

The 123's of ACT

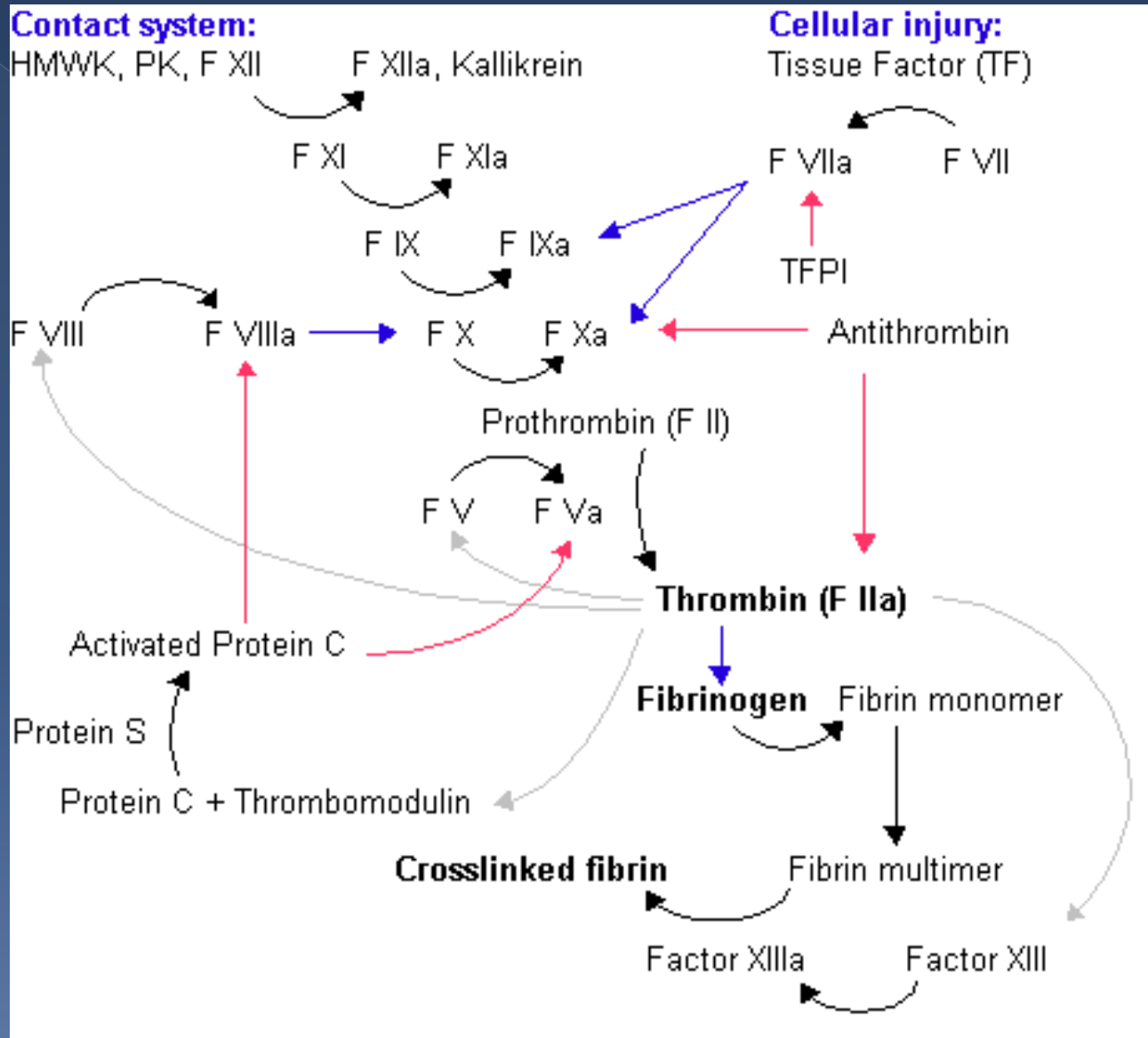
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Coagulation Testing

