The 123's of ACT

Marcia L. Zucker, Ph.D.
ZIVD LLC

Objectives

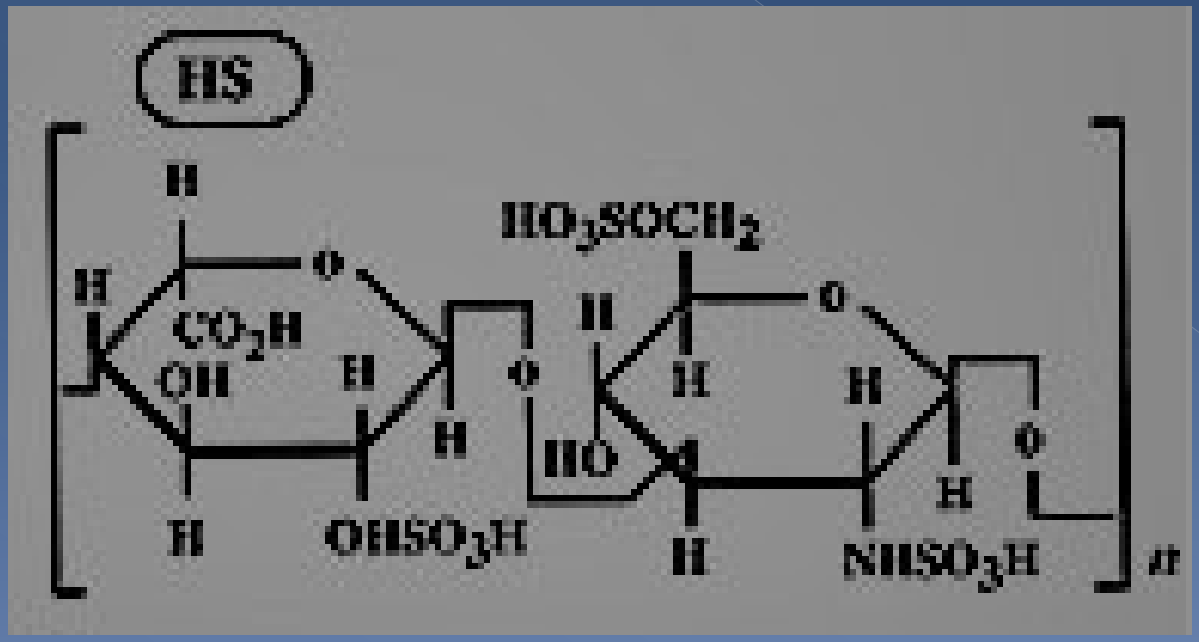
- Explain why ACTs from different systems are not the same
- Develop a plan for switching from one ACT system to another
- Describe why ACT and aPTT are not interchangeable

What is an ACT?

