
Point-of-Care Coagulation Testing

What is it?

Why do we need it?

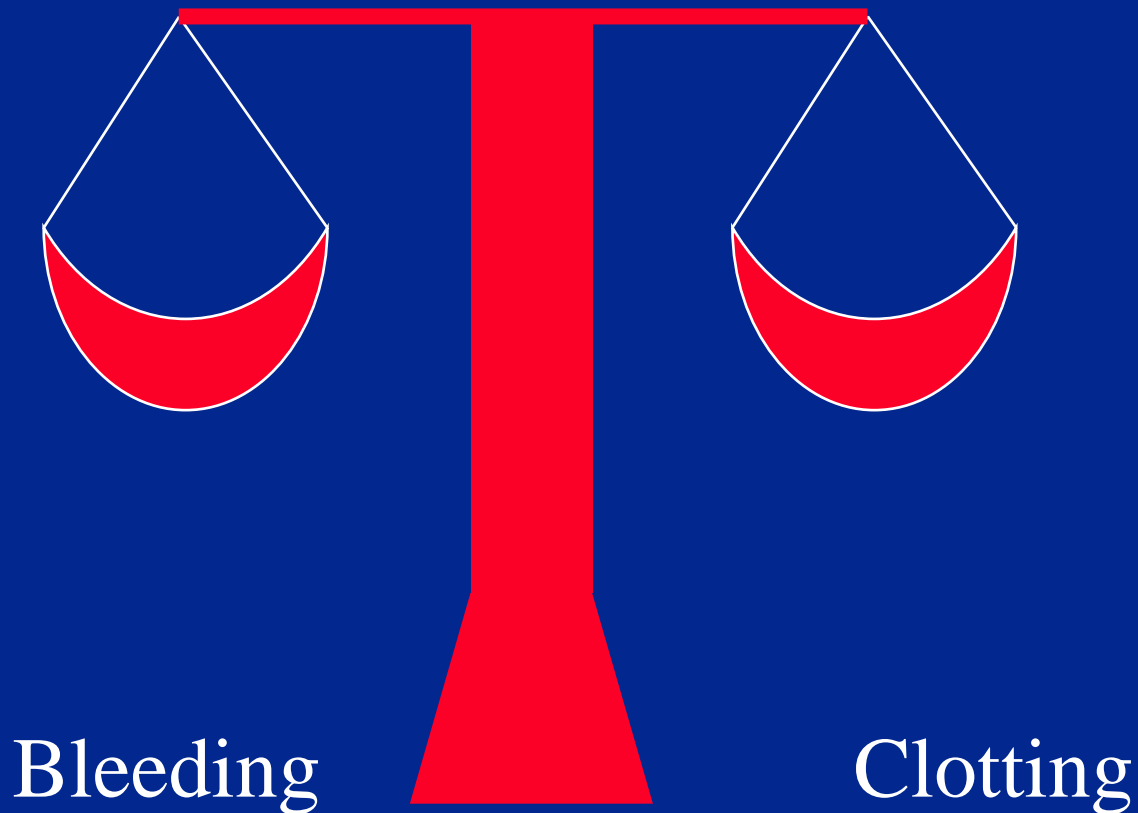
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Director of Clinical Research



Educational Services,
Edison, NJ

Coagulation Testing

◆ Monitoring hemostasis



Coagulation Testing

◆ Monitoring therapy

Heparin

Monitor with
ACT / aPTT

Coumadin/ Warfarin

Monitor with PT



Direct thrombin
inhibitors

Common Pathway

Monitor with ??????

Thrombolytics

CLOT

Monitor with
TT / Fibrinogen

Common Coagulation Tests

◆ Laboratory

- Anti Xa
- Anti IIa
- Factor Assays

PT

aPTT

TT

Fib

◆ Point of Care

– ACT

- » Celite[®]
- » Kaolin
- » Glass beads
- » Silica
- » thromboplastin

Differences in test methods

◆ Standard Laboratory

- Platelet Poor Plasma
- Sodium Citrate Anticoagulant
- 1:9 Dilution
- Variable Preanalytical Delay

◆ Point of Care

- Whole Blood
- No Added Anticoagulant
- No Dilution
- No Preanalytical Delay

POC Coagulation Analyzers

- ◆ HEMOCHRON 401 / 801 / Response
- ◆ HEMOCHRON Jr. *Signature* / *Signature+*
- ◆ ProTime
- ◆ Medtronic HMS / HemoTec ACT II
- ◆ Roche CoaguChek / S / Pro / Pro DM
- ◆ Bayer RapidPoint
- ◆ i-STAT
- ◆ Helena
- ◆ Others

Current choices

- ◆ HEMOCHRON Tube (401 / 801 / Response)
 - ACTs - Celite[®], kaolin, glass bead
 - RxDx Dosing assays (Celite, kaolin)
 - aPTT (fresh / citrated whole blood)
 - PT (fresh/ citrated whole blood)
 - HiTT, TT, HNNTT thrombin time based tests
 - Fibrinogen

Current choices

- ◆ HEMOCHRON Jr / Signature / Signature+
 - ACT - Celite (ACT-LR), Combination (ACT+)
 - aPTT (fresh / citrated whole blood)
 - PT (fresh/ citrated whole blood)
- ◆ ProTime (ITC)
 - PT only

Current choices

- ◆ Medtronics / ACT II / HMS / HMS+
 - ACT - kaolin (HR-ACT, LR-ACT)
 - Heparinase ACT
 - Dosing assays – thromboplastin based
- ◆ i-STAT
 - ACT – Celite
 - PT – FDA cleared, not yet available
 - Endpoint measure of thrombin generation

Current choices

- ◆ Bayer RapidPoint
 - ACT - Celite (HMT)
 - Dosing assays (Celite based)
 - APTT (fresh / citrated whole blood)
 - PT (fresh / citrated whole blood)
- ◆ Helena Actalyke
 - ACT – Celite, kaolin, glass, combination (MAX-ACT)

Current choices

- ◆ Roche CoaguChek Pro / DM
 - ACT -Tissue factor / factor VII activation
 - aPTT
 - PT
- ◆ Roche CoaguChek / S
 - PT only

POC Coag Analyzers Differ

- ◆ Test methodology
 - Sample size and application
 - » Microliters to milliliters
 - Sample measurement
 - » Manual vs automated
 - Clot detection method
 - » Enzyme detection method
 - Reagent composition
 - Results

Clinical Applications

- ◆ Operating Room
 - Cardiac Surgery
 - Interventional Cardiology and Radiology
- ◆ Critical Care
- ◆ Satellite Sites
 - Dialysis
 - ECMO
 - Emergency Room
 - Anticoagulation Clinic

