

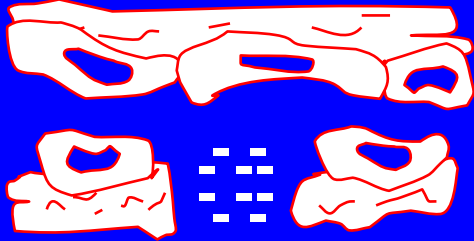
Michael Laposata, M.D., Ph.D.
Director, Clinical Laboratories
Massachusetts General Hospital
Professor, Harvard Medical School

OUTLINE OF THE PRESENTATION

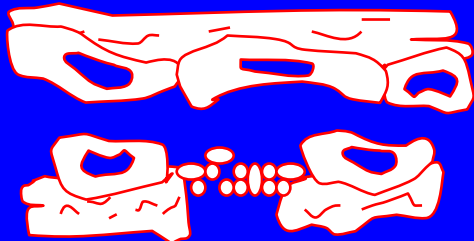
- **Background – Clot formation**
- **Coumadin action**
- **Coumadin monitoring**
- **Coumadin prophylaxis**
- **Coumadin in treatment of existing thrombosis**
- **Other anticoagulants and transitioning from another anticoagulant to coumadin**

Clot Formation

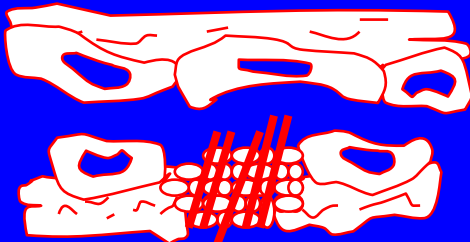
Vessel Wall Injury



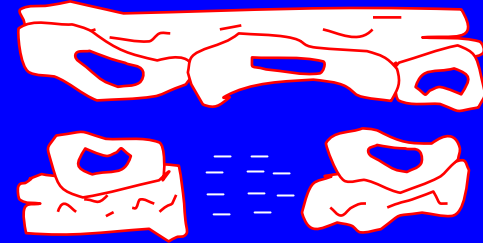
Platelet Adhesion



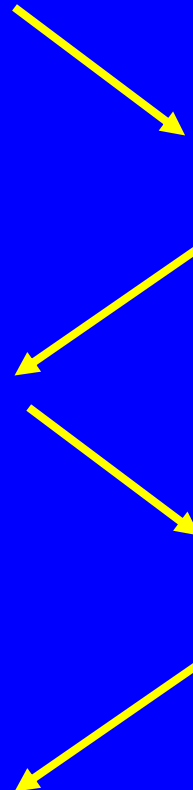
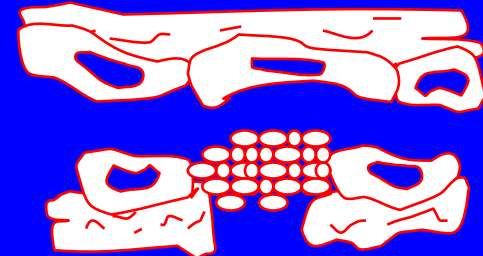
Fibrin Formation

