Coagulation: The Ins and Outs

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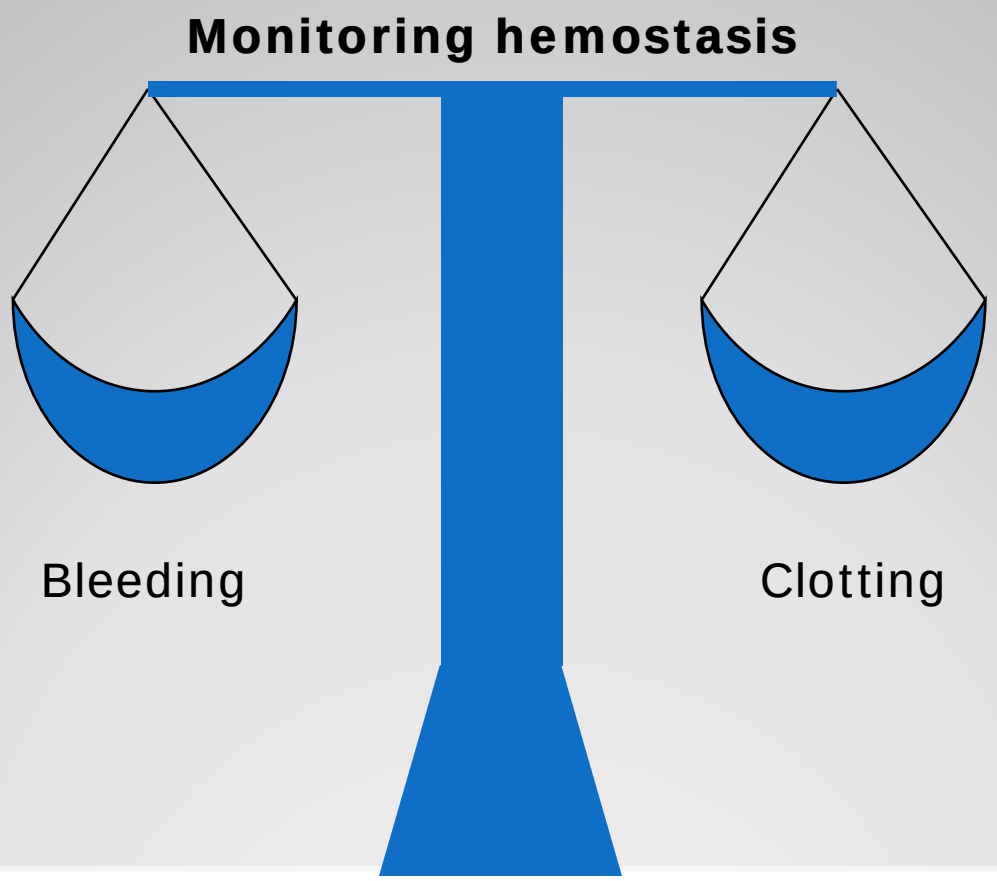
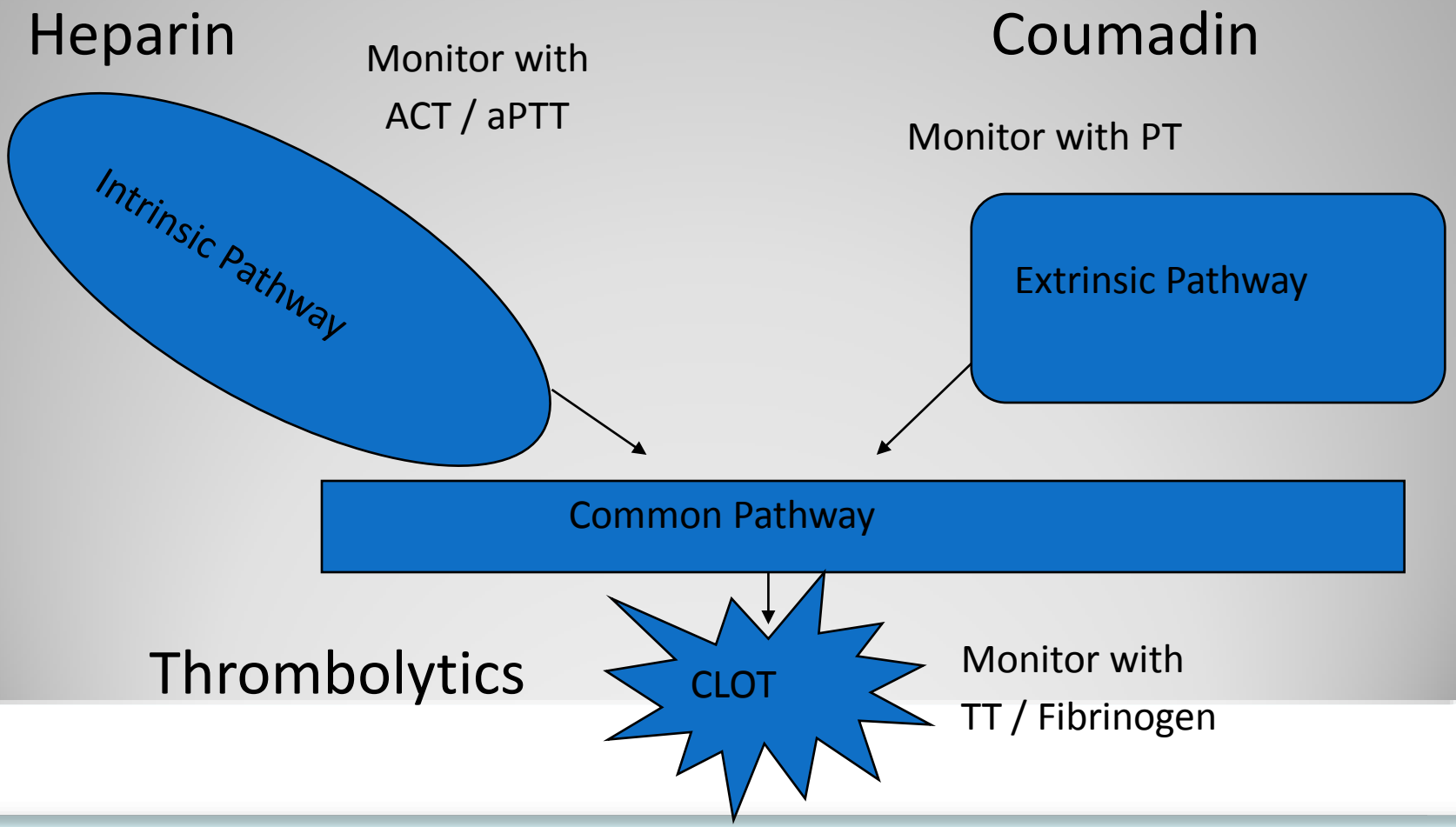
Coagulation Testing: What is it?



