? In clinical trials
  - No lab monitoring
  - Higher cost
  - Dosing controversy: 110 mg or 150 mg?
  - *Chris Ferrell (Dealing with Dabigatran 2011)*

Dabigatran etexilate (Pradaxa)

- Dabigatran is an oral anti IIa inhibitor very heavily advertised on TV for Atrial Fib.
- Available in US for just over 5 years.
- Short Half Life (12-17 hours). Peaks at 1.5-2.0 hours following the last tablet ingestion.
- 80% Renal clearance so really influenced by renal function. Will affect half-life.
- Biggest complaint is GI distress. Tend to cause more MI's than Coumadin
- Randomized Evaluation of Long-Term Anticoagulant therapy (RE-LY) trial: Reduced stroke deaths risk of dying by 70%. (Stroke April 2012). DOD study showed compliance was better with dabigatran than Coumadin: 64% vs 41%.

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Environmental Interactions Food

Drug	Interaction with Food	Recommendations
Rivaroxaban	Food increases plasma concentration 39%	Take with food
Apixaban	None	Take with or without food
Dabigatran	None Humidity affected!!! Do not dispense before taking medication. Might wind up with placebo!!!	Take with or without food? Dyspepsia major complaint.

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Dabigatran reversal

- Discontinue the drug: short half-life of 12-14 hours with normal renal function.
- Can be dialyzed within 2-3 hours with normal renal function (does not work for rivaroxaban, apixaban, edoxaban).
- Activated charcoal to remove drug from GI tract has been suggested in case of recent acute ingestion overdose.
- Discontinue other "blood-thinning drugs."
- In the case of life-threatening bleeds use APCC? In one study of 12 normal subjects this did not reverse prolongations of aPTT, ecarin clotting time or thrombin time. Use of PCC shows great promise in the Anti-Xa inhibitors. (Kcentra 4-factor PCC?) Used in Canada 2014.

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Dabigatran reversal: Breaking news! Boehringer-Ingelheim manufacturer makes announcement

- June 26, 2014-Fab idarucizumab gets FDA OK for "fast track review," for antidote for Pradaxa
- Results from phase ½ study showed agent can produce sustained reversal of dabi-anticoagulation in healthy human volunteers. No toxicity.
- Phase 3 trial: RE-VERSE AD underway.
  - Boehringer-Ingelheim's investigational antidote press release.

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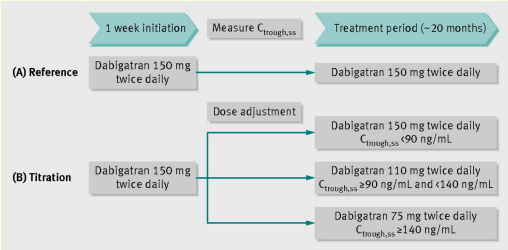
Boehringer's proposed dose adjustments for dabigatran



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Impact of bleeding complications in patients receiving TSOACs

- Blood 2014, 24(15): 2450-2458.
- Chai-Adisaksopha C et al: Looked at 12 Randomized clinical trials for all TSOACs compared to warfarin.
- Involved 102,607 subjects/
  - TSOACs reduced the risk of major bleeds (RR 0.72, p<0.01)
  - Clinically relevant non-major bleeds (RR 0.78, p<0.01)
  - No significant difference in major GI bleeding between TSOACs and VKAs (RR 0.94, P=0.62)
  - Total bleeding (RR 0.76, P<0.1)

  When compared with VKAs, TSOACs have less major bleeding, fatal bleeding, ICH, clinically relevant non-major bleeding and total bleeding. Do not increase the risk of GI bleeds.

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When to Assay Dabigatran

- Renal disease with CrCl <30 mL/min
- Noncompliance or underdosing
- Screening for co-medication interference
- Determining cause of acute hemorrhage (ER or surgery)
  - To identify anticoagulant or monitor its reversal
- Bridging from one anticoagulant to another
- Discontinuation before surgery
- Resumption of anticoagulation after surgery
- Unstable coagulation: pregnancy, liver disease, renal disease, malignancy, DIC
- Patients >75 years old (excluded from clinical trials)
- Patients with marginal fluid compartment (excluded from clinical trials)
  - >150 kg: proportionally reduced plasma volume
  - <40 kg or pediatric: proportionally increased plasma volume

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Bleeding problems with Anticoagulants: Coumadin, Pradaxa and Xarelto (ISMP 2014)

- Xarelto blood clots more frequent in 10 mg qd after hip or knee replacement compared to 20 mg in AF.
- PE and DVT in lower dose after surgery compared to AF (56% vs 17%) adjusted OR 7.0 95% CI 3.9-12.6.
- Unavailable in the US is an assay to determine the plasma concentrations of dabigatran.
- "This rapid, standardized and calibrated assay should provide accurate and consistent results." The test, called the Hemoclot Thrombin Inhibitor assay, is available in Europe, Australia, and Canada; RUO in US.
- FDA should strongly consider this important additional information about dabigatran, reassess the one-dose-fits-all recommendation, and reevaluate the Hemoclot Thrombin Inhibitor assay to reduce the risk of serious injury from one of the highest risk outpatient drug treatments.