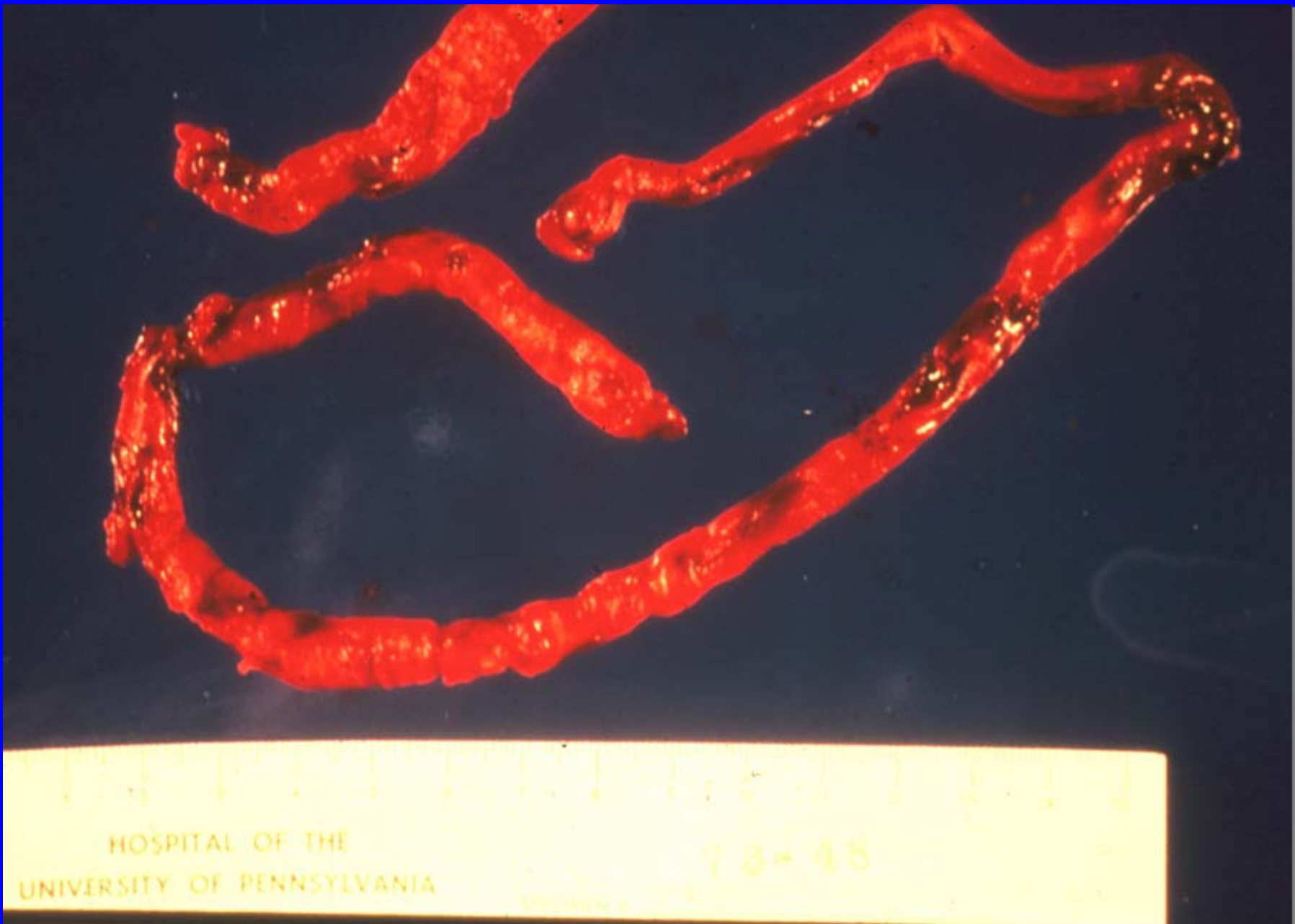


Vessel Wall Contraction



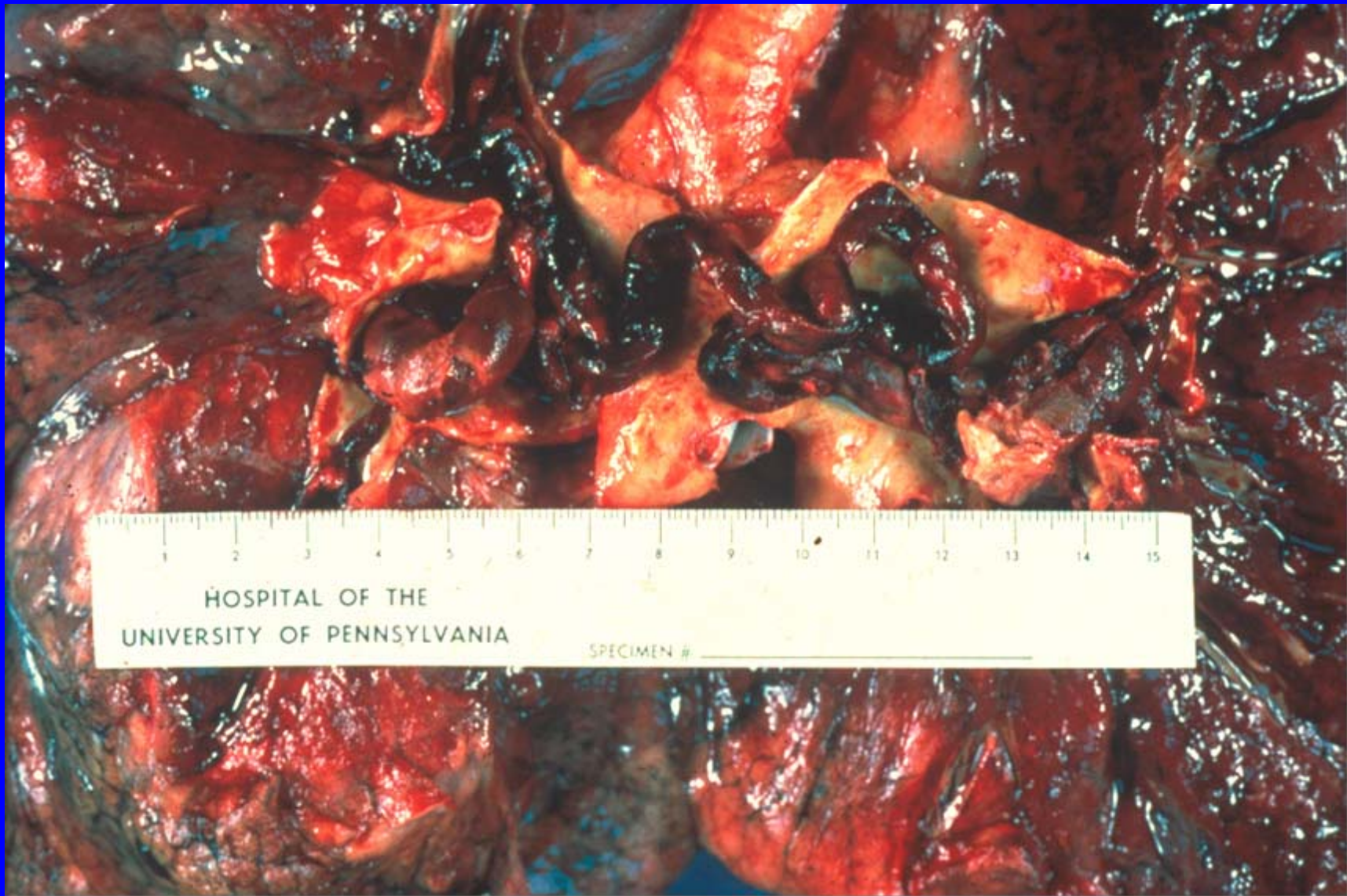
Platelet Aggregation





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SPECIMEN # _____



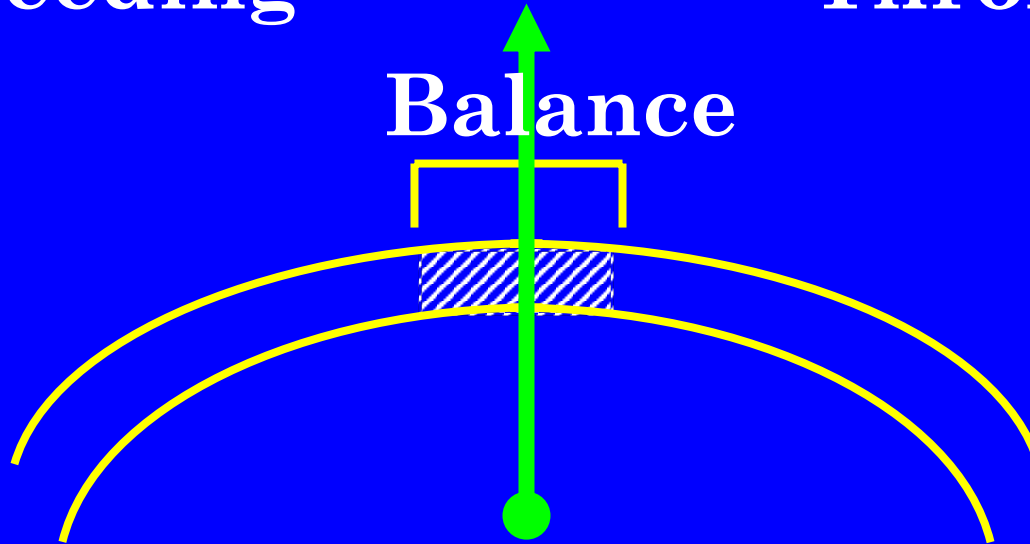
Patient's fingers at 12 hours (left) and 3 weeks (right).