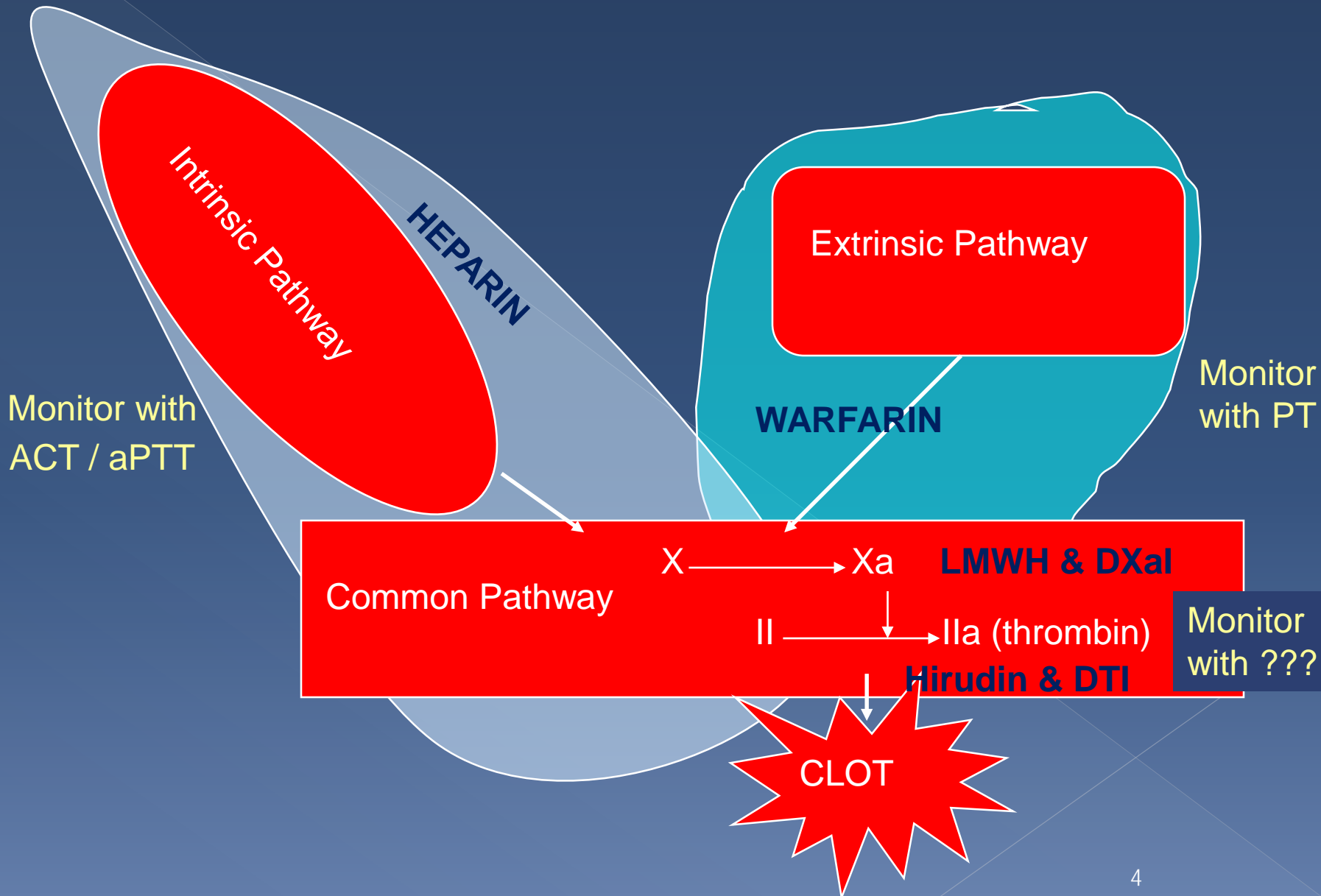
- Monitoring hemostasis



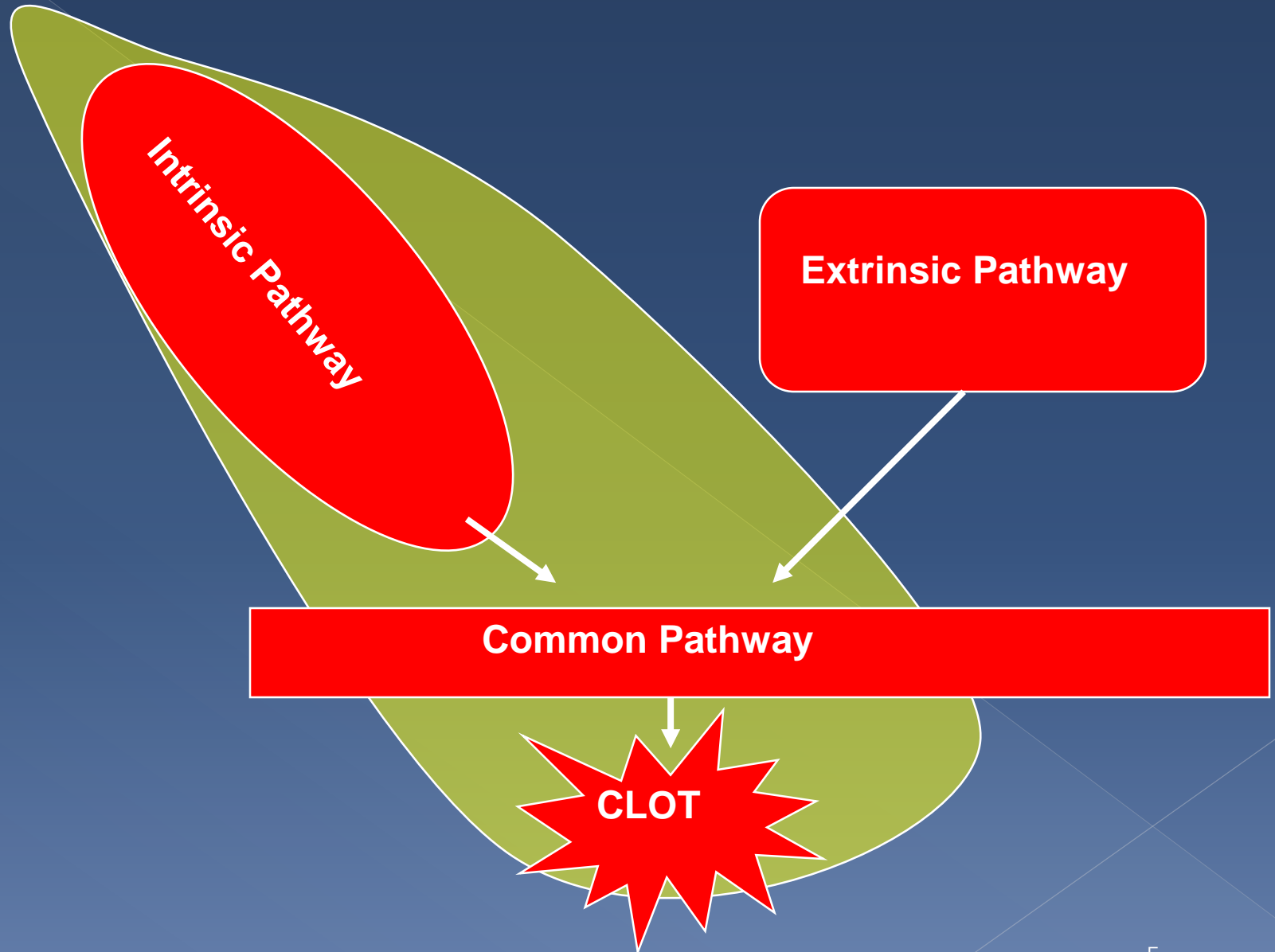
Coagulation is Complex



Coagulation Testing



Activated Clotting Time



What is an ACT?

- In the beginning.....
- The Lee-White clotting time
 - Add blood to glass tube, shake
 - No activator required
 - Manual method
 - Place in heat block
 - Examine for clot every 30 seconds
