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Clumsy Coagulation Communication
Let's Blame the Lab!

George A Fritsma MS, MLS
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Lab–Clinician Communication

- Barriers and opportunities
- Where are the errors made?
- How do we enhance patient experience?

"This concludes my lecture on non-verbal communication. Any comments or questions?"

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Heparin: Crude Extract of Porcine Mucosa

Unbranched sulfated mucopolysaccharide glycosaminoglycan

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Coronary Bypass Graft Unfractionated Heparin (UFH)

- UFH bolus: 5000–10,000 units; 60–80 units/kg
  - Two hours after termination of thrombolytic therapy
  - Simultaneous with IV platelet glycoprotein inhibitors
- Maintenance: 1600 IUs/hour; 12–18 units/kg/h
- Terminate at discharge, max 5 days
  - Risk of heparin-induced thrombocytopenia with thrombosis (HIT) after 5 days of UFH
  - May substitute low molecular weight heparin

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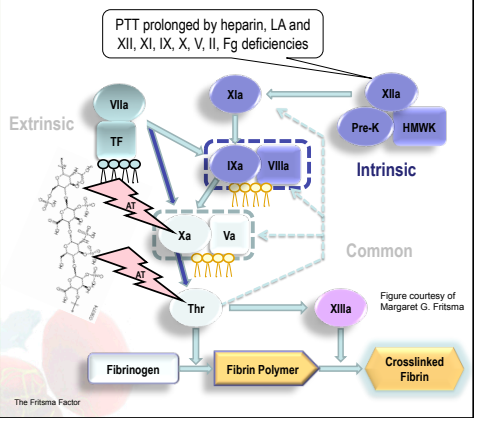

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Monitoring UFH Therapy Standard Schedule

- Perform "baseline" PTT to r/o factor deficiency, inhibitors, lupus anticoagulant
- Initiate therapy: bolus + continuous infusion
- At least 4–6h after initiation, not >24h, perform second PTT
- Adjust dose to PTT therapeutic range
  - *Never use* 1.5–2.5 x mean of normal range
  - Use laboratory-published range: laboratory operator generates range using Brill-Edwards *ex vivo* curve

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

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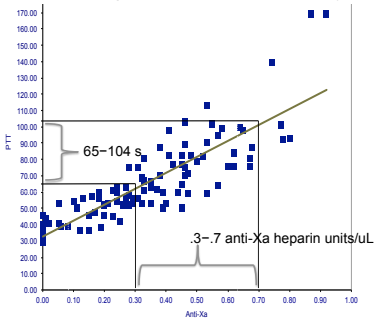
Develop UFH therapeutic range using the Brill-Edwards curve comparing PTT to the chromogenic anti-Xa heparin assay



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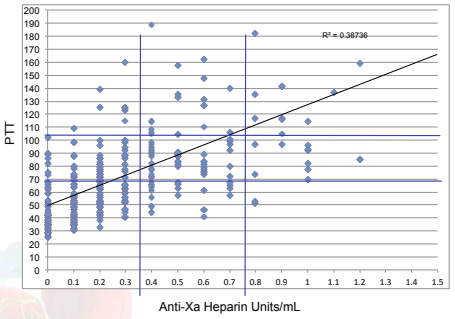
PTT/Anti-Xa Data, Three Routine Days



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Limitations of PTT in UFH Monitoring

- Lupus anticoagulant, present in 1–2% of unselected individuals, prolongs PTT
- Coagulopathy or coag factor inhibitor prolongs PTT
- Elevated FVIII renders PTT insensitive to heparin
- Antithrombin deficiency or consumption renders PTT non-responsive, “heparin resistance”
- Reagent variations require recalibration to the anti-Xa heparin assay, new target ranges with each lot

Eikelboom, JW, Hirsh J. Monitoring unfractionated heparin with the APTT; time for a fresh look. Thromb Haemost 2006; 96: 547–52.