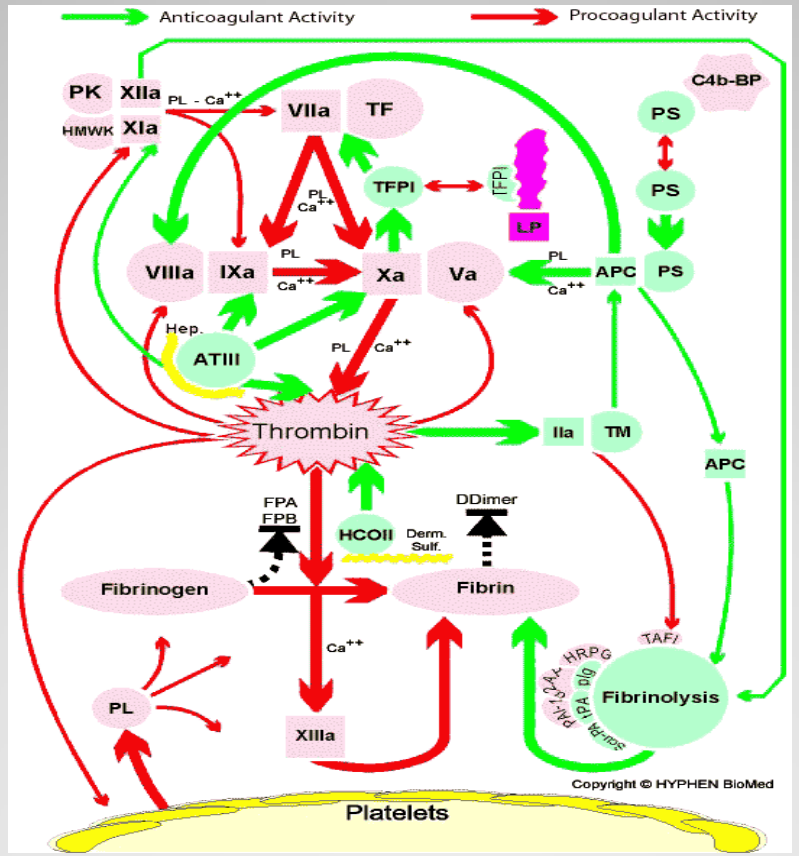
Coagulation Testing

- Monitoring therapy



Coagulation Testing is Complex

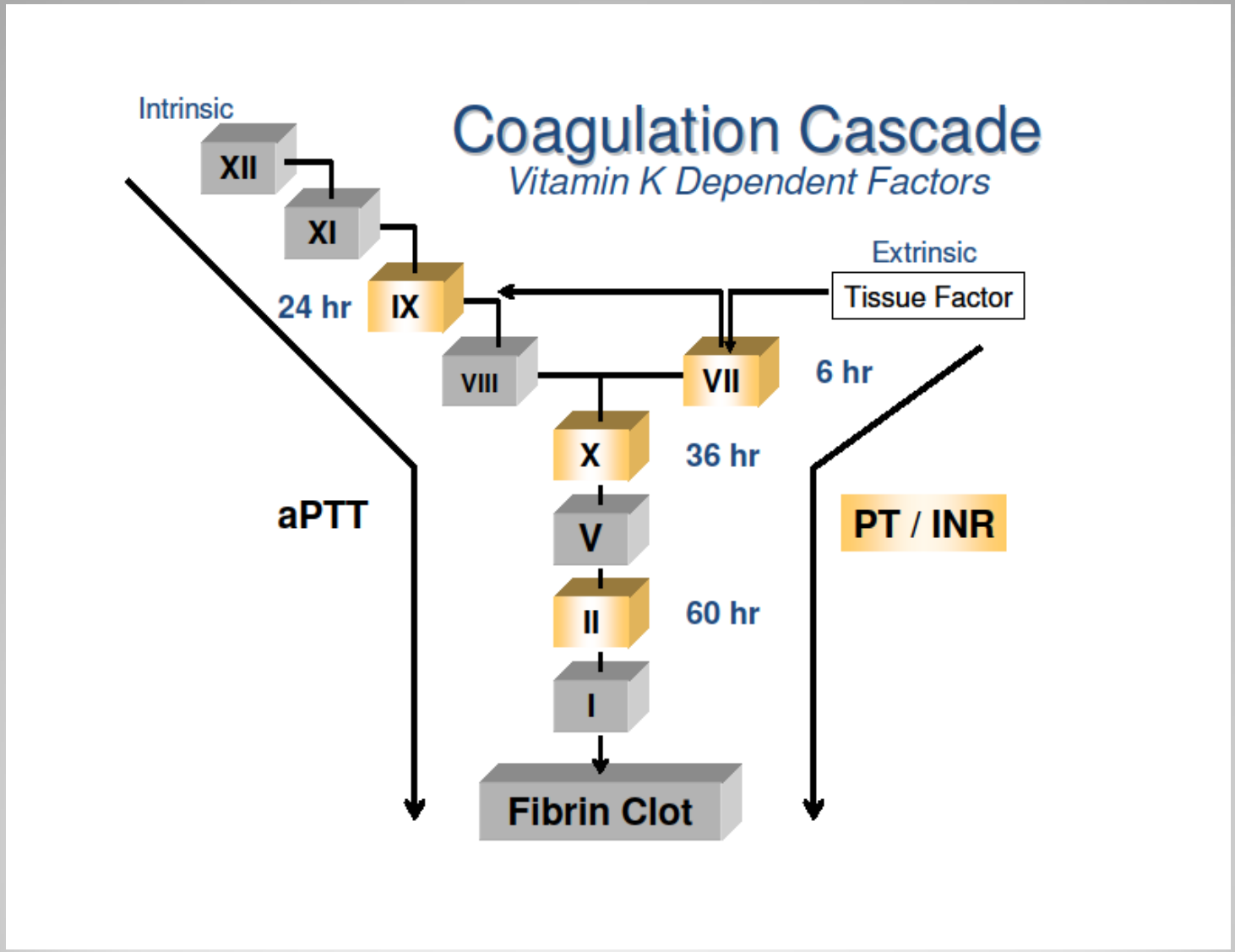
Platelets



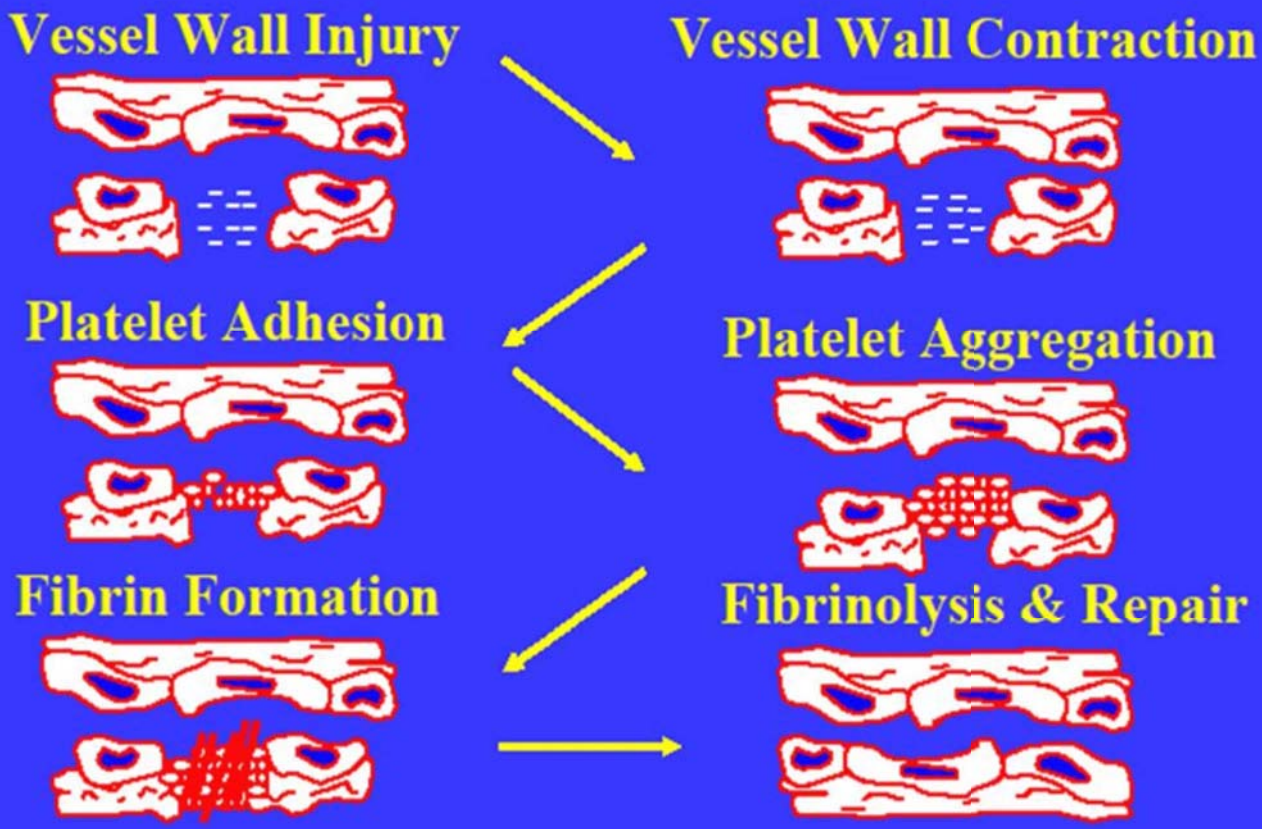
Factors

Pathways

Graphic from Diapharma.com


Coagulation Cascade
Vitamin K Dependent Factors
Intrinsic
XII
XI
24 hr
IX
VIII
Extrinsic
Tissue Factor
VII
6 hr
X
36 hr
V
II
60 hr
I
Fibrin Clot
aPTT
PT / INR

Clot Formation & Fibrinolysis



Coagulation Tests

PT/INR
aPTT
ACT (Celite, Kaolin)
TT
FIB
TEG

Lab:

- Anti Xa
- Anti IIa
- Factor Assays

Differences in Test Methods

LAB	Point of Care
Platelet Poor Plasma	Whole Blood
Sodium Citrate Anticoagulant	No Added Anticoagulant
1:9 Dilution	No Dilution
Variable Pre-analytical Delay	No Pre-analytical Delay

Reagent
Instrument
Clot detection methodology

Clinical Applications

Critical Care
- Emergency Department
- Interventional Radiology
- Cath Lab
- OR

Units
- NICU/PICU (ECMO)
- Cardiovascular ICU/Step Down Unit
- Dialysis

Outpatient Clinic/POL
- Coumadin Clinic

Coagulation Analyzers

- HEMOCHRON Response
- HEMOCHRON Jr. Signature / Signature +/Signature Elite
- ProTime
- Medtronic HMS/HMS+/ ACT II / ACT Plus
- CoaguChek XS Pro/XS
- i-STAT
- Helena Actalyke
- HemoSense INRatio
- TEG
- Others?

Choosing an Instrument

- CLIA licensure
  - Waived vs. Moderately complex