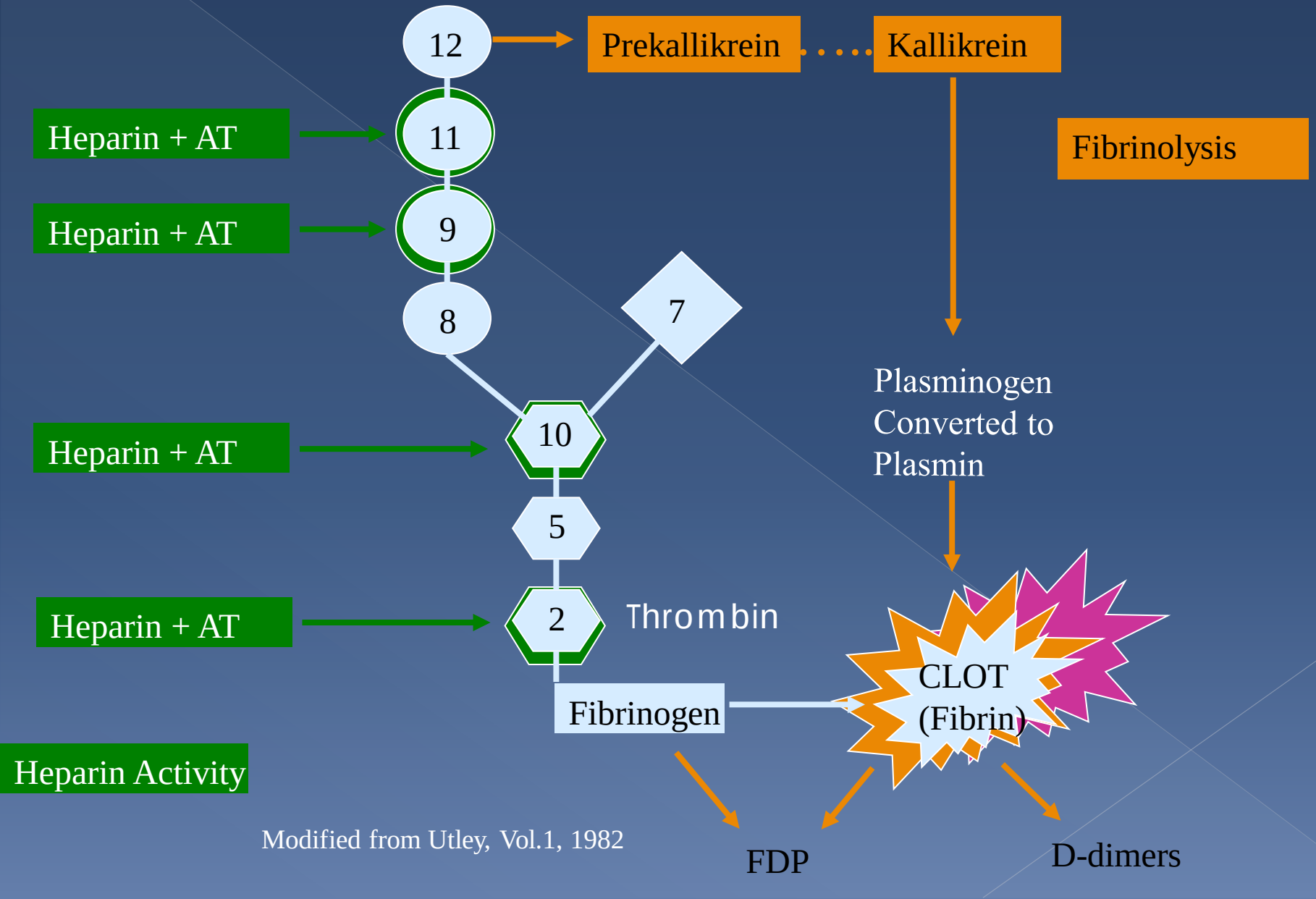
- Modified Lee-White clotting time
  - Add blood to glass tube, shake
    - Place in heat block
    - Visual clot detection
- First described in 1966 by Hattersley
  - Activated Clotting Time
    - Add blood to glass tube with dirt, shake
      - Diatomaceous earth activator
      - Place in heat block
      - 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



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

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 1º 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

