

Point of Care Testing in Coagulation: The Key Question

**Will a test performed –
with less accuracy or precision by a
lesser trained healthcare worker or
by a patient –
improve outcome or possibly incur
less cost to the institution with no
loss in quality of care?**

Higher Cost Per Test But Decreased Cost Per Patient Encounter



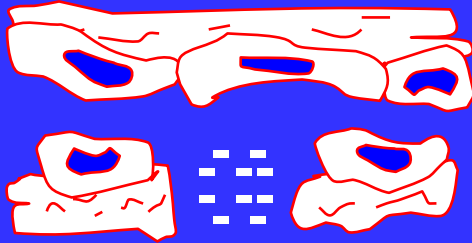
is not as good as



The Basics of Point of Care Coagulation Testing

Clot Formation & Fibrinolysis

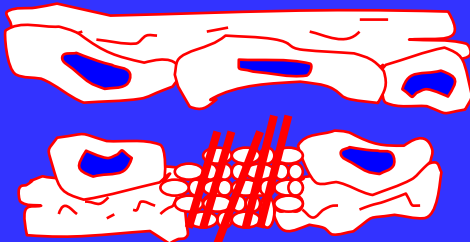
Vessel Wall Injury



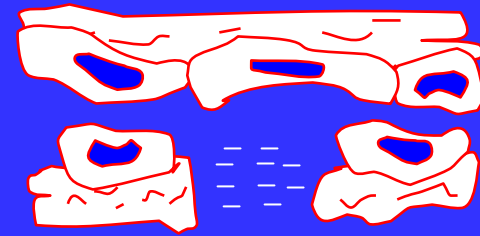
Platelet Adhesion



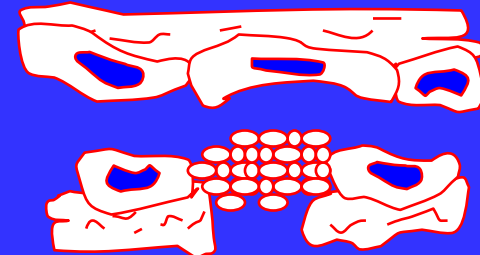
Fibrin Formation



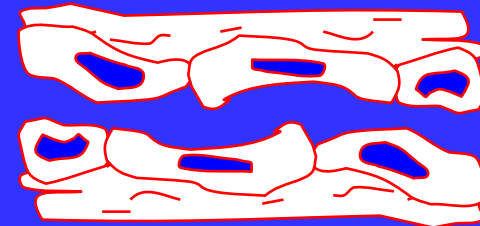
Vessel Wall Contraction



Platelet Aggregation



Fibrinolysis & Repair



What is Point of Care Testing in this Presentation?

- Patient self testing
- Testing within a care unit or clinic
- Physicians Office Lab Testing

but not

- Main Laboratory Testing

Samples for Point of Care Coagulation Testing

- **For most systems, the sample is fresh, non-anticoagulated venous whole blood, obtained either by fingerstick or by venipuncture**
- **For some systems, there is an option for citrated whole blood**
- **For some systems, there is an option for citrated plasma**
- **Serum, which is clotted plasma and therefore depleted of several of the clotting factors, is never an option for coagulation testing**

There are Many Mechanisms for Clot Detection in Point of Care Devices

- **Clot formation resists plunger that moves through the sample**
- **Thrombin from coagulation cascade releases an electroactive compound**
- **Clot formation prevents movement of iron particles in a magnetic field**
- **Thrombin from coagulation cascade cleaves a chromogenic substrate releasing fluorescent rhodamine**

There are Many Mechanisms for Clot Detection in Point of Care Devices

- **Light transmittance decreases with clot formation**
- **Amount of current passing through specimen decreases when blood clots**
- **Clot formation prevents blood from moving back and forth across a detector**
- **Clot formation prevents blood from moving along a channel by capillary action**

Coagulation Testing Opportunities with a Point of Care Testing Platform

In Common Use

- PT and PTT
- Activated Clotting Time (ACT)
- D-Dimer
- Thromboelastography

Not in Common Use

or

In Development

or

Growing Clinical Need

- Platelet Count
- Platelet Function
- Anti-Factor Xa for LMWH Monitoring
- Antibody to Heparin – PF4
- Ecarin Clotting Time
- Chromogenic Factor X
- ADAMTS –13 activity

Devices for Point of Care Coagulation Testing by Capability

PT and PTT

Healthcare worker operated device that can perform the PT only, the PT and PTT, the PT and the ACT, the PTT and the ACT, or the PT, PTT and ACT

Device for self-testing that monitors the PT/INR only

Activated Clotting Time (ACT)

Device that can perform ACT alone or ACT with PTT, PT, or both

D-Dimer

Separate device or one device which is used in the detection of D-dimers and cardiac markers

Devices for Point of Care Coagulation Testing by Capability

- **Thromboelastography** Separate Device
- **Platelet Count** Separate Device
- **Platelet Function** Separate Device
- **Anti-Factor Xa for LMWH Assay** Separate Device
- **Antibody to Heparin – PF4** Separate Device
- **Ecarin Clotting Time** Separate Device
- **Chromogenic Factor X** Separate Device
- **ADAMTS –13 activity** Separate Device

Coagulation Testing NOT Likely To Be Improved By a Point of Care Testing Platform

With minor exceptions for specific clinical circumstances –

- **Hypercoagulation Testing**
- **von Willebrand Disease Evaluation**
- **Coagulation Factor Assays**
- **Antiphospholipid Antibody Testing**