- Moderate complexity licensure
  - Any instrument can be used
  - Bells and whistles
    - OID
      - Operator lock-out
    - PID
    - QC lock-out
    - Connectivity

How Do Analyzers Differ?

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

Clinical Awareness

Starts at the onset of POC request and continues as an on-going process.

Onset Education?

Continuing Education through life of POC testing?

Have the processes impacted been indentified?

Have the processes impacted change to include POC testing?

Have all personnel involved been identified? (physicians, nurses, technicians, unit clerks, RT, lab)

The Joint Commission-NPSG

National Patient Safety Goal (Anticoagulation)*

Hospital
Ambulatory
Home health
Long Term Care
Critical Access Hospital

*** 2008: 1 year phase in, 2009: Full implementation**

TJC's: National Patient Goals 3E & Anticoagulation (AC)

- Goal: HCP are to reduce the likelihood of patient harm
- Purpose: Standardize prescribing practice
  - Reduce the risk of adverse drug events
  - Systematic & sustainable approach to AC management
- ASHP[1] 2015 Health System Initiatives
  - Increase pharmacist involvement
  - Decrease high-risk medications

HCP:health care providers
TJC: www.thejointcommission.org

American Society of Health System Pharmacy – ASHP 2015 Initiative. http://www.ashp.org/s_ashp/cat1c.asp?