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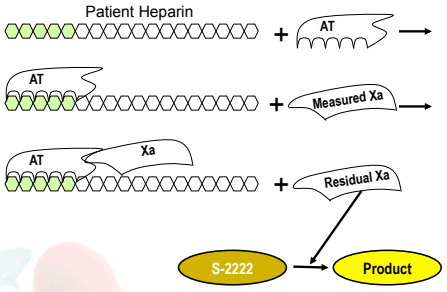
Chromogenic Anti-Xa Heparin Assay



Intensity at 405 nm is inversely proportional to patient heparin concentration

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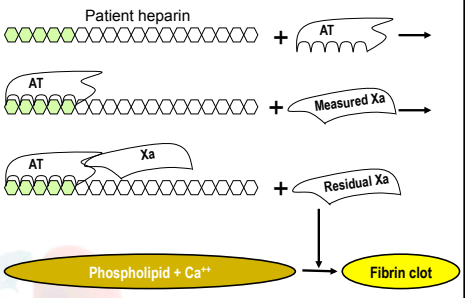
Sekisui® (formerly ADI) HEPTEST®



Clot interval inversely proportional to heparin concentration

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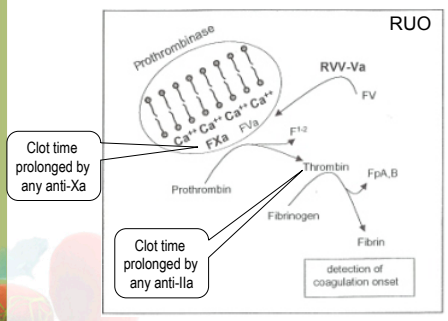
Pentapharm® Pefakit®
Prothrombinase-induced Clot Time (PiCT®)



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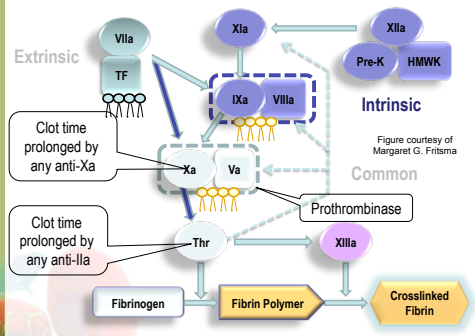
PiCT®

pentapharm benefiting society through science
RUO



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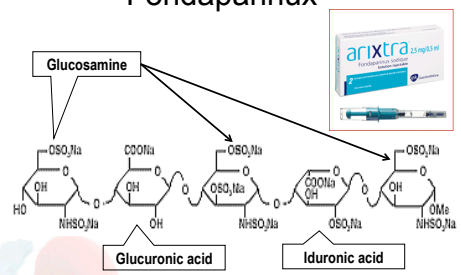
Synthetic Pentasaccharide, Fondaparinux



Turpie AGG. Pentasaccharides. Semin Hematol 2002;39:158-171

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Chromogenic Anti-Xa Heparin Curve

- Separate curves for UFH and LMWH?
- Hybrid curve: one curve fits all
- Different LMWH formulations
  - Aventis 5/1/09 loses Lovenox patent
- Separate curve for fondaparinux?
  - Synthetic pentasaccharide
  - Marilyn Johnston, McMaster: uses same curve as LMWH

McGlasson DL, Kaczor DA, Krasuski RA, et al. Effects of pre-analytical variables on the anti activated factor X chromogenic assay when monitoring unfractionated heparin and low molecular weight heparin. Blood Coagul Fibrinolysis 2005;16:173–6.

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Analytical Error: Thrombophilia Screen

Assay	Patient	RI
Protein C *antigen*	73%	>70%
Protein S *antigen*	99%	>65%
Antithrombin *antigen*	93%	78–126%
Factor VIII	125%	50–186%
APCR	2.4	>1.8
Factor II 20210	Wild-type	Wild-type
PTT-LA	39 s	30–40 s
Homocysteine	3.9 ηmol/L	<4.3 ηmol/L
45-YO woman, three DVTs in five years		

What do you recommend?

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Post-post: Thrombophilia Report

Assay	Patient	RI
Protein C activity	35%	>70%
Protein S activity	39%	>65%
Antithrombin activity	57%	78–126%
Factor VIII	125%	50–186%
APCR	2.4	>1.8
Factor II 20210	Wild-type	Wild-type
PTT-LA	39 s	30–40 s
Homocysteine	3.9 ηmol/L	<4.3 ηmol/L

- Triple heterozygote?
- Terminate pregnancies?
- Increase Coumadin?
- Start heparin?
- Consult with the lab?