PT / INR
Monitoring by
Healthcare
Workers

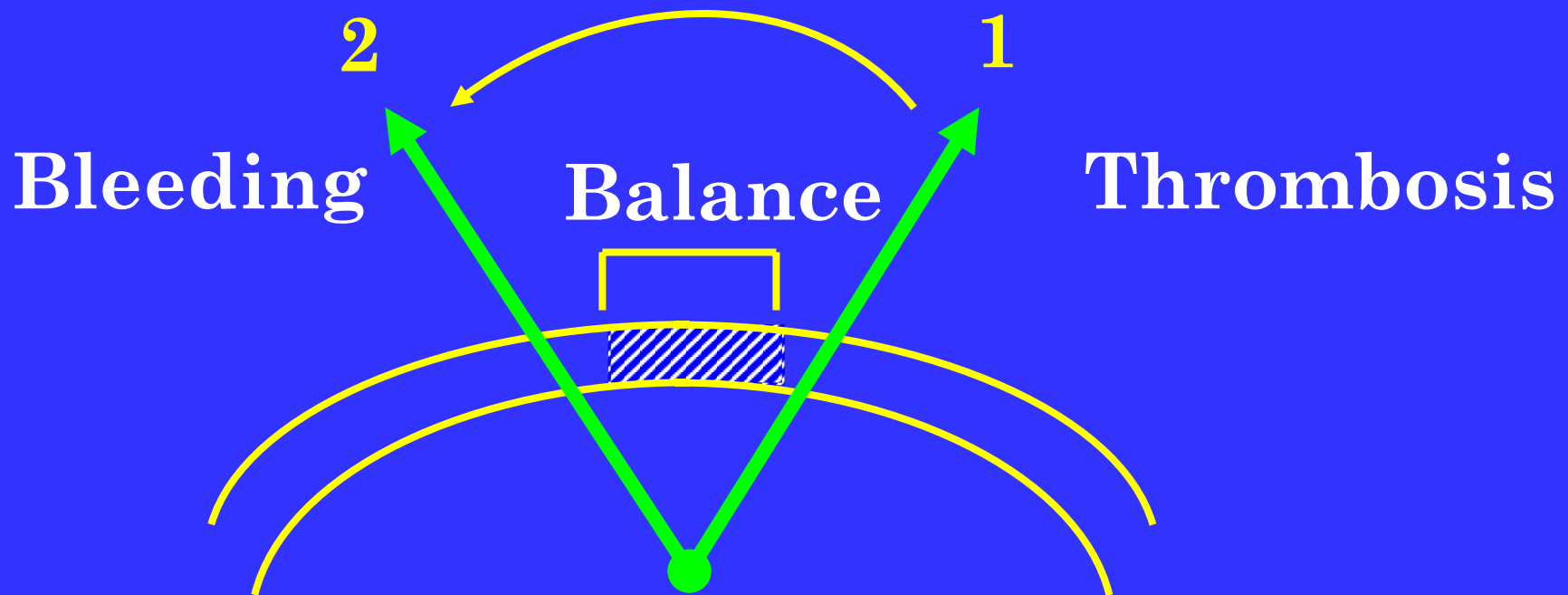
Point of Care Testing for Warfarin Management

The Issues:

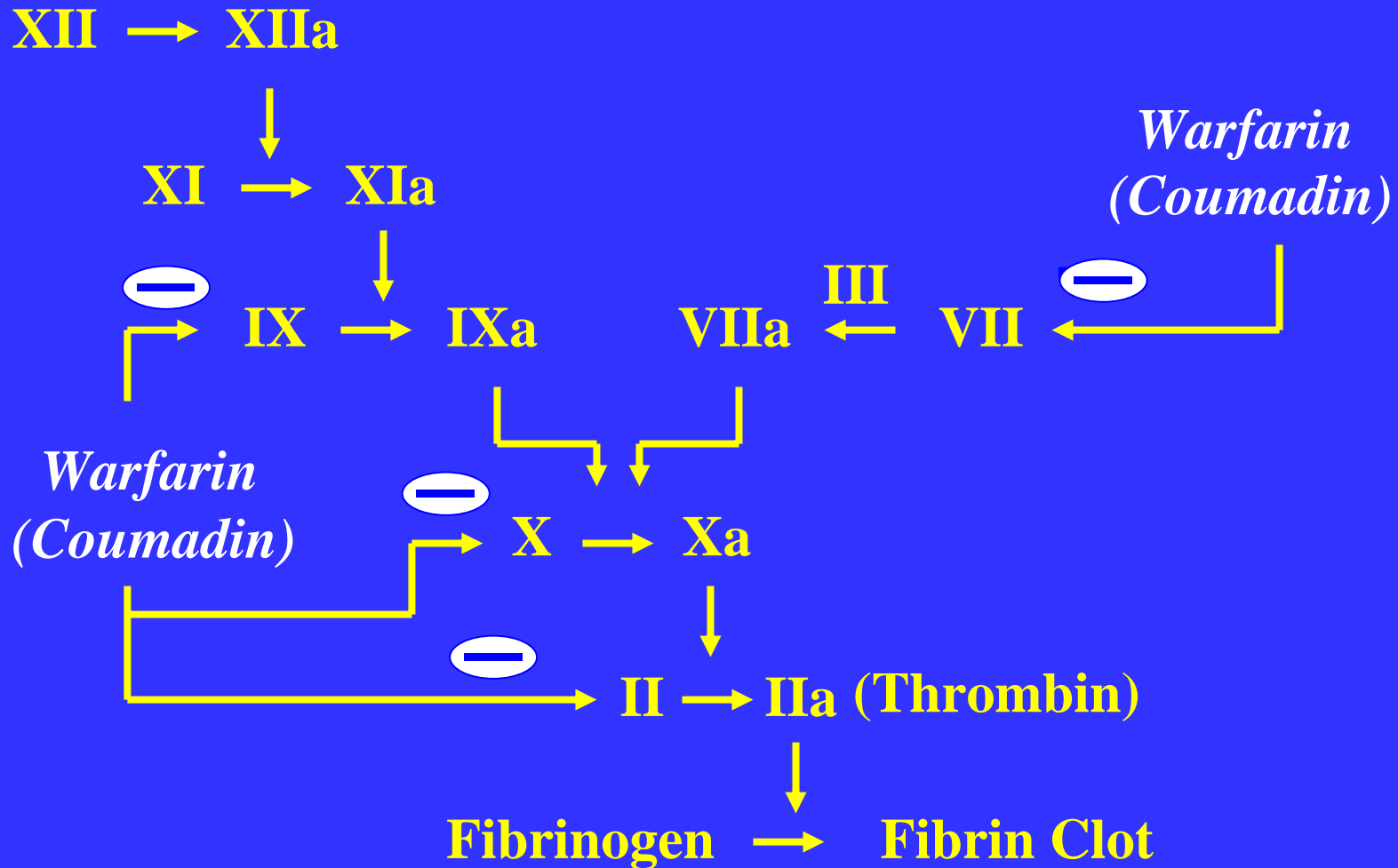
- Approximately 1% of the population of a non-developing country is taking coumadin
- ~40% of anticoagulation clinics in US have POC testing
- Physician offices are not uncommonly equipped with a POC test for anticoagulant monitoring

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Too Much Anticoagulation in a Thrombotic Patient



Inhibition of the Coagulation Cascade by Warfarin (Coumadin)



PT Testing: Main Lab vs. Point of Care Testing in Hospital for Warfarin Management

The Issues:

- **POC & Main Lab results may not match**
- **POC Brand A & POC Brand B results may not match**
- **Testing is much more convenient for patient by fingerstick vs. venipuncture**
- **If Main Lab Service is optimized & phlebotomy is excellent, there may be less institutional interest in POC testing within the hospital because of the items in bullets 1 and 2 above**