 - Very slow process
 - Subjective clot detection



1966 - Hattersley

- Activated Clotting Time
 - Add blood to glass tube with dirt and shake
 - Diatomaceous earth activator
 - Manual method
 - Place in heat block
 - Visual clot detection
 - Subjective clot detection



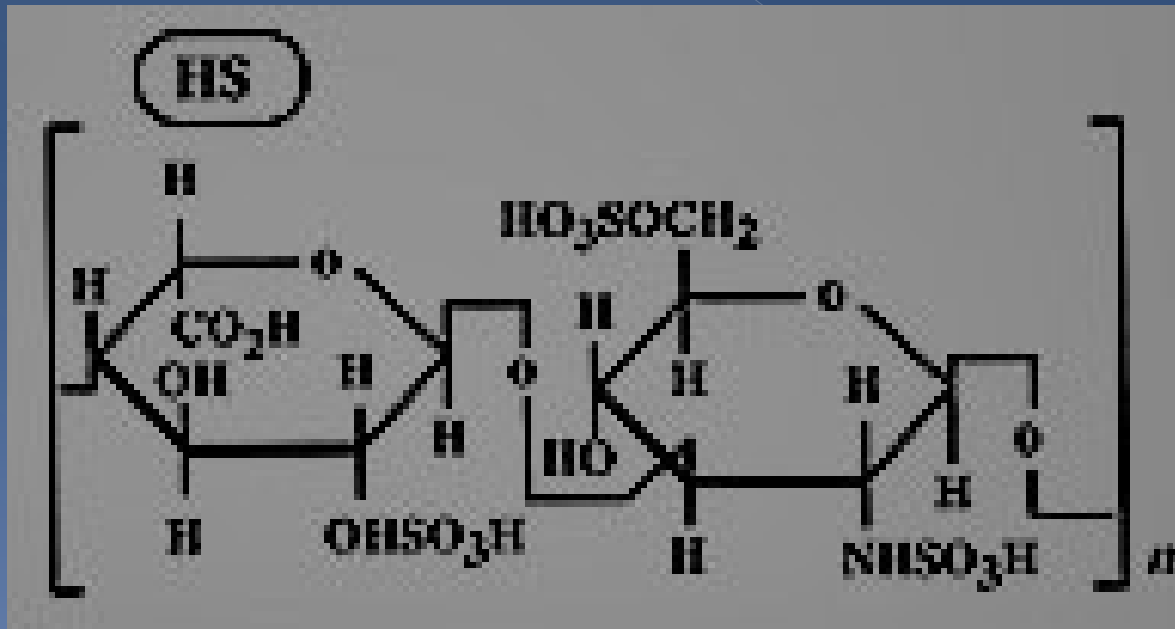
Hattersley PG. Activated coagulation time of whole blood. JAMA 1966 May 2;196(5):436-40.