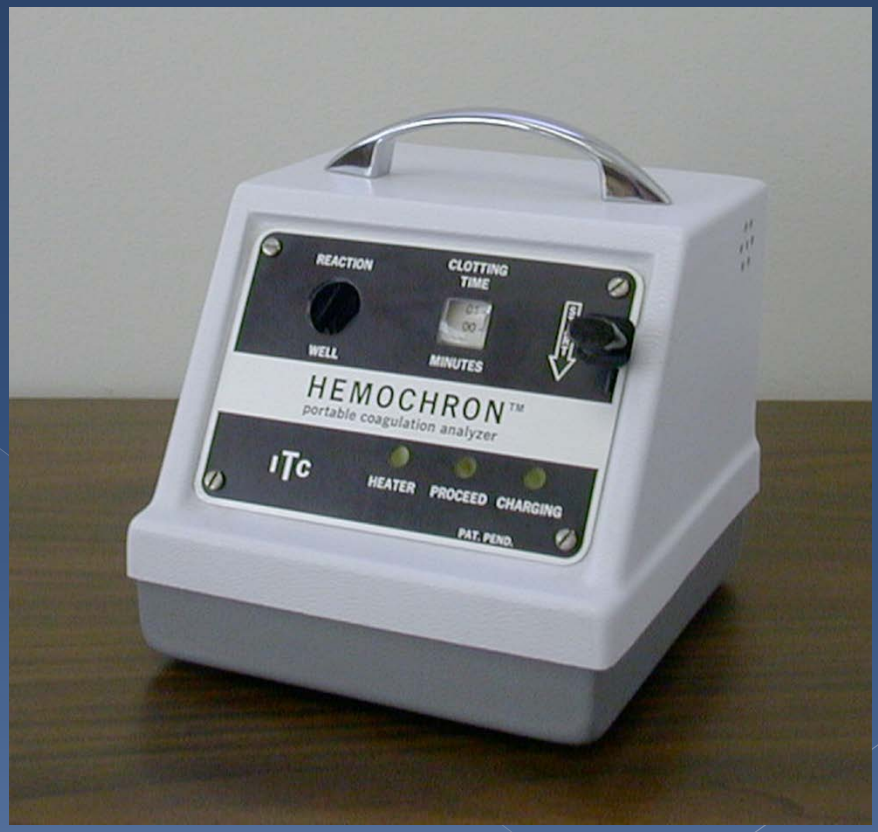
- ACT
  - Activated clotting time
  - POC Only
  - Low, moderate or high dose heparin
    - System dependent
- aPTT
  - Activated partial thromboplastin time
  - Laboratory or POC
  - Low dose heparin only