ACT

- Maintain Balance
  - Bleeding  Thrombosis
- Heparin
  - Rapid anticoagulant effect
    - Individual sensitivities vary significantly
    - Potency differences
      - Source: Bovine or Porcine
      - Lot to Lot variability
  - Rapidly Reversible with Protamine

AACC Clinical Lab News-Dec 09

New Heparin Standards

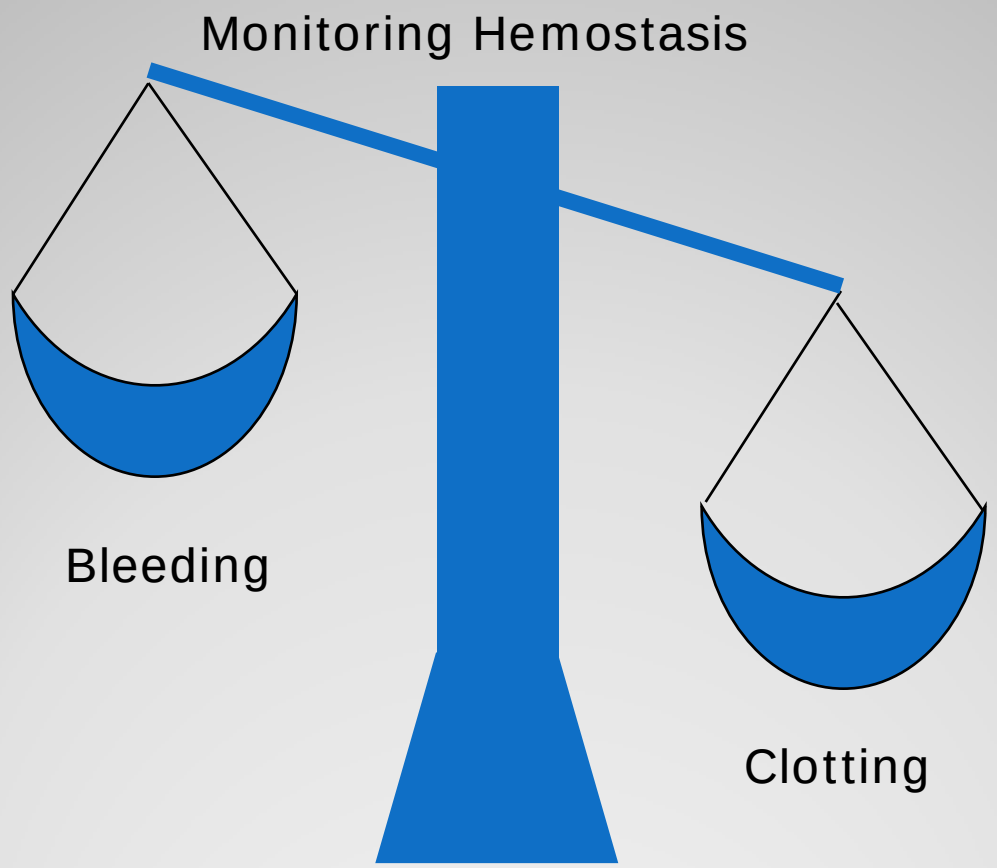
Will the Change Make a Discernable Difference in Coagulation Monitoring?

A recent update to the U.S. Pharmacopeia heparin monograph has added another potential confounding factor in dosing and monitoring, leaving coagulation experts wondering about the ultimate impact of the change. The update, which became effective October 1, 2009, resulted in an approximate *10% reduction in heparin potency in the U.S*. and brought U.S. and international units of unfractionated heparin in line with each other.

As lots of the new heparin formulation make their way into hospitals across the country, laboratorians should be on the front lines of developing communication and monitoring plans with their pharmacist and physician colleagues, according to Dr. Paula Santrach. “You have to talk about it so everyone is aware and there’s a plan”.

http://www.aacc.org/publications/cln/2009/December/Pages/CoverStory1Dec09.aspx

ACT- Surgical Impact on Coagulation



Traditional Activated Clotting Time

- Whole blood test, performed at patient site
- Monitor anticoagulant heparin given during:
  - Cath Lab (PTCA)
  - CVOR (CABG)
  - Renal dialysis
- Results available in minutes
- General assessment of “delay” in normal clotting

