Coagulation Testing
at the Point of Care

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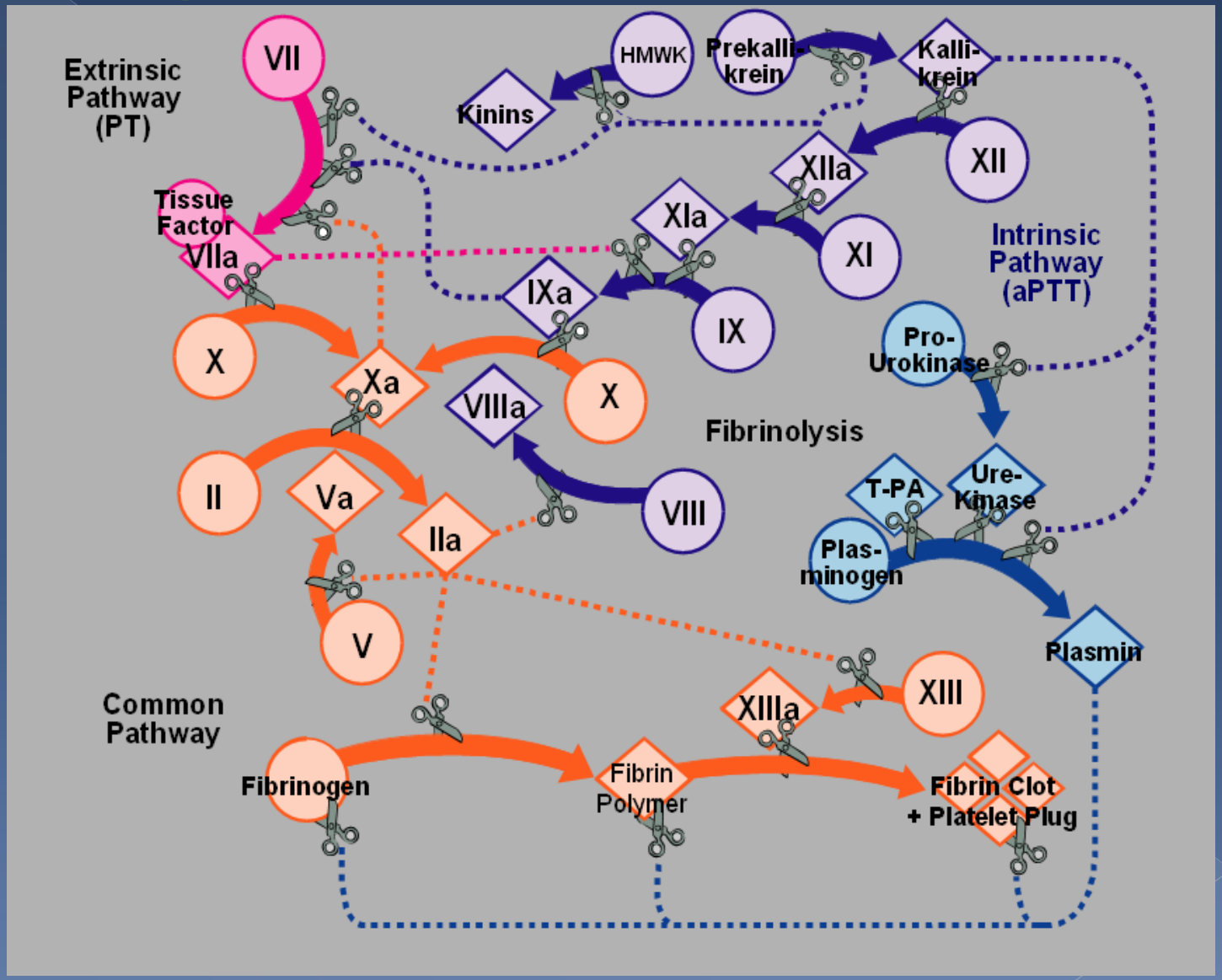
Coagulation Testing