    - System dependent upper limit

ACT and aPTT

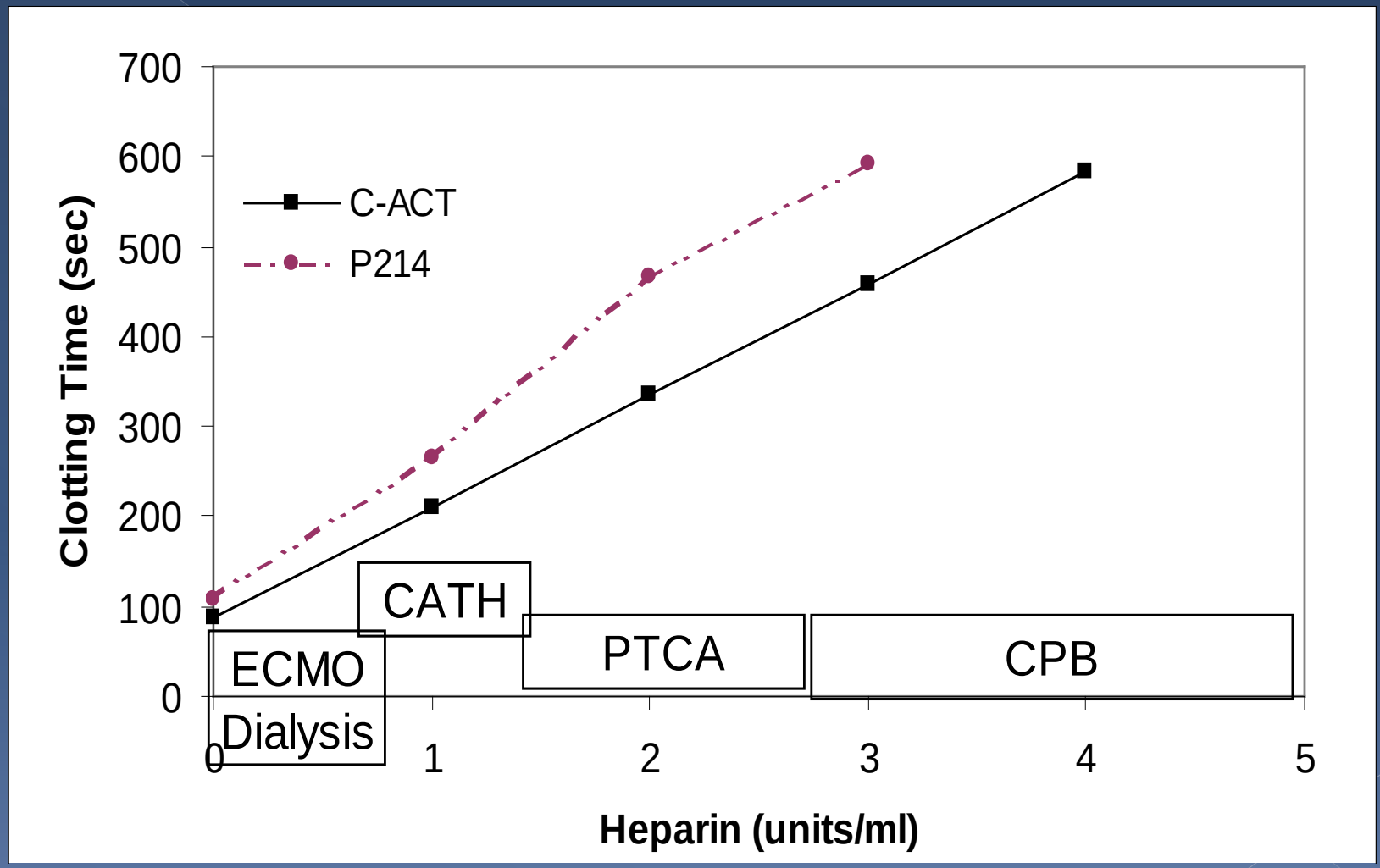
- Why are the results from different systems SO VERY different?
  - Multiple activators
  - Multiple detection mechanisms
  - NO standardization
- ACT Differences

