

# The 123's of ACT

Marcia L. Zucker, Ph.D.  
ZIVD LLC

# Objectives

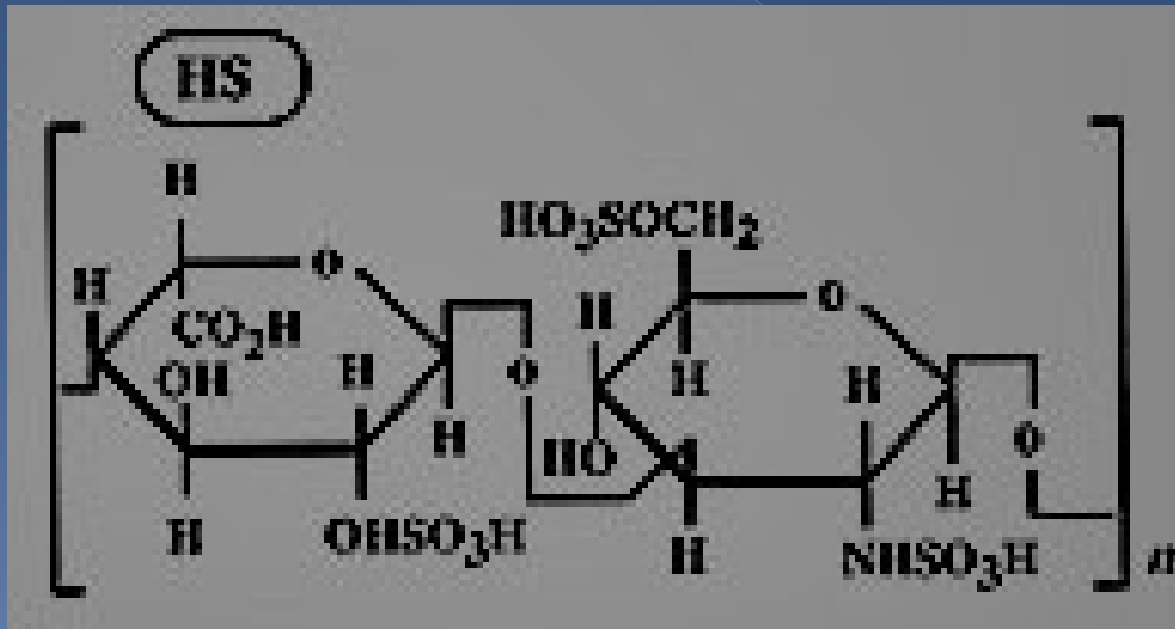
- Explain why ACTs from different systems are not the same
- Develop a plan for switching from one ACT system to another
- Describe why ACT and aPTT are not interchangeable