J Stangier Blood Coag Fibrino 2012;23:138-143.

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FDA Study of Medicare patients: Lower risk for stroke and death, but higher risk for GI bleeding with Pradaxa (dabigatran) compared to warfarin

- Study included information from 34K Medicare patients, 65 years or older.
- Lower risk of clot-related strokes, ICH, and death than warfarin
- Increased risk of GI bleeds and MI risk similar for both drugs
- Study findings except with regards to MI consistent with clinical trial results despite using older population
  - IMS National Prescription Audit (NPA and IMS, Vector One: Total Patient Tracker (TPT) Databases. Oct 2010-December 2013. Extracted Feb 2014.

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Dabigatran Interferences

- Verapamil, Amiodarone, Clarithromycin (strong P glycoprotein inhibitors).
- Elevation of plasma concentration: reduce dosing of 300 mg to 150 mg daily.
- Treatments not recommended concomitantly with Pradaxa:
- -UHF and heparin derivatives.
- -LMWH
- -Fondaparinux, desirudin, thrombolytic agents.
- -GPIIb/IIIa receptor antagonists, clopidogrel, prasugrel, aspirin, dextran, sulfinpyrazone,
- -Vitamin K antagonists

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RE-LY sub analysis of gene variant

- 33% of Europeans carriers of gene variant CES1 (SNP) rs2244613.
- Blunts transformation of oral etexilate form to active dabigatran accentuating trough serum levels.
- Each minor allele of the SNP associated with a 15% drop.
- Corresponded to a 27% decrease in risk of bleeding.
- May explain why drug levels varied in subjects and also explained association with any bleeding and minor bleeds.
- *Could herald personalized dosing?
- Pare G et al: European Society of Cardiology 2012.

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RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy): Dabigatran

- Effect of Dabigatran Plasma Concentrations and Patient Characteristics on the frequency of ICH and Major Bleeds in AF Patients:
  - J of the Am Coll Cardiol 2014;63:321-328
  - Therapeutic concentration never defined
  - Dosing of 110 and 150 mg BID correlated with clinical outcomes.
  - 110: 28.2 ng/mL-275 ng/mL; 150: 39.8 ng/mL-383 ng/mL

  Median trough and post doses concentrations 55% and 36% higher in events.

  Results: 9,183 patients, with 112 ischemic strokes/systemic emboli (1.3%) and 323 major bleeds (3.8%) recorded

  Dabigatran levels depended on renal function, age, weight. Gender issue?

  Risk of ischemic events was related to trough dabigatran levels with age and previous stroke (p<0.0001) and renal function

  Major bleeding risk increased with dabigatran levels, age, ASA use and diabetes.

  Conclusions: Most severe problems directly related to dabigatran levels and age. Tailoring dosing might be required?

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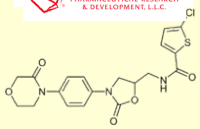
Rivaroxaban (Xarelto®)

- An oxazolininone derivative direct anti-Xa
- Safety and efficacy exceed Lovenox in three out of four phase III trials



Bauer KA, Homering M, Berkowitz SD. Effects of age, weight, gender and renal function in a pooled analysis of four phase III studies of rivaroxaban for prevention of venous thromboembolism after major orthopedic surgery. Blood 2008; 112: Abstract 436

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Rivaroxaban (Xarelto) Prescribing Information

- Factor Xa inhibitor
- Indicated for non valvular AF, VTE, THR, TKR, Stroke, SE, DVT, PE in most countries
- No monitoring necessary?
- No antidote?
- Require CrCl for dose determination (3months)
- -Do not use if CrCl <15
- Dose of 15 mg if CrCl is 15-50; 20 mg if CrCl>50.
- Adjust accordingly.
- Elective Surgery discontinuation 3-5 days? Arbitrary….