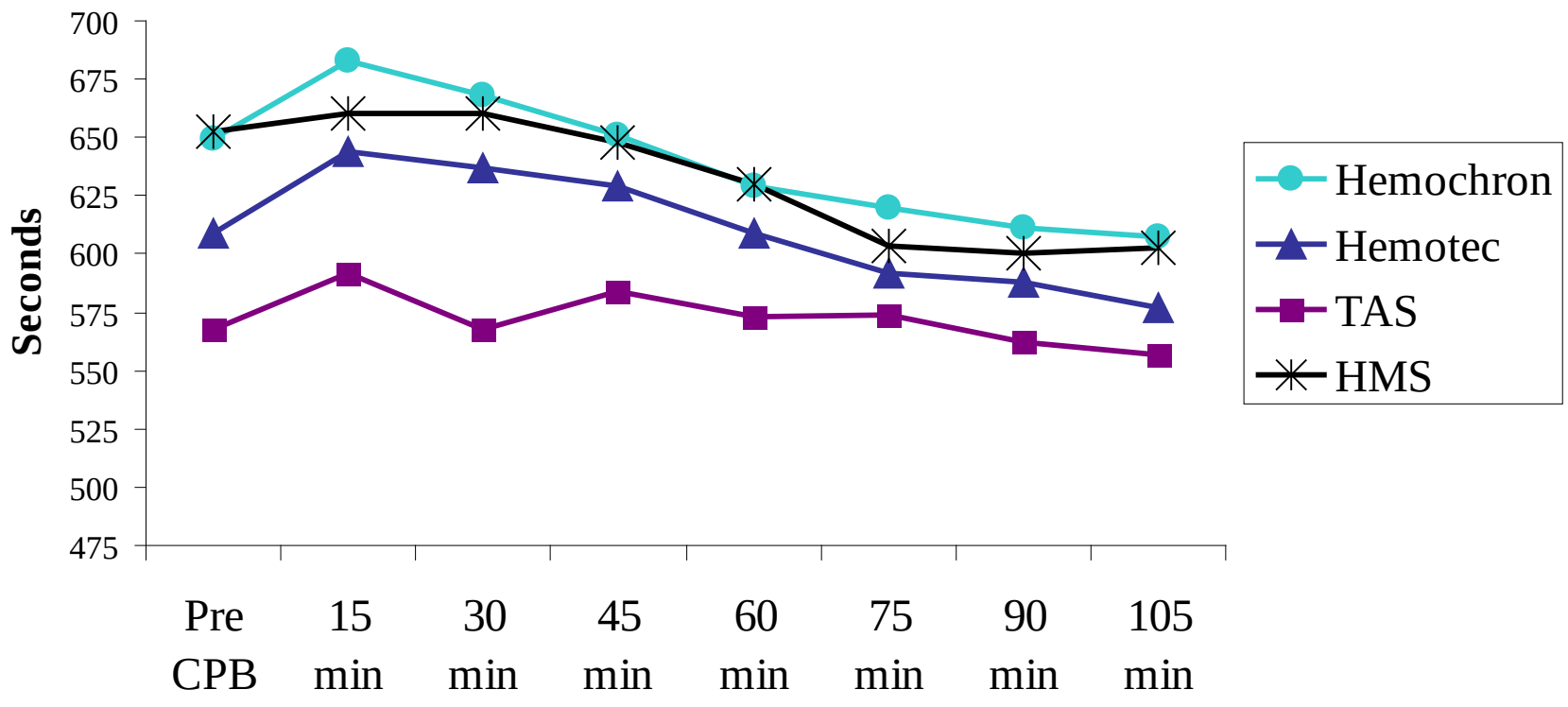
ACT Monitoring

- Benefits
  - Industry Standard Since 1970s
  - 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

ACT History

- Shortly after ACT discovery, CPB was growing
- Brian Bull, MD
  - Cardiac anesthesiologist read article on ACT
  - Thought would help the largest CPB problem
    - Heparin therapy guidance
  - Performed many studies
    - 480 target time study
    - Used 2 point dosing curve and physical oxygenator (for clots) evaluation
    - Did ENTIRE study with handheld ACT test

Heparinized ACT-CPB



Data from Huffman, et.al. 1998 AmSECT meeting

ACT-Troubleshooting

- Relies on physical blood clot to turn off instrument
  - Affected by hemodilution
  - Affected variably by platelet dysfunction
  - Affected by fibrinogen
- ACT tests have traditionally had marginal reliability due to operator variances

So what do we do?

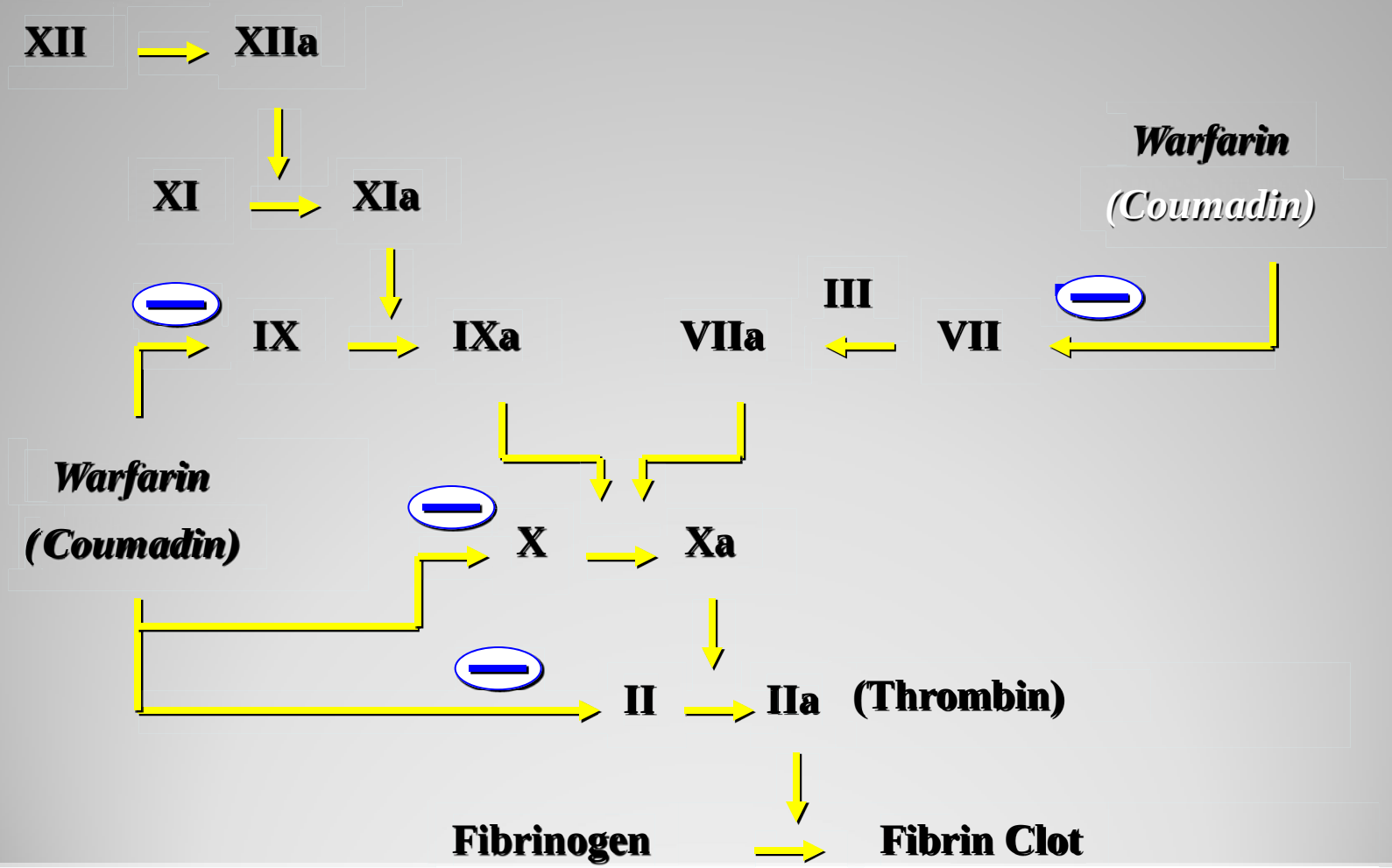
✓ Ensure good technique in collection and application.

✓ Repeat at the POC and use lab when needed.