# What is an ACT?

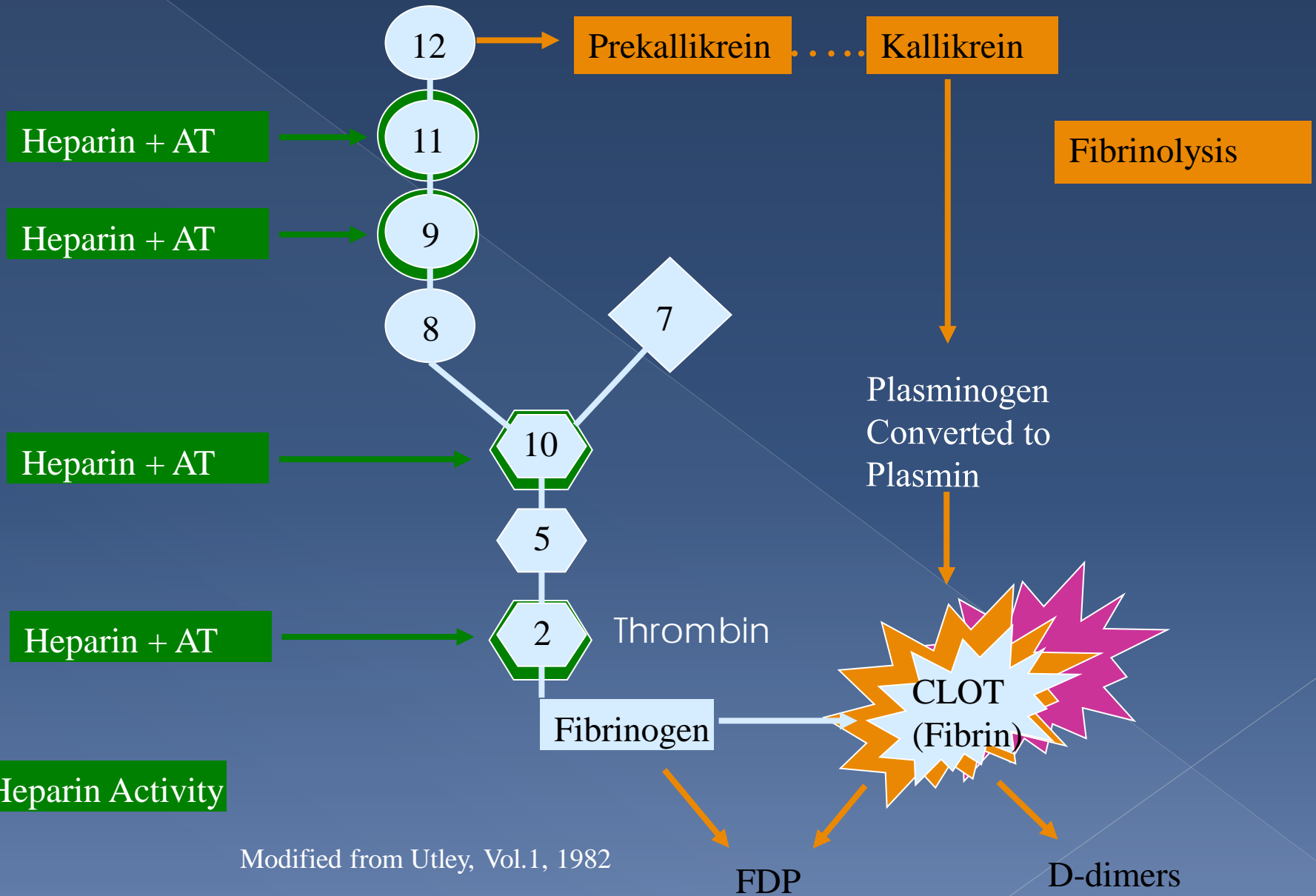
- ◉ Modified Lee-White clotting time
  - Add blood to glass tube, shake
    - Place in heat block
    - Visual clot detection
- ◉ First described in 1966 by Hattersley
  - > Activated Clotting Time
    - Add blood to glass tube with dirt, shake
      - Diatomaceous earth activator
      - Place in heat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

# 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



# 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

# Why Use an ACT?

- Monitoring hemostasis for heparin anticoagulated patients



# Why do we use an ACT?

## ● Point of Care

- › Immediate turn around
- › Rapidly adjust anticoagulant dosing as needed
  - Heparin – half life varies by patient
    - Dose required varies by patient
    - Potency varies by lot
  - IV Direct thrombin inhibitors – very short half life
    - Require immediate intervention
    - No antidote available



# Where is an ACT Used?

- Cardiac surgery
- Percutaneous coronary intervention (PCI)
- Interventional cardiology
- ECMO
- Critical care
- Interventional radiology
- Electrophysiology
- Vascular surgery
- etc.

# Cardiac Surgery

- ◉ Industry Standard Since 1970s
- ◉ Recommended as 1<sup>o</sup> method in AmSECT guidelines
- ◉ ACT improves outcome in CPB, PCI
  - › AACC NACB LMPG for POCT
    - Strongly recommend ACT monitoring of heparin anticoagulation and neutralization in cardiac surgery. (Class A, Level I)
  - › Insufficient evidence to recommend specific target times for use during cardiovascular surgery. (Class I – conflicting evidence across clinical trials).
- ◉ Easy to run

# Cardiac Surgery

- ◉ Disadvantages
  - › Each system yields different numbers
  - › Most sensitive to hypothermia and hemodilution
  - › Little or no correlation to heparin level
    - especially true for pediatric patients
- ◉ “Standard” target time = 480 seconds
  - › Developed with manual ACT
  - › Suggested due to high variability

# Catheterization Laboratory

## ⦿ Diagnostic

### > Catheterization

- locate and map vessel blockage(s)
- determine need for interventional procedures

### > Electrophysiology

## ⦿ Interventional

### > Balloon angioplasty

### > Atherectomy (roto-rooter)

### > Stent placement

# Dosing & Target Times

- Angioplasty, Atherectomy, Stent placement
  - › 10,000 unit bolus dose or 2 - 2.5 mg/kg
  - › target ACT 300 - 350 seconds
  - › Target time be reduced if ReoPro Used
    - ReoPro is one of 3 "GPIIb/IIIa" Inhibitors
- Catheterization and Electrophysiology
  - › Same dosing and targets for vascular surgery
  - › 2500 - 5000 unit bolus dose
  - › frequently not monitored
  - › if monitored – Targets ~ 200 seconds OR twice baseline