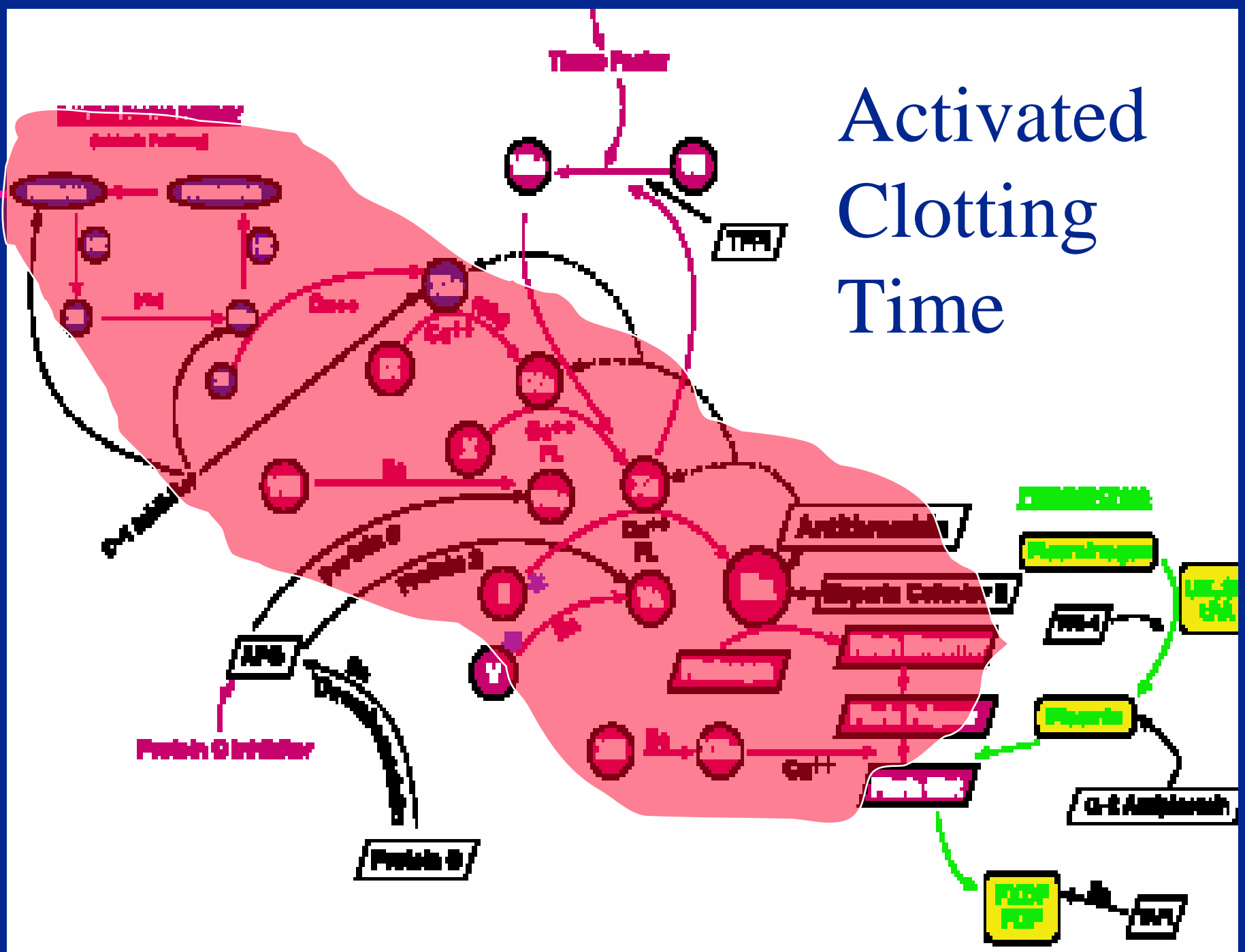
History of the ACT

- ◆ Lee-White clotting time
 - Manual
 - No activator
 - Very slow
- ◆ 1966 –Hattersley- Activated Clotting Time
 - Diatomaceous earth activator
 - Operator defined mixing and clot detection
 - Global assay - Contact activation of cascade

Particulate Contact Activation

- ◆ Initiation of intrinsic coagulation cascade
 - Factor XII (Hageman factor)
 - Prekallikrein (Fletcher factor)
- ◆ Dramatically shortens contact activation period over Lee-White time
- ◆ Proposed as both screening assay for coagulation defects and for heparin monitoring

Activated Clotting Time



ACT Automation - 1969

◆ HEMOCHRON introduced

- semi-automated
- less operator dependence
- two assays

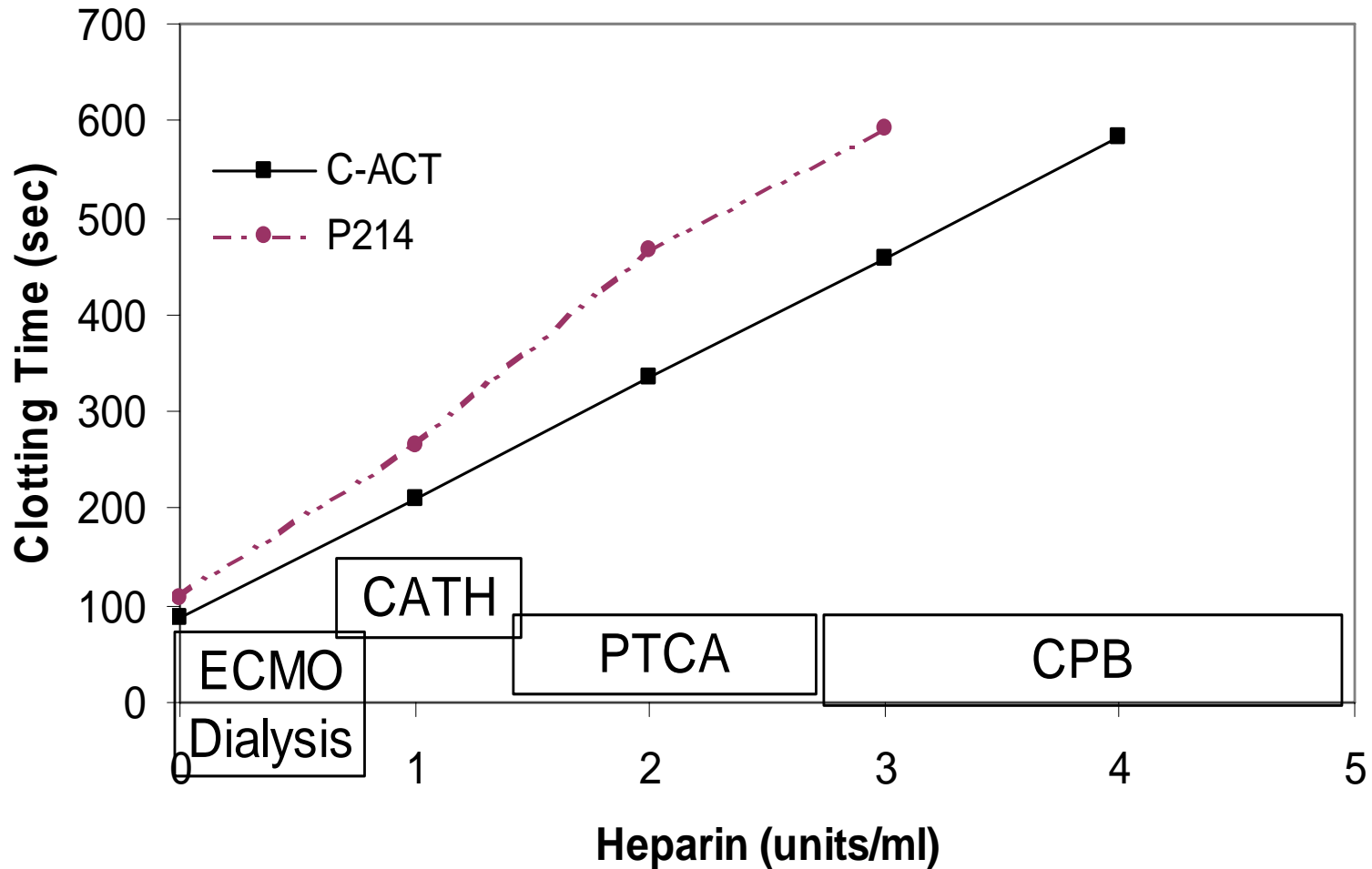
» CA510 (later FTCA510)

◆ diatomaceous earth
activated

» P214 glass bead activated

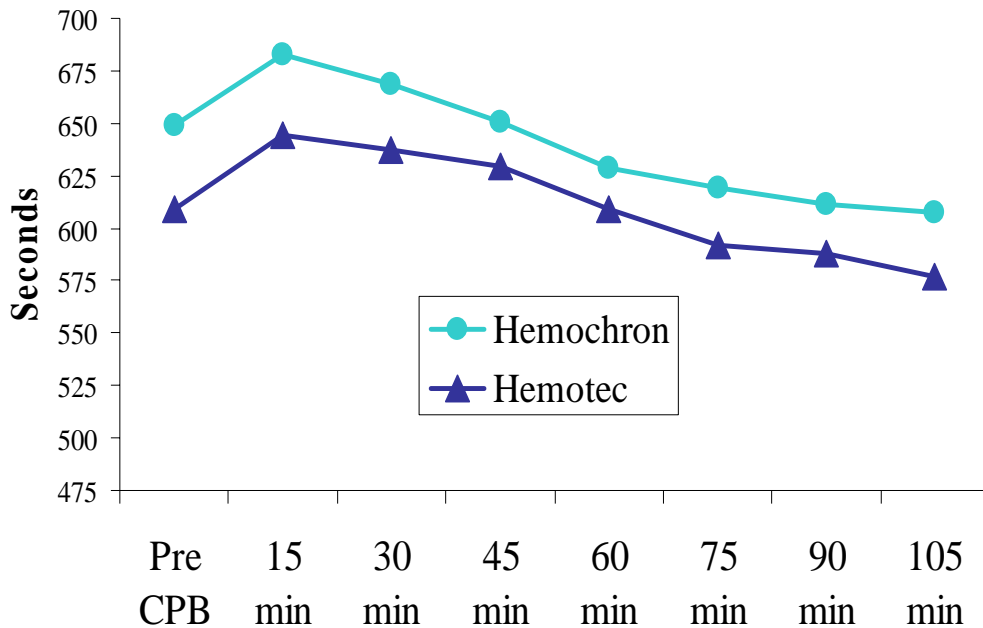


2 assays for separate applications



1980's HemoTec ACT

- ◆ Liquid kaolin activator
- ◆ Different technology
 - Different results



ACT Differences

- ◆ Recognized in literature >20 years
 - Clinical evaluations of Hemochron appeared in journals mid 1970's
 - By 1981, papers appeared showing little correlation between ACT and heparin level
 - By 1988, papers clearly showed clinically different results between Hemochron and HemoTec
- ◆ Differences ignored by clinicians