PT Testing: Point of Care by Healthcare Professional vs. Self Testing

The Issues:

- POC self testing has clearly better outcomes – bleeding, thrombosis, in range results % - than management by a physician practice, with testing 2 – 4 times as often
- **POC self testing has similar outcomes to management by an anticoagulation clinic**
- Is the ideal situation home testing 2 – 3x/week and testing in lab through anticoagulation clinic 3 – 4 times/yr?
- **The cost of the monitoring instrument is a major barrier to many patients who would otherwise use it**

PT Testing: Point of Care by Healthcare Professional vs. Self Testing

The Issues:

- **Purchase of instrument is US largely through physicians with prescription**
- **Only FDA approved use for self-testing is for monitoring of patients with artificial heart valves**
- **Of ~2.5 million US patients on warfarin, only about 10,000 using self testing –with slow growth expected in the years ahead – after which an oral anticoagulant other than warfarin may dominate the market**

**PT / INR Monitoring
by Self Testing –
with or without
warfarin dose
adjustment**

**Conclusion from a Recent Meta-Analysis to
Determine Clinical Outcome for Patients
Self-Testing for INR**

Lancet 2006; 367:404-11

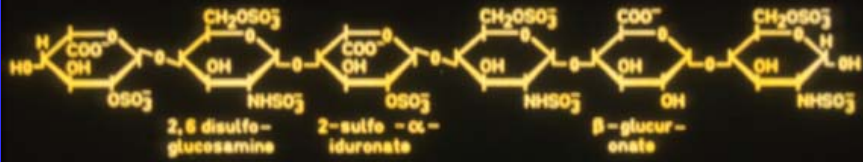
**Home INR testing may be better than
INR testing by others –**

**but only if you compare self testing to
management of anticoagulation by
physician practices or single physicians–**

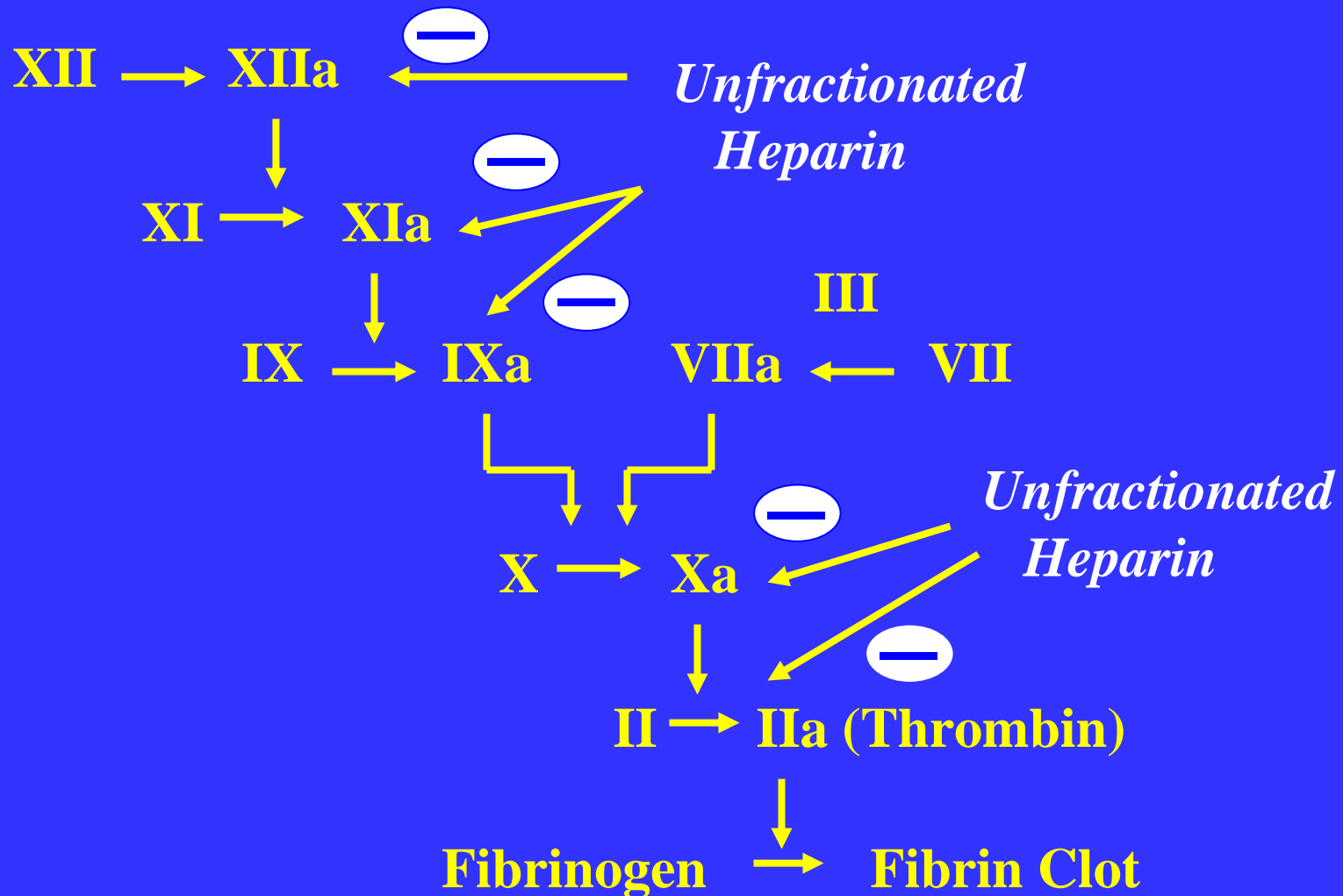
**not if you compare home testing to
anticoagulation clinics managed by a
staff of trained nurses**

**PTT Monitoring
for Standard
Heparin Therapy**

HEPARIN: STRUCTURE



Inhibition of the Coagulation Cascade by Unfractionated Heparin



PTT Testing: Heparin Monitoring

The Issues:

- Quicker turnaround time to roughly approximate heparin concentration in selected clinical situations – such as the operating room – may be very important to optimize outcome
- **Institutional factors that influence decision include pneumatic tube/transit time optimization of STAT service by lab; increased budget costs for point of care testing relative to total cost per encounter**

PTT Testing: Heparin Monitoring

The Issues:

- The issue of matching POC values for the PTT to those obtained in the main laboratory are the same as for the PT – POC devices do not often match each other and a POC device may not match the main laboratory result
- **A major reason why results often do not match is that the sample for POC is often whole blood and the sample for the main laboratory is plasma – and the RBC do influence the result**