Particulate Contact Activation

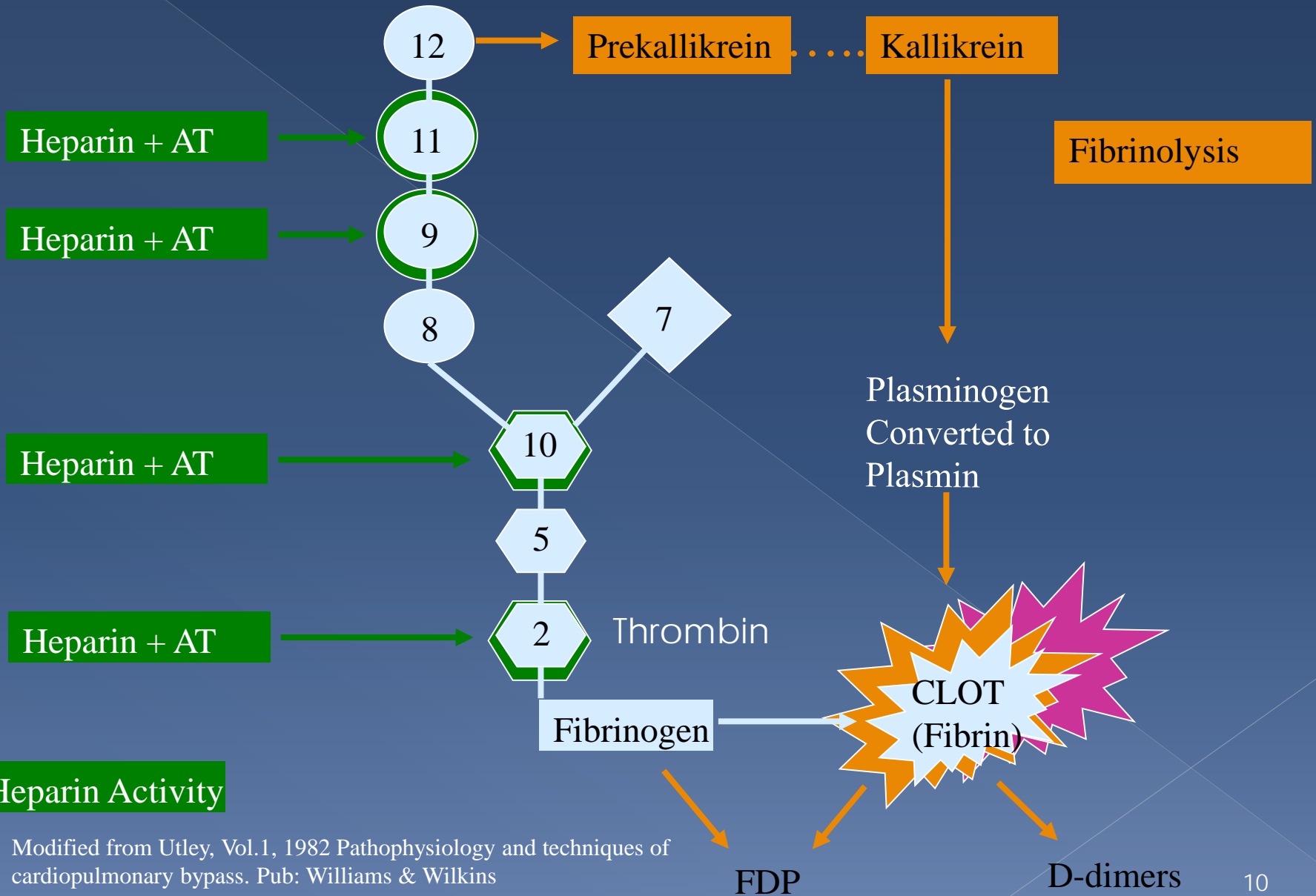
- ⦿ Initiation of intrinsic coagulation cascade
 - Factor XII (Hageman factor)
 - Pre-kallikrein (Fletcher factor)
- ⦿ Shortens contact activation period
- ⦿ Proposed as both screening assay for coagulation defects and for heparin monitoring

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 Pathophysiology