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WARFARIN COMPARISON TRIALS TO RIVAROXABAN (Xarelto)

TRIAL	EINSTEIN-DVT 2010- DVT	ROCKET-AF 2012	EINSTEIN –PE 2012
N=	3449	14,264	4832
Drug (brand name)	Rivaroxaban 15mg bid x 3 weeks, 20 mg daily	Rivaroxaban 20 mg qd	Rivaroxaban 15 mg BID for3 wk then 30 mg qd
Mean age (yrs)	71.5	73	65
CHADS score	N/A	3.5	N/A
TTR (%)	57.7%	57.8%	62.7%
Efficacy % vs Warfarin (%)	1.70 vs 1.11; p<.0.02	2.42 vs 2.12; p 0.12	1.60 vs 1.27; p<.001
Major Bleeding %; ICH% **Conclusion**	3.57/3.32; p=0.31 0.74 vs 0.3; p<.001 **Superior efficacy, less ICH**	3.45 vs 3.6; p=0.58 0.74 vs 0.49; p=0.19 **Non-inferior on efficacy and safety**	3.09 vs 2.13; p<.001 0.47 vs 0.24 p,.001 **Superior efficacy, less ICH, lower**

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Rivaroxaban interactions

- Interaction with CYP3A4 inducers: Use of rivaroxaban with rifampicin, phenytoin, carbamazepine, phenobarbital or St John's Wort may lead to reduced rivaroxaban plasma concentrations. Co-administer with caution.
- CYP3A4 and P-gp inhibitors: Co-administration with ketoconazole X 1/day or ritonavir X 2/day led to a 1.7 or 1.6 respectively fold increase. May lead to a bleeding risk.
  - Erythromycin (500 mg 3 X daily which may inhibit CYP3A4 and P-gp moderately causing a 1.3 fold increase in mean rivaroxaban levels.
    - Amiral Portland 2010

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Rivaroxaban: For and Against

- **For**: Convenience; once daily dosing; Not inferior to Warfarin on efficacy and safety; Superior in ICH risk.
- **Against**: Not more effective than Warfarin; no less bleeding than Warfarin; Cost $180-300/ mo.; More drug interaction than dabigatran; Black Box warning with spinal hematomas and drug cessation.
- Reduced overall major bleeding compared to Coumadin and other DOAC's.
  - BMJ 2012;345:e7498.

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Questions:

- FDA allowed dose not studied in trial
- Allowed Dabigatran and Rivaroxaban to be used with CrCl < 30 even though subjects excluded in trial
- Safe? Should we limit CrCl>40 in elderly?
- Should epidural anesthetics be avoided?
- Might Xa drugs be preferred in patients with concomitant CAD?

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Potentially useful tests for rivaroxaban and their characteristics

Characteristics	TESTS			
	PT	APTT	Anti-Xa	Ecarin
Linearity	Neoplastine or Neoplastine CI+	Less sensitive than PT	Standards (Stago/Aniara)	+
Standardization	Assay specific calibrators can be made-	None –very variable	Commercial available:	?
Responsiveness	+	+	++	++

Favaloro EJ. Biochemica Medica 2012;22:329-41.Euro space 2013;15:625-651.

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Apixiban in VTE Prophylaxis fritsma factor

- 12 days, 2.5 mg twice a day
- Comparator: enoxaparin
- Primary safety: major bleeding
- Primary efficacy: composite VTE

Study	N	Enox	Safety	Efficacy
ADVANCE 1	3195	30 mg	0.7 V 1.4%	9% V 8.9%
ADVANCE 2	1973	40 mg	0.6 V 0.93%	15% V 24%

Bristol-Myers Squibb Company

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Apixaban (Eliquis®)

- Oral factor Xa inhibitor
- Half life of 12 hours
- Developed for treatment of AF
- AVERROES: ASA vs Apixaban [trial stopped early because of clear benefits in regard to stroke reduction favoring Apixaban].
- Hazard ratio 0.46%; 95% CI 0.33-0.64; p<0.001.
- Results showed rates of major bleeding similar to ASA. Better tolerated than ASA with fewer study drug stoppages.

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Apixaban (2)

- ARISTOTLE trial compared Apixaban with warfarin for prevention of stroke and system embolism (SE) in AF subjects.
- Compared with Warfarin Apixaban reduced stroke and SE by 21% (p<0.01), resulted in 31% less bleeds (p<0.001); 11% lower mortality (p=0.047)
- Apixaban better tolerated than Warfarin with fewer drug discontinuations.
  - Now FDA cleared for atrial fibrillation;
  - Major bleeding with increased CHA_2DS_2-VASc scores
    - Lancet 2012;380:1749-58.

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Edoxaban (Liliana)

- Oral direct inhibitor of factor Xa
- Max concentration 1-2 hours after administering
- Half-life 8-10 hours
- 40% elimination is renal
- ENGAGE AF-TIMI 48 trial randomized >20,000 subjects with AF and elevated CHADS score compared to warfarin.
  - Just FDA cleared in January 2015. Used extensively in Japan and Europe.