The Appropriate Level of Hemostasis

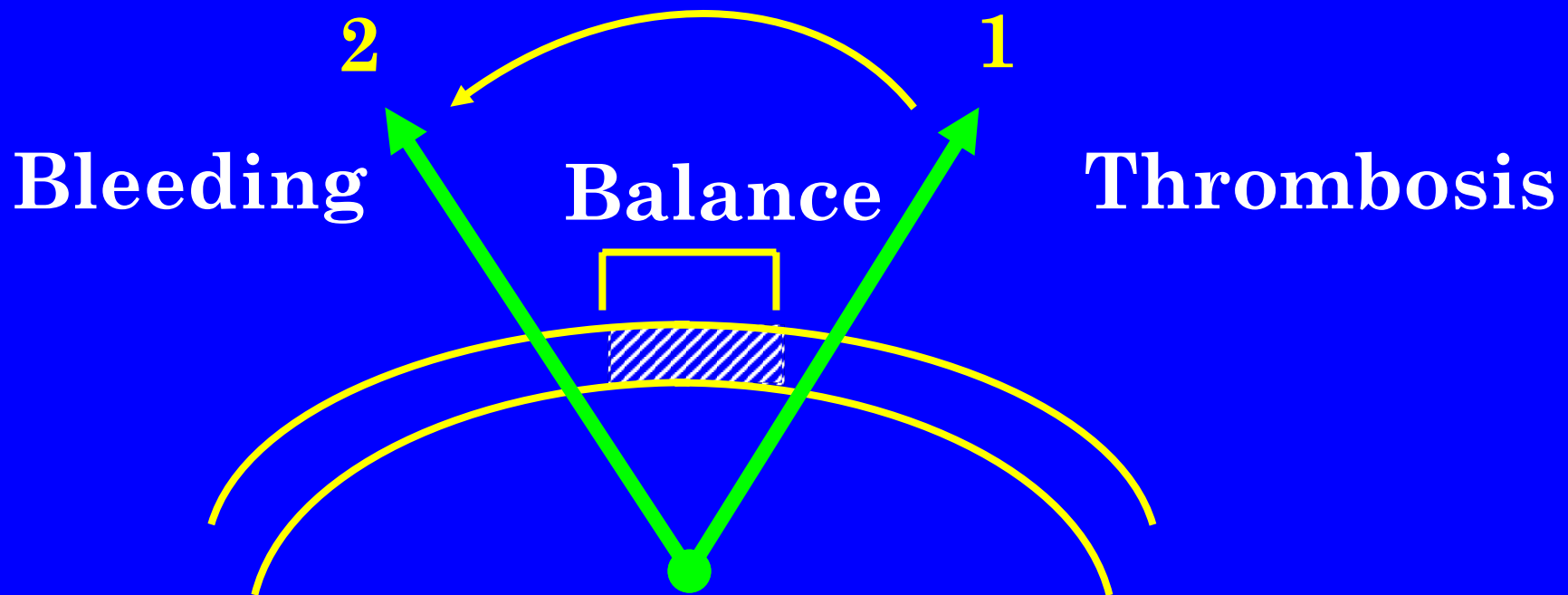
Bleeding

Thrombosis

Balance



Too Much Anticoagulation in a Thrombotic Patient



Primary Prophylaxis

**Preventing the first
thrombotic event**

Secondary Prophylaxis

**Preventing a
recurrence of a
thrombotic event**

DRUG CLASSES: TREATMENT OF THROMBOSIS

- **Anticoagulants: prevent clot formation and limit extension**
 - Oral-Warfarin (Warfarin = Coumadin)
 - Subcutaneous – Unfractionated Heparin, LMW Heparin, Fondaparinux
 - Intravenous - Unfractionated heparin, argatroban, lepirudin
- **Antiplatelet drugs: impair platelet function**
- **Thrombolytic agents: dissolve existing thrombi**

Treatment of an Existing Thrombosis

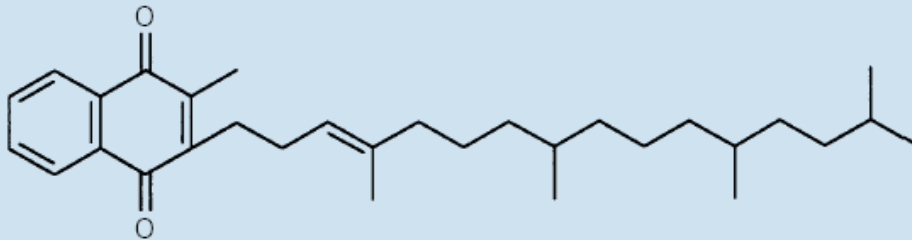
- **Venous Thrombosis – Deep Vein Thrombosis and Pulmonary Embolism**
- **Acute Coronary Syndrome**
- **Arterial Thrombosis**

Coumadin: Drug Action

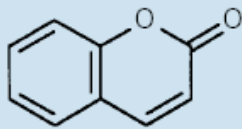
HISTORICAL BACKGROUND: WARFARIN

- **In the Great Depression, farmer Ed Carson fed his cattle with spoiled sweet clover. Cattle eating the spoiled clover bled to death.**
- **In 1930, he provided a large container of blood which could not clot and many pounds of spoiled sweet clover to Karl Paul Link a biochemist at the Wisconsin Agricultural Research Foundation. Dr. Link identified the toxic substance as Dicoumarol. Spoilage of the clover permitted conversion of Coumarol to Dicoumarol, the anticoagulant agent.**
- **Dicoumarol was first used as rat poison**