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Post-post: Thrombophilia Report

Assay	Patient	RI
Protein C activity	35%	>70%
Protein S activity	39%	>65%
Antithrombin activity	57%	78–126%
Factor VIII	125%	50–186%
APCR	2.4	>1.8
Factor II 20210	Wild-type	Wild-type
PTT-LA	39 s	30–40 s
Homocysteine	3.9 ηmol/L	<4.3 ηmol/L

Or: "*Protein C, S, and AT appear deficient, probably Coumadin interference, reflex INR = 2.1, suggesting Coumadin is present. Other risk factor assay results are within reference interval. No evidence for thrombotic risk, repeat profile 2 weeks after discontinuing Coumadin.*"

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Post-post Issue: Pre-op Screen

Assay	Patient	RI
HGB	14.2 g/dL	13.5–15.6 g/dL
PTT	59 s	25–35 s
PT	12.4 s	9.8–12.6 s
TT	18.2 s	<21 s
PLT count	310,000/µL	250–450,000/µL
Fibrinogen	270 mg/dL	150–400 mg/dL
No bleeding Hx, surgeon postpones procedure		

- Heparin present?
- Risk: bleeding? Thrombosis?
- Repeat PTT until negative?
- Consult with laboratory?
- Laboratory immediate reflex to…

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Post-post Issue: How About This?

Assay	Patient	RI
HGB	14.2 g/dL	13.5–15.6 g/dL
PTT	59 s	25–35 s
PT	12.4 s	9.8–12.6 s
TT	18.2 s	<21 s
PLT count	310,000/µL	250–450,000/µL
Fibrinogen	270 mg/dL	150–400 mg/dL
No bleeding Hx, surgeon postpones procedure		

"*Isolated prolonged PTT may indicate coagulation factor deficiency, coagulation factor inhibitor, or lupus anticoagulant. Normal TT indicates no heparin present. Laboratory reflex to PTT mixing study, results follow.*"

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Mixing Study: New Specimen, Next Day

Assay	Result	RI	Comment
PTT	57 s	25–35 s	Confirms previous PTT
PTT/control 1:1 immediate mix	38.5 s	Control value 27.5 s	Commercial platelet-free normal control plasma

- Uncorrected?
- Should lab have done incubated mix?
- Do you send this result to the surgeon?
- Continue to delay surgery?
- Consult with laboratory?
- Laboratory immediate reflex to…

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Mixing Study: How About This?

Assay	Result	RI	Comment
PTT	57 s	25–35 s	Confirms previous PTT
PTT/control 1:1 immediate mix	38.5 s	Control value 27.5 s	Commercial platelet-free normal control plasma

Interim report: "*Patient plasma mixed 1:1 with normal plasma, PTT performed immediately after mix remains prolonged (uncorrected). Presumptive evidence of lupus anticoagulant. LA profile follows.*"

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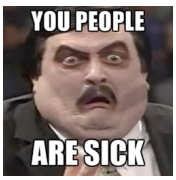
LA Profile: Third Day of Hospital Stay

Assay	Result	RI	Comment
PTT-LA	47.9 s	30–40 s	Confirms PTT
PTT-LA /control 1:1	38.5 s	Control 34.5 s	Possible LA
Staclot LA kit	12 s correction	> 8 s correction	Confirms LA
DRVVT	52.5 s	35–45 s	Possible LA
DRVVT confirm	1.4 ratio	> 1.2 correction	Confirms LA

- Send this result to the surgeon w/o comment?
- Delay surgery?
- Consult with laboratory?



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LA Profile: How About This?

Assay	Result	RI	Comment
PTT-LA	47.9 s	30–40 s	Confirms PTT
PTT-LA /control 1:1	38.5 s	Control 34.5 s	Possible LA
Staclot LA kit	12 s correction	> 8s correction	Confirms LA
DRVVT	52.5 s	35–45 s	Possible LA
DRVVT confirm	1.4 ratio	> 1.2 correction	Confirms LA

Or: "*Patient plasma tested using LA-sensitive PTT reagent and dilute Russell viper venom reagent, both prolonged, both corrected by high phospholipid neutralization reagent, confirming LA. No bleeding risk, may indicate thrombosis risk if LA is chronic. Repeat after 12 weeks to determine persistence.*"

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Pre-op Coags Look the Same as Before "Will This Never End?"