and techniques of cardiopulmonary bypass. Pub: Williams & Wilkins

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^o 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

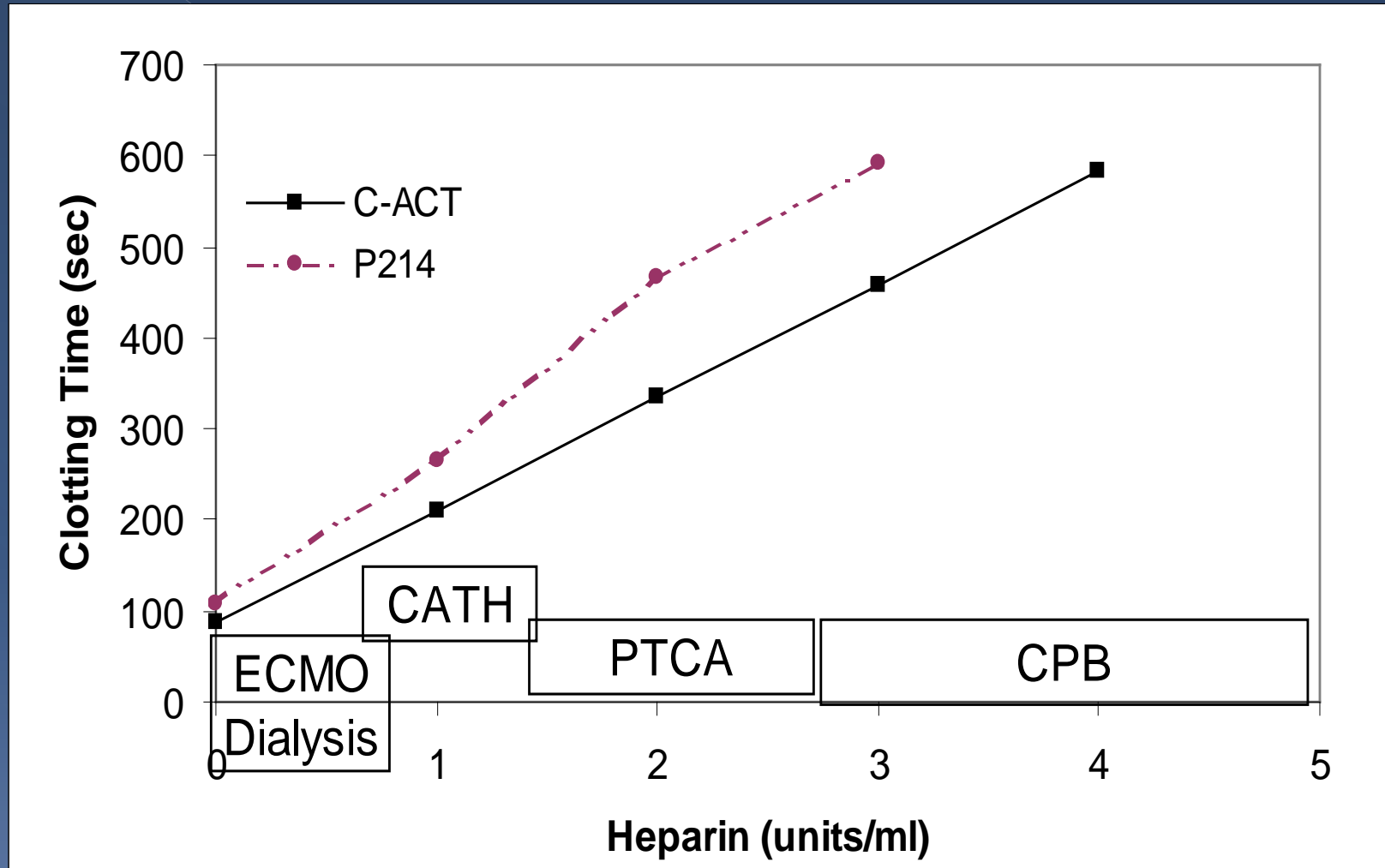
- ◉ Why are the results from different systems SO VERY different?
 - > Multiple activators
 - > Multiple detection mechanisms
 - > NO standardization
- ◉ ACT Differences