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Edoxaban (2)

- Reversal of effects in emergency situation were studied on bleeding times ("curses") in rats PT in human plasma.
- Prothrombin concentrate (PPSB-HT); activated prothrombin complex concentrate (FEIBA) and recombinant rFVIIa were the agents used.
- Study indicated that all 3 agents have potential to be reversal agents for edoxaban.
  - » Fukuda T et al: Thromb Haemost 2012;107:253-259.

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Edoxaban vs Warfarin in Patients with AF: Results of ENGAGE AF-TIMI 48 trial

- Warfarin TTR was 68.4% as compared with 1.18% high-dose edoxaban and 1.61% for non-inferiority to Warfarin.
- Trend favoring high-dose edoxaban vs Warfarin:
- 3.43% major bleeds with Warfarin vs 2.75% with edoxaban high dose and 1.61% with low dose edoxaban
- Stroke, SE, cardiovascular causes: Warfarin 4.43%; edoxaban 3.85% and 4.23%
- Conclusion: both once-daily doses of edoxaban were non-inferior to Warfarin with respect to stroke or SE but significantly lower rates of bleeding and mortality from cardiovascular issues
- N Engl J Med 2013;369:2093-104

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INDIRECT COMPARISONS OF NEW ORAL ANTICOAGULANT DRUGS FOR EFFICACY AND SAFETY WHEN USED FOR STROKE PREVENTION IN ATRIAL FIBRILLATION

- Lip GY et al: J Am Coll Cardiol: 2012;60:738-746
- No profound difference between oral anticoagulants, comparison suggests using indirect comparison study.
- Comparison of RE-LY, ARISTOTLE, and ROCKET-AF against a common comparator: Warfarin. Using the Bucher method they estimated the hazard ratios for safety and efficacy when comparing against one another.
- 26% reduction of risk of stroke of SE favoring dabigatran.
- Compared with rivaroxaban, dabigatran significantly reduced the risk of hemorrhagic stroke 56% and non-disabling stroke 40%.

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INDIRECT COMPARISONS OF NEW ORAL ANTICOAGULANT DRUGS FOR EFFICACY AND SAFETY WHEN USED FOR STROKE PREVENTION IN ATRIAL FIBRILLATION (2)

- Apixaban reduced the risk of major bleeding 26% compared with 150mg dabigatran (HR 0.74; 95% CI 0.61-0.91) and 34% compared with rivaroxaban (HR 0.66; 95% CI 0.54-0.81
- Dabigatran 110mg reduced the risk of major bleeds 23% compared with rivaroxaban (HR 0.77;95% CI 0.83-0.94).
- Combined the new OA's reduced the risk of stroke or SE 21% hemorrhagic stroke by 53% and all-cause mortality by 12% for all comparisons vs warfarin.
- Major bleeding was 13% lower for ANY new OA when compared with warfarin

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INDIRECT COMPARISONS OF NEW ORAL ANTICOAGULANT DRUGS FOR EFFICAY AND SAFETY WHEN USED FOR STROKE PREVENTION IN ATRIAL FIBRILLATION (2)

- Dr. Lip quotes: "Patients frequently do not obey textbooks or inclusion criteria for clinical trials leaving clinicians to find appropriate dose."
- European MD's have 110 mg dose of dabigatran: not available in US (150 or 75mg)
- Lower dose could be used in elderly subjects at risk for bleeding or taking concomitant meds such as verapamil
- "These drugs will work when used correctly."

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Laboratory assays for Anti Xa's

- Anti-Xa tests are usable: high variability between assays.
- Factor Xa assays designed for heparin need to be adapted: too sensitive and developed for the catalytic inhibitor heparin; incubation times have strong interference in individual methods.
- Specific calibrators for the tested anti-Xa's need to be used and matrix effect checked.
- Assays need to cover the expected therapeutic range (100-400 ng/ml) present good linearity and recover in plasma.
- Not FDA cleared for measuring apixaban or rivaroxaban.

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SUMMARY OF DIFFERENT ASSAYS FOR TSOAC anti-Xa AND DABIGATRAN

ASSAY	AVAILABILITY	APIXABAN	RIVAROXABAN	EDOXABAN	DABIGATRAN
PT	Widely used	Not useful	Qualitative only	Not useful	Not useful
APTT	Widely used	Not useful	Not useful	Not useful	Qualitative only
Hemoclot /DTT	Not FDA cleared	Not useful	Not useful	Not useful	Quantitative assessment good
ANTI-Xa	Widely used	Quantitative	Quantitative	Quantitative	Not useful
Ecarin	Not FDA cleared	No effect	No effect	No effect	Quantitative assessment good
DRVVC	FDA cleared for LA testing	?	?	?	Quantitative assessment good

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Safety is Paramount

- If we have learned nothing during the past 50 years it's that the idea of anticoagulant drugs never requiring monitoring is flawed, no matter what the FDA says.
- Drug company studies are carefully chosen so that there tends to be monopathology in patients and control groups. (i.e. few risk factors)

– Dr. S Duncan GNOCC 2012

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Safety (2)

- In the trials of Dabigatran v Warfarin, Pradaxa was safer and more effective.
- Why are we seeing so many bleeds?
- Real world older patients are not the same as a drug study population.
- They take multiple drugs, often skipping or doubling doses. They have multiple pathologies.