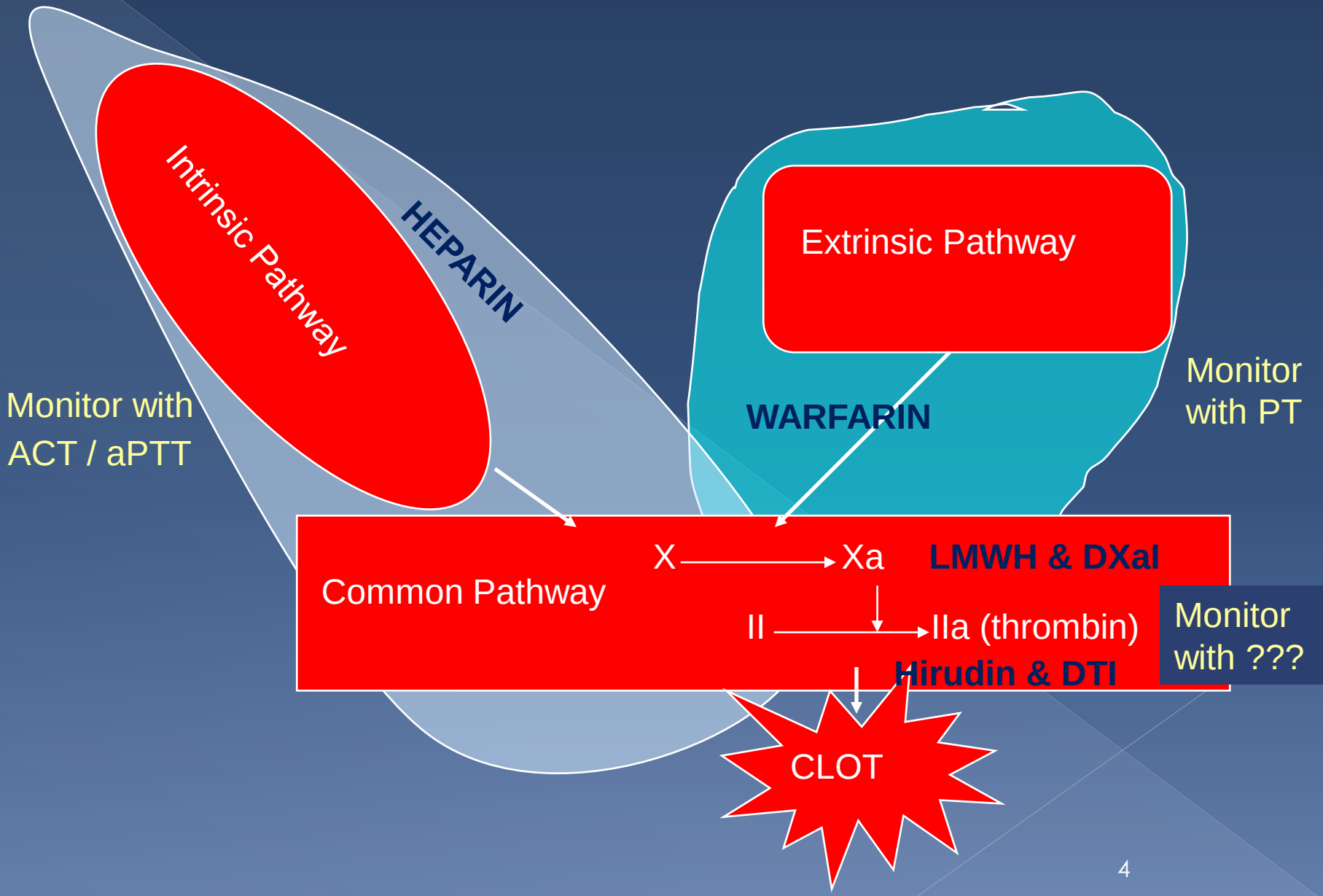
- Monitoring hemostasis

Coagulation Made Simple



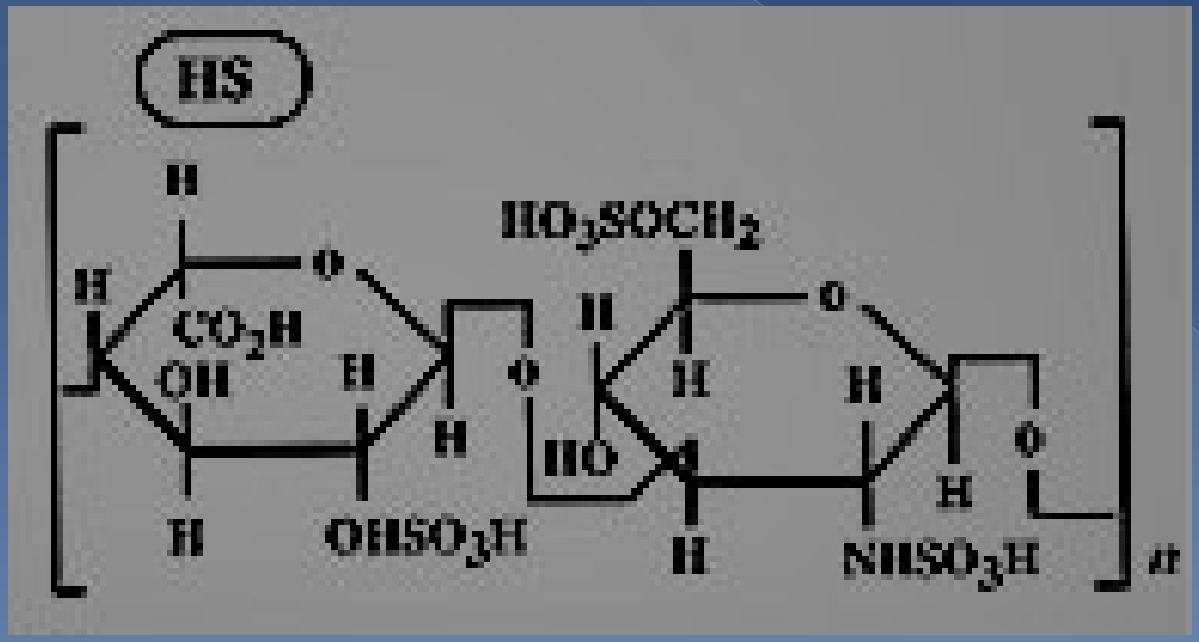
Picture courtesy of Helena Laboratories

Coagulation Testing

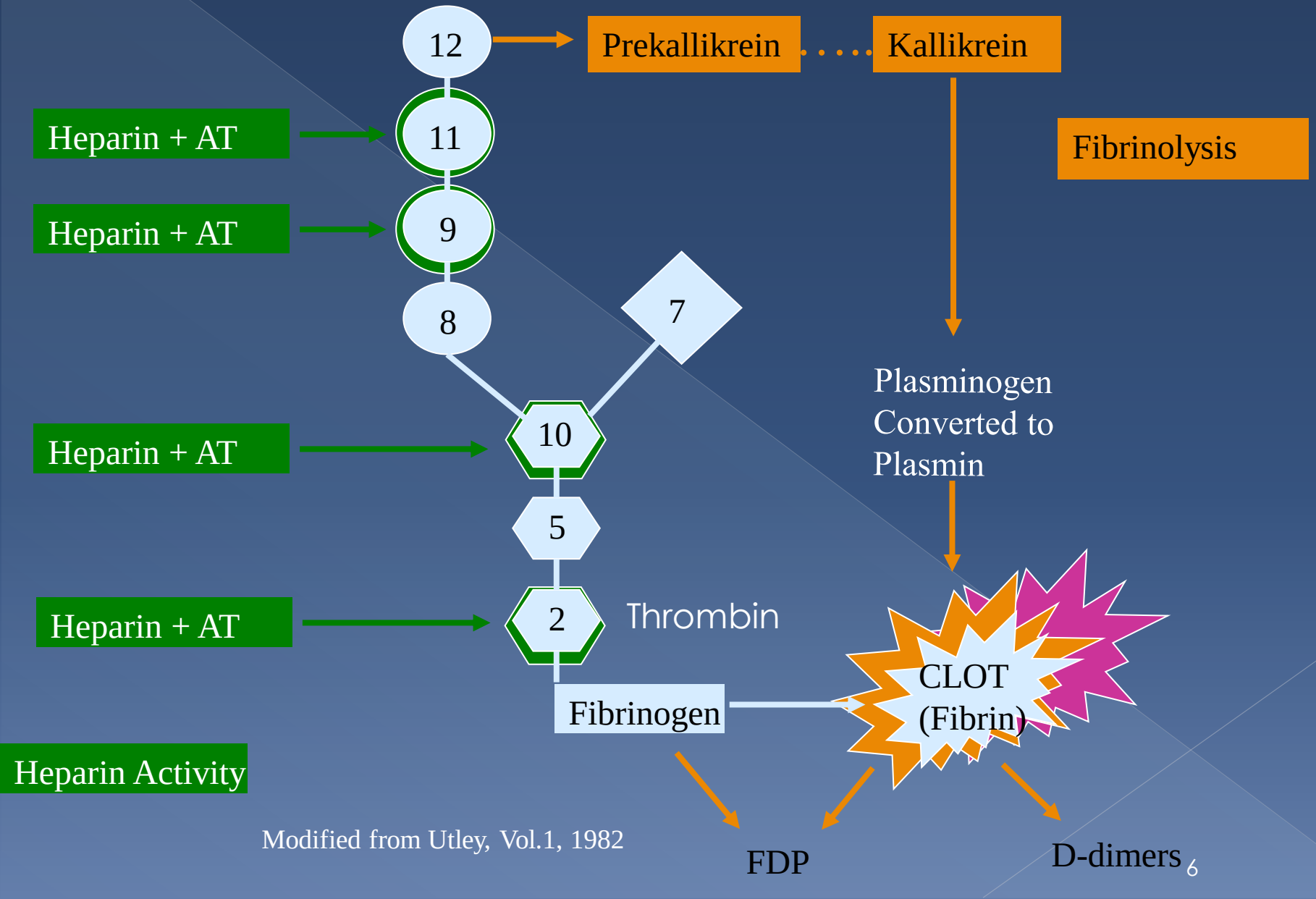


What is Heparin?

- Glucopolysaccharide
- MW range: 6,000 - 25,000 daltons
- Only ~1/3 molecules active
  - Must contain specific sequence of glucosaccharides to function



Heparin Effects on Coagulation



Modified from Utley, Vol.1, 1982

Why Monitor Heparin?

- Potency varies by manufacturer
  - Potency varies by lot
- Dose response varies by patient
  - Half life ranges from 60 - 120 minutes
  - Non-specific binding
- Functions by accelerating action of antithrombin
  - Antithrombin level critical for appropriate response

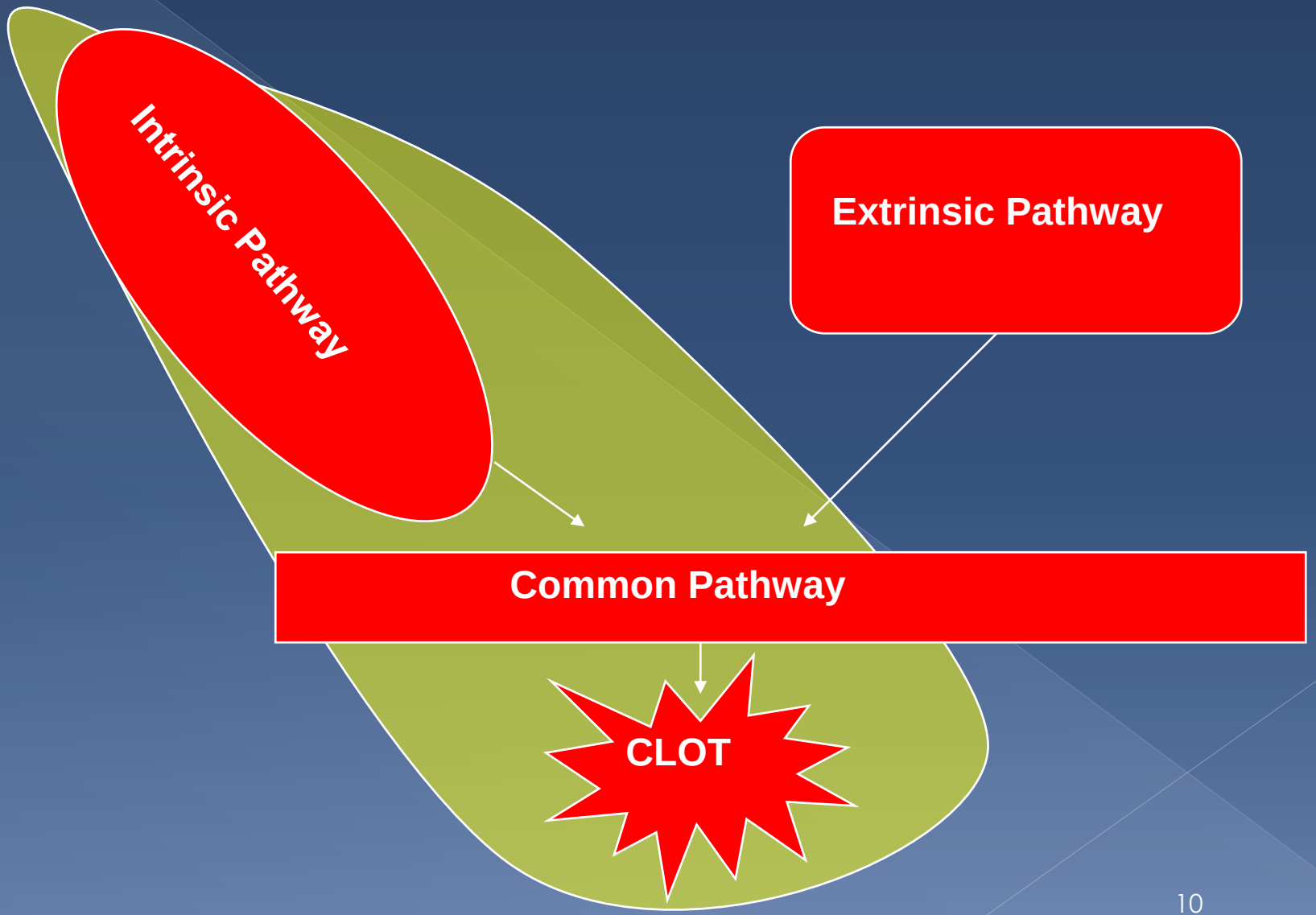
How to Monitor Heparin?