Heparin versus Warfarin

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

PT/INR


XII
XIIa
XI
XIa
Warfarin
(Coumadin)
IX
IXa
VIIa
III
VII
Warfarin
(Coumadin)
X
Xa
II
IIa
(Thrombin)
Fibrinogen
Fibrin Clot

PT/INR

- Monitor warfarin therapy
- Monitor heparin (LMWH)/warfarin crossover. (Be careful of the sensitive tests)
- Target times are set by

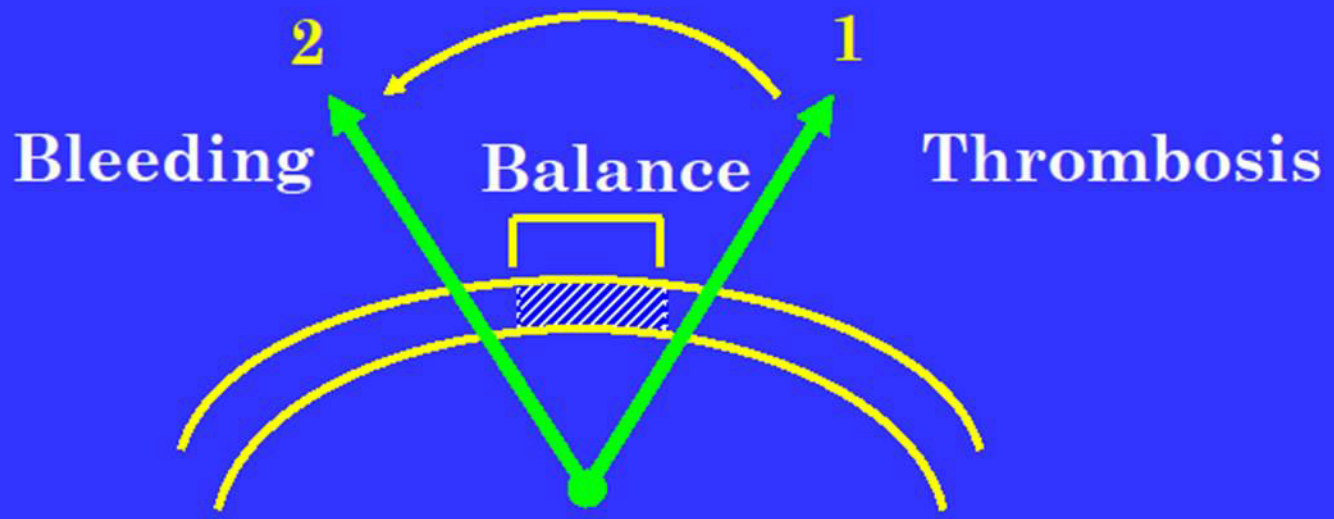
  International Normalized Ratio (INR)

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

  ISI = international Sensitivity Index

- INR target ranges are specified by patient populations
  - DVT, Afib, Atrial MHV: INR= 2.0 - 3.0
  - Mitral mechanical heart valve: INR= 2.5 – 3.5

Too Much Anticoagulation in a Thrombotic Patient



PT/INR- Coumadin Clinic

- Results Available While Patient is Present
  - Improved Anticoagulation Management
  - Improved Standard of Care
  - Staff Efficiency
- Immediate Retesting (if needed)
  - Fingerstick Sampling
- Same System for Clinic and Home Bound Patients
  - Standardized ISI / PT normal
    - Test System Specific

PT/INR- Patient Self Testing

Approximately 3-4 million patients on warfarin therapy in the US.

Indications are for warfarin therapy for approximately 7 million patients.

Why would a provider not put a patient on warfarin?

Complications of therapy and monitoring INR!

3 types of care:

- Usual medical care (UMC)
- Coumadin Clinic
- Patient Self testing (PST) (approximately 70K PST in the US)

CHALLENGE: Multiple sources of INR involved in patient management.

Optimal Management

- 4.1.1. For health-care providers who manage oral anticoagulation therapy, we recommend that they do so in a systematic and coordinated fashion, incorporating patient education, systematic INR testing, tracking, follow-up, and good patient communication of results and dosing decisions as occurs in an anticoagulation management service (AMS) [Grade 1B].

Chest 2008;133:160s-198s

PT/INR-Patient Self Testing

Barriers to Patient Self-Testing

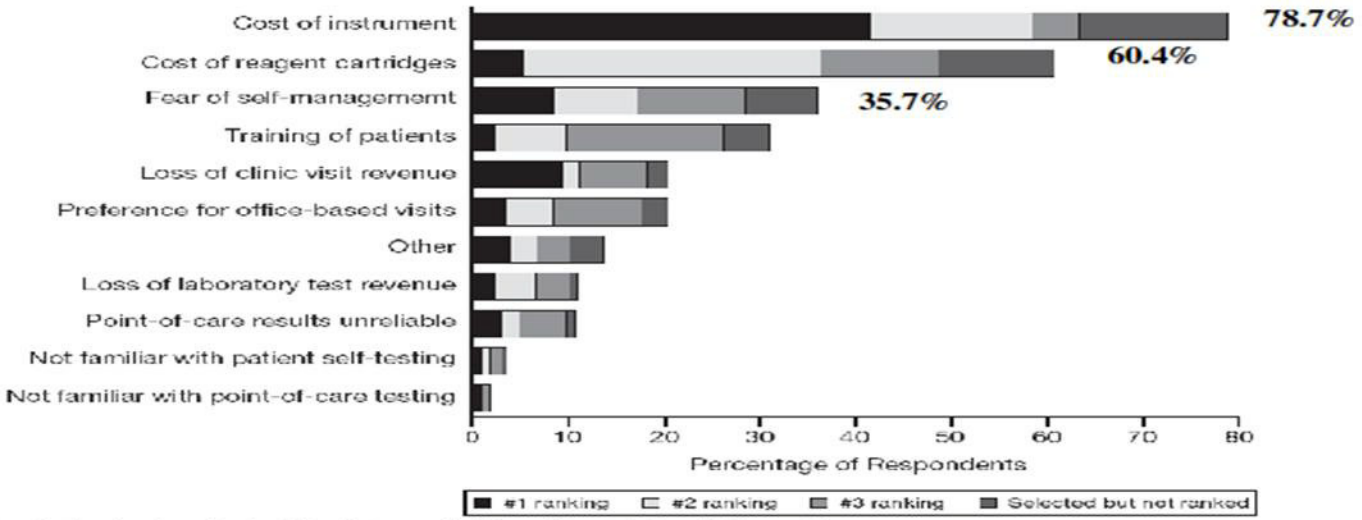


Figure 1. Barriers to patient self-testing as ranked by anticoagulation clinic providers.