A Little History

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



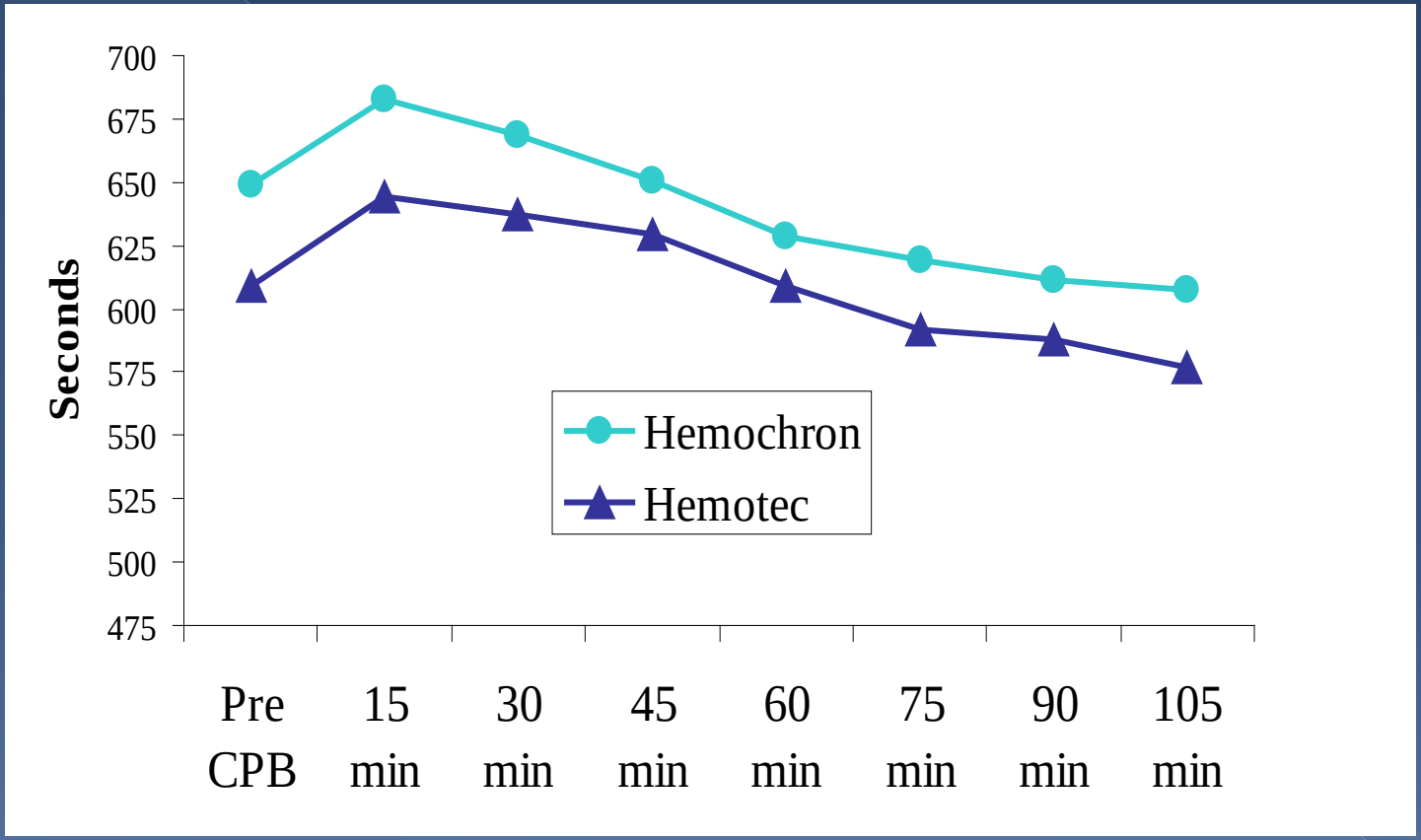
Two assays for separate uses



1980's

- HemoTec ACT
  (later Medtronics 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 –