# ECMO

- ◉ ExtraCorporeal Membrane Oxygenation
  - > Very small window of safety
  - > NACB Guidelines:
    - Strongly recommend ACT monitoring to control heparin anticoagulation during ECMO. (Class A – Level III)
    - Target times for ECMO based on the ACT system. (Class B – Level III)
  - > Target often 180 – 200 seconds
    - Based on Hemochron P214/215 tubes

# Critical Care

- ◉ 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
- ◉ Monitor heparin therapy
  - > Target times determined by each facility
  - > ACT or aPTT

# 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



# ACT and aPTT

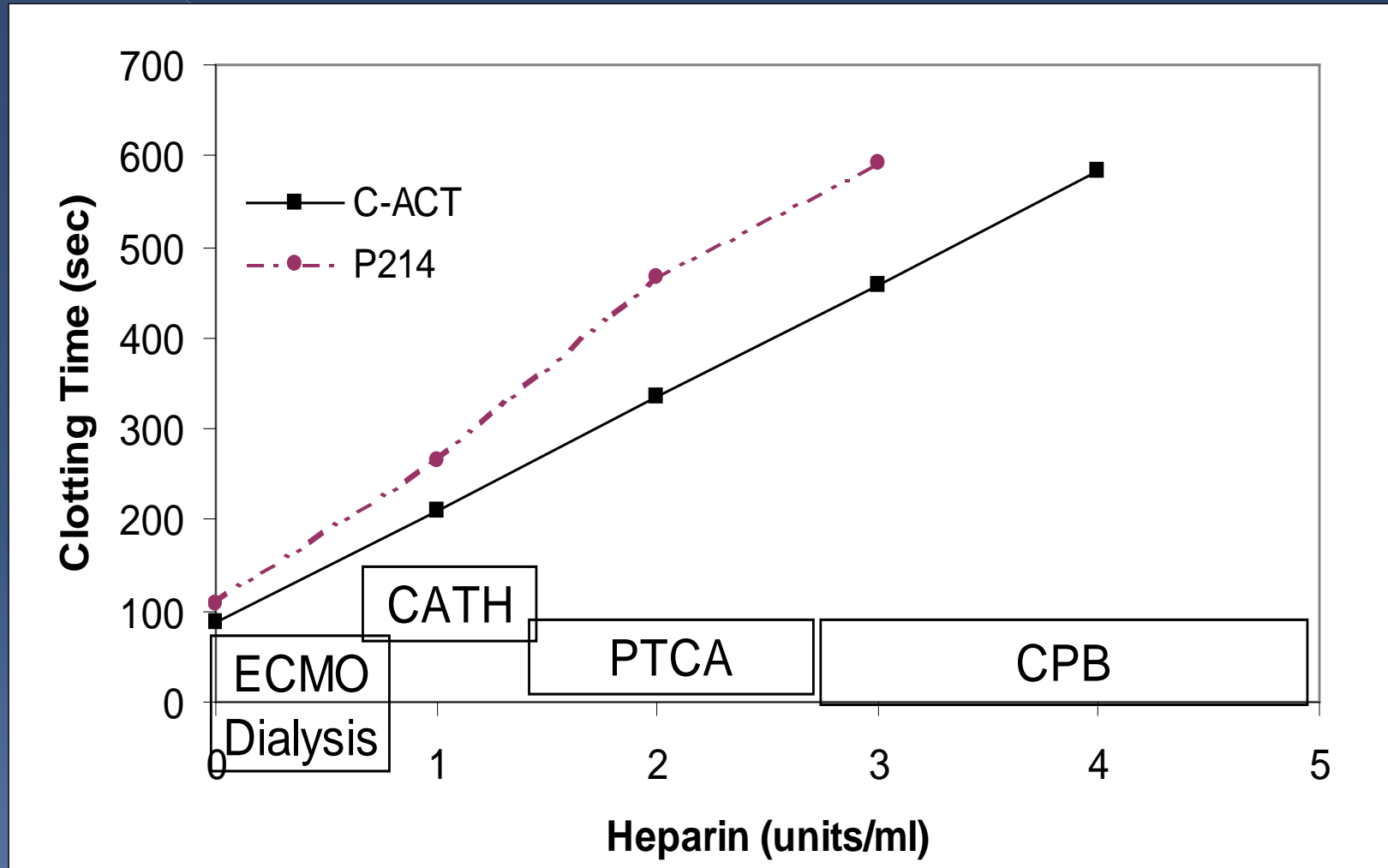
- ◉ Why are the results from different systems SO VERY different?
  - > Multiple activators
  - > Multiple detection mechanisms
  - > NO standardization
- ◉ ACT Differences