Pharmacotherapy 2005;25:265-269

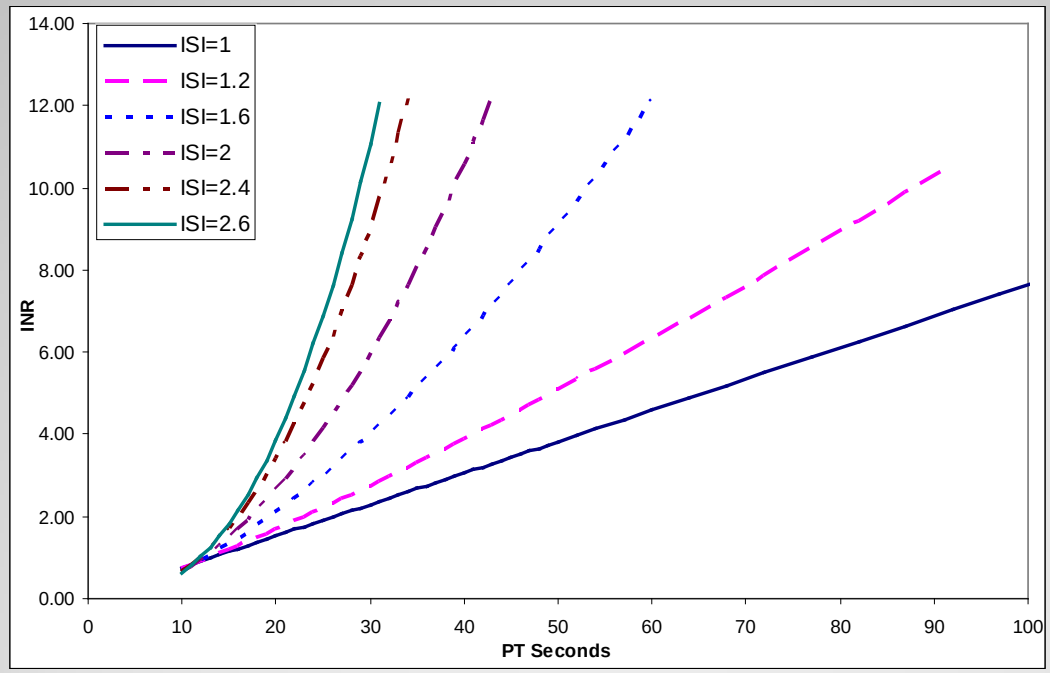
PT/INR

Will POC Results Match the Lab?

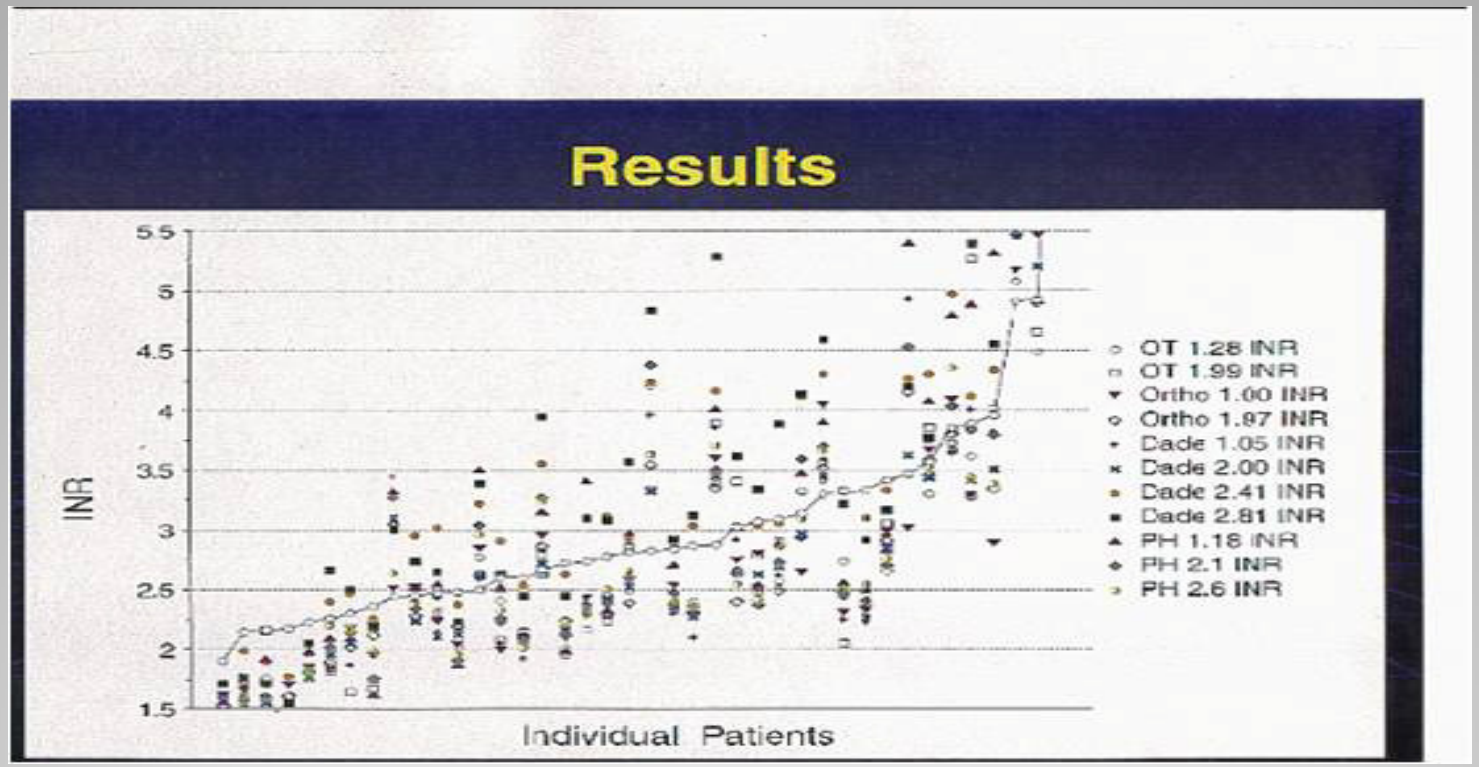
(Probably Not-Hopefully they WILL correlate)

PT/INR Troubleshooting

Effects of ISI on INR



Variability of INR across Multiple Lab Systems



INR Expectations

INR within 0.4 of lab $\geq$ 80%

INR within 0.7 of lab $\geq$ 90%

INR within 1.0 of lab $\geq$ 95%

Reference: Jacobson et al, 2001

How to Compare INR Results

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

- Test Again?
- Test more often?

Other POC Coag in the OR

- aPTT / PT
  - Pre- and post-procedural screening
- Fibrinogen
  - Pre- and post-procedural screening
- Dosing Assays
  - Customize heparin and protamine for each patient

Procedure

CLSI format?

Available to all personnel 24/7?

Contain all limitations?

Pertinent to all departments? Tests?

Current to Operator's Manual? package insert?

Signed off/reviewed by all required personnel? (multi-departmental)

Quality Control Requirements

Verification of Performance Specifications

CLIA
- 493.1253

CAP
- GEN.42020
- POC.04525
- GEN.42085

TJC
- QC.1.70

COLA
- VER1, VER2, VER3, VER4

Verify the manufacturer's analytical claims before patient testing. Perform for all analytes on all handhelds.