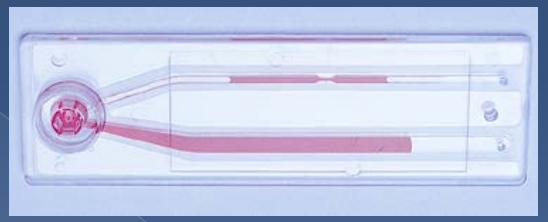
differences ignored by clinicians

1980's - ACT Differences

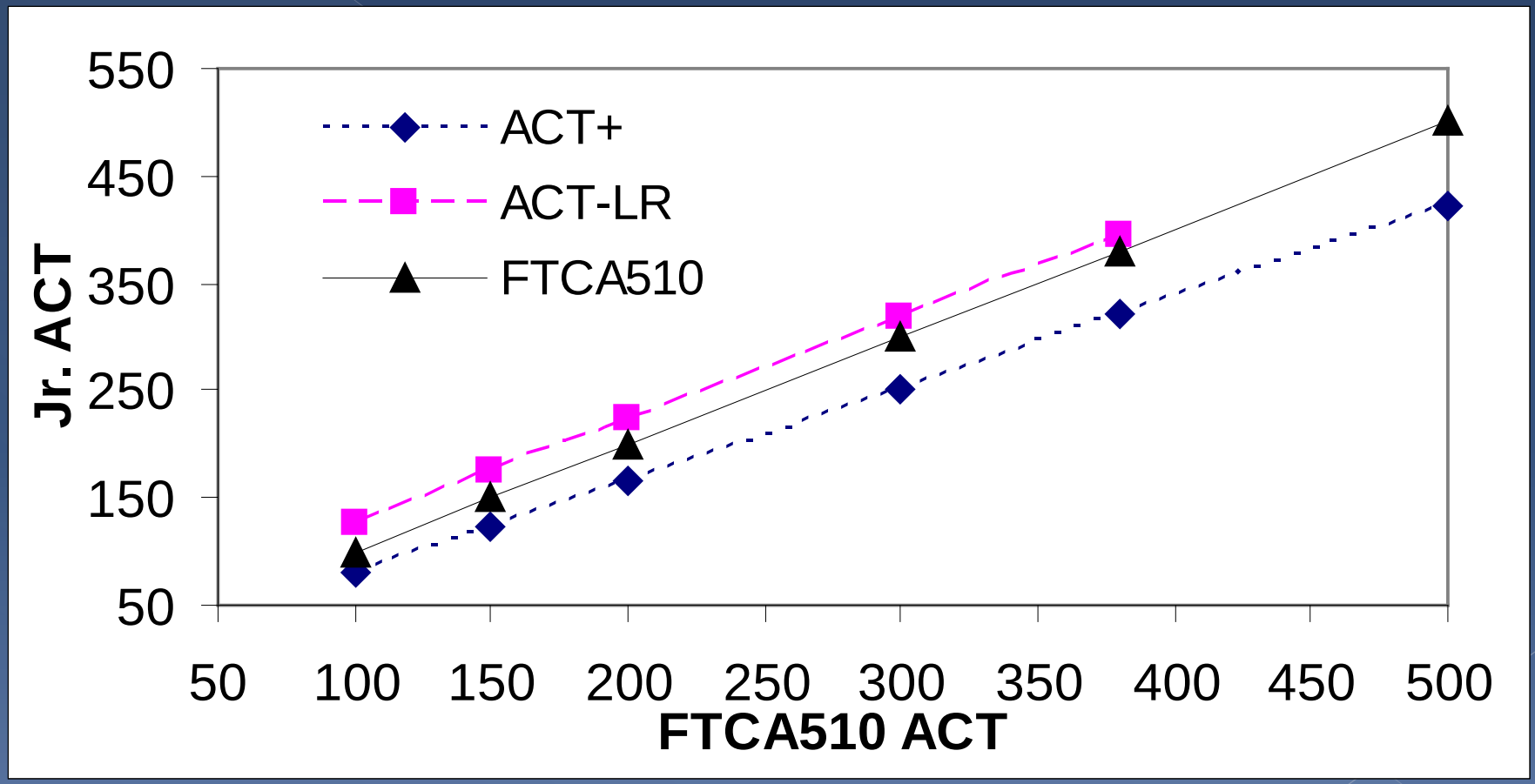
- Reported in literature >20 years
  - Clinical evaluations of Hemochron - mid 1970's
  - By 1981 –
    - poor correlation between ACT and heparin level
  - By 1988
    - Hemochron and HemoTec clinically different
- Early '80's to Present
  - Improved clinical outcome with ACT use
    - NACB Laboratory 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