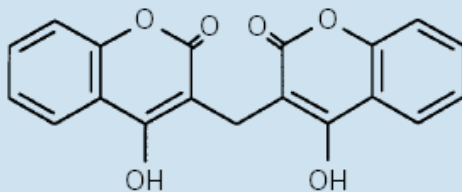
WARFARIN IS A COMPETITIVE ANTAGONIST OF VITAMIN K



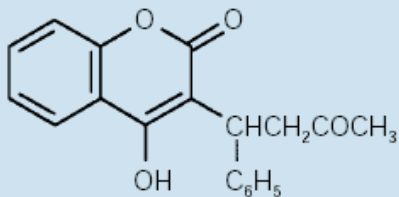
Vitamin K₁
(Phylloquinone)



Coumarin



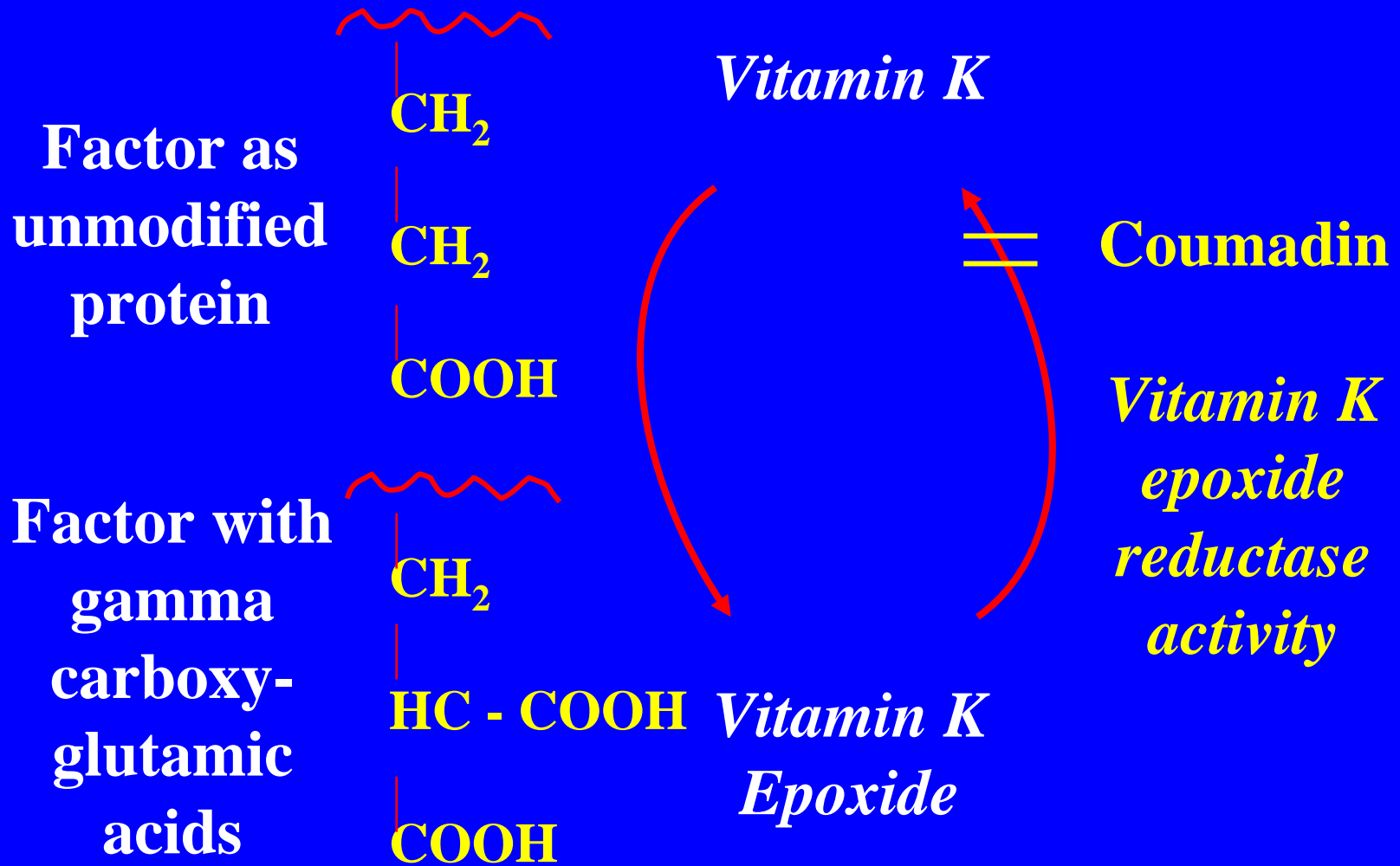
Dicumarol



Warfarin

Scully, M. The Biochemist. 2002.

ACTION OF VITAMIN K



Anticoagulants Inhibit the Coagulation Cascade

XII → XIIa

XI → XIa

IX → IXa VIIa ← III ← VII

Warfarin
(Coumadin)

X → Xa

II → IIa (Thrombin)

Fibrinogen → Fibrin Clot

Warfarin
(Coumadin)

Coumadin: Monitoring

**DIFFERENCES BETWEEN THROMBOPLASIN
PREPARATIONS IN GREAT BRITAIN AND U.S.**

Primary Tissue Source

<i>Great Britain</i>	Previously human brain Currently rabbit brain / lung
<i>U.S.</i>	Rabbit brain / lung

CONSEQUENCES OF GREATER SENSITIVITY OF HUMAN BRAIN THROMBOPLASTIN TO FACTOR DEFICIENCIES

	<u>U.S.</u>	<u>Great Britain</u>
Normal Range	9 - 11	9 - 11
Low Dose Warfarin	13	19
	2 seconds	8 seconds
	Prolonged	Prolonged



*Adequate Anticoagulation?
Higher Dose Warfarin Administered*

*Clinical Consequences:
Bleeding Episodes in U.S. >> Bleeding Episodes in Great
Britain*

Differences Between Rabbit Brain/lung Thromboplastins in the U.S.