- Laboratory measures of activity
  - a Factor Xa
  - a Factor IIa (thrombin)
  - No clear correlation between heparin activity and patient outcome
  - TAT generally too long for peri-procedural use
- Viscoelastography
  - TEG / ROTEM
  - Reflects entire coagulation process
    - Requires interpretation
  - TAT generally too long for peri-procedural use
- ACT

What is an ACT?

- Modified Lee-White clotting time
  - Add blood to glass tube, shake
    - Place in heat block
    - Visual clot detection
- First described in 1966 by Hattersley
  - Activated Clotting Time
    - Add blood to glass tube with dirt, shake
      - Diatomaceous earth activator
      - Place in heat block
      - Visual clot detection
    - Proposed for both screening for coagulation defects and for heparin monitoring

Activated Clotting Time



Why do we use an ACT?

- Point of Care
  - Immediate turn around
  - Rapidly adjust anticoagulant dosing as needed
- Literature supports use of ACT
  - Poor correlation between ACT & heparin level (1981)
  - Hemochron and HemoTec clinically different (1988)
  - Differences ignored by clinicians, yet…
  - Improved clinical outcome with ACT use
    - Reviewed: 2007 NACB Laboratory medicine practice guideline for point of care coagulation testing
      - https://www.aacc.org/science-and-practice/practice-guidelines/point-of-care-testing

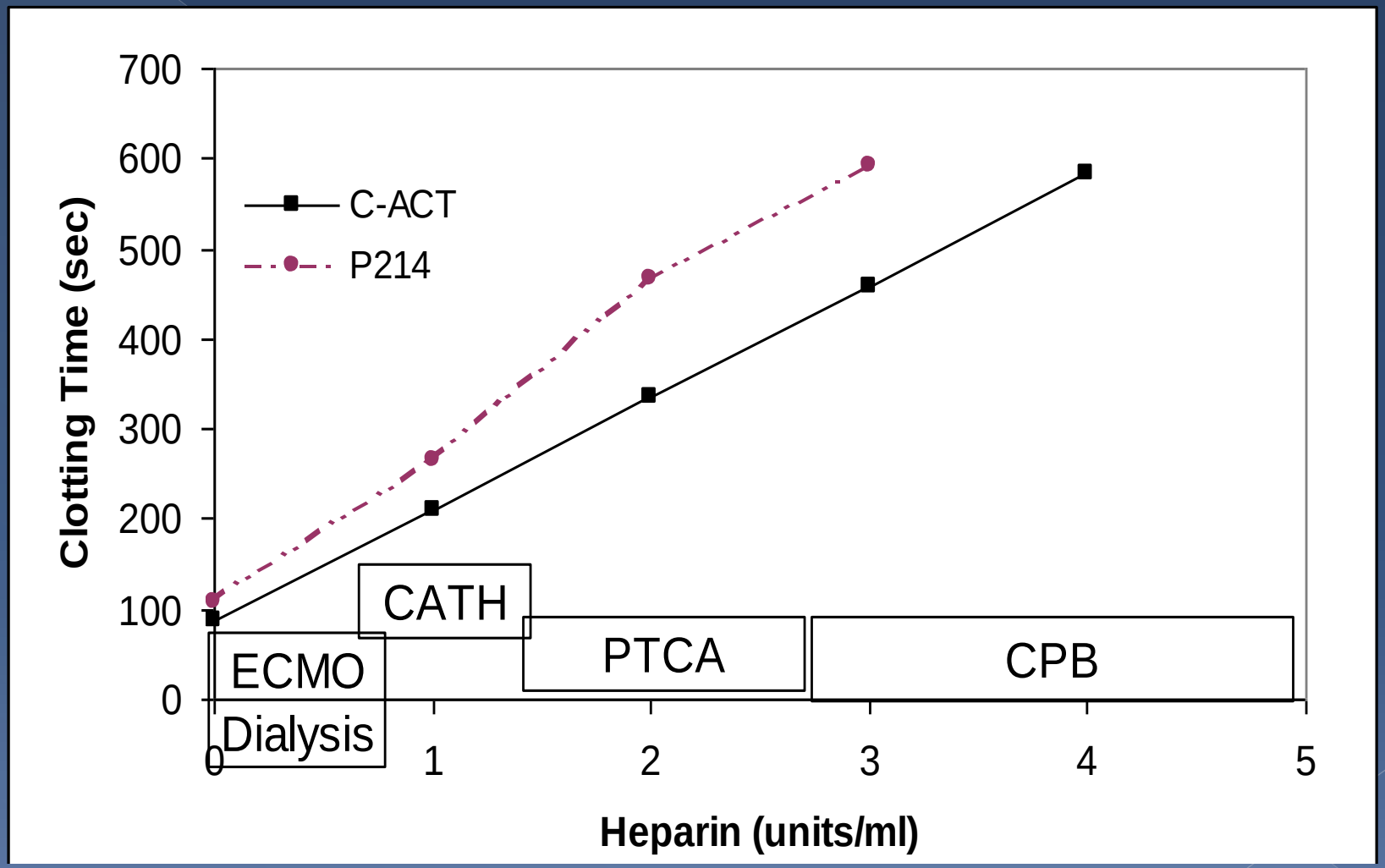
Why do ACTs Differ?

- Activator
  - diatomaceous earth; kaolin; glass beads; thromboplastin; combinations
- Sample measurement
  - Manual; automated
- Sample mixing
  - Manual; automated; physical; chemical
- Endpoint detection
  - Clot; surrogate marker
- By design!

Semi - Automation - 1969

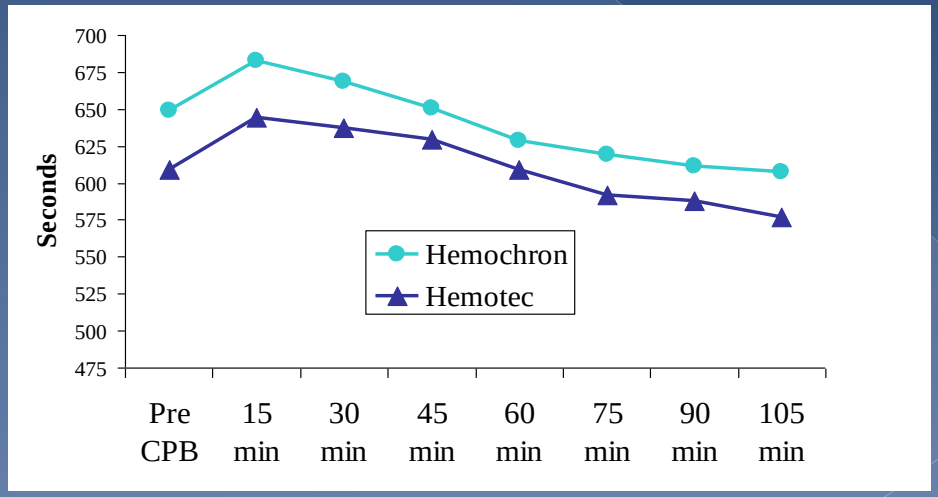
- HEMOCHRONOMETER
  - Later - HEMOCHRON
  - Add blood to tube, shake
    - Manual sample treatment
  - Place in test well
    - Automated heating
    - Mechanical, objective fibrin clot detection
  - Two different activators
    - CA510 (later FTCA510)
      - Diatomaceous earth
      - P214 glass bead

Two assays for separate uses



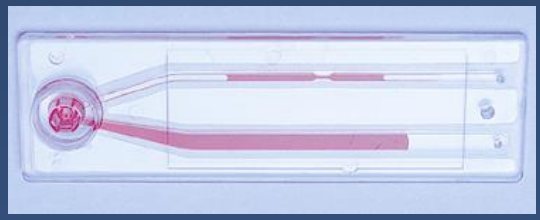
1980's

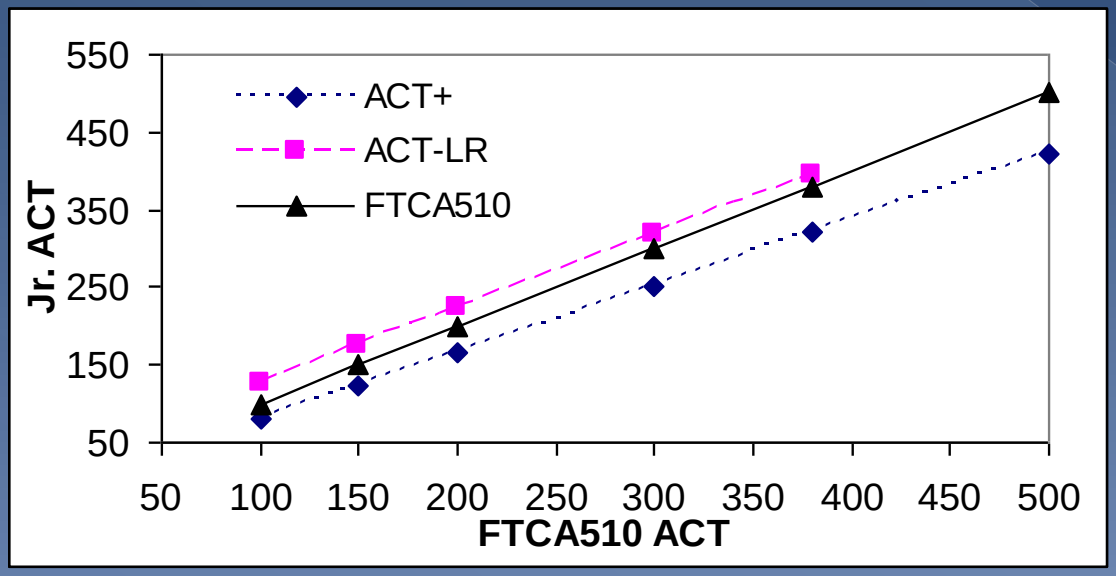
- HemoTec ACT
  (later Medtronics ACTII)
  - Add blood to dual cartridge
    - Liquid kaolin activator
  - Place in instrument
    - Automated mixing
- Results don't match Hemochron