# A Little History

- 1969 -  
HEMOCHRONOMETER
  - > Hattersley ACT
    - Automated heating
    - Objective fibrin clot detection
  - > two different activators
    - CA510 (later FTCA510)
      - diatomaceous earth
      - P214 glass bead



# Two assays for separate uses

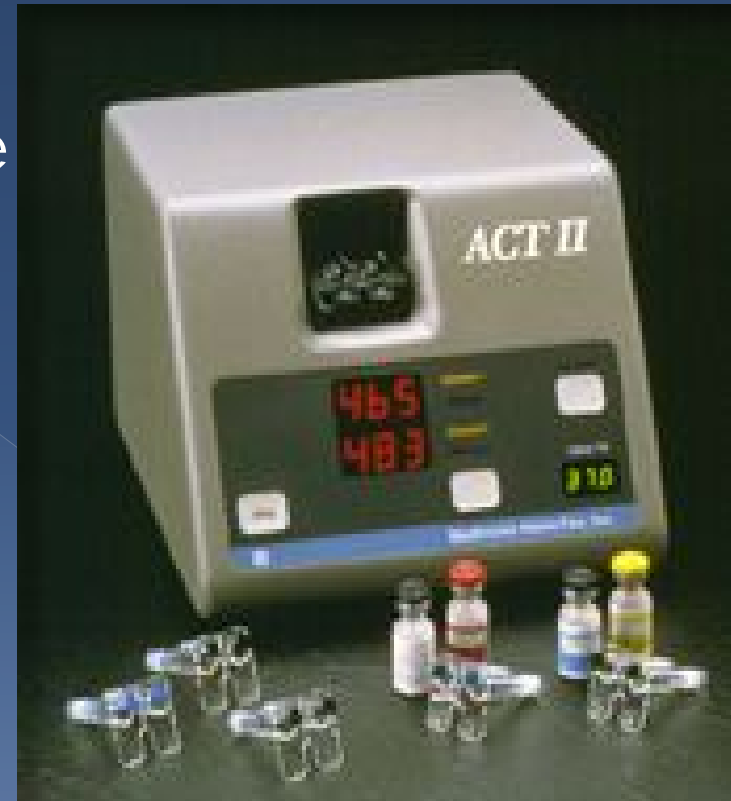


# 1980's

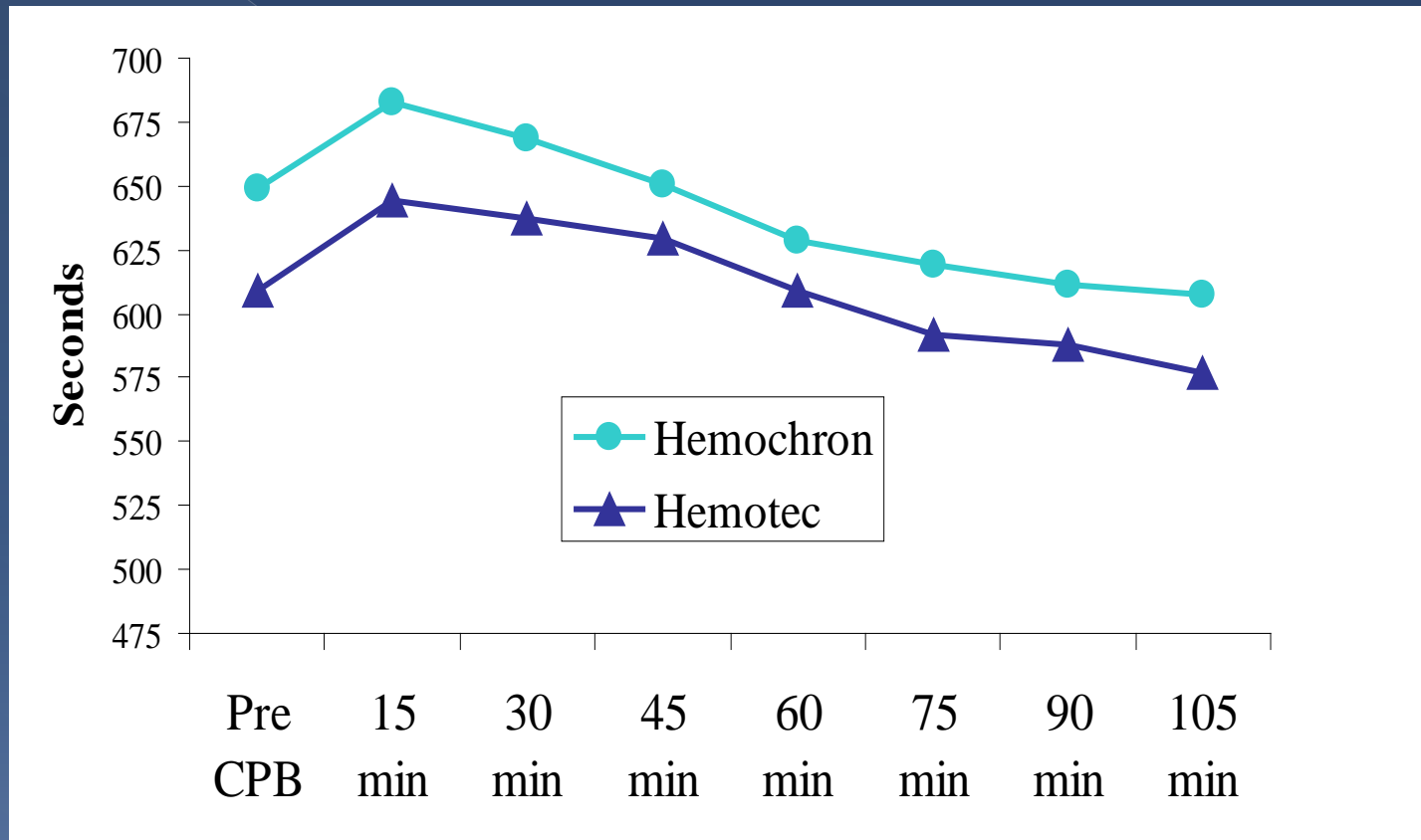
## ● HemoTec ACT

(later Medtronic ACTPlus)

- Add blood to dual cartridge
  - Liquid kaolin activator
  - Flag moves up and down
  - As fibrin forms, motion slows
  - Instrument displays clotting time



# Lower values than CA510 –



differences ignored by clinicians

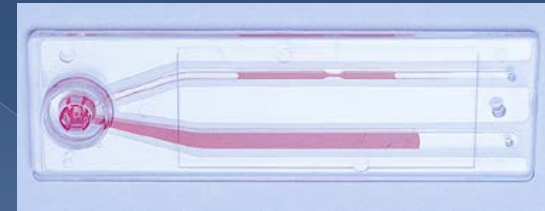
# 1980's - ACT Differences

- Reported in literature >20 years
  - > Clinical evaluations of Hemochron - mid 1970's
  - > By 1981 –
    - poor correlation between ACT and heparin level
  - > By 1988
    - Hemochron and HemoTec clinically different
- Early '80's to Present
  - > Improved clinical outcome with ACT use
    - NACB Laboratory medicine practice guideline for point of care coagulation testing 2007
    - <http://www.aacc.org/SiteCollectionDocuments/NACB/LMPG/POCT/Chapter%204.pdf>