1 Plasma Sample Split into 3 for
PT Determinations in 3 Different Laboratories

Hospital A

13 Seconds

Hospital B

15 Seconds

Hospital C

17 Seconds

*1 Sample Tested Using 3 Different Lots of Same
Thromboplastin Reagent from Same Manufacturer*

14 Seconds

15 Seconds

16 Seconds

The International Normalized Ratio - INR

$$\text{INR} = \left[\frac{\text{Patient PT}}{\text{Mean of Normal PT Range}} \right]^{\text{ISI}}$$

**ISI: International Sensitivity Index for Thromboplastin
Used for PT Determination**

*Low ISI = High Sensitivity
to Factor Deficiencies*

*High ISI = Low Sensitivity
to Factor Deficiencies*

Example:

INR = 3.0

$$\text{ISI} = 2$$
$$3.0 = \left[\frac{17.3}{10} \right]^2$$

PT = 17.3 Seconds

$$\text{ISI} = 3$$
$$3.0 = \left[\frac{14.4}{10} \right]^3$$

PT = 14.4 Seconds

DETERMINATION OF THE ISI

*Determination for each lot of thromboplastin
by the manufacturer*

Derived from orthogonal regression analysis of 60 PT values from patients stabilized on oral anticoagulants and 20 normal controls using the test thromboplastin and an international reference preparation derived from human brain

SELECTED THROMBOPLASTINS FROM U.S. SOURCES IN 1992

Arch. Int. Med. 152: 278, 1992

<u>Manufacturer</u>	<u>Reagent Name</u>	<u>ISI</u>
Dade	Thromboplastin C	2.6 - 2.8
	Thromboplastin C Plus	2.0 - 2.16
	Thromboplastin IS	1.2 - 1.4
Organon Technica	Simplastin XL	2.0 - 2.1
	Simplastin Auto	1.9 - 2.0
	Simplastin	1.9 - 2.0
	Simplastin A	1.7
	Simplastin XLS	1.3
Ortho Diagnostics	Ortho - Brain Thromboplastin	1.75 - 2.22

Coumadin: Use in Prophylaxis

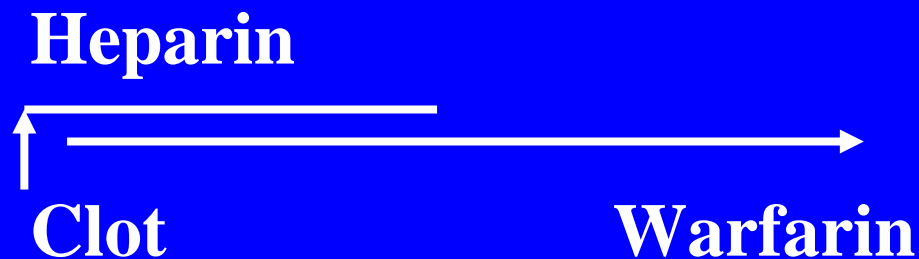
Recommended Intensity of Oral Anticoagulation for Common Indications

<u>Indication</u>	<u>INR</u>
DVT / PE	2.0 - 3.0
MI	2.0 - 3.0
Cardiogenic Embolus	2.5 - 3.5
Tissue Heart Valve	2.0 - 3.0
Valvular Heart Disease	2.0 - 3.0
Atrial Fibrillation	2.0 - 3.0
Mechanical Heart Valve	2.5 - 3.5

Coumadin: Use in Treatment

INDICATIONS FOR WARFARIN THERAPY

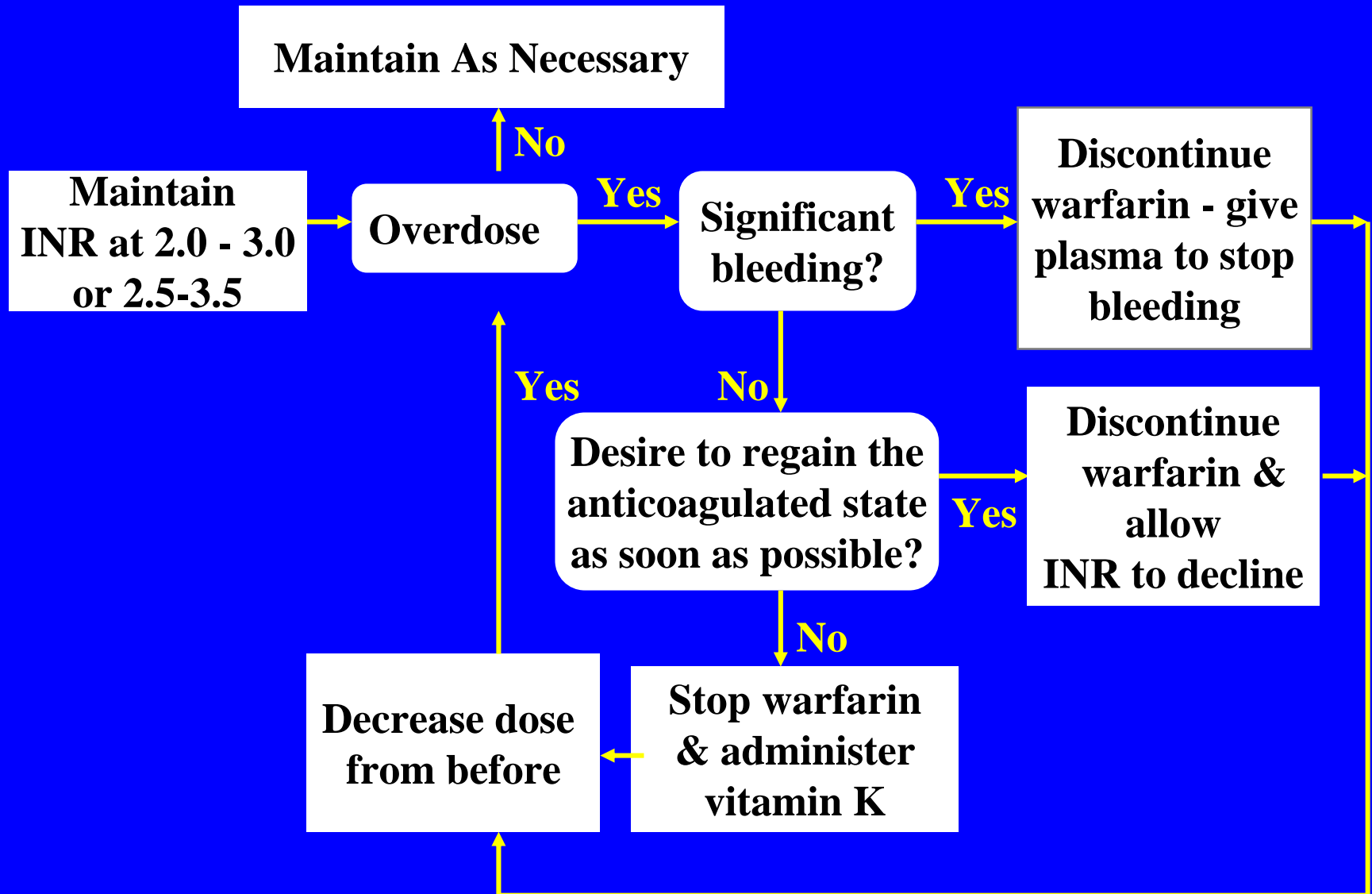
1) **Thrombosis/embolism - primary or recurrent**