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

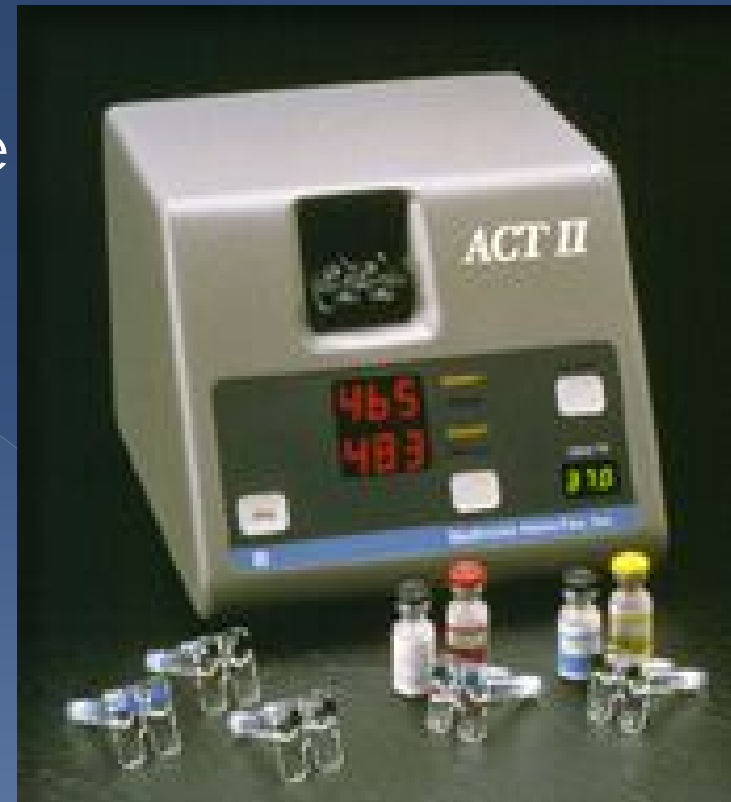


1980's

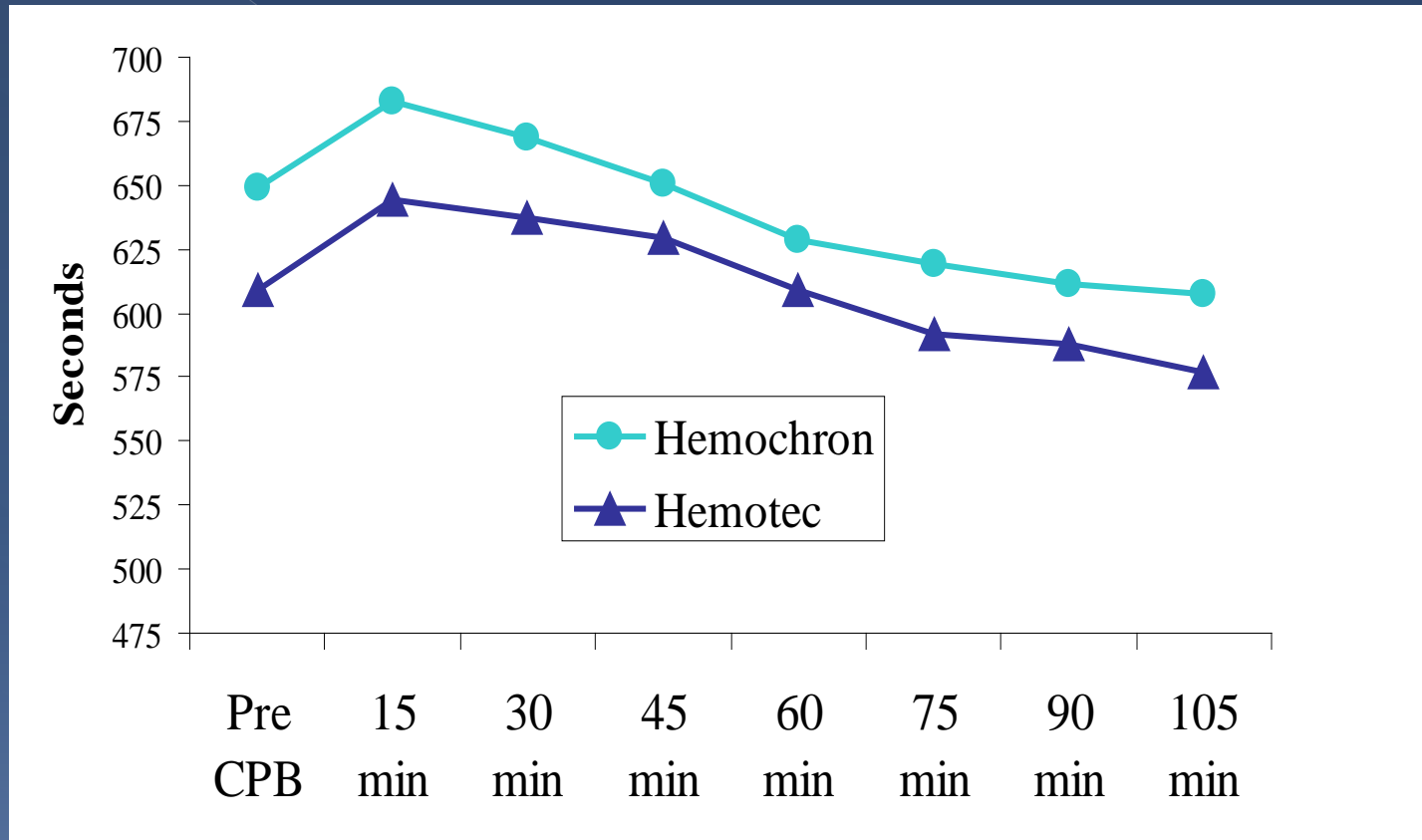
● HemoTec ACT

(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>

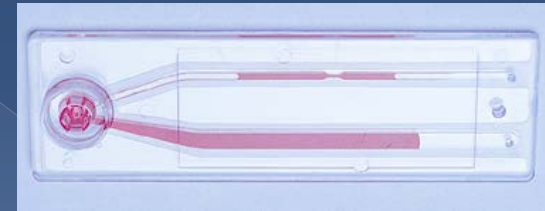
Multiple Activators

- Diatomaceous earth (Celite[®])
 - Used in original Hatterley and Hemochron tube ACT
- Kaolin (clay)
 - Used in suspension in original HemoTec ACT
 - Used as powder in Hemochron tube ACT
 - Unaffected by the use of aprotinin
 - CVOR to reduce blood loss; no longer marketed
- Glass beads
 - Used in Hemochron low dose tube ACT
- Phospholipids
 - Used in Roche ACT, HMS HDR and Hemochron Jr ACT+
- Mixtures used in lots of different ACTs