Monitoring - ACT

◆ Benefits

- Industry Standard Since 1970s
- Recommended as 1^o method in perfusion guidelines
- Easy to run

◆ Disadvantages

- Each system yields different numbers
- High sensitivity to hypothermia and hemodilution (with exceptions)
- Little or no correlation to heparin level
 - » especially true for pediatric patients

Monitoring - Heparin Level

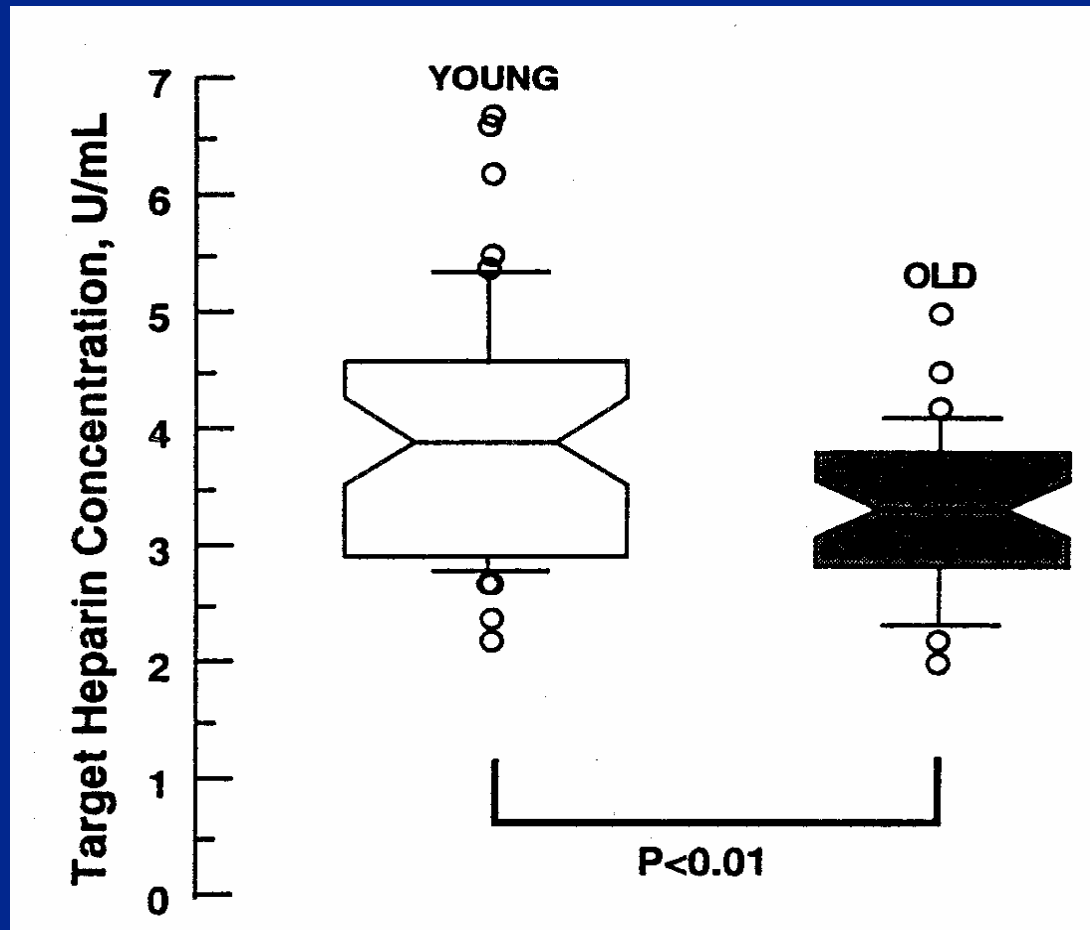
◆ Benefits

- Measures concentration, not activity
- Correlates with laboratory standards

◆ Disadvantages

- Each system yields different numbers
 - » apples and oranges do not compare
- Correlation to anticoagulation status is still disputed
- Target for neonate, pediatric and adult patients may differ

Monitoring - Heparin Level



- ◆ Young: <4.5 years
- ◆ Shayevitz, JR and O'Kelly, SW Progress in Anesthesiology, vol. IX, chapter 16 1995

Heparin Monitoring Dilemma

ACT



Heparin
Level

Which Value Determines
Response?

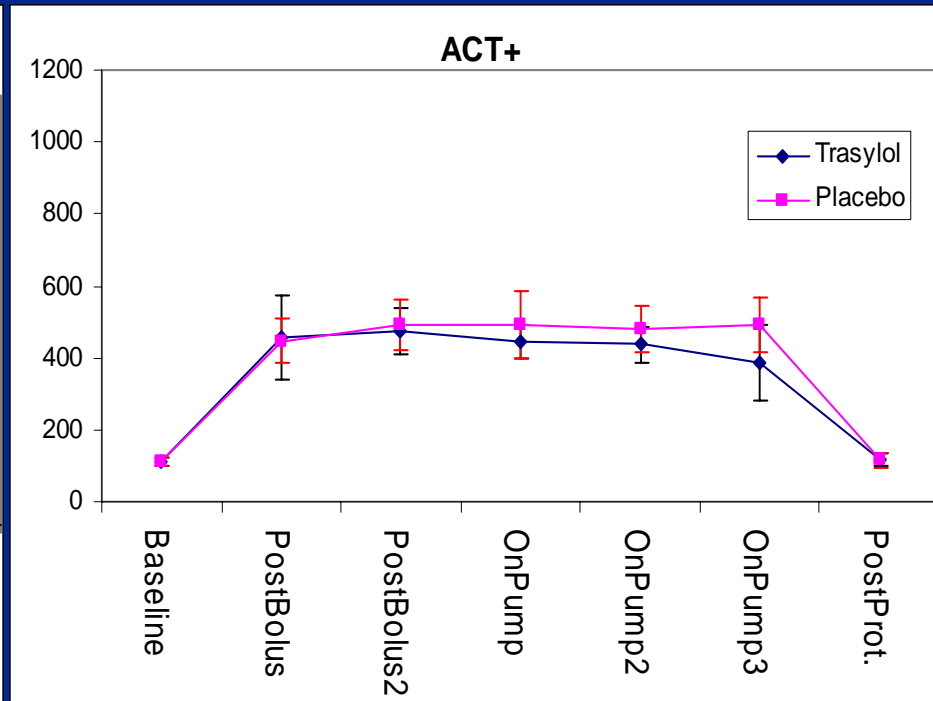
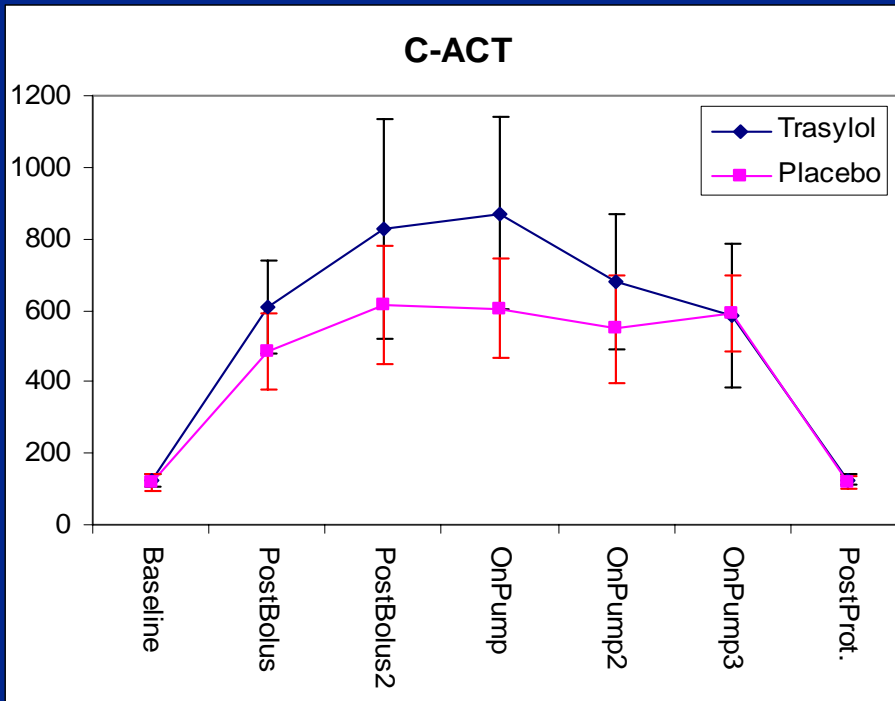
Pharmaceutical Intervention