**ACT Monitoring
for High Dose
Heparin Therapy**

ACT Testing: POC only

The Issues:

- **When the amount of heparin is so great that the PTT is beyond the upper limit of detection, the ACT is used to monitor heparin therapy**
- **Testing at site is essential-no actual in lab solution**
- **Standardization of test & comparability between instruments is very limited**

**D-Dimer
Measurement for
Rule-Out of Venous
Thrombosis :
DVT and PE**

D-Dimer Testing: To Rule out DVT or PE

The Issues:

- **There is a major cost reduction when a patient who is short of breath and low risk for venous thrombosis “rules out” with a negative D-Dimer test**
- **Less use of Spiral CT, VQ Scans, anticoagulants and decreased length of stay in emergency room**
- **Institutional factors that influence decision include turnaround time from main lab (<60 min) and use of a test that is widely perceived by treating physicians as effective in ruling out thrombosis**

**Platelet Function
Testing for
Monitoring
Platelet Activity**

Clinical Indications for Aspirin Therapy

12,900,000

Heart Attack & Angina

4,700,000

Stroke

16,000,000

Diabetics > age 30

12,000,000

Peripheral Arterial Disease

45,600,000

Total Clinical Potential

Tables/figures courtesy Gordon Ens, BA, MT (ASCP)

Advance for Medical Laboratory Professionals, December 1, 2003

Platelet Function Testing

The Issues:

- Physicians have long been searching for a replacement for the bleeding time to assess platelet function
- **Platelet function testing could emerge to detect aspirin resistance or inhibition of platelets by GP IIb/IIIa inhibitors**
- Institutional factors that influence the decision include degree of interest in testing for platelet function by the medical and laboratory staff; perceived credibility of data from methods regarding platelet function

Thromboelastography for Monitoring Clot Formation and Dissolution

Thromboelastography

The Issues:

- Anesthesiologists are interested in whole blood clotting tests to personally follow clotting status in the operating room, especially for liver transplantation
- **Anesthesiologists have variable triggers from a TEG tracing for transfusion with plasma, platelets, and cryoprecipitate – and administration of amicar**
- Institutional factors that influence the decision include degree of interest in TEG by specific anesthesiologists; the willingness of the laboratory to assist the anesthesiologists to validate the use of the instrument for clinical decision making

**Platelet Count
Determination for
Monitoring
Platelet Number**

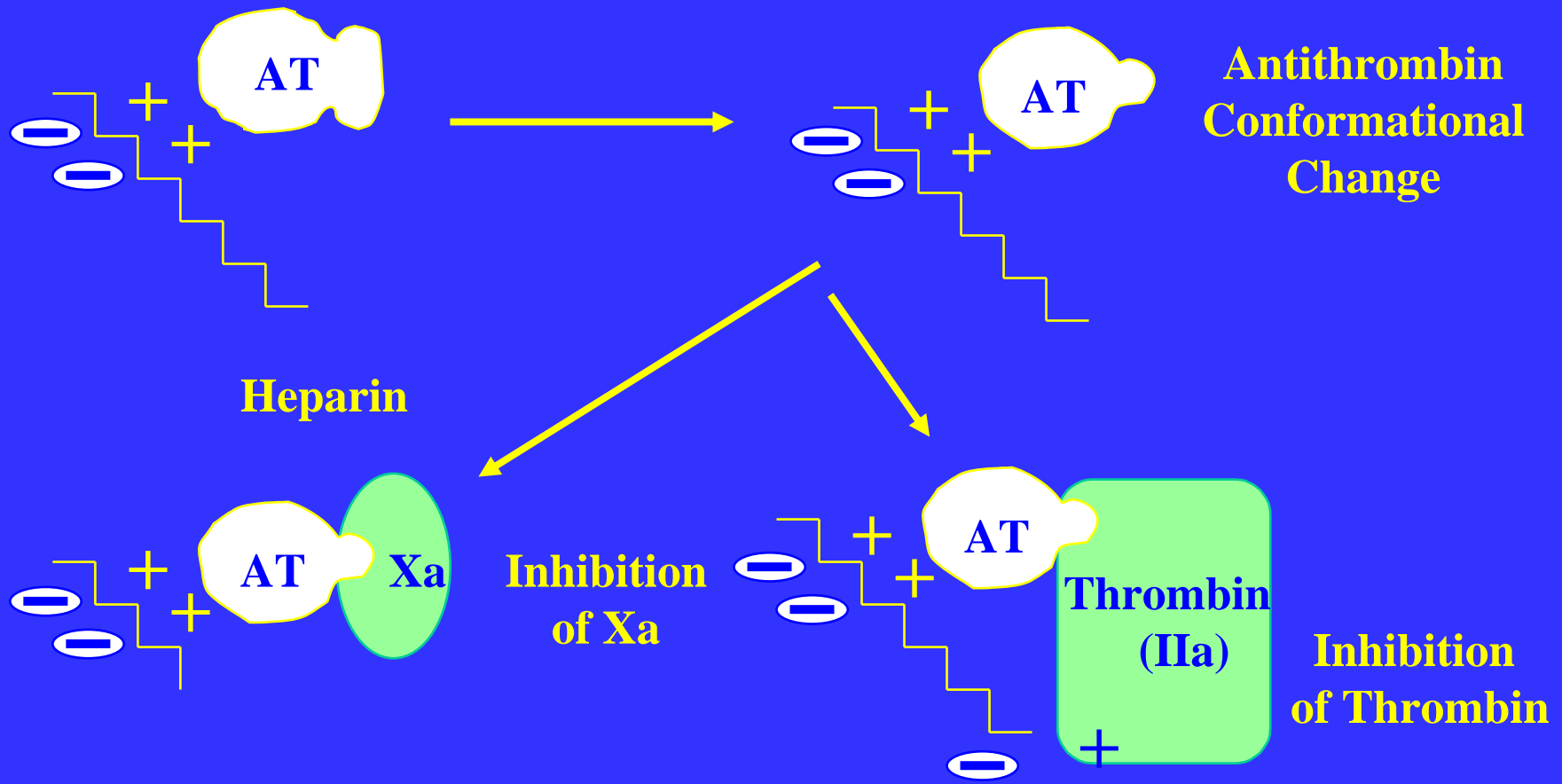
Platelet Count: POC in Selected Sites

The Issues:

- Common practice as part of CBC in physician office lab to obtain platelet count – not usually for STAT purposes
- **A platelet count in an OR with 2-5 minute turnaround time may decrease transfusion of platelet concentrates**
- Institutional factors to consider include the reluctance of non-laboratorians, notably nurses and many anesthesiologists, to perform laboratory testing; effectiveness of communication between laboratory & clinical service for instrument implementation and maintenance