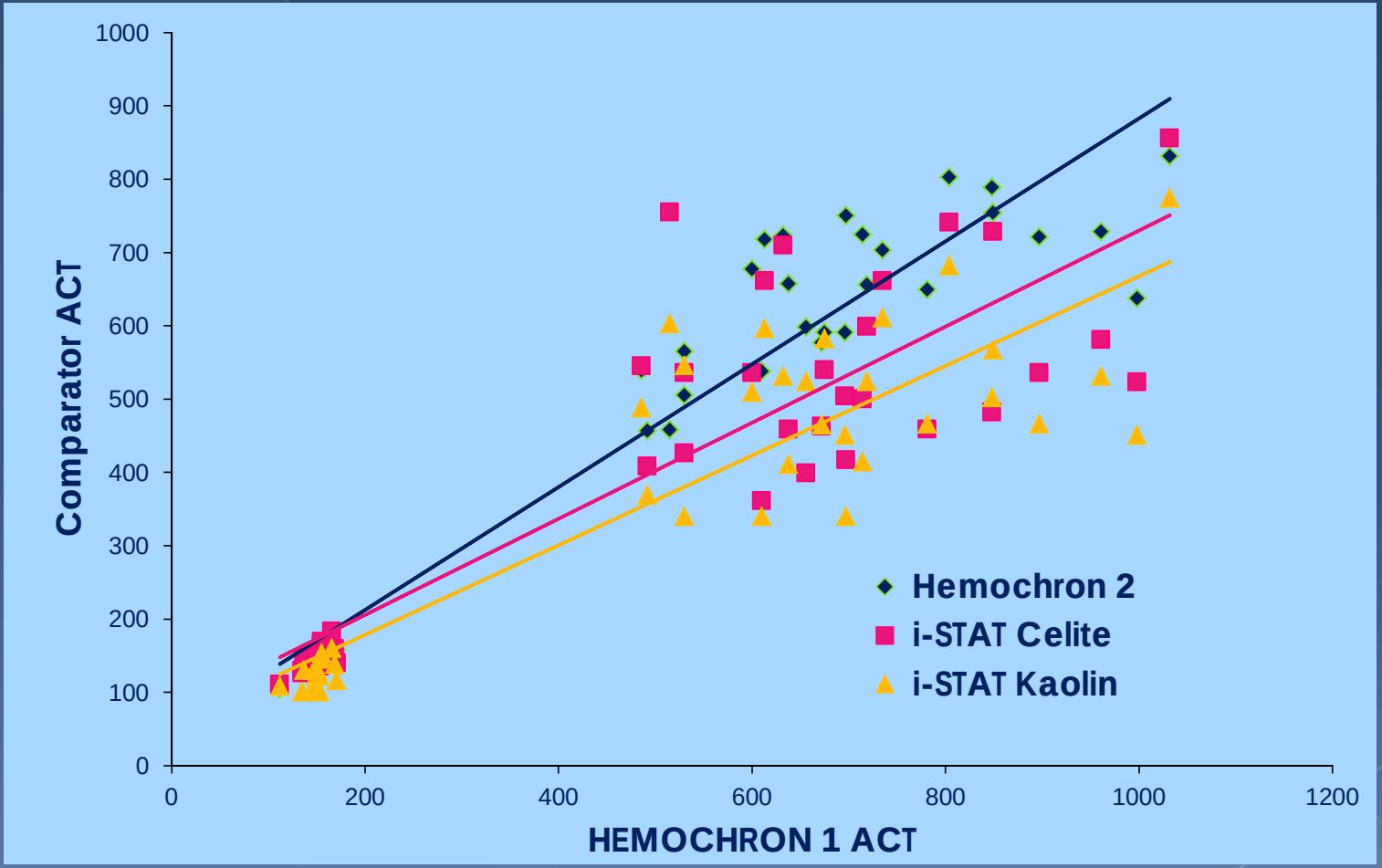
Clotting Times Different



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!



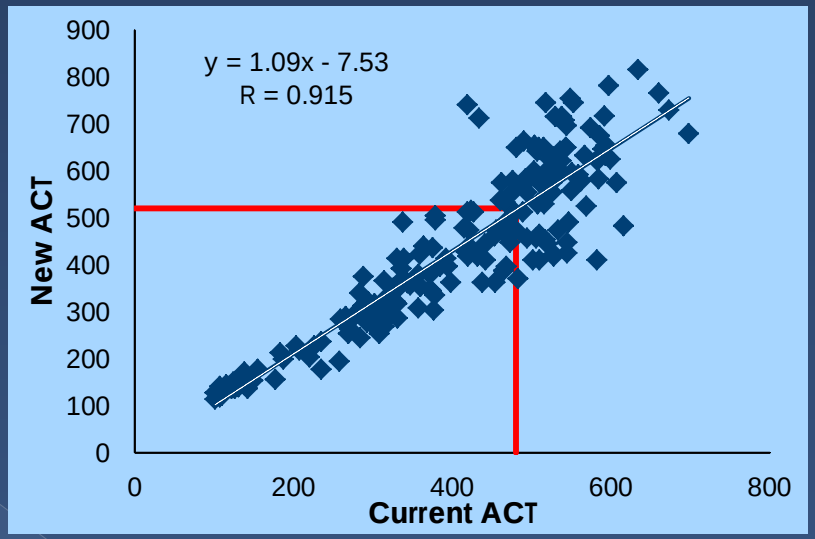
How can a new ACT be used?