- ◆ Amicar or Tranexamic Acid
 - No effect on standard celite ACT
- ◆ Aprotinin
 - Significant elevation of celite ACT
 - Two dosing regimens
 - » Full or Half Hammersmith
 - » Both independent of patient size

ACT Monitoring-Aprotinin Treatment

- ◆ Celite ACT
 - Not recommended
 - Still used with target times of >750 seconds
- ◆ Kaolin ACT
 - Unaffected by moderate doses of aprotinin
 - Used with target times of > 480 seconds
- ◆ ACT+
 - Unaffected by ALL doses of aprotinin
 - Used with target times of > 400 seconds

Monitoring in CPB - Aprotinin



◆ Data from clinical evaluation, on file, ITC

Other POC Coag in the OR

◆ Dosing Assays

- Customize heparin and protamine for each patient
 - » HEMOCHRON HRT / PRT
 - » Hepcon HMS
 - » RapidPoint Accent
- Heparin level

◆ Heparin neutralization verification

- Ensure complete removal of circulating heparin
 - » aPTT
 - » PDA-O - ACT based
 - » TT/HNTT - TT based
 - » heparinase ACT

Outcome studies - POC in OR

- ◆ Reduced Blood Loss/Transfusion
 - Use of HRT and PRT (RxDx System)
- ◆ Reduced Cost Resulting from Use of POC Assays
 - RxDx combined with TT / HNTT
- ◆ Reduced Complication Rates
 - TT / HNTT
 - Re-Exploration for Bleeding Reduced from 2.5% to 1.1%
 - Re-Exploration for Coagulopathy Reduced from 1.0% to 0.0.
 - J Thorac Cardiovasc Surg 110:36-45, 1995;
 - Am Soc Anesth Mtg 1996;
 - Point of Care 1:224, 2002

Clinical Applications

- ◆ Operating Room
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 - Interventional Cardiology and Radiology
- ◆ Critical Care
- ◆ Satellite Sites
 - Dialysis
 - ECMO
 - Emergency Room
 - Anticoagulation Clinic

Procedures

◆ Diagnostic

– Catheterization

» locate and map vessel blockage(s)

» determine need for interventional procedures

– Electrophysiology

◆ Interventional

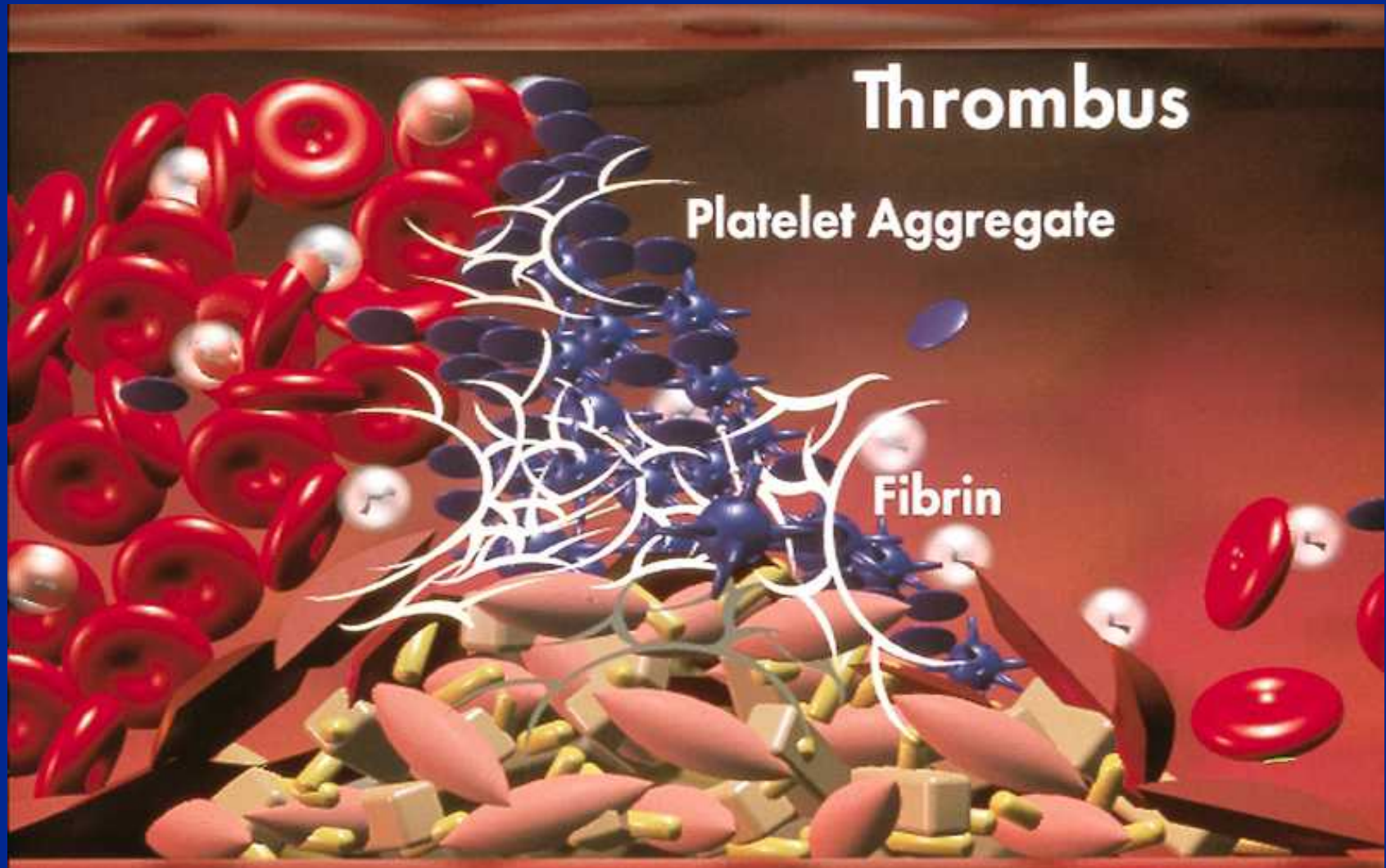
– Balloon angioplasty

– Atherectomy (roto-rooter)

Cath Lab Applications

- ◆ Catheterization and Electrophysiology
 - Low dose (2500 - 5000 unit bolus)
 - frequently not monitored
 - if monitored – ACT or aPTT
- ◆ Angioplasty and Atherectomy
 - 10,000 unit bolus dose or 2 - 2.5 mg/kg
 - target ACT 300 - 350 seconds
 - » unless platelet inhibitors used
 - ◆ 200 – 300 in presence of ReoPro

Angioplasty promotes aggregation



Platelet Inhibitors

◆ ReoPro

- elevates ACTs
- target time = 250 sec with ReoPro
 - » determined using FTCA510 tube

◆ Integrelin

- No reported clinically significant effects on ACT

◆ Aggrastat

- No reported effects on ACT

Clinical Applications

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◆ Critical Care

◆ Satellite Sites

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ACT or aPTT

- ◆ Determine when to pull the femoral sheath
 - Premature sheath pull can lead to bleeding.
 - Delayed removal can increase time in CCU.
 - Target set at each site.
 - » ACT targets range from 150 – 220 seconds
 - » aPTT targets range from 40 – 70 seconds
 - ◆ Highly dependent on reagent used

ACT or aPTT

- ◆ Monitor heparin therapy
 - Target times determined by each facility
 - POC aPTT outcome study
 - » Reduce time to result (112 vs <5 minute)
 - » Reduce time to stabilization
 - » Reduce dose adjustments
 - » Reduce length of stay
 - » By using POC aPTT instead of lab
 - ◆ Poster at AACC 2000 – Staikos, et.al.