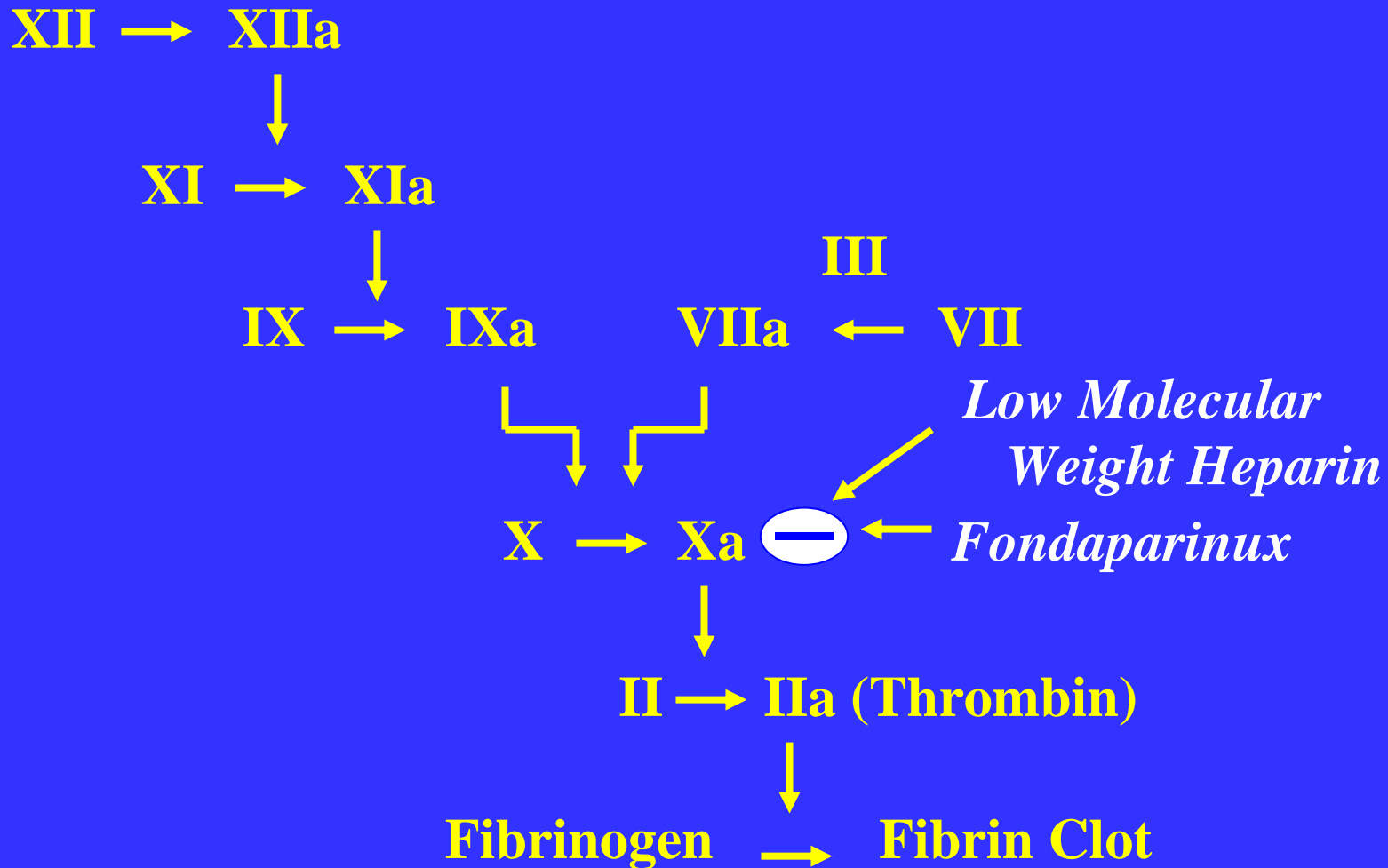
**Anti-Factor Xa
Monitoring for
Low Molecular
Weight Heparin
Therapy**