Quality Control Requirements

42 CFR 493.1253

Each laboratory that introduces an unmodified, FDA-cleared or approved test system must do the Following before reporting patient test results:
(i) Demonstrate that it can obtain performance specifications comparable to those established by the manufacturer for the following performance characteristics:
(A) Accuracy.
(B) Precision.
(C) Reportable range of test results for the test system.

GEN.42020

Has the laboratory verified or established and documented analytic accuracy and precision for each test?

NOTE: Where current technology permits, accuracy is established by comparing results to a definitive or reference method, or may be verified by comparing results to an established comparative method. Use of reference materials or other materials with known concentrations or activities is suggested in establishing or verifying accuracy. Precision is established by repeat measurement of samples At varying concentrations or activities within-run and between-run over a period of time.

Quality Control Requirements

Comparison of Test Results

CLIA
- 493.1281

CAP
- POC.07568
- CHM.13800

TJC
- QC.1.80

COLA
- QA12

Understand the relationship between results produced by each test system method and verify that this relationship does not change over time.

Quality Control Requirements

493.1281 Standard: Comparison of test results.

(a) If a laboratory performs the same test using different methodologies or instruments, or performs the same test at multiple testing sites, the Laboratory must have a system that twice a year evaluates and defines the relationship between test results using the different methodologies, instruments, or testing sites.
(b) The laboratory must have a system to identify and assess patient test results that appear inconsistent with the following relevant criteria, When available:
(1) Patient age.
(2) Sex.
(3) Diagnosis or pertinent clinical data.
(4) Distribution of patient test results.
(5) Relationship with other test parameters.
(c) The laboratory must document all test result comparison activities.

POC.07568

For quantitative tests, if the laboratory/POCT program uses more than one instrument to test for a given analyte, are the instruments checked against each other at least twice a year for correlation of patient results?

NOTE: This includes the same or different instrument makes/models.

Quality Control Requirements

Equivalent Quality Control Study

CLIA
- 493.1256

CAP
- POC.07300

TJC
- QC.1.77
- QC.6.20

COLA
- QC 24

Optional study to validate the adequacy of limiting daily QC to the electronic/built in controls.

Quality Control Requirements

493.1256 Standard: Control procedures.

(a) For each test system, the laboratory is responsible for having control procedures that monitor the accuracy and precision of the complete analytic process.

(b) The laboratory must establish the number, type, and frequency of testing control materials using, if applicable, the performance specifications verified or established by the laboratory as specified in § 493.1253(b)(3).

(c) The control procedures must—

(1) Detect immediate errors that occur due to test system failure, adverse environmental conditions, and operator performance.

(2) Monitor over time the accuracy and precision of test Performance that may be influenced by changes in test system performance and environmental conditions, and variance in operator performance.

POC.07300

Are controls run daily for quantitative and qualitative tests?

NOTE: For quantitative tests, 2 controls at 2 different concentrations must be run daily, except for coagulation. **For coagulation tests, 2 levels of control must be run every 8 hours.**

Daily controls may be limited to electronic/procedural/internal controls for test systems that meet all of the following criteria:

- *The system is FDA-cleared or approved*
- *The system is classified as waived or moderately complex under CLIA-88*
- *The POCT program has performed and documented studies to validate the adequacy of limiting daily QC to the internal controls*
- *External controls are run for each new lot number or shipment of test materials*

Quality Control Requirements

Liquid Quality Control

CLIA
- 493.1256

CAP
- POC.07300

TJC
- QC.187

COLA
- QC 14

Intended to monitor the complete analytical process.

Quality Control Requirements

Calibration Verification

CLIA
- 493.1255

CAP
- POC.08300
- POC.08450
- POC.08500 (AMR)

TJC
- QC.1.75

COLA
- CA2
- CA5
- CA6

Confirm that calibration setting continues to provide accurate results over the reportable range of the test system.

Quality Control Requirements

§ 493.1255 Standard: Calibration and calibration verification procedures.

Calibration and calibration verification procedures are required to substantiate the continued accuracy of the test system throughout the laboratory's reportable range of test Results for the test system.

CAP.08300

Are criteria established for calibration Verification, and is compliance documented?

CAP.08450

Are upper and lower limits of the ANALYTICAL MEASUREMENT RANGE (AMR) for all analytes defined, so that results falling outside these limits are appropriately reviewed and reassayed if necessary before reporting?

CAP.08500

Is validation of the analytic measurement range (AMR) performed with matrix-appropriate materials of known analyte value appropriate to the AMR of the instrument, and is the process documented?

Quality Control Requirements

New or replacement devices

CLIA
- 493.1253

CAP
- GEN.042020

TJC
- QC.1.70

COLA
- VER1, VER2, VER3, VER4

Verify accuracy, precision, reportable range (AMR for CAP), reference range for each analyte to be tested on each device.

Quality Control Requirements

New Lot of Controls

CLIA
- 493.1256

CAP
- POC.07456

TJC
- QC.6.30
- QC.6.50

COLA
- QC5

Establish or verify the criteria for acceptability of all control materials; determine if the stated limits of control materials can be used.

Quality Control Requirements

POC.07456

Are tolerance limits defined for control procedures?

NOTE: The POCT program must verify the tolerance limits for control materials that have numeric limits established by the manufacturer. For unassayed control materials, a valid acceptable range must be established by repetitive analysis in runs that include previously tested control material.

Quality Control Requirements

New Lot of Reagents / Strips / Cartridges / Cuvettes / Disposables

CLIA
- 493.1255
- 493.1256
- 493.1267

CAP
- POC.08300
- POC.08450
- POC.08500
- POC.07300

TJC
- QC.1.75
- QC.1.77

COLA
- QC14
- QC15

Quality Control Requirements

Proficiency Testing (PT)

CLIA
- 493.801

CAP
- POC.03250

TJC
- QC.1.40

COLA
- PT5

493.801 Condition: Enrollment and testing of samples.

Each laboratory must enroll in a proficiency testing (PT) program that meets the criteria in subpart I of this part and is approved by HHS. The laboratory must enroll in an approved program or programs for each of the specialties and subspecialties for which it seeks certification. The laboratory must test the samples in the same manner as patients' specimens.

Training

- ✓ Knowledge Based Competency
- ✓ Observation Checklist

Who does your training?

Do you use your feedback processes (QC, errors, etc) to modify your Competency and Checklist regularly?

Questions?

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Thanks!