Heparin versus Warfarin

Drug	Action	Mechanism	Monitoring	Effective
Heparin	Direct Inhibition of Thrombin	ATIII cofactor	APTT ACT	Immediate
Warfarin	Decreases Production of factors	Vitamin K	PT	Delay 3-5 days

Prothrombin Time

◆ Monitor warfarin therapy

◆ Target times are set by

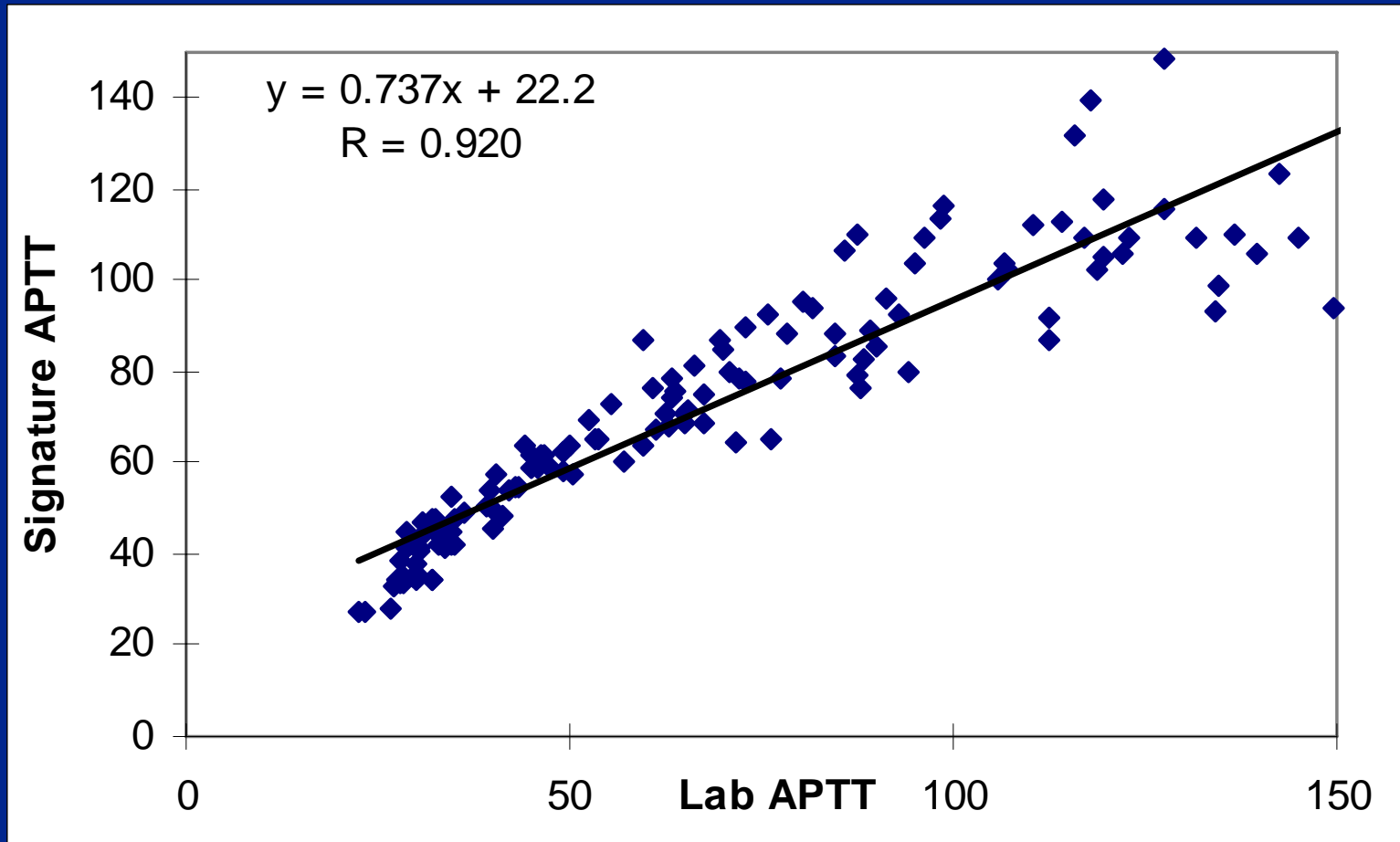
$$INR = \left(\frac{PT_{patient}}{PT_{meannormal}} \right)^{ISI}$$

International Normalized Ratio (INR)

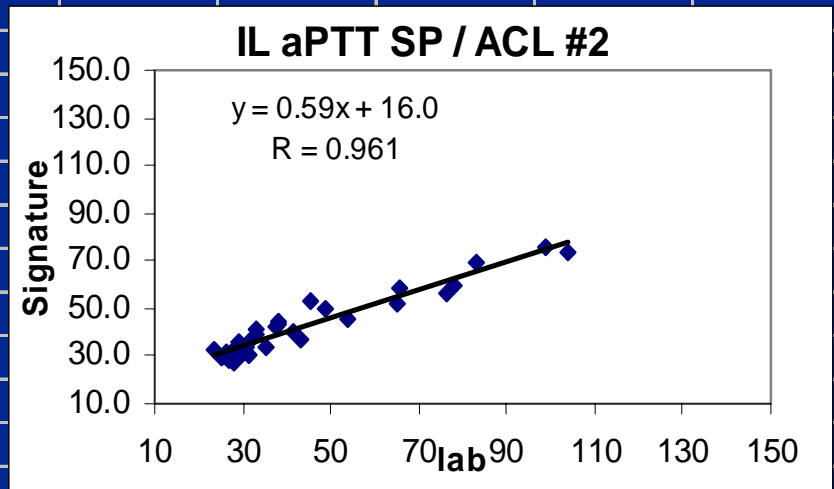
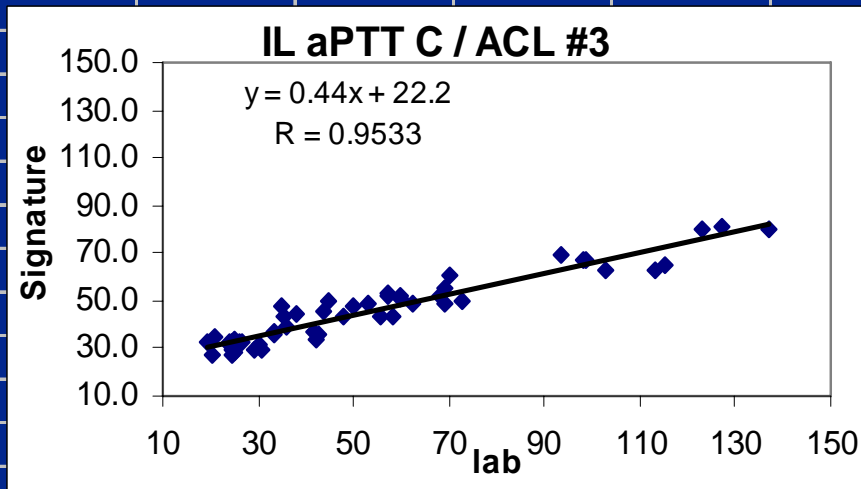
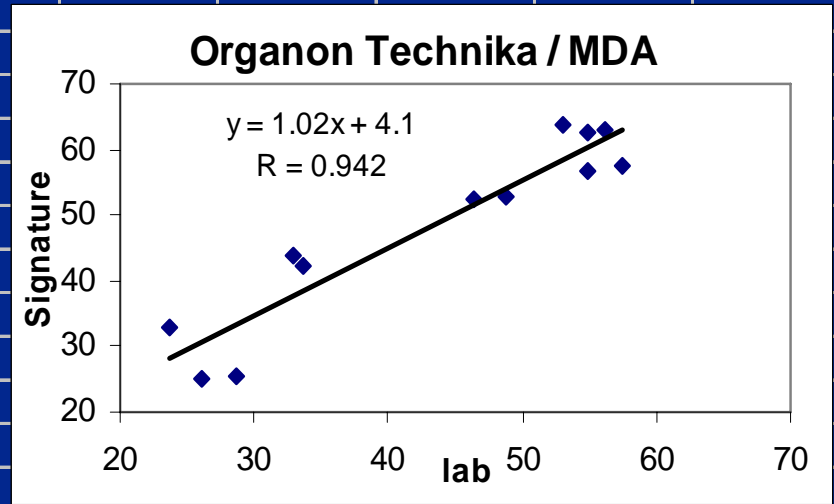
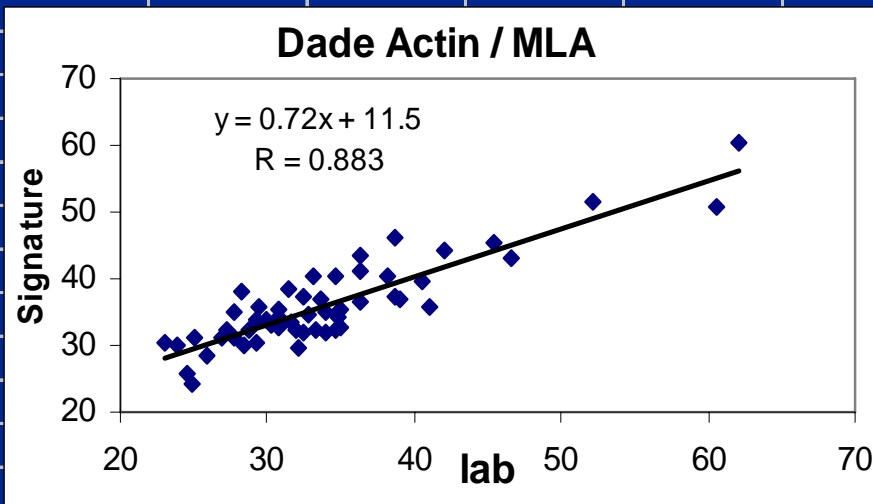
ISI = International Sensitivity Index