Heparin and Shorter Derivatives : Interaction with Antithrombin

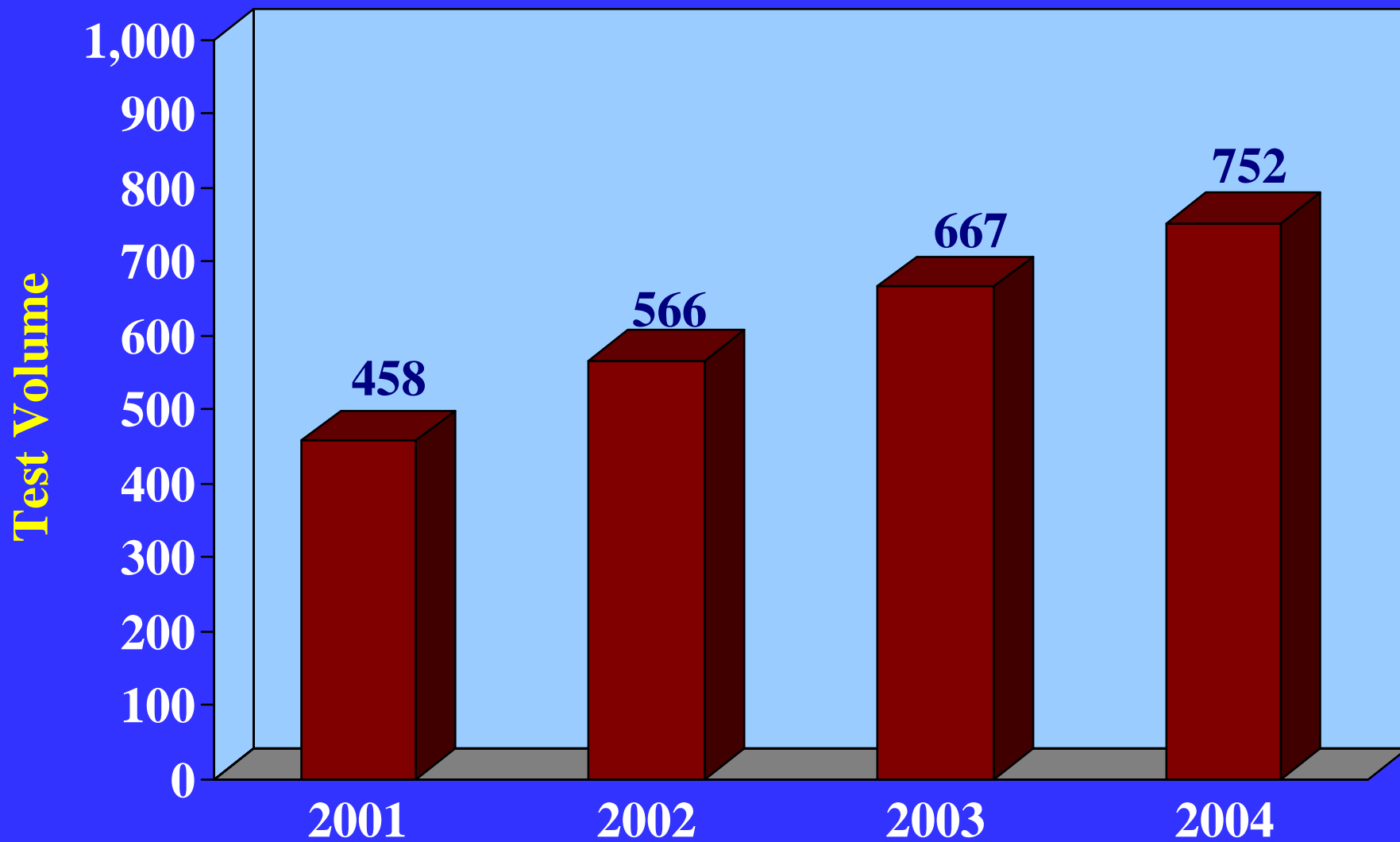


Low Molecular Weight Heparin &
Fondaparinux (only 5 sugars long)

Inhibition of the Coagulation Cascade by LMW Heparin and Fondaparinux



ANTI-FACTOR Xa

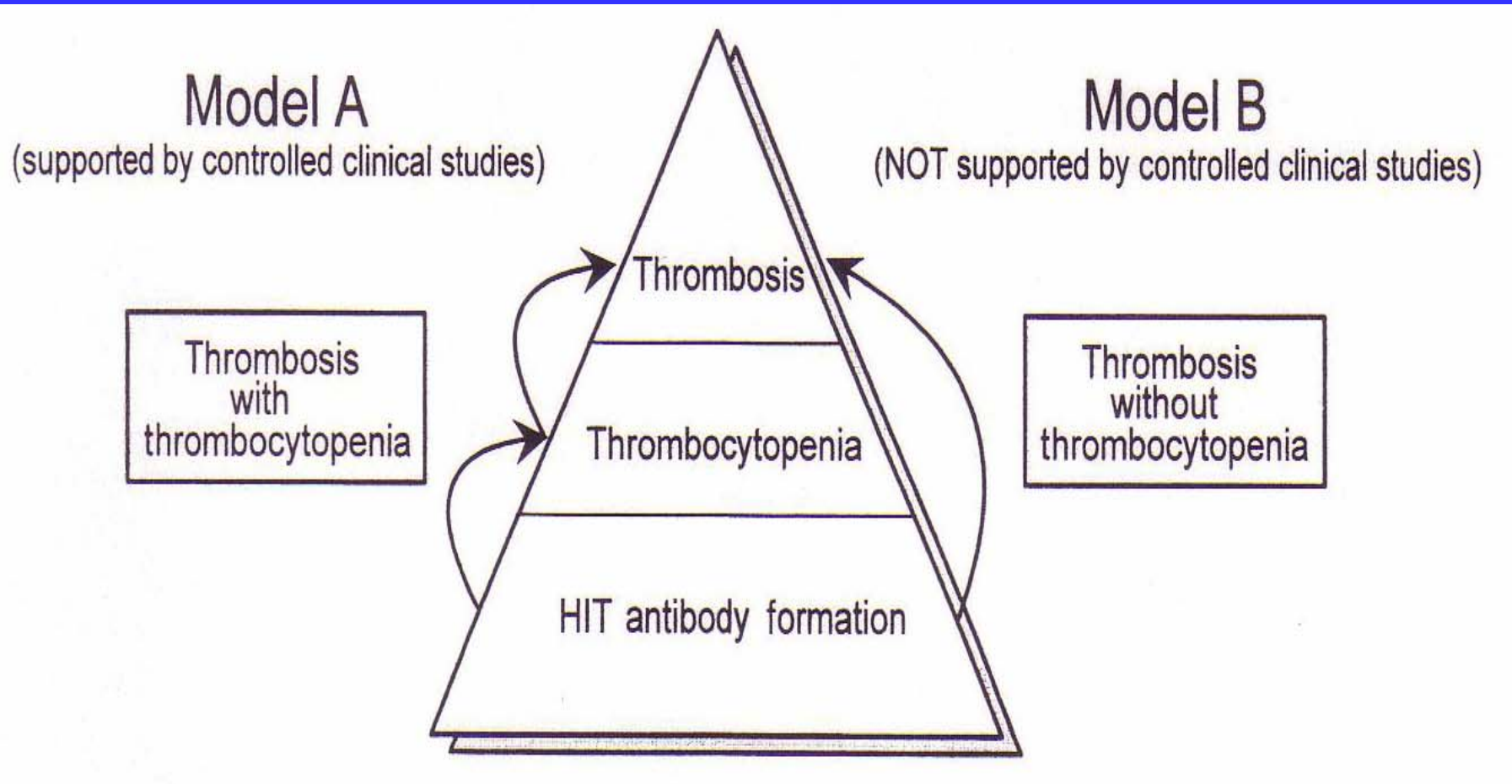


Anti-Factor Xa for LMWH Monitoring in Selected Clinical Sites

The Issues:

- **Interventional cardiology is greatly affected by positive ELISA Tests for heparin – PF4 antibodies – and subsequent uncertainties about anticoagulant use**
- **The use of LMWH is associated with a much lower incidence of heparin – PF4 antibodies and most cardiologists demand a POC monitoring assay that would replace the ACT-test development sponsored by pharmaceutical company may influence choice of LMWH preparation**
- **Institutional factors to consider include the willingness of cardiologists to switch from heparin to LMWH; the sensitivity & clinical response to a positive Elisa Test for heparin – PF4 antibodies**

**Assay for Antibodies
to Heparin-Platelet
Factor 4 Complexes in
the Assessment for
Heparin-Induced
Thrombocytopenia**



Warkentin, T., A. Greinacher. 2001. Heparin-Induced Thrombocytopenia: Second Edition. Marcel Dekker, Inc. New York, NY