1990's

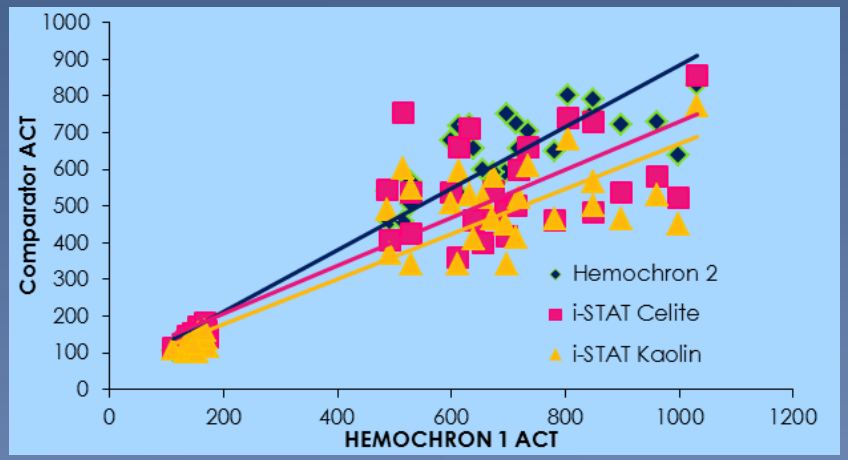
- Microsample ACTs - Hemochron Jr
  - Add blood to sample well, press start
    - Automated sample measurement
    - Automated mixing
    - Objective clot detection
- Results still don't match





2000

- Abbott Point of Care - i-STAT
  - Thrombin detection
    - Synthetic thrombin substrate
    - Electro-active compound formed, detected amperometrically
    - Clotting time reported
  - First non-mechanical clot detection
  - Direct chemical assessment of the appearance of active thrombin



Where is an ACT Used?

- Cardiac surgery
  - Recommended as 1° method in AmSECT guidelines
- Percutaneous coronary intervention (PCI)
- Interventional cardiology
- ECMO
- Critical care
- Interventional radiology
- Electrophysiology
- Vascular surgery
- etc.

Dosing & Target Times

- "Standard" target times
  - Most developed with manual ACT
  - Suggested due to high variability
  - No evidence for optimal ACT targets
- Drug defined targets
  - GPIIb/IIIa Inhibitors; Angiomax
  - Drug manufacturer defines ACT target
    - Does not specify ACT type
    - Ignores "off-label" indications

How to Compare ACTs?

- Clinical Correlation
  - In clinical setting to be used
    - Do not compare in CVOR to change in cath lab
  - Data MUST span current target times
  - Correlation coefficient
    - $R \geq 0.88$

CORRELATE DOES NOT MEAN MATCH

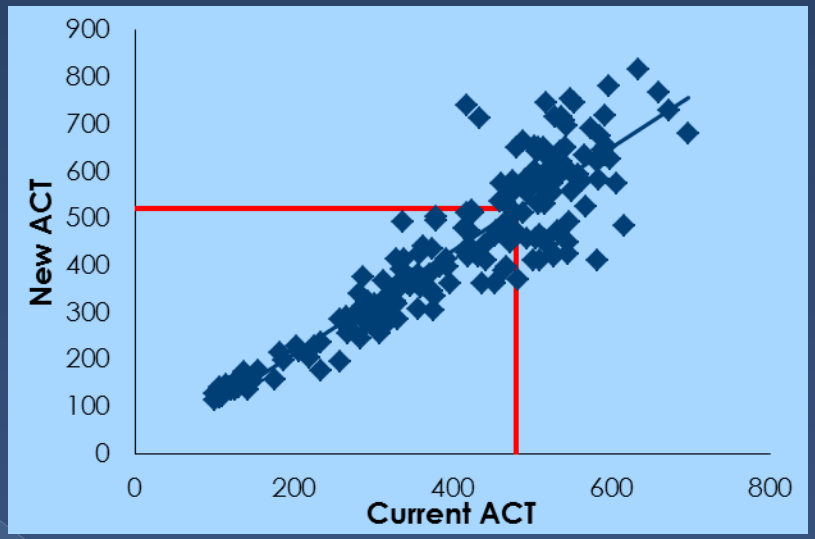
Clinical Comparison

- Data used to predict new target time
- Clinical agreement determined from predicted target time
  - Only method of value in ECMO, sheath pull
    - Range of values too small for correlation analysis

Evaluate Clinical Agreement

- CVOR example

Current	New	N	%
≥ 480	≥ 520	72	34%
≥ 480	< 520	19	9%
< 480	≥ 520	7	3%
<480	<520	117	54%



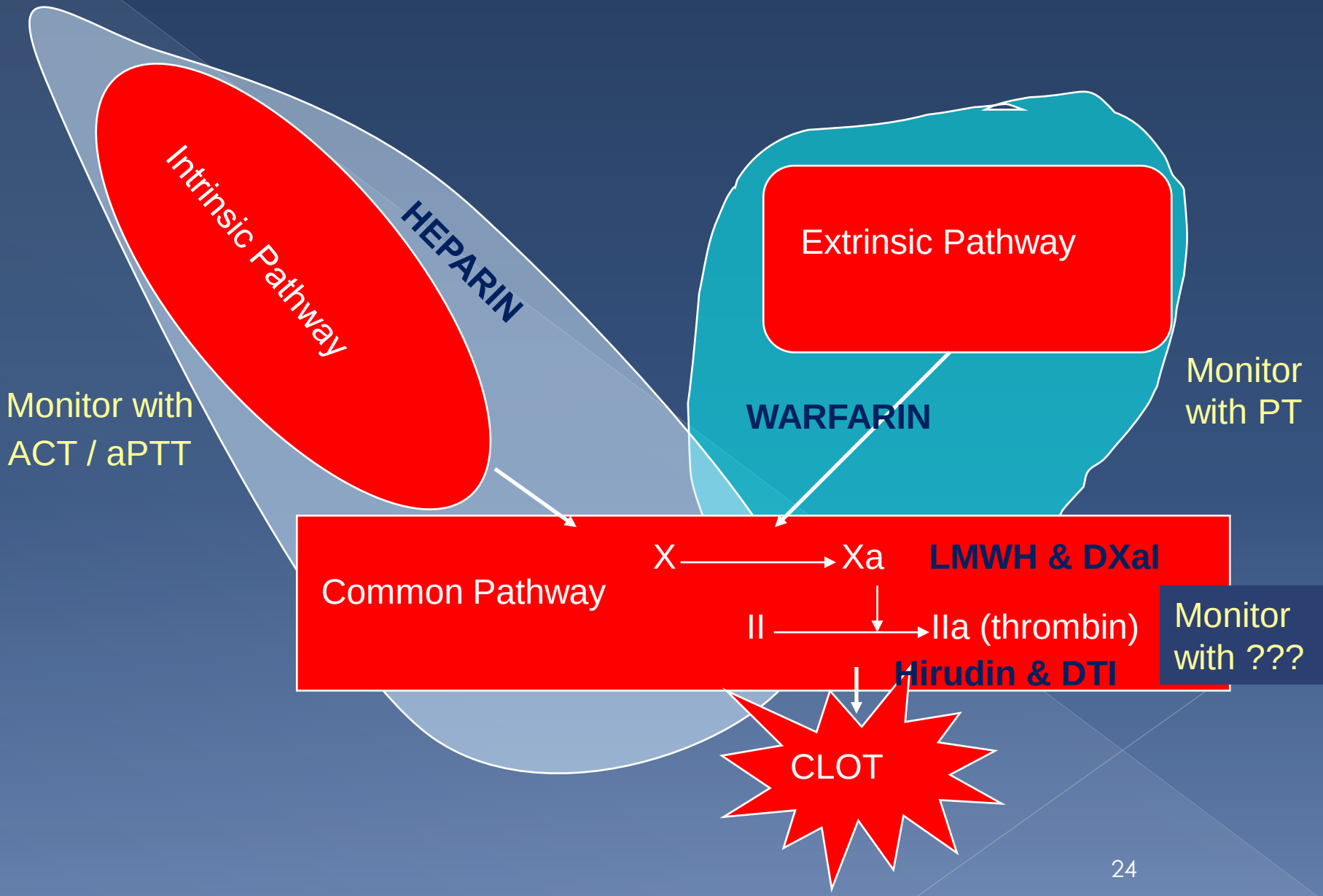
- 88% agreement
  - 21 of 26 discrepancies
    - Current value within 10% of 480
  - 5 of 26 discrepancies
    - New leads to additional heparin given