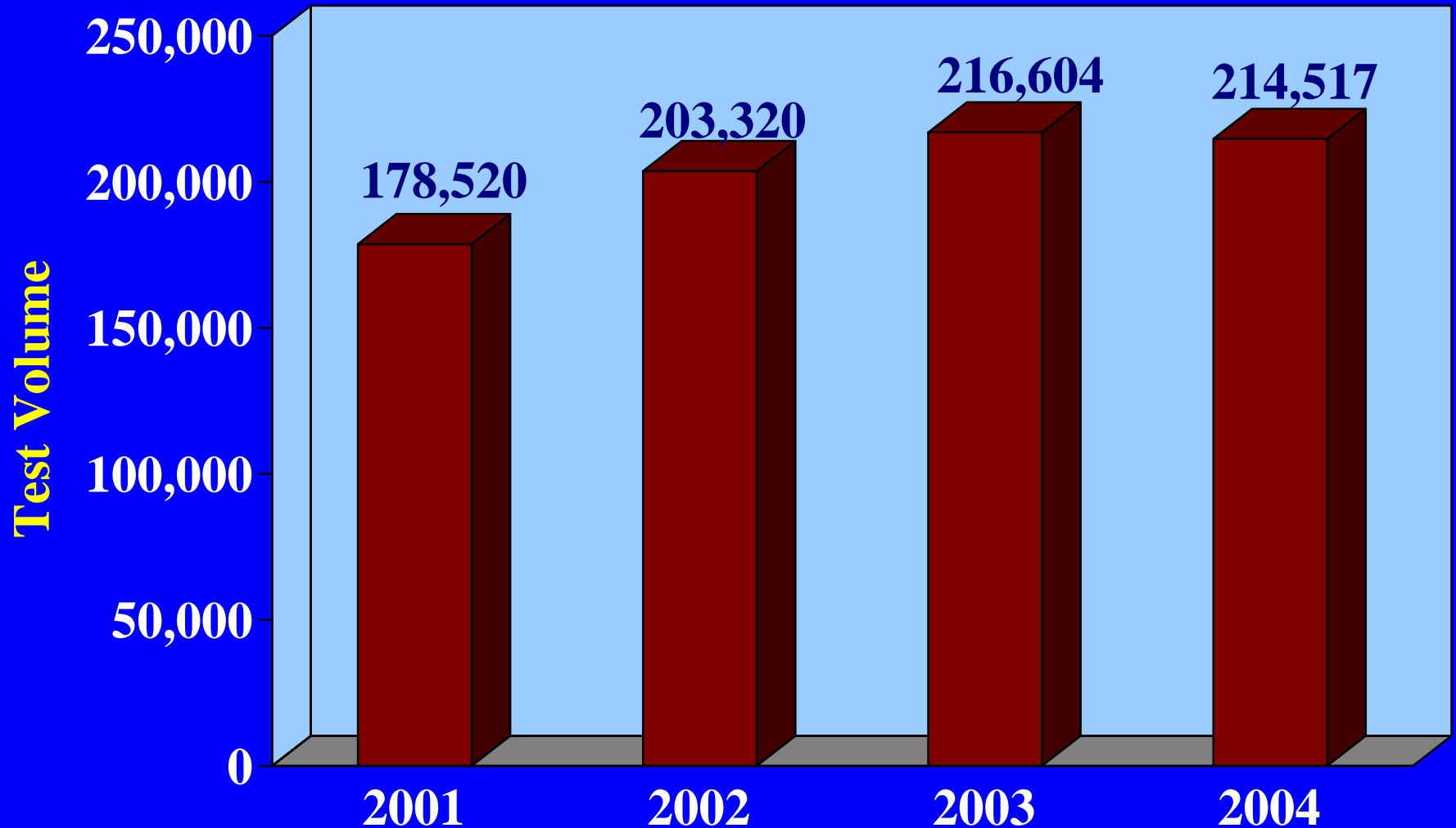
2) **Anticipated thrombosis from atrial fibrillation**

3) **Anticipated thrombosis from presence of prosthetic heart valves**

ALGORITHM FOR WARFARIN USE



PT volume at MGH



How Long Until Warfarin Affected Factors Decrease?

<i>Factor</i>	<i>Approximate Half Life</i>
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VII

4 - 7 hours

IX

12 - 24 hours

X

40 - 45 hours

II

60 – 70 hours

Consequences of an INR Miscalculation

INR Goal = 3.0 and PT = 20 sec
Actual ISI = 2.0 and Mistaken ISI = 1

$$\left(\frac{20}{10} \right)^2 = 4$$

(Actual)

$$\left(\frac{20}{10} \right)^1 = 2$$

(Mistaken)