- 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	%
≥ 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

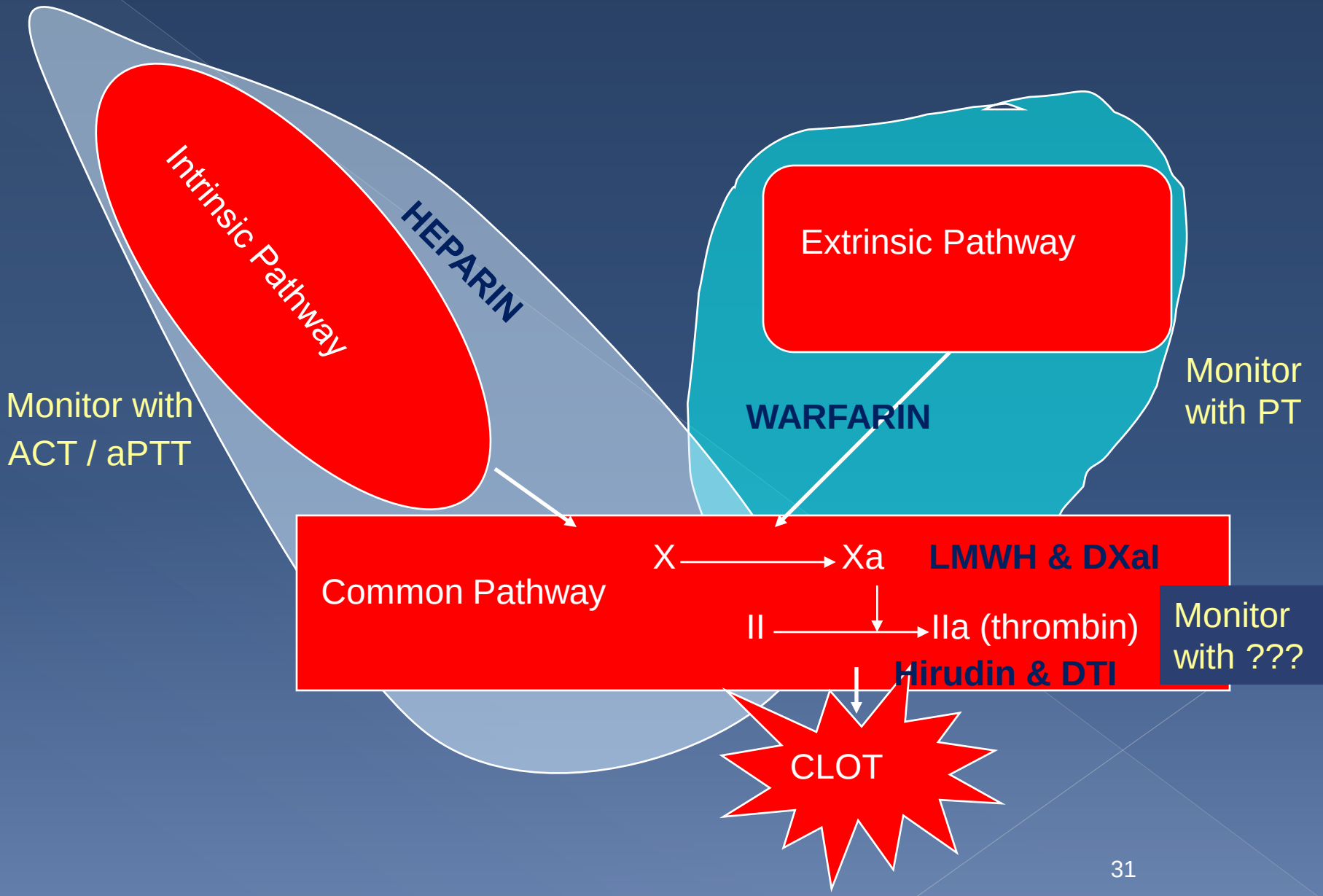
Clinical Comparison

- 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