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Safety (3)

- " A lot of people think that when you don't need to monitor a drug, you don't' need to test for the drug"

Dr. Michael Laposata MD, Ph.D quoted in CAP Today, January 2012.

"Short half life of new drugs means missing a dose could lead to clotting issues quicker than missing a warfarin dose." Compliance is a huge issue!

Dr. Mark Wuster M.D. THSNA 2012 (?) LATER!!!

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Drug Safety & Lab Support

- If we accept that the efficacy of these new oral anticoagulants is established, then the safety issue becomes paramount
- Needs support from lab.
- How do you set up a test for a drug not requiring monitoring ?
- Are there any tests available ?
- Can we modify what we currently do?

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Conclusions

- Despite the FDA mandate for no monitoring, past experience tells us that is not going to be true.
- The same rationale for testing children, the obese, pregnant woman, acutely ill patients, elderly & other "special" populations will likely force safety testing.

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Managing bleeding in subjects on TSOAC's

- No clinically available specific antidote
- Discontinuation of drug
- Supportive care (IVFs, PRBCs etc.)
- Activated charcoal (if ingested in last 2 hours)
- Hemodialysis (dabigatran only-may or may not work?)
- Consider PCC, APCC or rVIIa for organ or life threatening bleeding. (ISTH 2014 SSC Does not recommend rVIIa)
- Suggested reading: Majeed A, Schulman S. Bleeding and antidotes in new oral anticoagulants. Best practice and Research Clinical Haematology 26;(2013) 191-202.

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Conclusions (2)

- The lack of FDA approved tests will be an impediment.
- Need for validation testing will not be easy.
- Impact of the FDA position needs to be clarified (risks of laboratory developed tests: LDTs). Where does CAP stand on this?
- These drugs are being used in an older higher risk population. Age & bleeding go together

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Conclusions (4)

- More oral drugs are on the horizon.
- Big Pharma is not going to suggest monitoring for any of these.
- Certain defined populations will be at higher risk for bleeding and maybe clotting.
- Labs will have to develop strategies to provide safety testing data for these new drugs.
- Who do we compare testing with?

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Update 2015 Portola Phamaceuticals (Andexanet Alfa)

- : IV administered synthetic small molecule; reverses rivaroxaban, apixaban and dabigatran, heparinoids and fondaparinux in preclinical studies (Phase II, Sanofi)
- Reduces aPTT in Xa drugs; PT in IIa meds
- Dose dependent reversal
- Directly binds anticoagulants with H+ binding
- Higher affinity to Xa than IIa.
- Used on healthy adults and reversed effect of apixaban
- Moving in to Phase 4 Clinical trials
- Presently being evaluated in Phase 3 trials for reversal of rivaroxaban and edoxaban (Daiichi Sankyo)

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Elective surgery: *When to stop*

	DABIGATRAN	
CrCl (ml/min)	Standard risk surgery	High risk surgery
>80	24 hrs	48 hrs
50-80	36 hrs	72 hrs
30-50	48 hrs	96 hrs
15-30	4 days	6 days

	Rivaroxaban and Apixaban	
CrCl (ml/Min)	Standard risk surgery	High risk surgery
>30	24 hrs	48 hrs
15-30	36 hrs	48 hrs

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Boston Scientific's Watchman Heart Device

- Device for the prevention of stroke and SE in patients with nonvalvular AF.
- Seals off left atrial appendage in the heart which is major source of stroke causing thrombus in AF subjects.
- PREVAIL Trial: 407 subjects. 95.1% implant success rate
- Seven day occurrence of issues was 2.7%
- Overall complications was 4.4%
- Scored better on quality of life issues than warfarin.(J American Coll of Cardiology, 2013).

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Comparison of Four Dabigatran Assays in an Anticoagulation Clinic Population

DL McGlasson (JBSA Lackland, TX); GA Fritsma (UAB, Birmingham, AL); EE Ezzell (Travis AFB, CA); NS Anderson (SAMMC, Ft Sam Houston, TX)

The contents of this presentation are the opinions of the authors only and not the United States Air Force.