Assay	Result	RI
PT	14.2 s	12.6–14.6 s
PTT	42.5 s	25–35 s
TT	17.5 s	< 21 s
PLT	245,000/µL	150–450,000/µL

- Heparin present?
- Risk: bleeding? Thrombosis?
- Repeat PTT until negative?
- Consult with laboratory?
- Laboratory reflex to…

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Pre-op Coags Look the Same as Before How About This?

Assay	Result	RI
PT	14.2 s	12.6–14.6 s
PTT	42.5 s	25–35 s
TT	17.5 s	< 21 s
PLT	245,000/µL	150–450,000/µL

Or: "*Isolated prolonged PTT may indicate coagulation factor deficiency, coagulation factor inhibitor, or lupus anticoagulant. Normal TT indicates no heparin present. Laboratory reflex to PTT mixing study, results follow.*"

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Mixing Study: How About This?

Assay	Result	RI	Comment
PTT	42.5 s	25–35 s	Confirms previous PTT
PTT/control 1:1 mix immediate	31.1 s	Control 27.5 s	Commercial platelet-free normal control plasma
PTT/control 1:1 mix 2 h at 37°C	33.4 s	Control 31.3 s	Control is incubated alone and with mix

- Corrected?
- Send results to surgeon w/o comment?
- Delay surgery?
- Consult with laboratory?
- Laboratory reflex to…

Or: "*Patient plasma was mixed 1:1 with normal plasma, PTT within 10% of control immediately and after incubation (corrected). Presumptive evidence of factor deficiency, factor assays follow.*"

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VWD Profile

Assay	Result	RI	Comment
FVIII	40%	50–150%	Mildly decreased
VWF:Ag	37%		VWD type 1
VWF:RCo	45%		
VWF:Act	48%		
VWF:CBA	37%		

- Send this result to the surgeon w/o comment?
- Delay surgery?
- Consult with laboratory?

Or: "*Results indicate von Willebrand disease type 1, risk of mucocutaneous bleeding may require pre-operative corrective therapy.*"

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Consultative Lab Testing

- "Goal-oriented" ordering: assays keyed to condition
- Assess causes for long PT or PTT: Hx of bleeding or thrombosis, interfering drugs, summarize results
- Initial profile with algorithm-based reflex additions
- Reduce cost by selecting correct assays
- Fewer repeat samples, less blood volume
- Conclude on abnormalities efficiently
- Shortened TAT and stay
- Interpret results, indicating cause and significance of the coagulation abnormality, bleeding and thrombotic risk, recommendations for therapy

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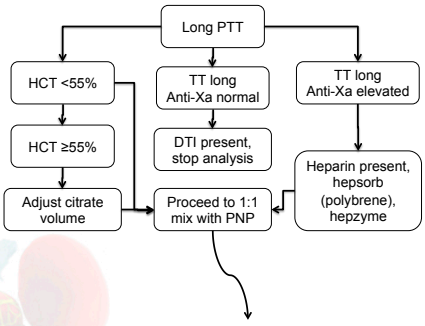
Prolonged PTT Workup



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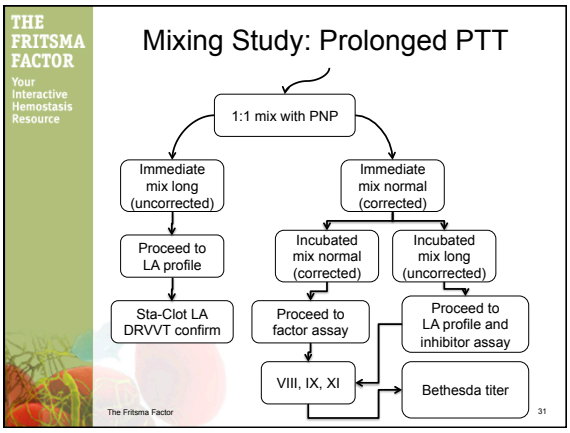
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Mixing Study: Prolonged PTT
1:1 mix with PNP
Immediate mix long (uncorrected)
Immediate mix normal (corrected)
Proceed to LA profile
Incubated mix normal (corrected)
Incubated mix long (uncorrected)
Sta-Clot LA DRVVT confirm
Proceed to factor assay
Proceed to LA profile and inhibitor assay
VIII, IX, XI
Bethesda titer
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