Help clinician overcome differences

- Source:
  - Reagent differences
  - Technology differences
  - No standardization

Alter target times to Maintain clinical protocols

Coagulation Testing



ACT versus aPTT

- ACT
  - Activated clotting time
  - POC Only
  - Low, moderate or high dose heparin
    - System dependent
- aPTT
  - Activated partial thromboplastin time
  - Laboratory or POC
  - Low dose heparin only
    - System dependent upper limit

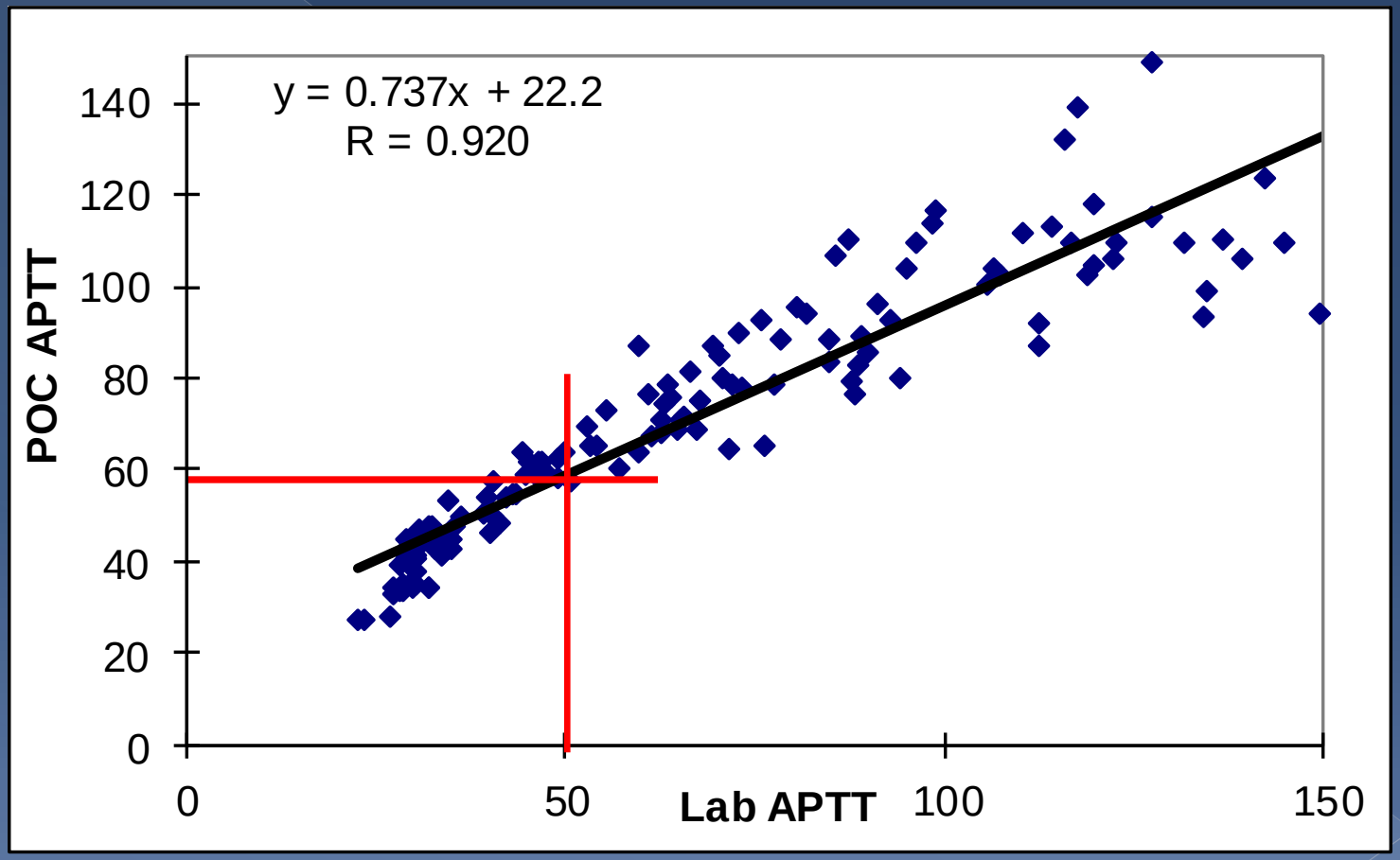
Where is an aPTT Used?

- Critical care
  - Heparin drip maintenance
- Unusual, but possible:
  - Interventional radiology
  - Electrophysiology
  - Vascular surgery
  - ECMO
- Any low dose heparin application

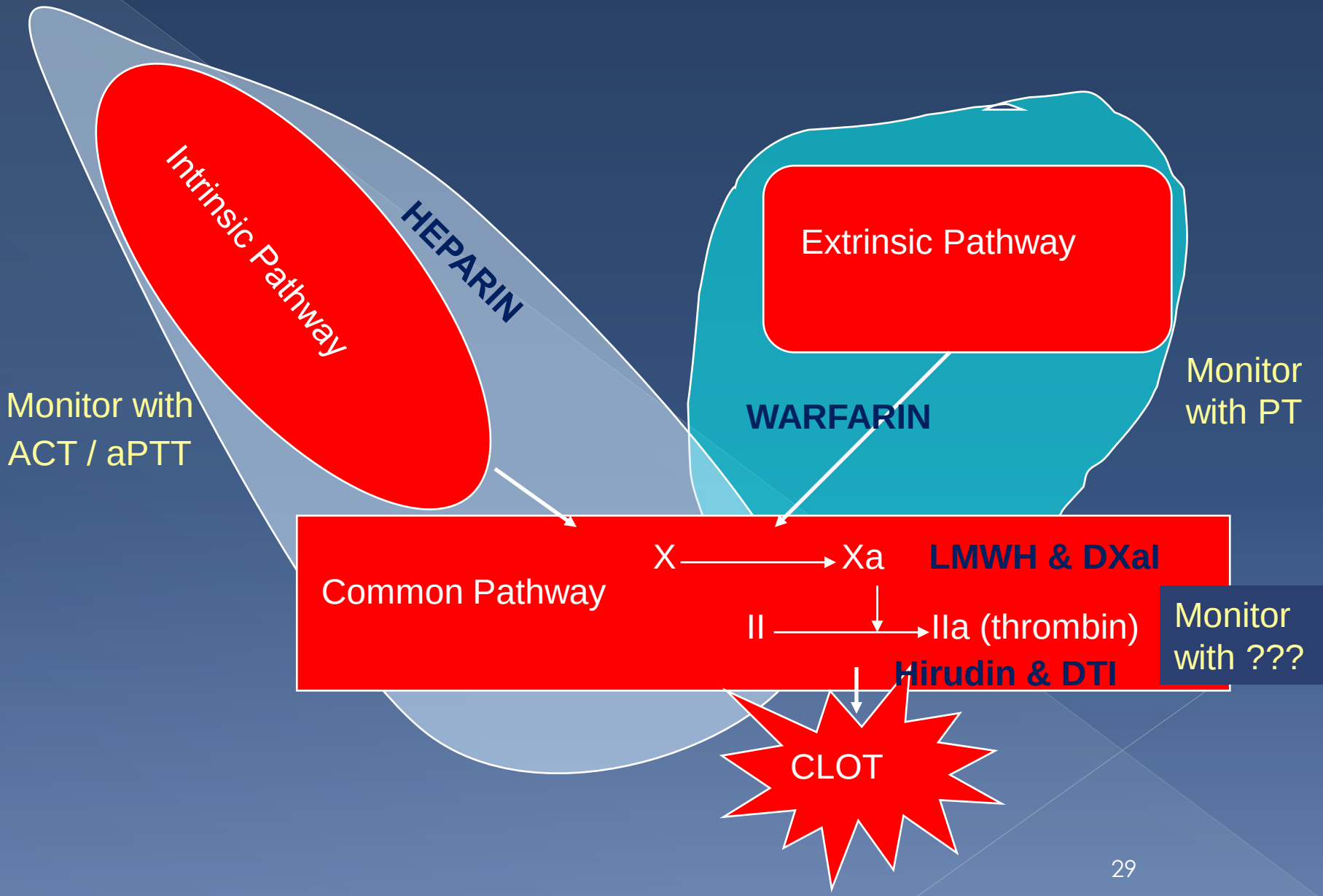
aPTT test methods

- Standard Laboratory
  - Platelet Poor Plasma
  - Sodium Citrate Anticoagulant
  - Dilution in testing
  - Variable Preanalytical Delay
  - Instruments
  - Reagents
- Point of Care
  - Whole Blood
  - No Added Anticoagulant
  - No Dilution
  - No Preanalytical Delay
  - Instruments
  - Reagents