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MATERIALS AND METHODS

- Protocol FWH21020123H sponsored by the Air Force office of the Surgeon General.
- Enrolled 102 subjects: Men: 64 (Average age 77; Females: 38 (Average age: 76)
- All receiving Pradaxa (dabigatran) 150 mg/bid
- Exception if renal insufficiency, dose is 75 mg/bid

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Objectives

- We evaluated the capacity of four coagulation assays to measure oral dabigatran in 432 aliquots from 72 anticoagulation clinic patients and 30 locally collected normal, non-dabigatran subjects
- We compared the results of the partial thromboplastin time (APTT Automated, Stago); Ecarin Chromogenic Assay (ECA-T, Stago); Hemoclot Thrombin Inhibitor (HTI, Aniara); and Prothrombinase-Induced Clotting Time (PiCT, Enzyme Research Laboratory)

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Materials and Methods

- We obtained Informed consent for all subjects. All subjects were >18 years and had a creatinine clearance >30 mL/min.
- All subjects had been taking 150 mg dabigatran BID for at least one month prior to enrollment except one who took 75 mg BID due to having one kidney. None were excluded for parallel medications or other health issues.
- We originally enrolled 64 males, average age 77, and 38 females, average age 76. Average $CHAD_2VAS_c$ score was 3.2; average BMI 29.8.
- Seventy-two subjects completed the 6 month collection period.

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Material and Methods (2)

- A 3 mL 3.2% sodium citrate whole blood specimen was collected from each patient monthly for 6 months on a date ± 5 days of the start date for that month.
- Specimens were centrifuged immediately to prepare platelet poor plasma, aliquoted, and stored at –70ºC until ready for testing.
- Aliquots were thawed rapidly and mixed immediately prior to testing.
- Aliquots were assayed for APTT, ECAT, HTI and PiCT.
- Assays were performed using the STAR-Evolution automated coagulation analyzer (Stago).

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Reference Interval and Range
30 Non-dabigatran Subjects

	APTT Seconds	ECAT ng/mL	HTI ng/mL	PiCT Seconds
Mean	30.7	0.0	0.0	40.1
± 2 SD	26.1–35.3	NA	NA	29.4–50.7
Range	27.4–36.4	NA	NA	32.9–56.8

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Monthly Means and SDs
72 Subjects, 432 Assays

	APTT Mean, SD	ECAT Mean, SD	HTI Mean, SD	PiCT Mean, SD
Month	Seconds	ng/mL	ng/mL	Seconds
1	53.7, 15.0	173.9, 129.4	190.1, 137.7	185.1, 61.9
2	51.7, 12.9	174.2, 141.2	174.3, 137.7	188.2, 67.5
3	51.9, 13.5	177.6, 132.2	189.7, 127.2	176.8, 55.4
4	55.8, 32.0	173.3, 124.6	178.3, 122.7	192.4, 62.5
5	54.2, 14.3	194.9, 168.3	206.7, 158.0	190.6, 59.0
6	52.0, 15.4	172.2, 155.3	173.5, 137.1	189.7, 66.2
Grand Mean, SD	53.7, 7.3	177.6, 16.9	185.3, 12.2	186.7, 4.5
Range	26.2–301	10–950	0.0–770	60.8–301

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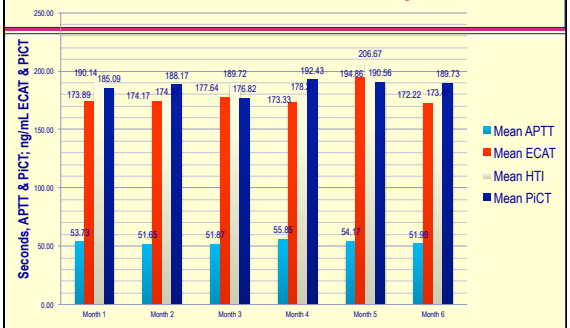
Comparison of Six Monthly Means



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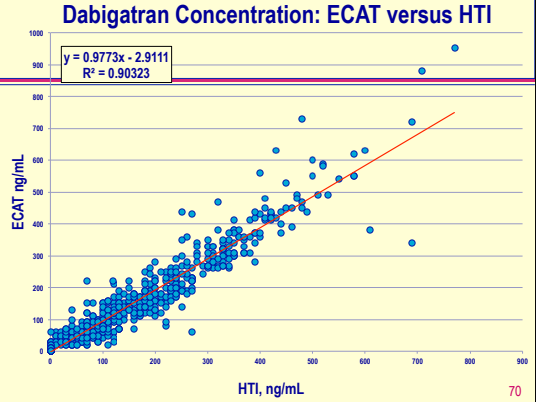
Dabigatran Concentration: ECAT versus HTI