- INR target ranges are specified by patient populations
 - » prophylactic therapy for DVT: INR= 2.0 - 3.0
 - » artificial heart valve: INR=2.5 – 3.5
 - » Other ranges on a patient by patient basis

Correlate Does Not Mean Match

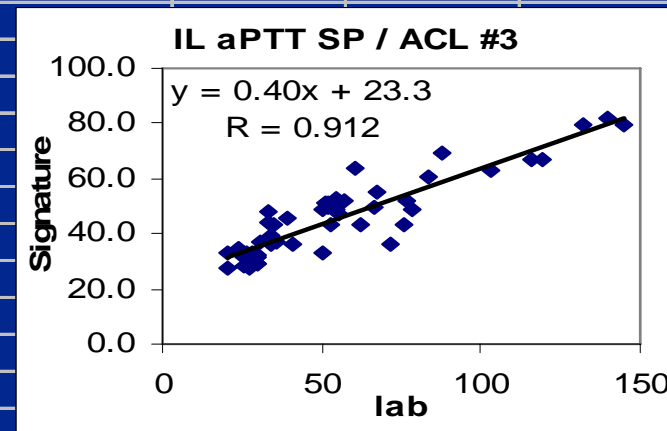
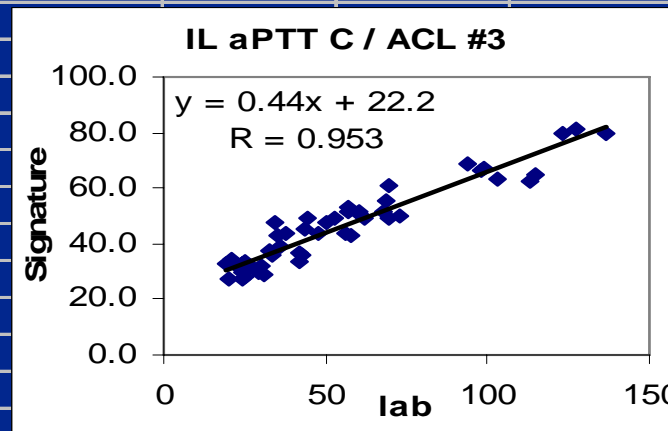
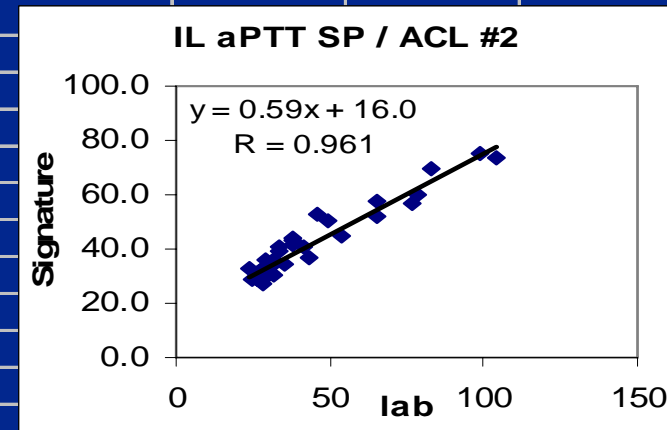
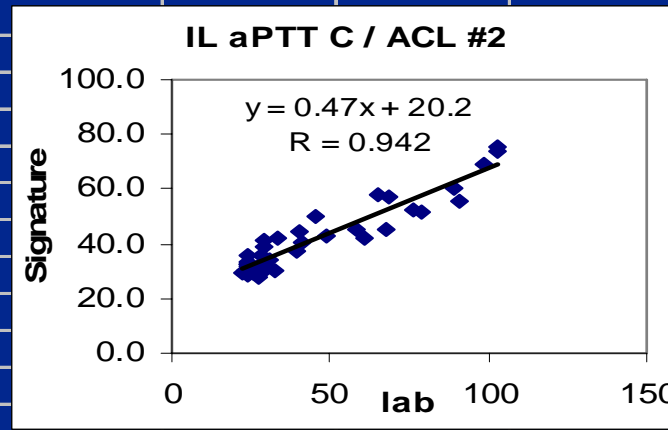
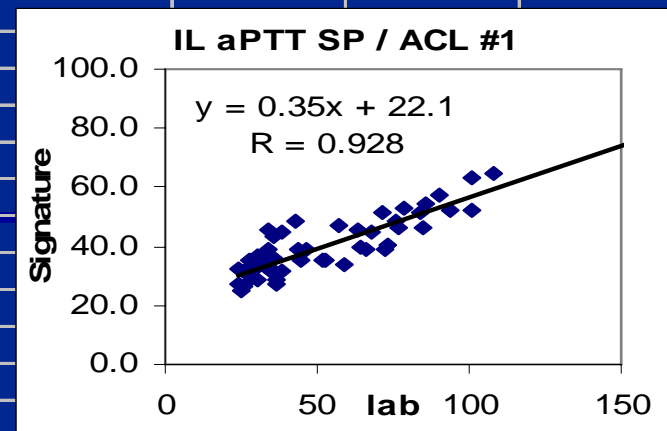
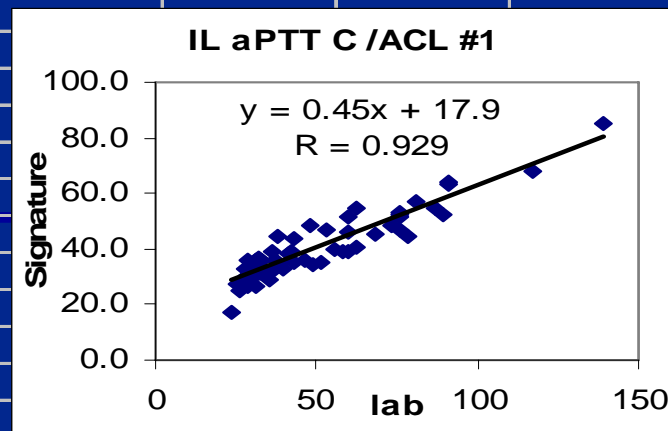


Coag is NOT Chemistry



Compare
for your
site.

Same
System /
Multiple
Sites



Are differences important?