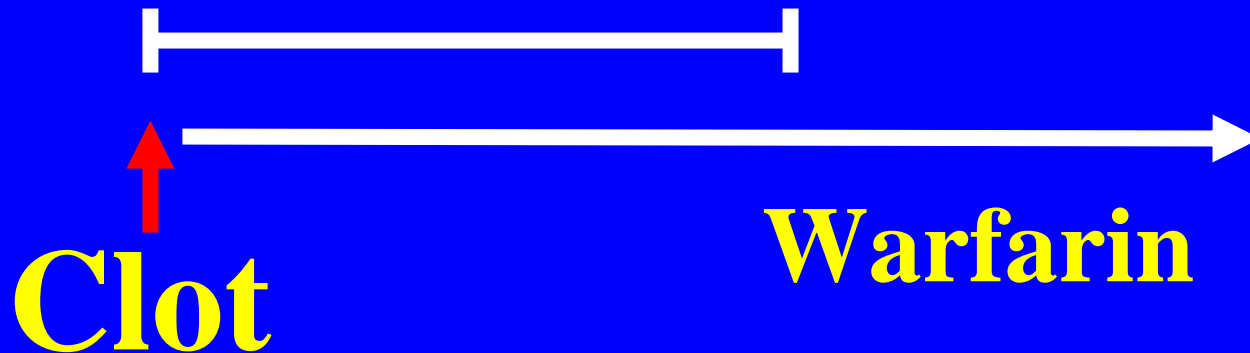
For INR = 4, withhold dose

For INR = 2, increase dose

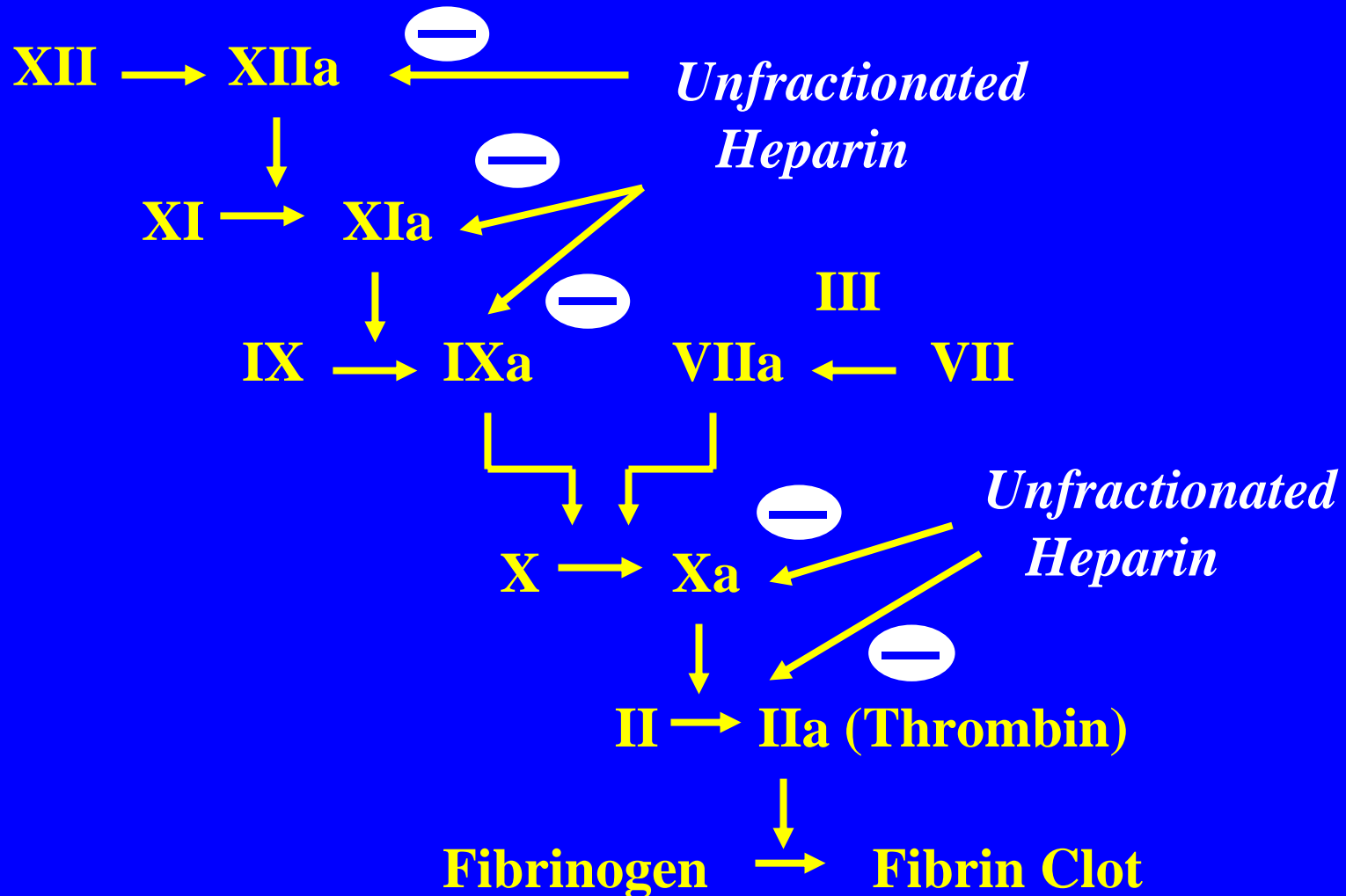
**Other anticoagulants
and transitioning from
another anticoagulant
to warfarin**