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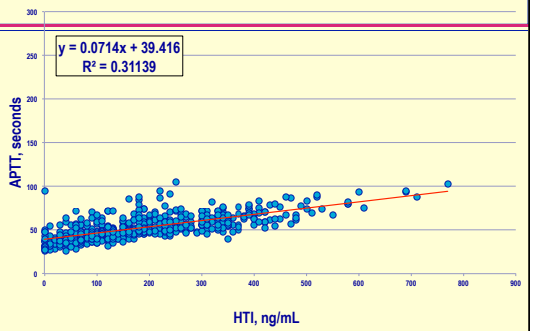
Dabigatran APTT Activity versus HTI Concentration



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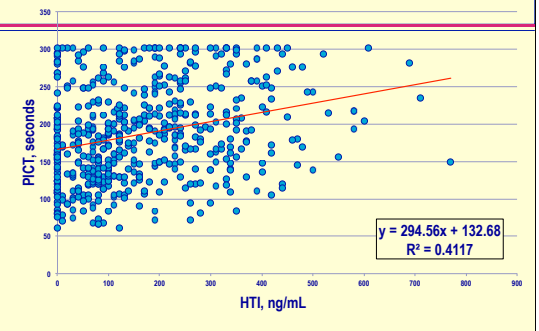
Dabigatran PICT Activity versus HTI Concentration



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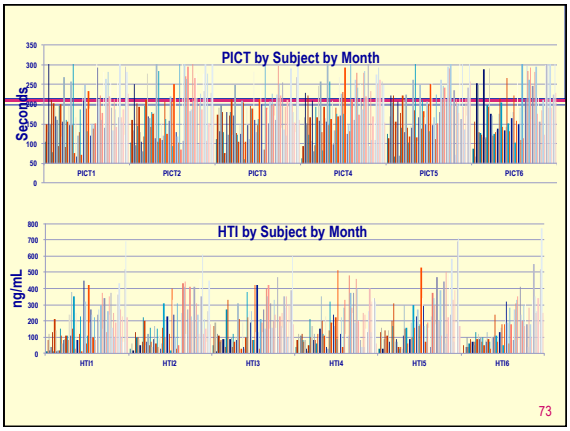

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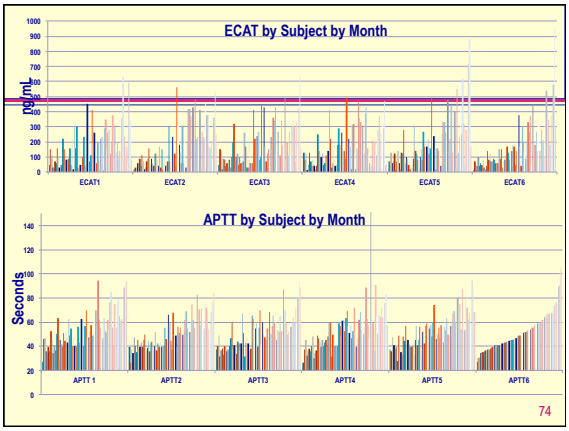

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Results

- Two-factor ANOVA (dabigatran, time) performed over 6 months with repeated measures indicated no significant difference between monthly results (p=0.234)
- Significant difference between all assays were indicated on Bonferroni corrected post hoc tests (p<0.001)
- To eliminate time as a variable we averaged across each of 6 monthly assays
- ECAT and HTI Spearman rank correlation coefficient: 0.988 indicating difference was not significant
- The APTT and PiCT assays showed poor correlation to the HTI assay

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Conclusion

- The ECAT and HTI assays may be employed to measure dabigatran in anticoagulation clinic patients
- The ECAT and HTI methods are superior to APTT and the PiCT assay for this purpose
- Our data imply reproducibility in the absence of strict control of dosage time versus specimen collection time
- This unexpected consequence suggests additional prospective studies that determine dabigatran anticoagulant effect versus time subsequent to dosage

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Measuring Dabigatran With the Dilute Russell Viper Venom Confirm Assay in an Anticoagulation Clinic Population

- This protocol was sponsored by the Surgeon General of the US Air Force and monitored by the 59th Clinical Research Division Institutional Review board, JBSA Lackland, TX 78236-9908. The Surgeon General of the US Air Force supplied all funding for this research.
- The views expressed are those of the [authors(s)]. [presenter(s)] and do not reflect the official views or policy of the Department of Defense or its components.