Correlate Does Not Mean Match



Coagulation Testing

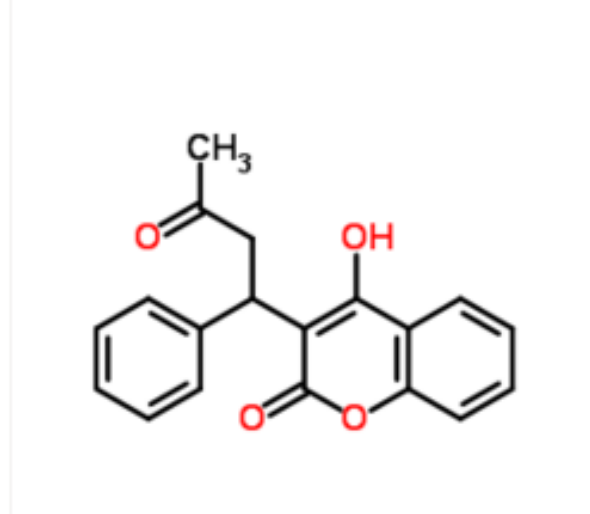


Heparin versus Warfarin

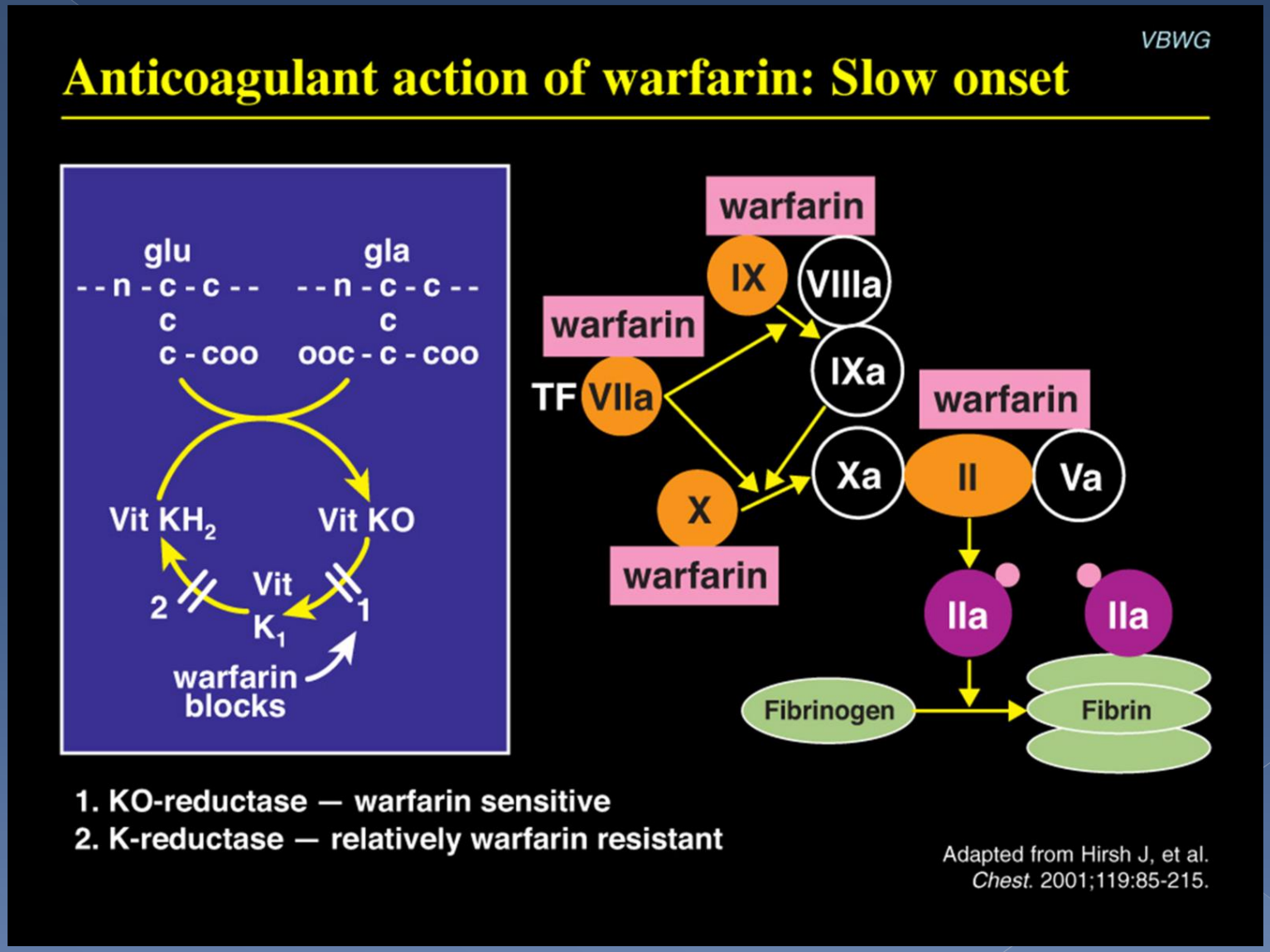
Drug	Mechanism of Action	Cofactor	Monitor	Effective
Heparin	Direct thrombin inhibition	Anti-thrombin	aPTT ACT	Immediate
Warfarin	Decrease factor production	Vitamin K	PT	3-5 day delay

What is Warfarin?

- Rat poison
- Cause of "sweet clover disease"
- Orally active anticoagulant



Warfarin Effects on Coagulation



Why Monitor Warfarin?

- Potency may vary by manufacturer
- Dose response varies by patient
  - Dietary interactions
  - Life-style influences
- Functions by decreasing production of Vitamin K dependent clotting factors in liver
  - Delayed onset of anticoagulation

How to monitor warfarin?

- Quick, et. al., 1937 – Prothrombin Time
  - Combine thromboplastin, calcium and patient plasma
    - Measures activity of factors I, II, V, VII, X
- 40 – 50 years pass
  - Thromboplastin isolated from:
    - Different species
      - pig; cow; human; etc.
    - Different organs
      - brain; thymus; lung; etc.
  - All yield different results
    - Results vary by instrument system in use
      - Manual tilt tube "gold standard"
      - Fibrometer; automated coagulation systems
  - PT ratios adopted to determine therapeutic range

INR

- 1983 – WHO and ISTH recommend the use of the INR to standardize PT result reporting
- International Normalized Ratio (INR)
  - ISI = international Sensitivity Index
  - INR target ranges are specified by patient populations, *e.g.*,
    - DVT, Afib, Atrial MHV: INR= 2.0 - 3.0
    - Mitral mechanical heart valve: INR= 2.5 – 3.5
    - Individual variation