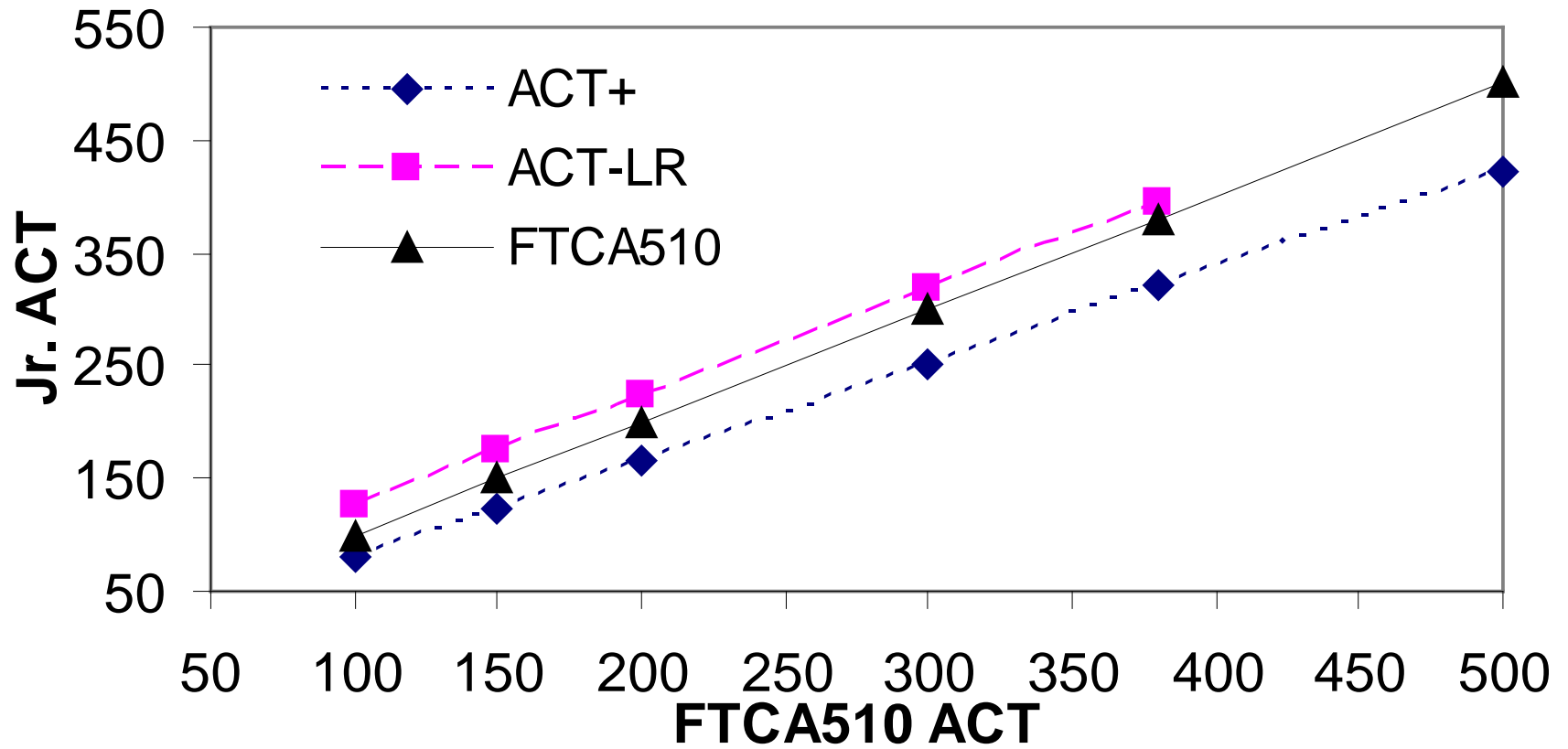
1990's

◉ 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



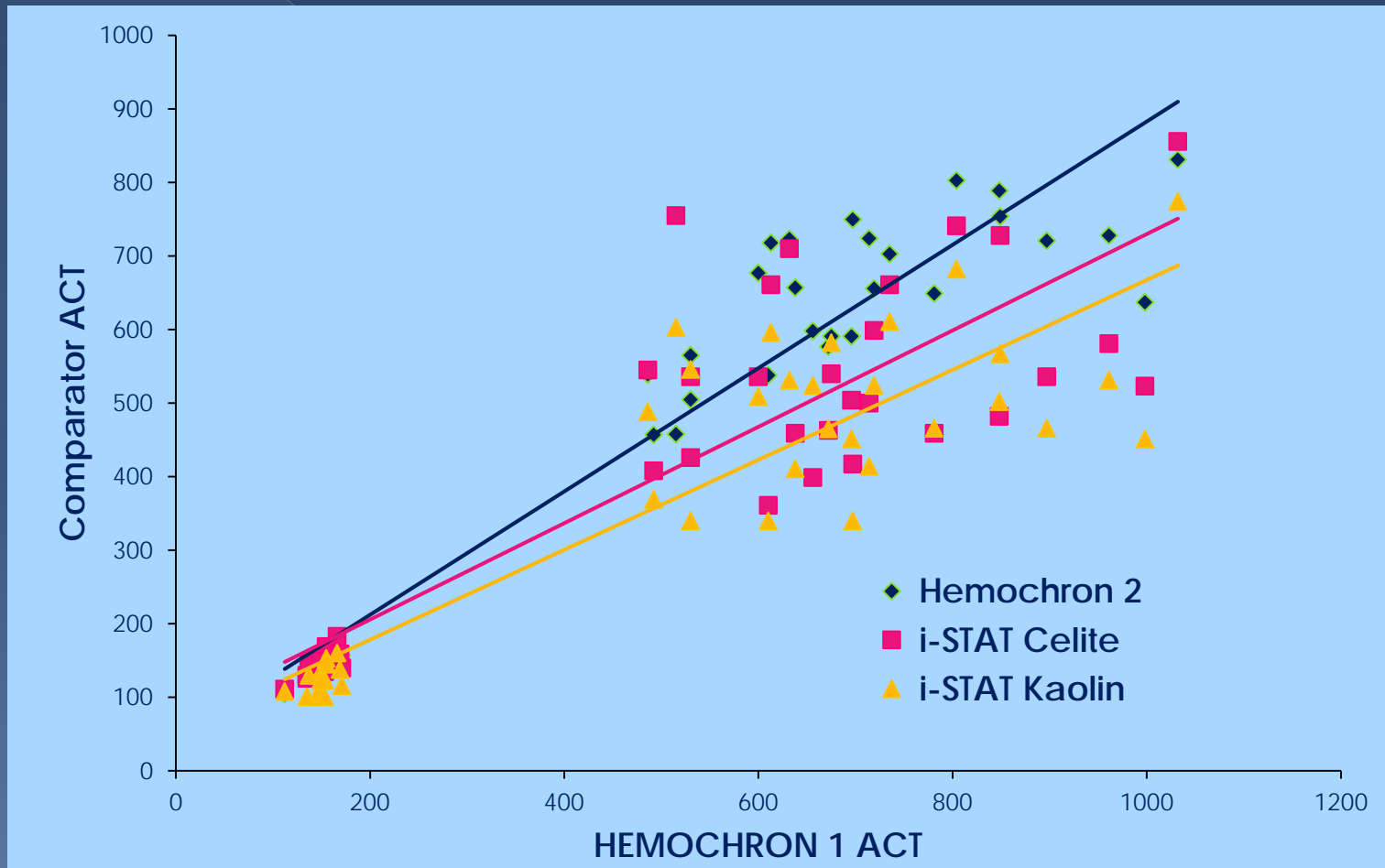
2000

● 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!