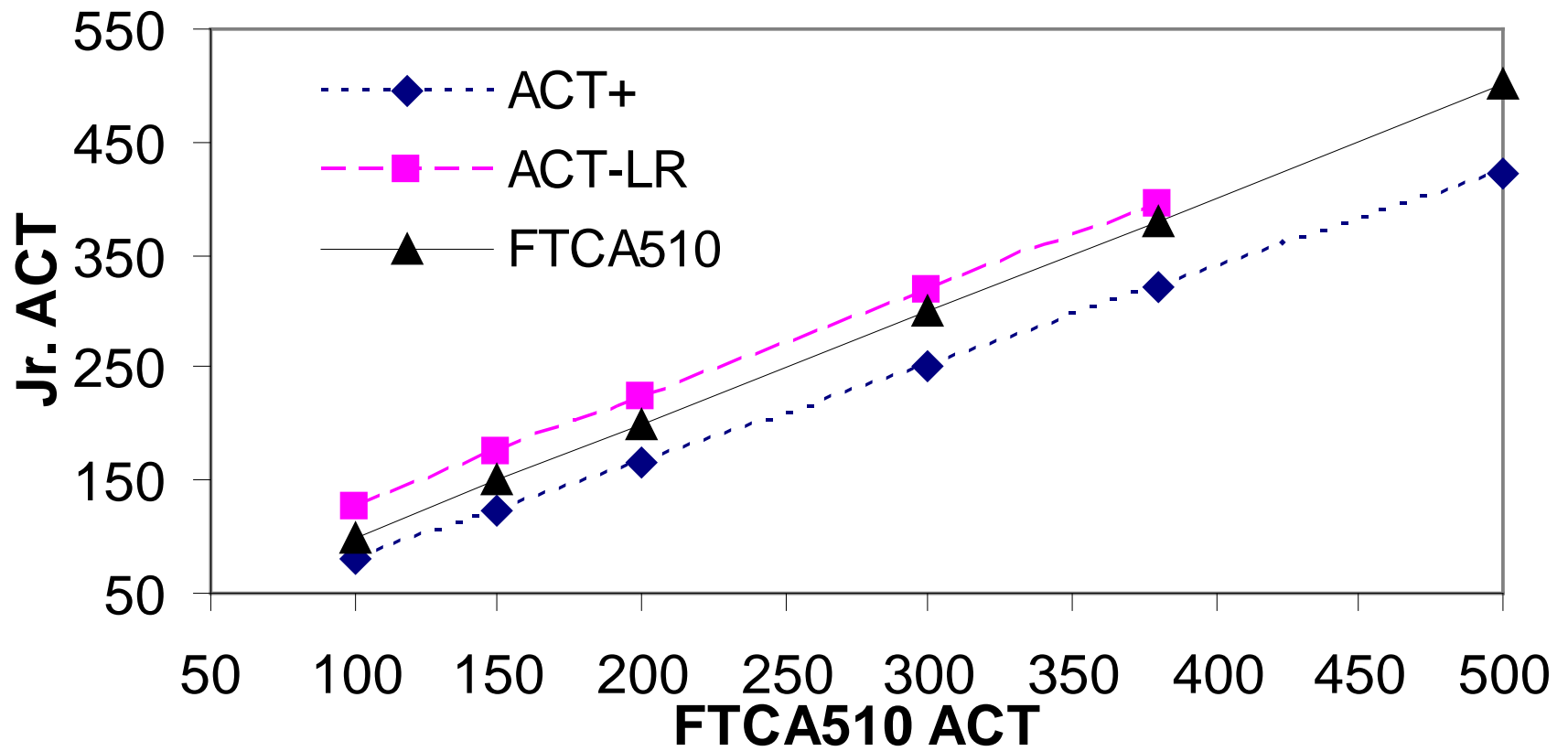
# 1990's

## ◉ Microsample ACTs - Hemochron Jr

- > Add blood to sample well, press start
  - Silica, kaolin and phospholipid (ACT+)
  - Diatomaceous earth (ACT-LR)
  - Sample pumped across restriction
  - Flow slows with clot formation
  - Optics measure motion
  - Clotting time displayed