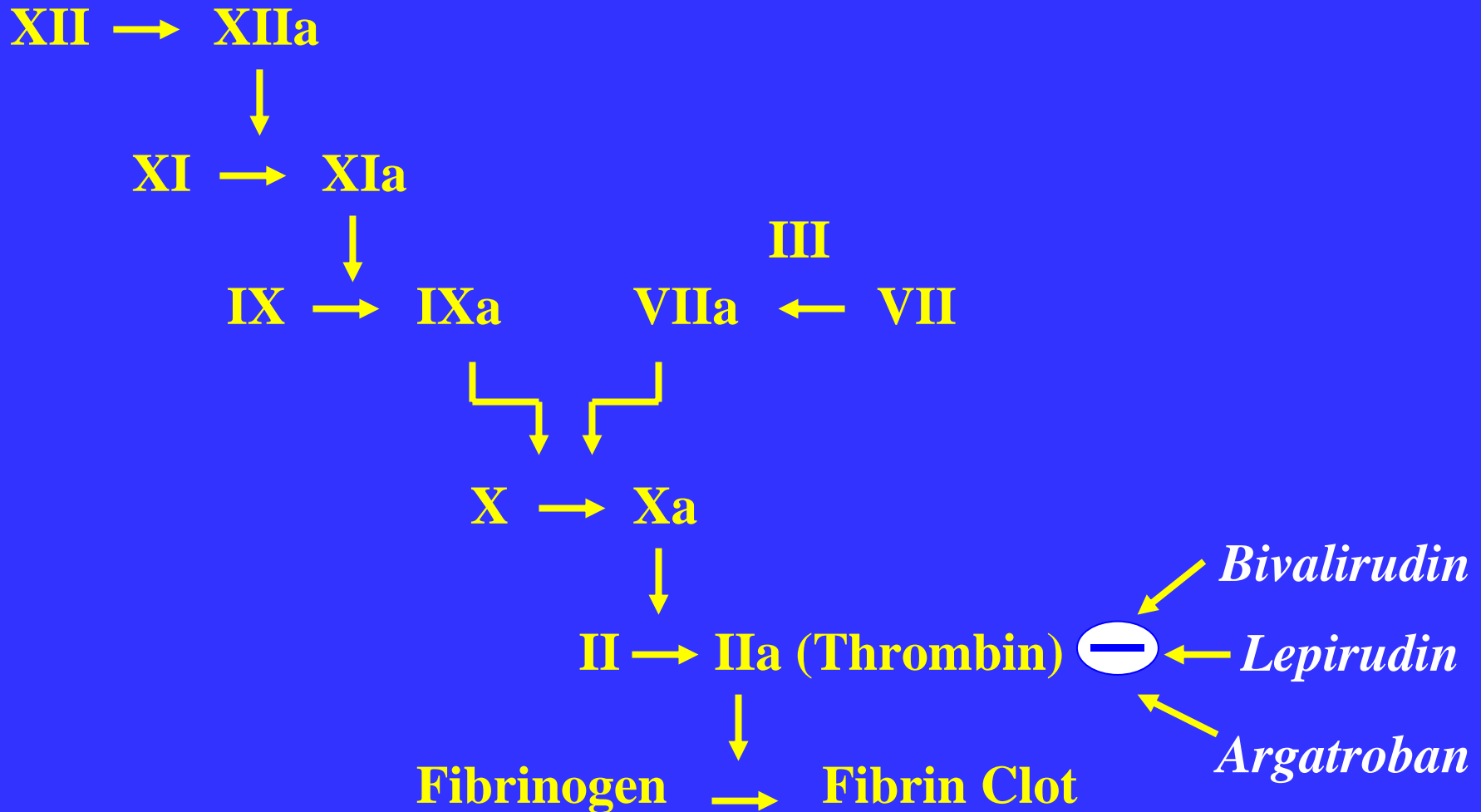
Antibodies to Heparin-PF4

The Issues:

- If the lab will not set it up, major often life threatening decision on anticoagulant selection looms while waiting for test result
- A major cost offset for a negative test is the ability to continue heparin use and avoid a more expensive alternative anticoagulant with its attendant complications
- Institutional factors to consider include the interest of physicians to identify HIT and their willingness to use and monitor alternative anticoagulants

**The Ecarin Clotting
Time for Monitoring
High Dose Therapy
with Direct Thrombin
Inhibitors**

Inhibition of the Coagulation Cascade by Direct Thrombin Inhibitors



Ecarin Clotting Time

The Issues:

- Useful for the monitoring of direct thrombin inhibitors when used in concentrations that exceed the dynamic range of the PTT
- Use is likely to grow as alternative anticoagulants are used instead of heparin for invasive cardiology and cardiac surgery
- Institutional factors to consider include the interest of physicians in the use of alternative anticoagulants

**The Chromogenic
Factor X Assay to
Monitor Warfarin in
the Presence of Direct
Thrombin Inhibitors**

Clinical Situations Where POC Testing Has Not Developed But Where There is a Clinical Need: Chromogenic Factor X

The Issues :

- **If the lab will not set it up, patients in an argatroban-coumadin overlap stay in hospital at great expense waiting for answer**
- **The MGH has spent more than \$400,000 per year in added length of stay holding patients over the weekend for a chromogenic factor X assay on Monday**