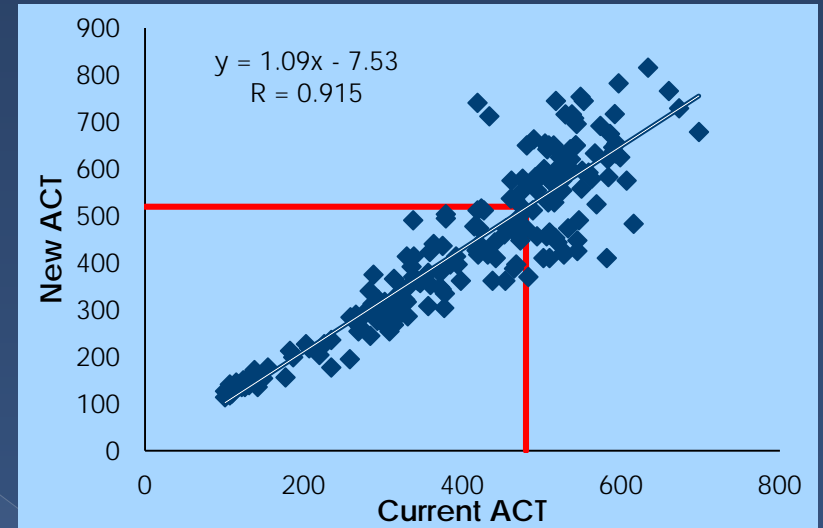
How can a new ACT be used?

- 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

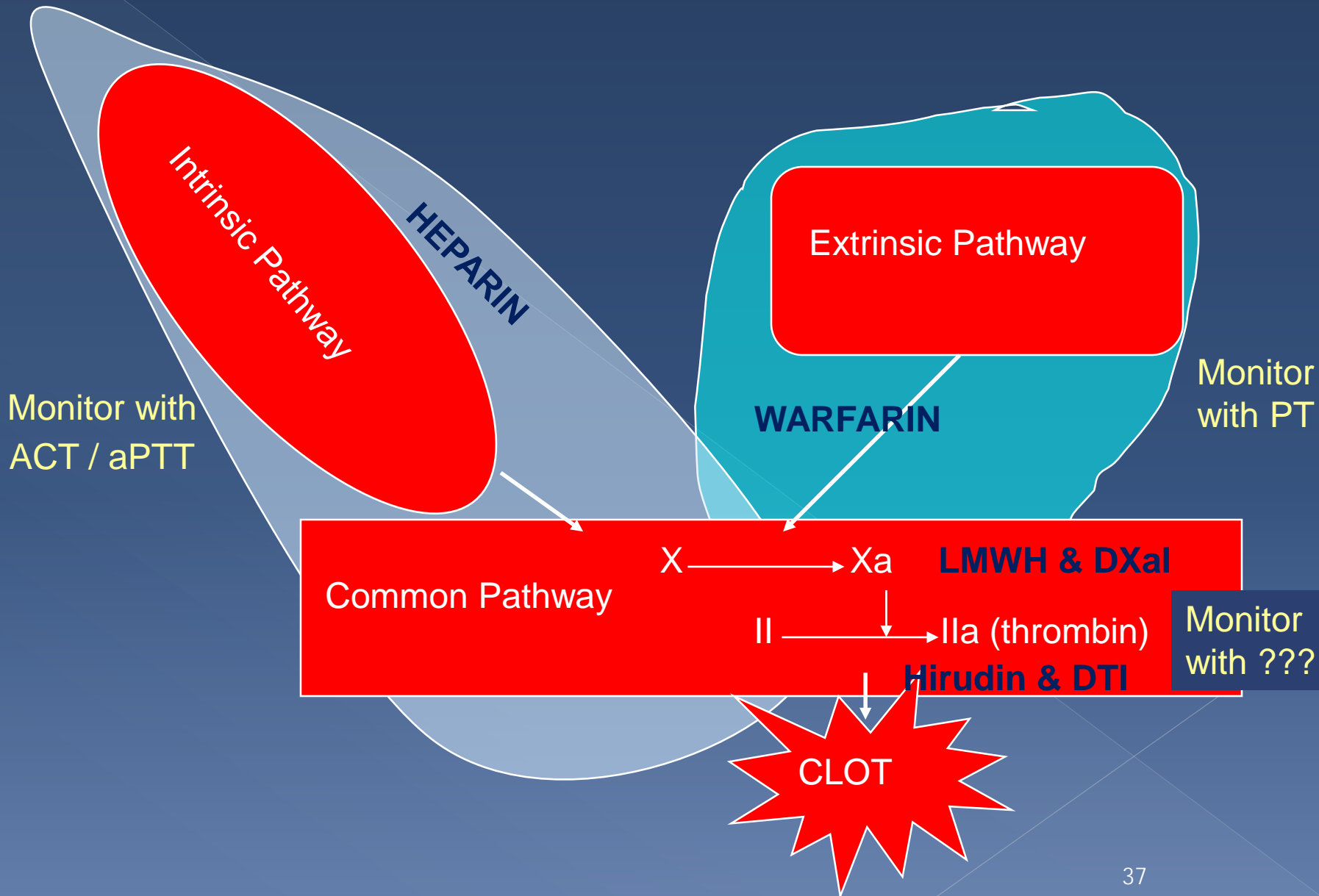
Clinical Comparison

- ◉ 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?

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