# Clotting Times Different





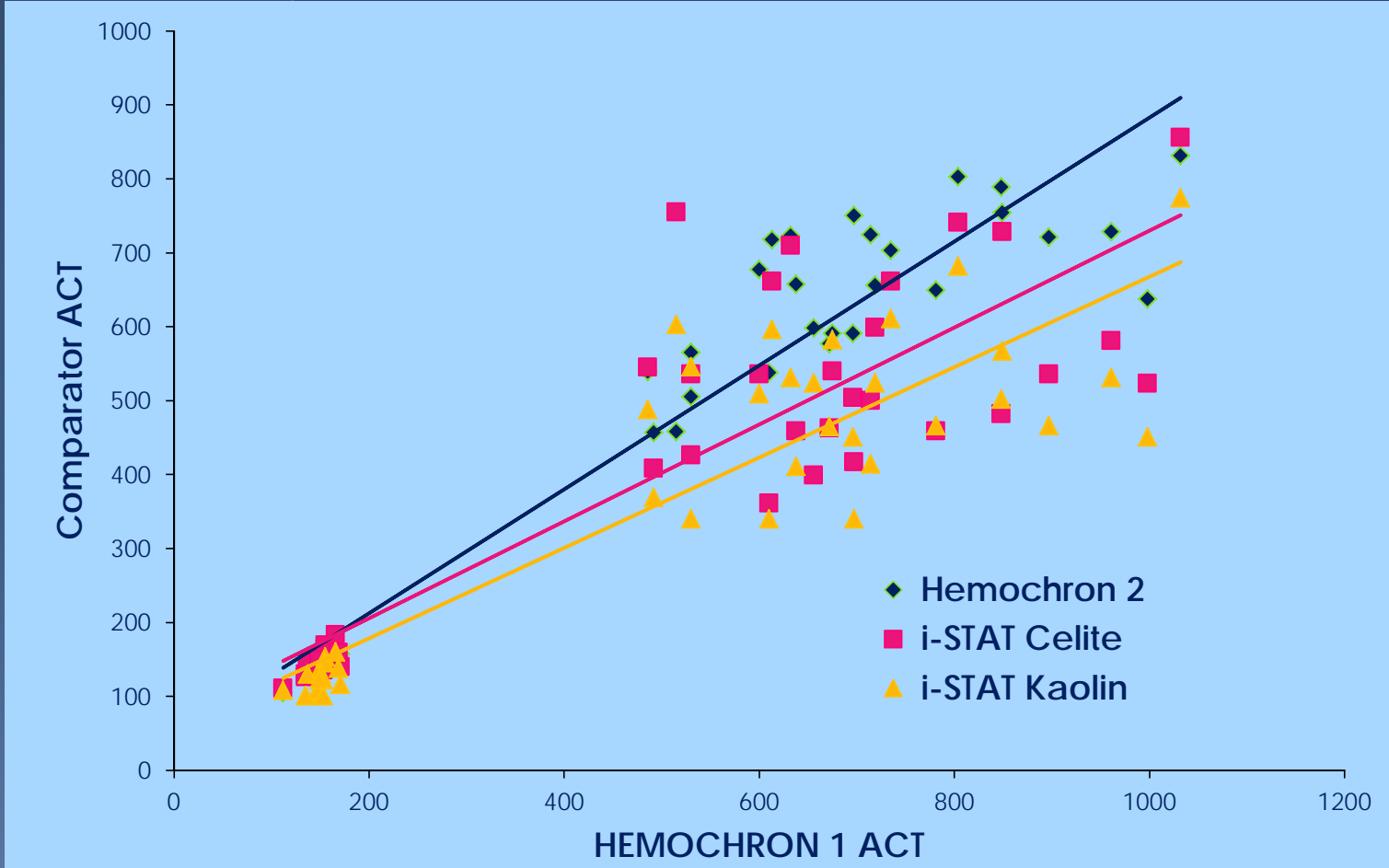
# 2000

## ● Abbott - i-STAT

- Add blood to cartridge, press start
  - Diatomaceous earth or kaolin
- Insert into instrument
- No clot detection
  - Synthetic thrombin substrate
  - Electro-active compound formed and detected amperometrically
  - "Clotting time" reported



# Number don't Match- Surprise!



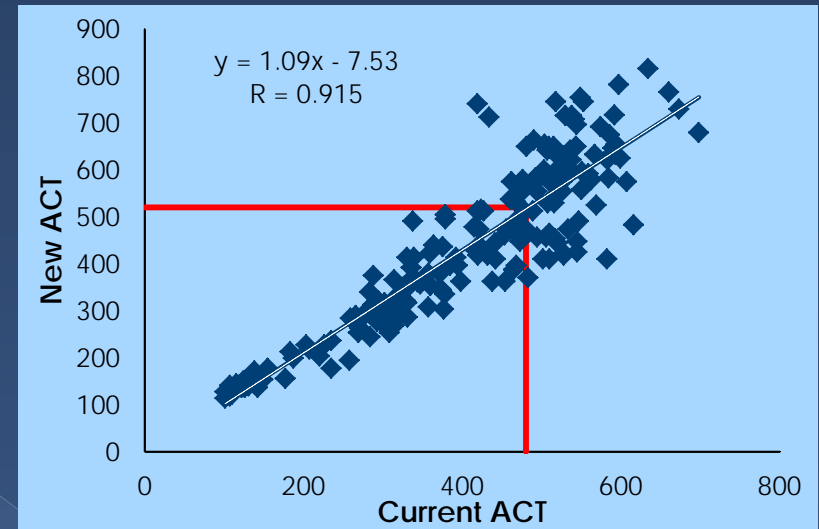
# How can a new ACT be used?

- Evaluate by clinical agreement
  - > Standard split sample correlation
  - > Samples across entire range
  - > Correlation coefficient
    - $R \geq 0.88$
  - > Two by Two table of agreement

# Clinical Correlation

## CVOR example

Current	New	N	%
$\geq 480$	$\geq 520$	72	34%
$\geq 480$	$< 520$	19	9%
$< 480$	$\geq 520$	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