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INTRODUCTION

- The dabigatran dose-response is predictable, however it is necessary to measure plasma levels in hemorrhage, hemostasis imbalance, renal and hepatic disease, in patients over 75, pediatric patients, and for patients over 140 kg.
- Currently there are no FDA cleared tests to measure any of the TSOAC's
- We measured plasma dabigatran and compared results from the Stago Sta-Clot dilute Russell viper venom confirm (DRVVC) assay, Stago Ecarin Chromogenic Assay, Biophen Hemoclot Thrombin Inhibitor, and to liquid chromatograph tandem mass spectrometry (LC/MS)

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MATERIALS AND METHODS

- We obtained dabigatran calibrators and controls from Biophen and performed the coagulation assays using a Stago STA-R Evolution coagulometer. LC/MS method specimens were performed at LabCorp using the AB Sciex instrument
- Enrolled 97 anticoagulation clinic patients, mean age 76, who were taking 150 mg dabigatran twice daily. All had creatinine clearances >30 mL/minute; subjects were not excluded for other medications or health issues. Citrated blood specimens were processed immediately, and stored at –70°C and we did not correlate collection time with medication time
- We employed descriptive statistics, ANOVA, and the Bland-Altman Difference plot to assess the data.

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RESULTS: Descriptive Statistics for Four Dabigatran Assays: ANOVA p=0.1

Method:	DRVVC	ECA	HTI	LC/MS
Mean (ng/mL)	269.0	228.4	215.8	225.1
Standard Deviation	175.4	160.3	142.1	156.6
Range	901	849.4	709.7	870.2
Minimum	16	11.6	20.8	34.5
Maximum	917	861	730.5	904.7
Confidence Interval (95.0%)	35.4	32.32	28.6	31.6

DRVVC, dilute Russell viper venom confirm assay; ECA, ecarin chromogenic assay; HTI, Hemoclot Thrombin Inhibitor assay; LC/MS, liquid chromatography and tandem mass spectrometry

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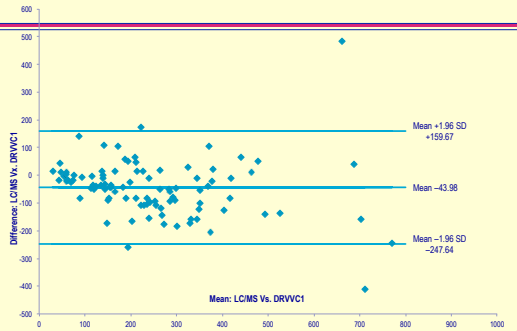
Bland-Altman: LC/MS Vs. DRVVC



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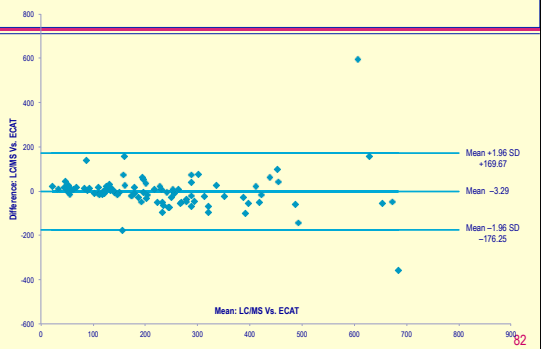
Bland-Altman: LC/MS Vs. ECAT



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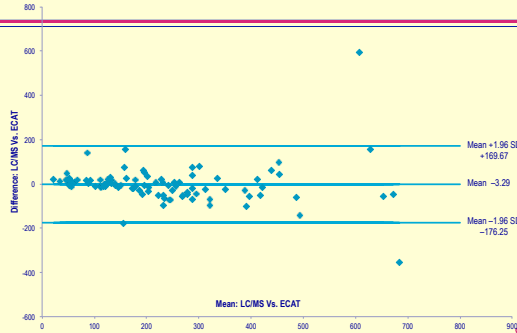
Bland-Altman: LC/MS Vs. ECAT



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CONCLUSIONS:

- The DRVVC Assay: use to confirm the presence of lupus anticoagulant (LA)
- Triggers coagulation at the level of factor X and is unaffected by any congenital coagulopathy other than rare X, V, or II coagulation deficiencies.
- DRVVC reagent is also unaffected by LA
- We have shown that the DRVVC, available to acute care facilities, may be used to monitor the direct thrombin inhibitor dabigatran. Owing to its dependence on coagulation factor X, we further predict that the DRVVC may also be employed to monitor direct anti-Xa inhibitors rivaroxaban, apixaban, and edoxaban. This consideration awaits laboratory confirmation. While there are several indications for laboratory measurement of TSOACs, one compelling argument for a broadly applicable assay is emergent hemorrhage in patients unable to report the identity of their anticoagulant therapy. In these instances, the DRVVC may become the assay of choice

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