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

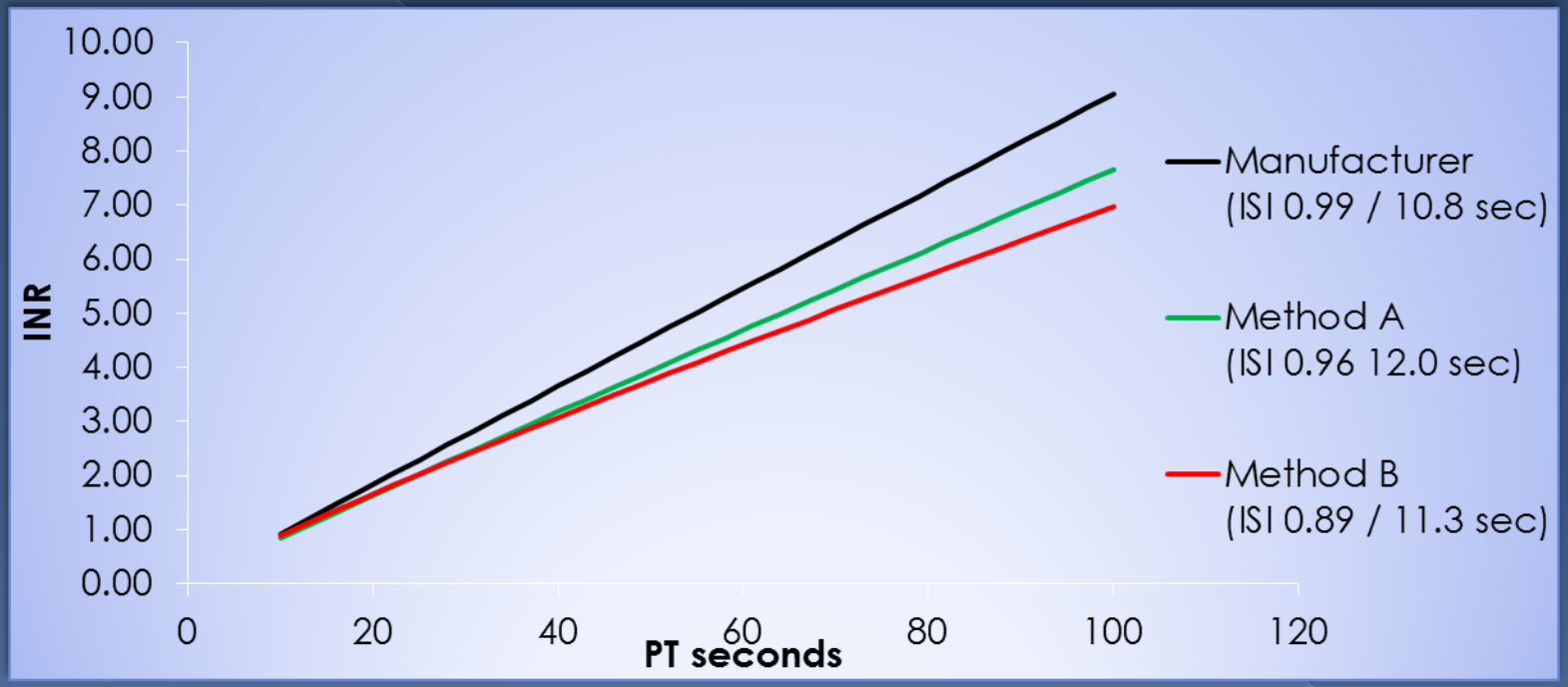
Key variables

- ISI
  - Initially determined by reagent manufacturer
  - Traceable to IRP
    - International Reference thromboplastin Preparation
  - WHO defined process
    - Calibration up to INR = 4.5
    - manual tilt tube method reference
  - Local calibrations can be performed to determine the instrument specific ISI[1]
- Mean normal PT
  - The mean normal PT should be determined for each new batch of thromboplastin with the same instrument used to assay the PT[1]

Antithrombotic therapy and prevention of thrombosis, 9th ed: ACCP guidelines. CHEST 2012; 141(2)(Suppl):e44S–e88S

Effect of Local Calibration

- Local calibration may introduce variability



  - Same sample yields different results depending on calibration method

ISI and MNPT from Poller et. al., J Thromb Haemost 2012; 10: 1379–84.

POC Calibration

- Manufacturer assigns ISI and mean normal PT (MNPT)
  - Lot specific
- Traceable to IRP
  - Often through secondary standard
- Cannot be changed by end user
  - Does not vary by location of testing

Will POC Results Match the Lab?

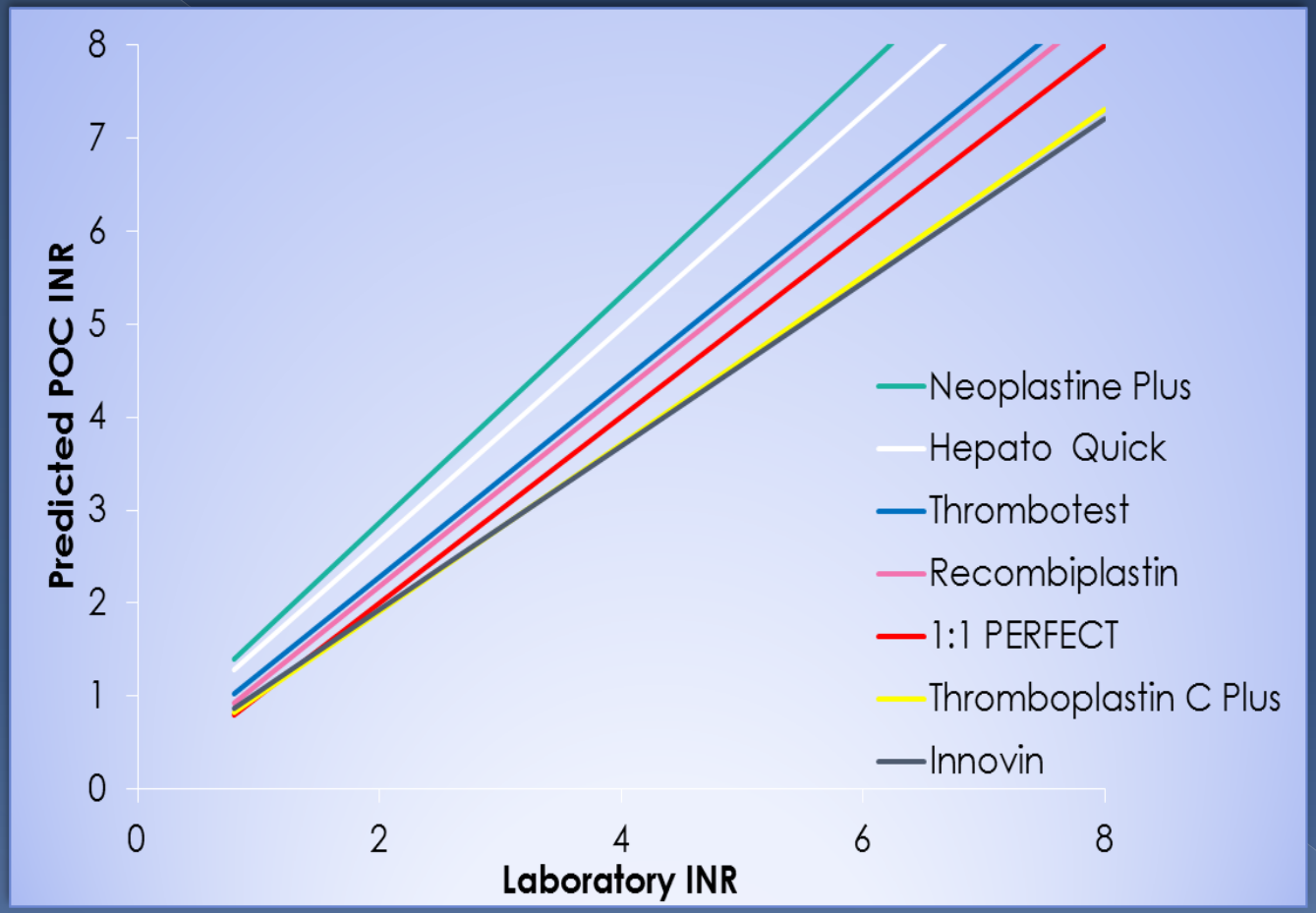
NOT Necessarily

but it WILL Correlate

Why not?

- Point of Care
  - Whole Blood
  - No Added Anticoagulant
  - No Dilution
  - No Preanalytical Delay
    - Reagent
    - Instrument
    - Clot detection
- Laboratory
  - Platelet Poor Plasma
  - Sodium Citrate Anticoagulant
  - 1:9 Dilution
  - Variable Preanalytical Delay

Correlation by lab system

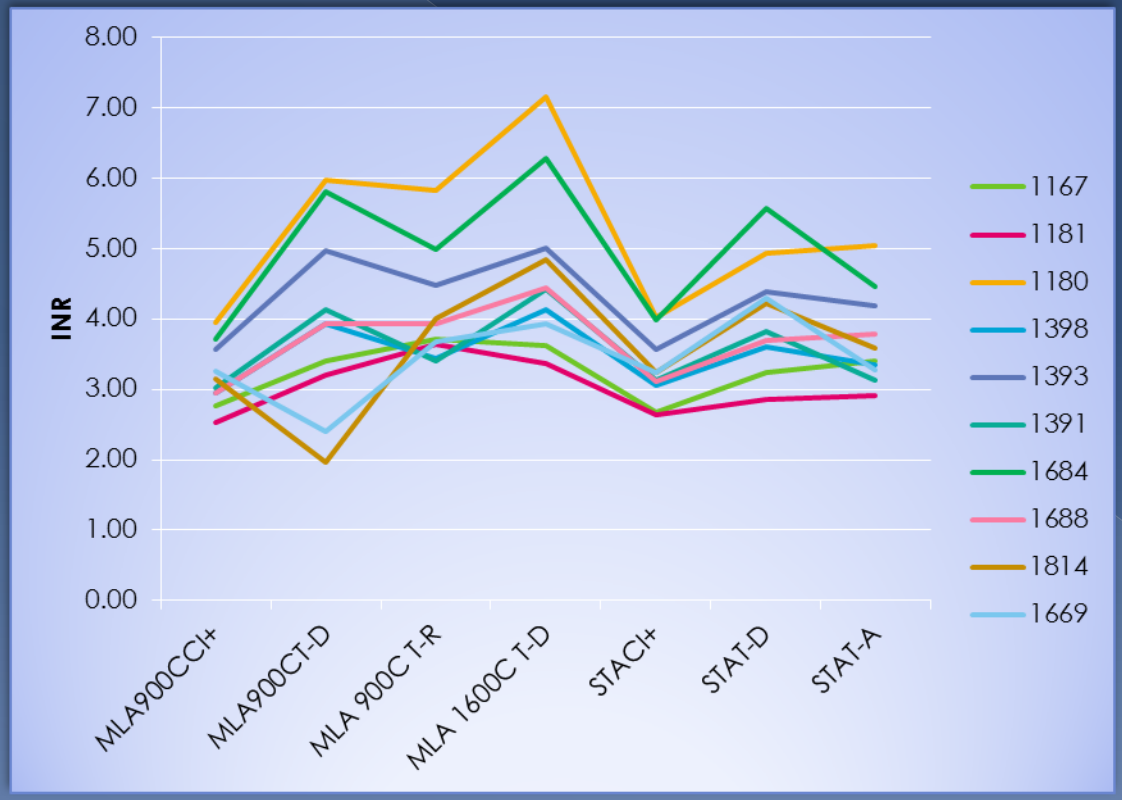


Correlation data from: Plesch et. al, Thromb Res 2008; 123:381–9

Thromboplastin	Analyzer	calibration	Thromboplastin	Analyzer	calibration
Innovin	CA1500	Local vs rTF/95	HepatoQuick	STA-R	Manufacturer
Recombiplastin	MLA1800	Local vs rTF/95	Thrombotest	KC10	Local vs OBT/79
Neoplastin Plus	STA-R	Manufacturer	Thromboplastin C Plus	CA1500	Manufacturer