◆ Sometimes no - aPTT C

Signature	site 1	site 2	site 3
30	27	21	18
40	49	42	41
50	71	63	64
60	94	84	87
70	116	105	109
80	138	127	132
90	160	148	155

◆ Sometimes VERY - aPTT SP

Signature	site 1	site 2	site 3
30	23	24	33
40	51	41	82
50	80	57	130
60	109	74	179
70	138	91	>200
80	167	108	>200
90	196	125	>200

Clinical Applications

◆ Operating Room

- Cardiac Surgery
- Interventional Cardiology and Radiology

◆ Critical Care

◆ Satellite Sites

- Dialysis
- ECMO
- Emergency Room
- Anticoagulation Clinic

Dialysis / ECMO

- ◆ ACT (or nothing in dialysis)
 - Majority use P214 glass activated ACT
 - Some use ACT-LR; ACT II LR-ACT
- ◆ Better Control of Anticoagulation Leads to Increased Dialyzer Reuse
 - Potential for Long Term Cost Savings
 - No Compromise in Dialysis Efficacy (Kt/V)
 - » Ouseph, R. et.al. Am J Kidney Dis 35:89-94; 2000

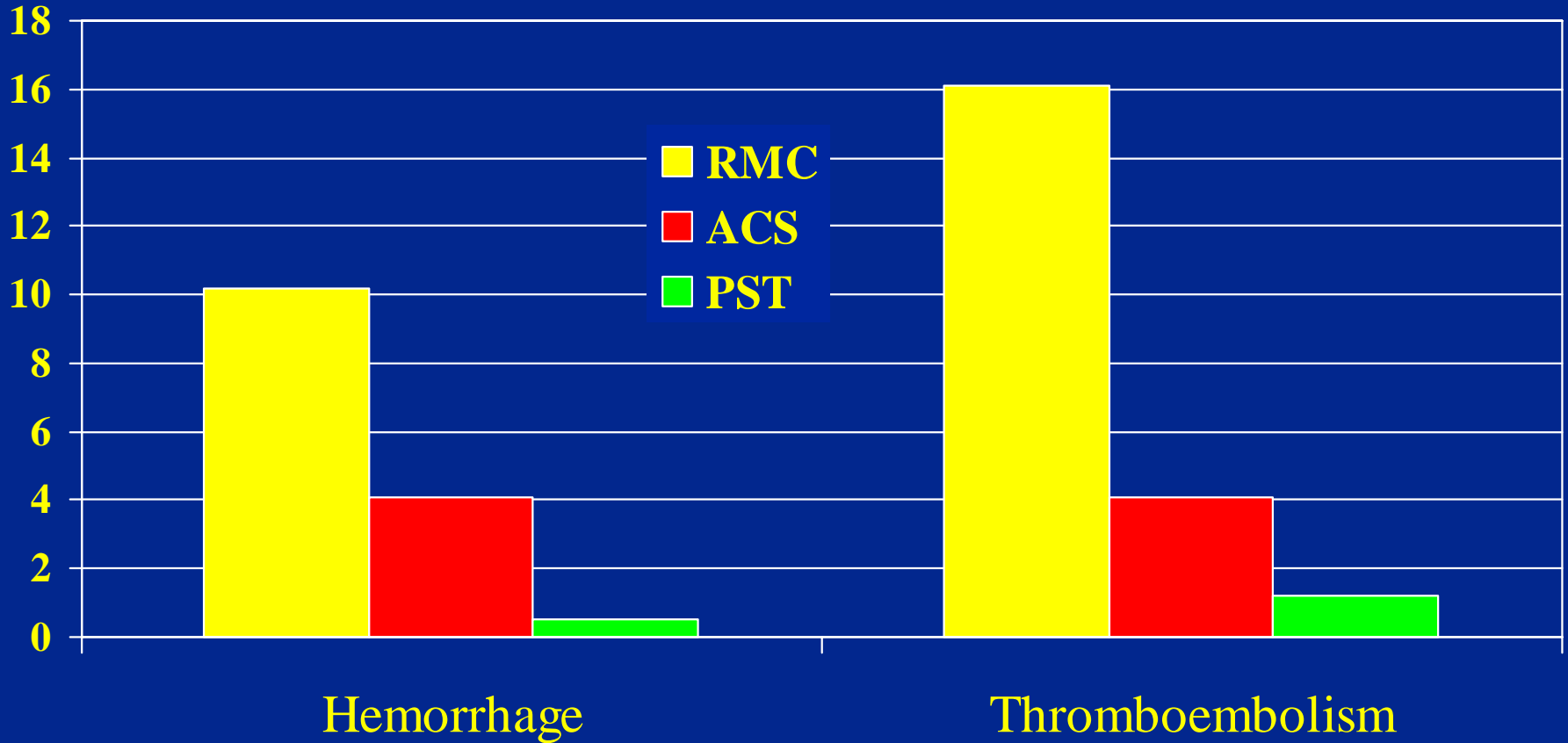
Emergency Room

- ◆ ACT; aPTT; PT; Fibrinogen
- ◆ Immediate Identification of Coagulopathies
 - Optimization of Critical Decision Pathways
- ◆ ACT Allows Early Detection of Traumatic Coagulopathy
 - Allows Early Treatment Decisions
 - Aids Damage Control Decisions
 - » Aucar, J. et.al. 1998 SW Surgeons Congress
- ◆ Optimize Staffing During Off Hours

Managing OAC Patients

- ◆ Routine Medical Care
 - RMC
- ◆ Anticoagulation Clinics
 - ACS
- ◆ Prothrombin Time Self-Testing
 - PST

Adverse Event Rates



Why the difference?

Increased PT Test Frequency



Increased Time in Therapeutic Range



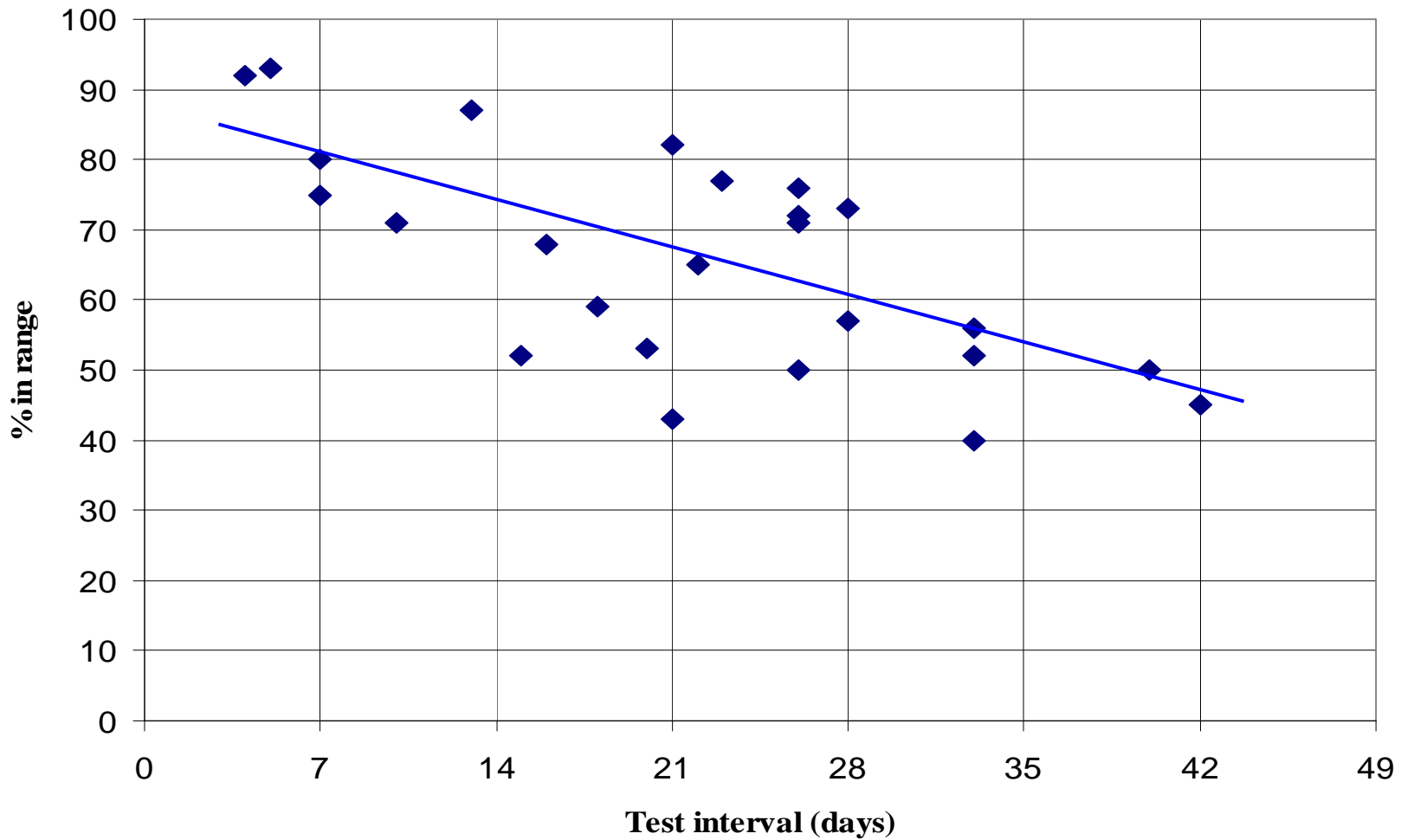
Reduced Complications

Improved Outcomes Through More Frequent Testing

Ansell, J. 1997 ISTH Mtg.