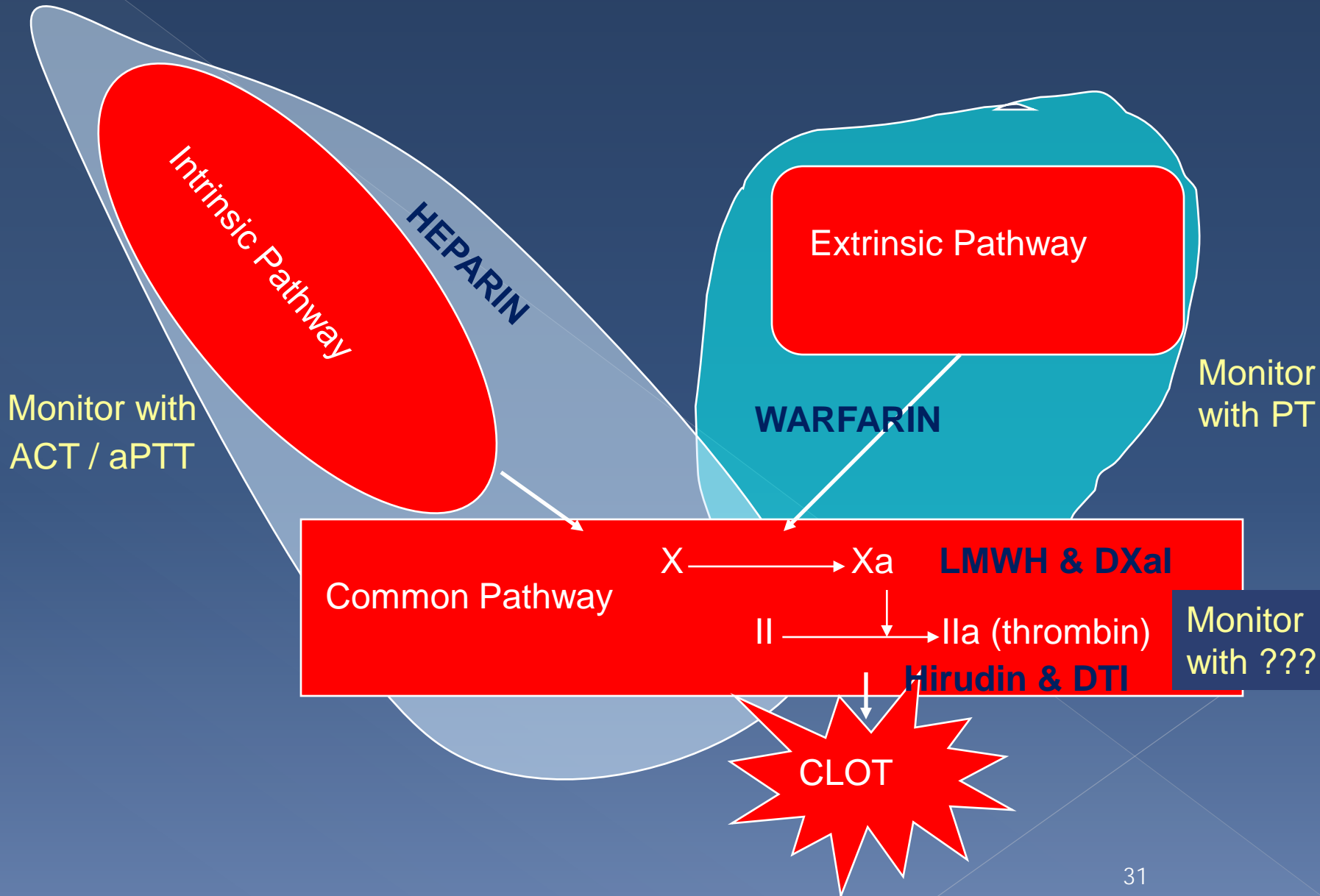
# Clinical Comparison

- ◉ 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

# Direct Thrombin Inhibitors

- Parenteral Direct thrombin inhibitors (DTIs)
  - > Used if patient at risk for HIT
    - Heparin induced thrombocytopenia
    - "Heparin allergy"
  - > Argatroban
  - > Angiomax
- No ACT FDA cleared for monitoring DTIs

# Coagulation Testing



# ACT Monitoring - DTIs

## ● Argatroban

- › Synthetic analog of L-arginine
  - Reversible binding to thrombin
- › PCI monitoring: ACT 300 – 450
  - Papers state standard ACT targets for CPB

## ● Angiomax

- › Synthetic analog hirudin (bivalirudin)
  - Reversible binding to thrombin
- › Labeling requires ACT after initial bolus
  - Original studies with Hemochron ACT-LR
  - Any ACT >250 sec



# Summary

- ◎ ACTs are Global Assays
  - > Used to monitor heparin
    - Heparin is non-homogenous
    - Difference by manufacturer & Lot
- ◎ ACTs differ:
  - > By manufacturer
  - > By activator
  - > By detection mechanism
- ◎ Must establish clinical equivalence
  - > New target times that reflect clinical practice

# QUESTIONS?

Marcia L. Zucker, Ph.D.  
ZIVD LLC  
Mlzucker.zivd@gmail.com