**Transition from Heparin to
Warfarin : No Interference
by Heparin in the INR to
Monitor Warfarin**

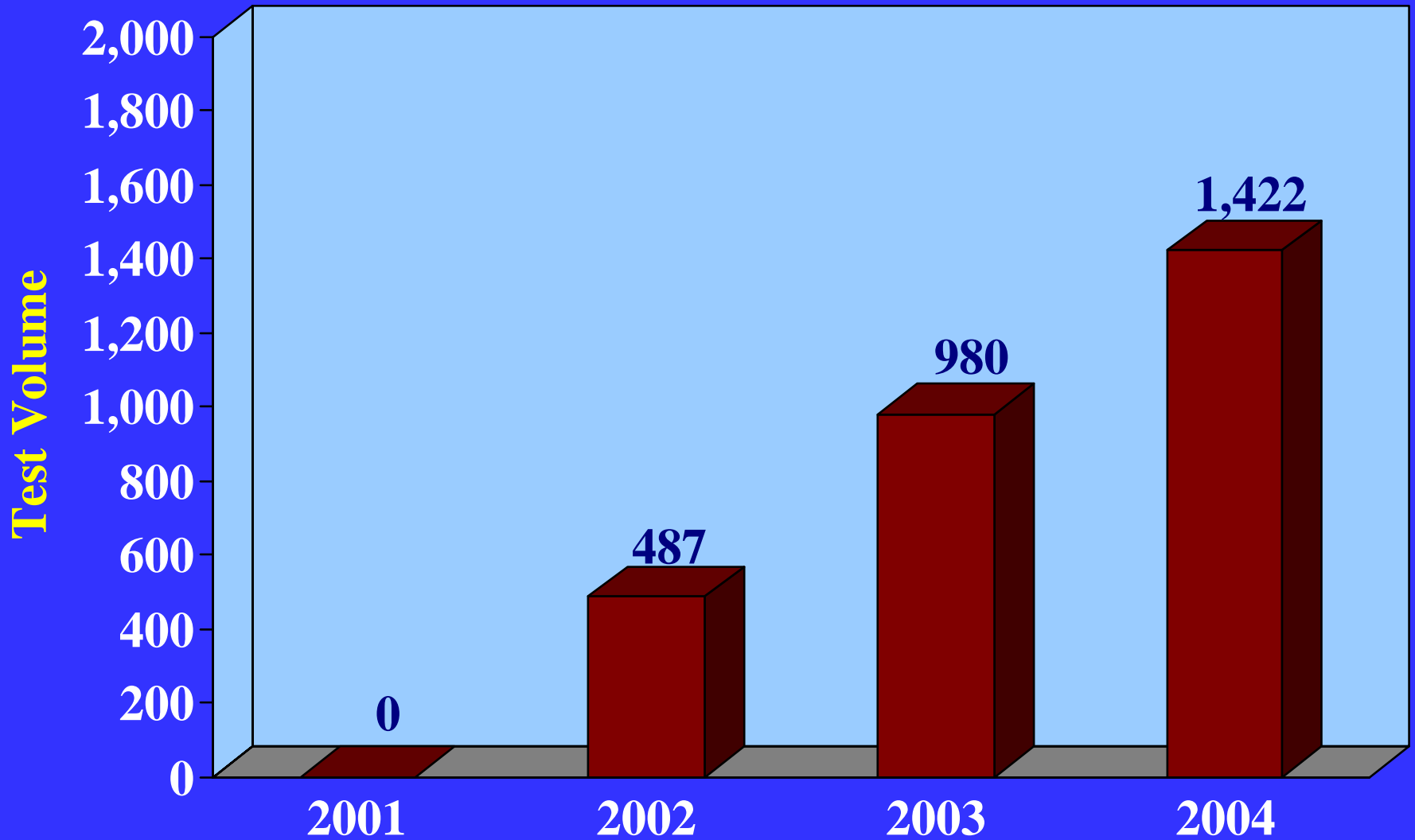


Transitioning from Argatroban to Coumadin – The Argatroban Makes INR Monitoring Impossible



**When is the warfarin effective allowing
the argatroban to be discontinued?**

CHROMOGENIC FACTOR X

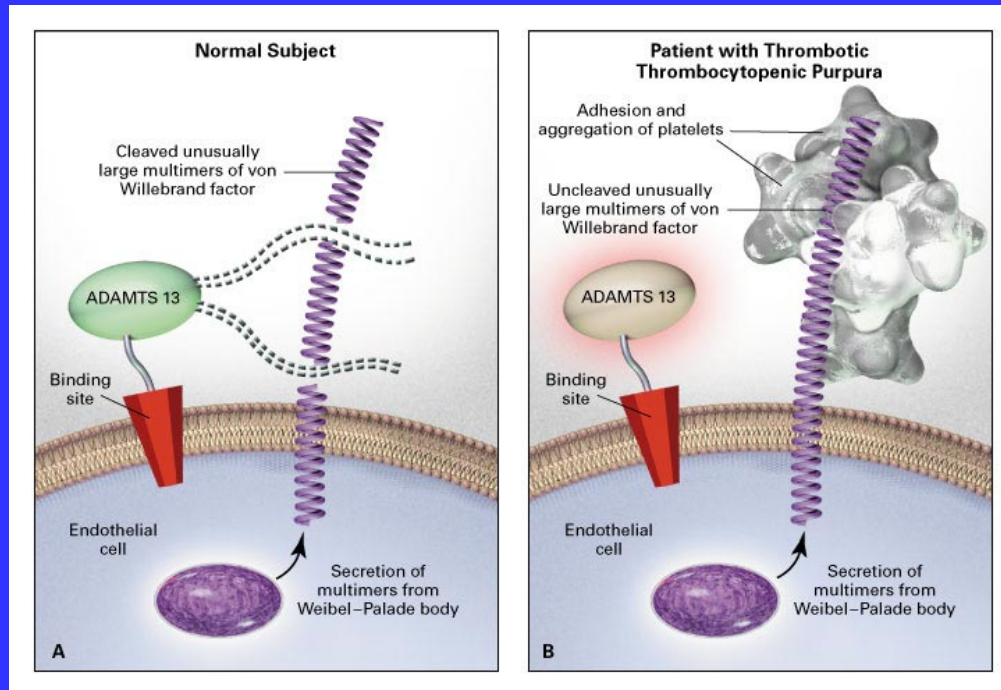


**The ADAMTS-13
Assay to Assess for
the Presence of
Thrombotic
Thrombocytopenic
Purpura (TTP)**

Clinical Situations Where POC Testing Has Not Developed But Where There is a Clinical Need: ADAMTS-13 Assay

- **The diagnostic dilemma for a thrombocytopenic patient not uncommonly involves consideration of Thrombotic Thrombocytopenic Purpura (TTP) – for which immediate treatment with apheresis is often life saving**
- **A POC ADAMTS-13 assay could greatly influence decision making on apheresis for questionable TTP**

THROMBOTIC THROMBOCYTOPENIC PURPURA



- TTP patients have large multimers of von Willebrand Factor
- ADAMTS-13 deficiency is found in patients with chronic TTP – either from a deficiency of ADAMTS-13 (familial deficiency or an inhibitor to ADAMTS-13)

**More Anticoagulant
Drugs are in the
Pipeline – Which Will
Need POC Testing ?**

Anticoagulants in Use or Under Evaluation – other than Warfarin and Heparin

Anticoagulant	Route	Target	Test to Monitor
•LMW Heparin	SC	Xa	Anti-Xa
•Fondaparinux	SC	Xa	Anti-Xa
•Idraparinux	SC	Xa	Anti-Xa
•Lepirudin	IV	IIa	PTT
•Argatroban	IV	IIa	PTT
•Bivalirudin	IV	IIa	PTT
•Bayer XXX	Oral	Xa	Anti-Xa?
•Dabigitran	Oral	IIa	PTT ?

POC Test Development Cannot Lose Focus of the Main Rationale for Point of Care Testing

**Improved patient outcome and/or
decrease in total cost of patient
encounter**

often despite

**Decrease in test accuracy & precision
increase in cost per test**

**Which laboratorians tolerate with
difficulty!**

Do the rapid turnaround time and convenience of point of care coagulation tests offset the disadvantages of multiple instrument platforms producing differing results which may not appear in the medical record?

The answer is not the same for all point of care coagulation tests and the answer for each is institution dependent!