Becker, D. et.al. 1997 Am Coll Cardiol Mtg.

Test Interval Vs. % In Range



Will POC Results Match the Lab?

NOT Necessarily

(It will be a lot closer than for aPTT)

but it **WILL** Correlate

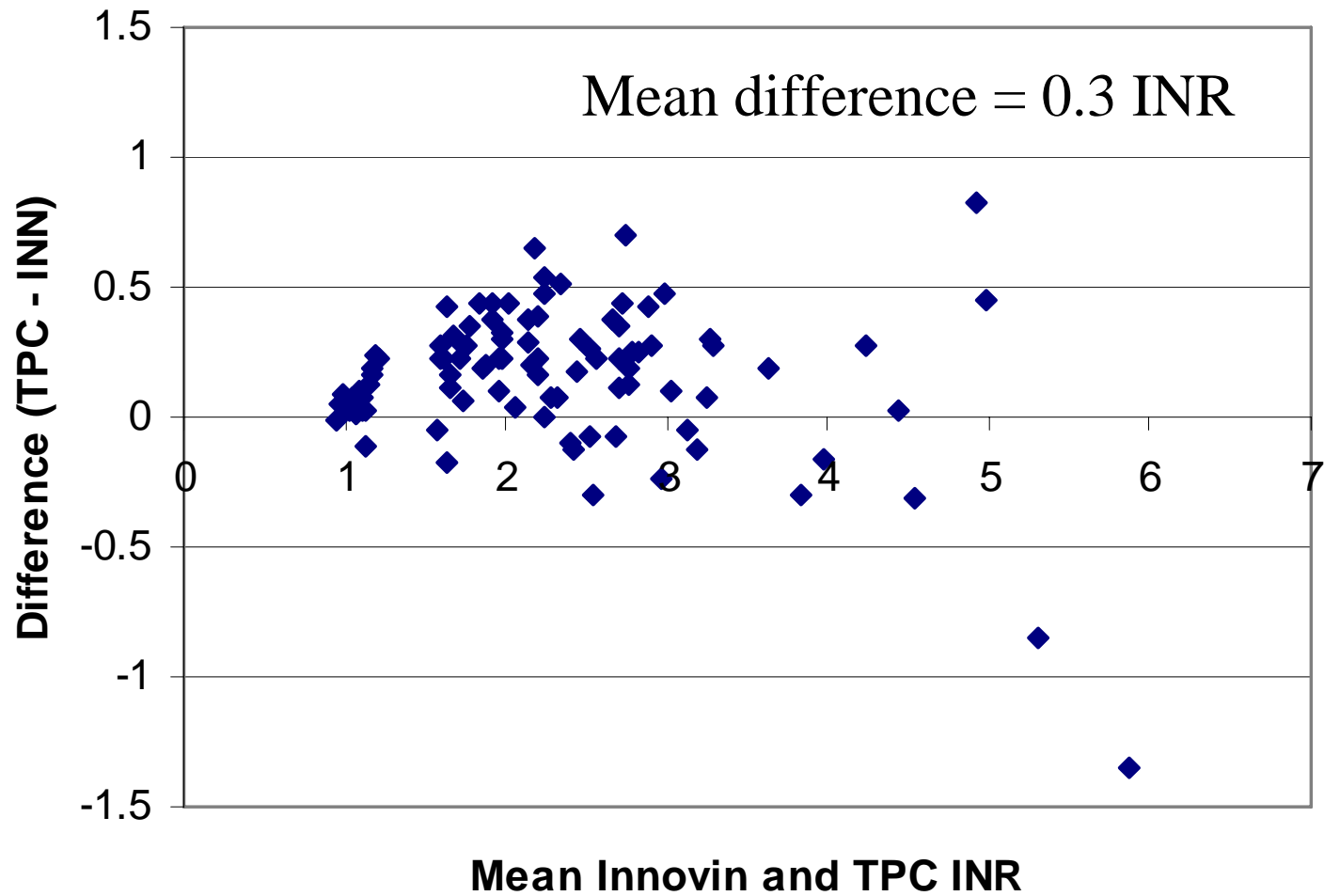
How to Compare INR Results



- ◆ Lower dose?
- ◆ Keep same dose?
- ◆ Raise Dose?

- ◆ Test Again?
- ◆ Test more often?

Lab to Lab Comparison



Why Bother with POC Coag?

- ◆ Improved TAT - Turn Around Time
 - Defined from the Clinician, not Lab view
 - When is Turn Around Important
 - » Emergency Room
 - » ICU/CCU Dose Adjustments
 - » Operating Room / Cath Lab
 - STAT Testing Turn Around

STAT Testing TAT

Lab (min)	CPB (N=40)	PVS (N=45)
Median	90.0	90.0
Mean	78.5	74.0
Minimum	38.0	21.0
POC (min)	All Groups	
Median	2.23	
Minimum	0.33	
Maximum	6.97	

Standardized Clinical Interpretation

- ◆ Defined Assay Sensitivity
 - Requires Lot to Lot Reproducibility
- ◆ Defined Reagent Variability
 - Identical Instrumentation and Reagents at All Testing Sites
- ◆ Defined Critical Clinical Decision Points
 - No Change of Normal Ranges or Target Times Between Lots of Test Reagents or Testing Locations

If POC is so good - What's the catch?

1. Regulatory compliance
2. Connectivity

Regulatory compliance

◆ Who sets the rules?

– JCAHO

» Joint Commission on Accreditation of Health Care Organizations

– CAP

» College of American Pathologists

– FDA

» Food and Drug Administration

– CMS

» Centers for Medicare and Medicaid Services

◆ formerly HCFA

CLIA Regulations for Coagulation

- ◆ Central Laboratory can hold the CLIA license
 - Satellites can have independent licensure
- ◆ Moderately Complex tests
 - Except - ProTime and Coaguchek are waived
- ◆ Requires
 - Certified Laboratory Director
 - Record Keeping
 - Training
 - Quality Policy

Implementing POC coag requires:

- ◆ Method Validation - accuracy
 - Comparison to current standard
 - Linearity may be used if no current standard
 - Is assay performance appropriate to clinical needs?
- ◆ Precision
 - Controls may be used to establish within and between run variability
- ◆ Training
 - competency evaluations at predetermined intervals
- ◆ Linearity and/or Cal/Ver not required for coag

Routine Quality Control

- ◆ Instrument Performance Verification
 - Electronic Quality Control with Numeric Output
 - Two levels per 8 hour shift
- ◆ Assay Performance Verification
 - Wet QC as per Manufacturer's Recommendation
 - » Varies by system
 - ◆ No external QC required for ProTime in most states
 - » Within system may vary by waived or moderate complexity licensure

Ensuring Compliance

◆ Required identification

- Mandatory operator ID
 - » Password control
 - » Reuse IDs for some applications
- Mandatory patient ID
 - » Reuse IDs for some applications

◆ Lockout

- Force QC at specific times
 - » QC must pass to run patient samples
- Lockout non-compliant or untrained operators

Why Bother with POC Coag?

- ◆ Once compliance issues addressed –
 - Improved Clinical Outcome
 - Reduced LOS – Length of Stay
 - Improved, timely patient care