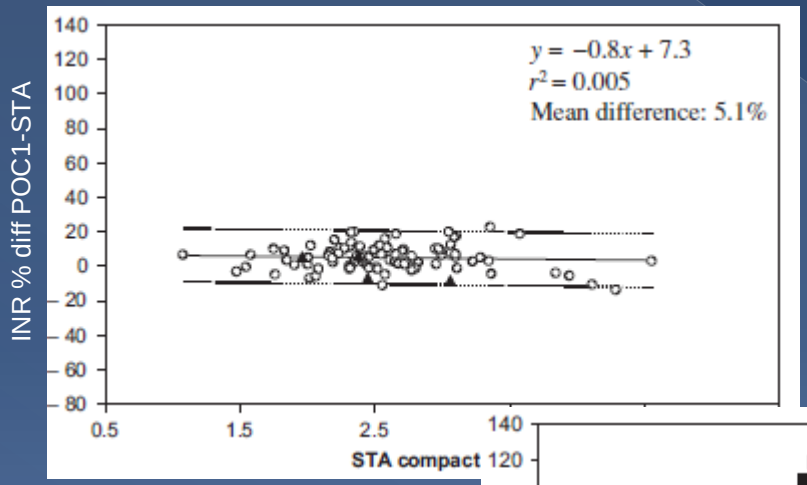
Expectations Lab to Lab

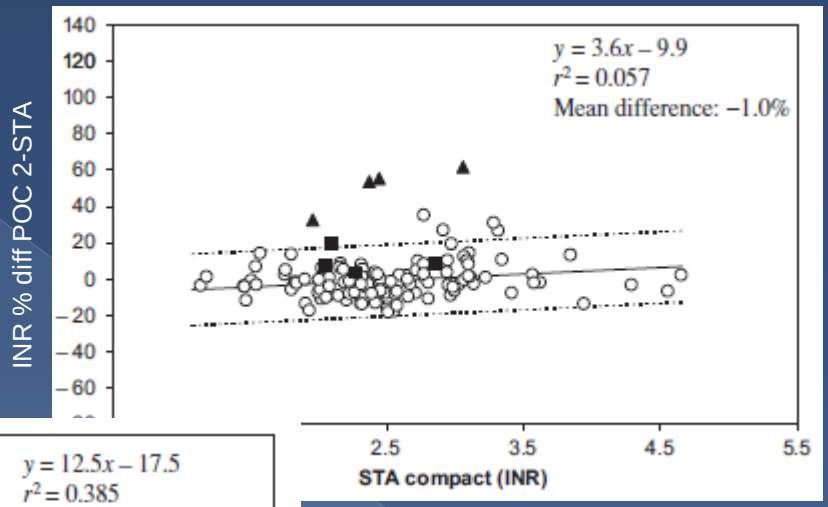
- 10 OAT patients across 7 analyzer/ reagent combinations
  - McGlasson, DL 2003: Lab Med 34: 124 – 9.

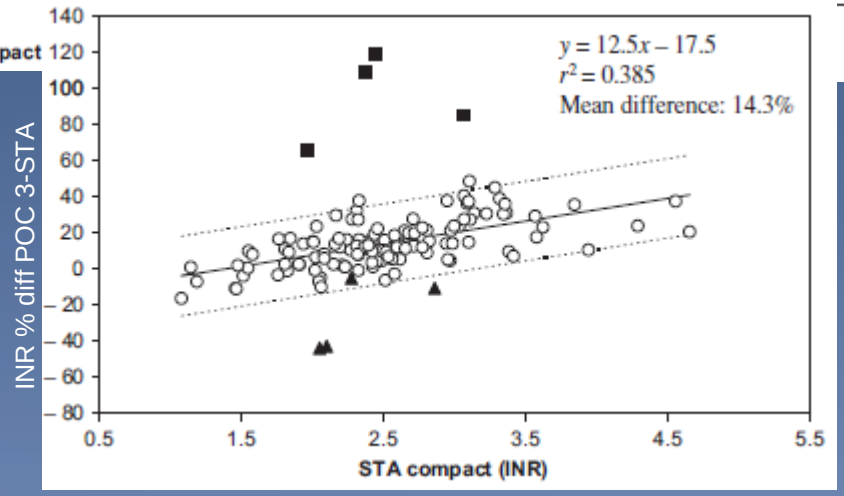


Expectations POC to lab

- 36 patients over 4 visits each
  - 3 POC; 1 lab
    - Solvik et. al., 2010: Clin Chem 56:1618–1626 (2010)







Variability of Lab INR

- Observed:
  - ± 0.4 at INR = 2.0
  - ± 0.8 at INR = 3.0
  - ± 1.2 at INR = 4.0
- Standardization as with glucose is unlikely
  - discrete analyte to be tested
  - versus a biologic process

Jacobson, J Thromb Thrombolysis (2008) 25:10–11

Patient Management

1. Understand limitations in the INR
   - Whenever a patient undergoes duplicate testing on different systems, there is the potential for disagreement
2. Attempt to have patients managed with a consistent methodology

Jacobson, J Thromb Thrombolysis (2008) 25:10–11

How to Compare INR Results

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

- Test Again?
- Test more often?

Why perform POC PT?

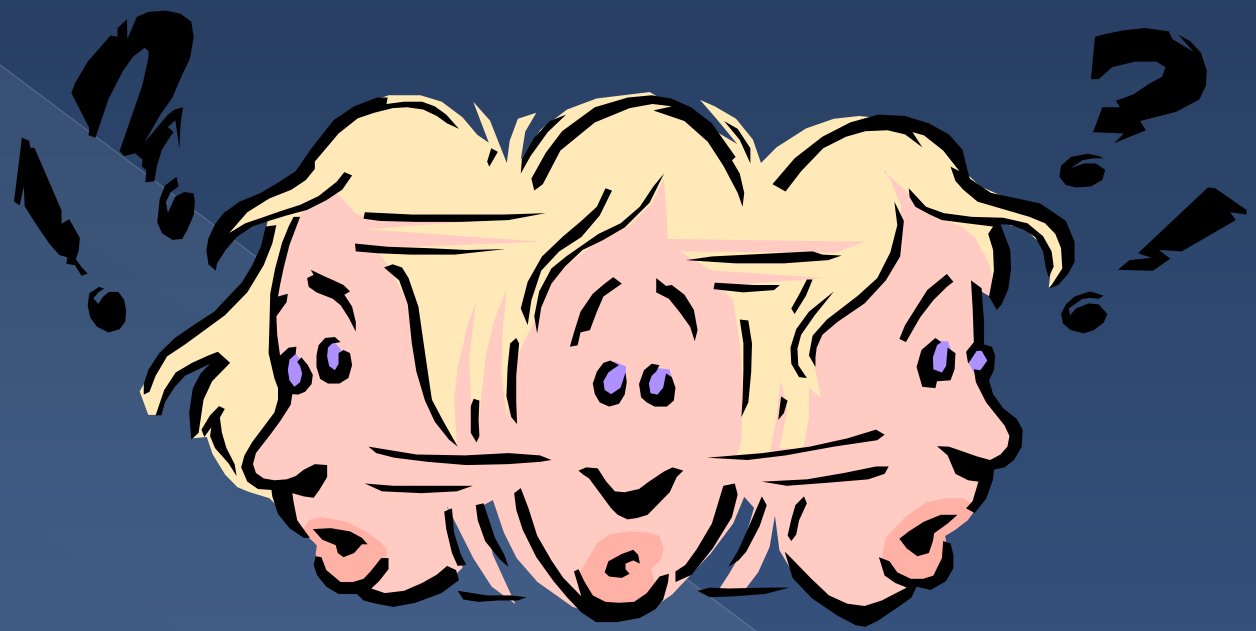
- Results Available While Patient is Present
  - Improved Anticoagulation Management
  - Improved Standard of Care
  - Staff Efficiency
- Immediate Retesting (if needed)
  - Fingerstick Sampling

LIMITATION!!!!!!!

- INR was developed to monitor effect of vitamin K antagonists (warfarin, others)
- INR is inappropriate scale for monitoring coagulopathies
- Most POC PT/INR tests cleared ONLY for monitoring patients receiving oral anticoagulation therapy such as Coumadin or warfarin.

POC Coagulation Testing

- Monitoring hemostasis



QUESTIONS?

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