Transitioning from another anticoagulant to Warfarin

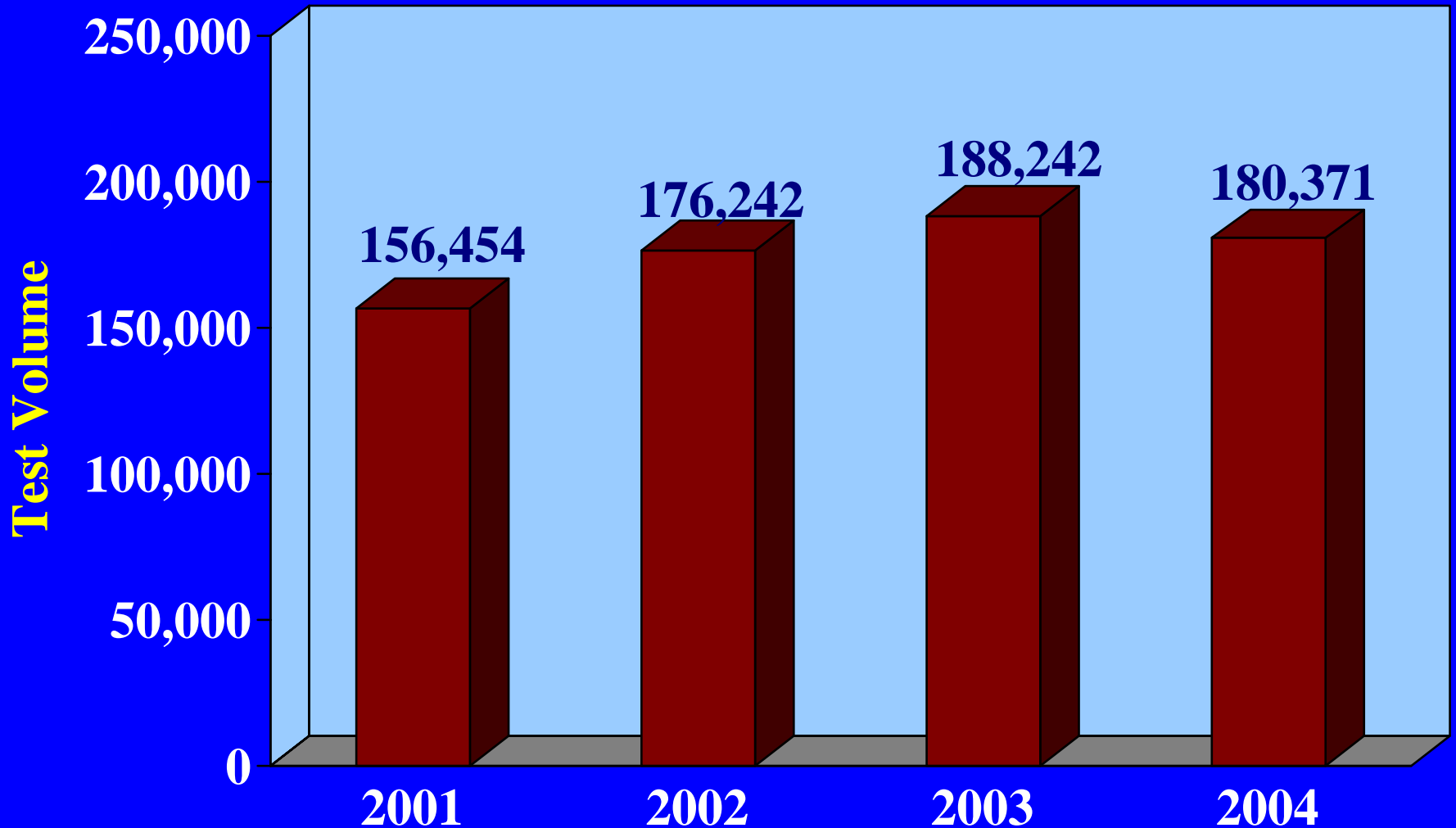
Heparin/LMW heparin/Fondaparinux



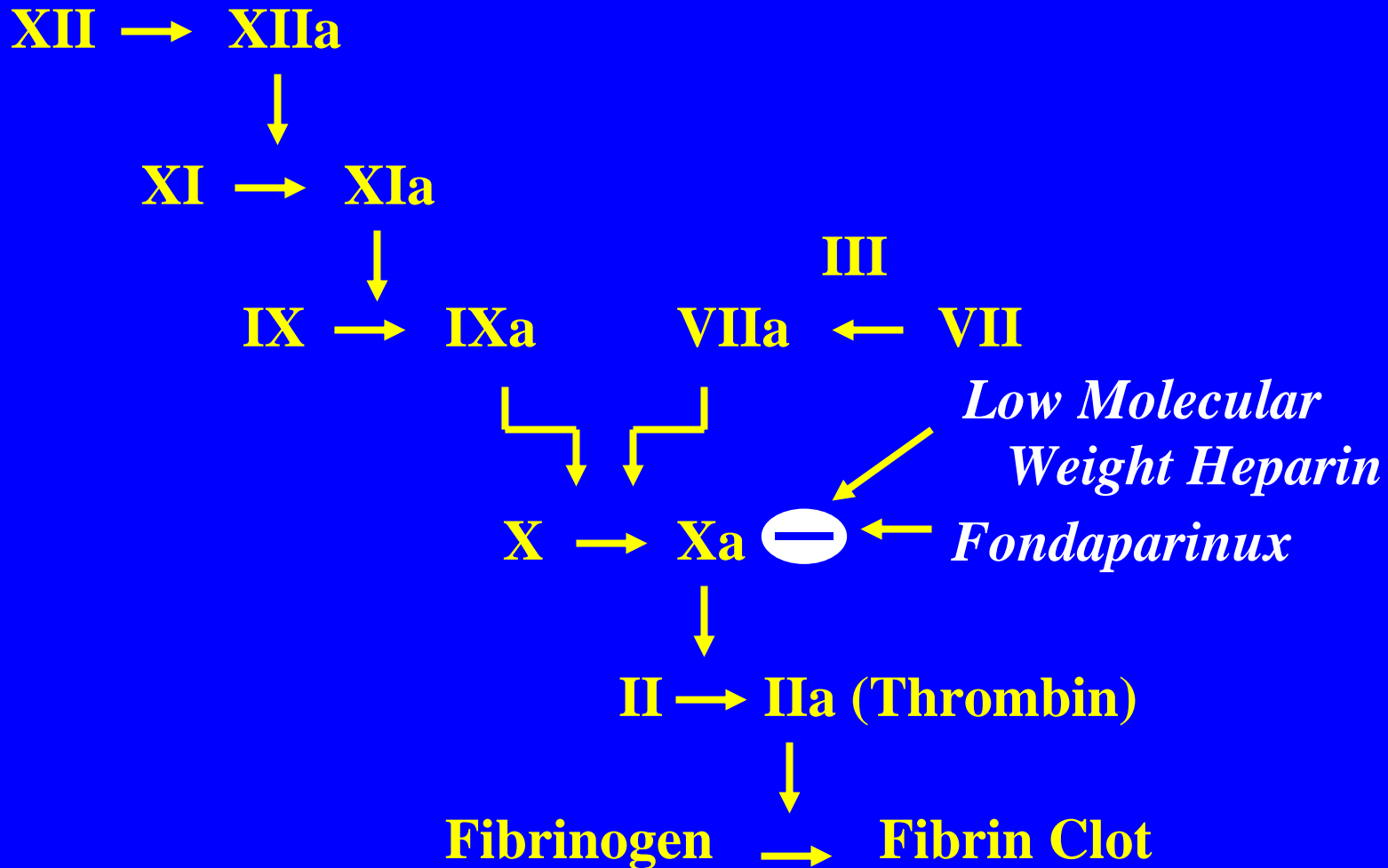
Heparin Inhibition of the Coagulation Cascade – PTT to monitor



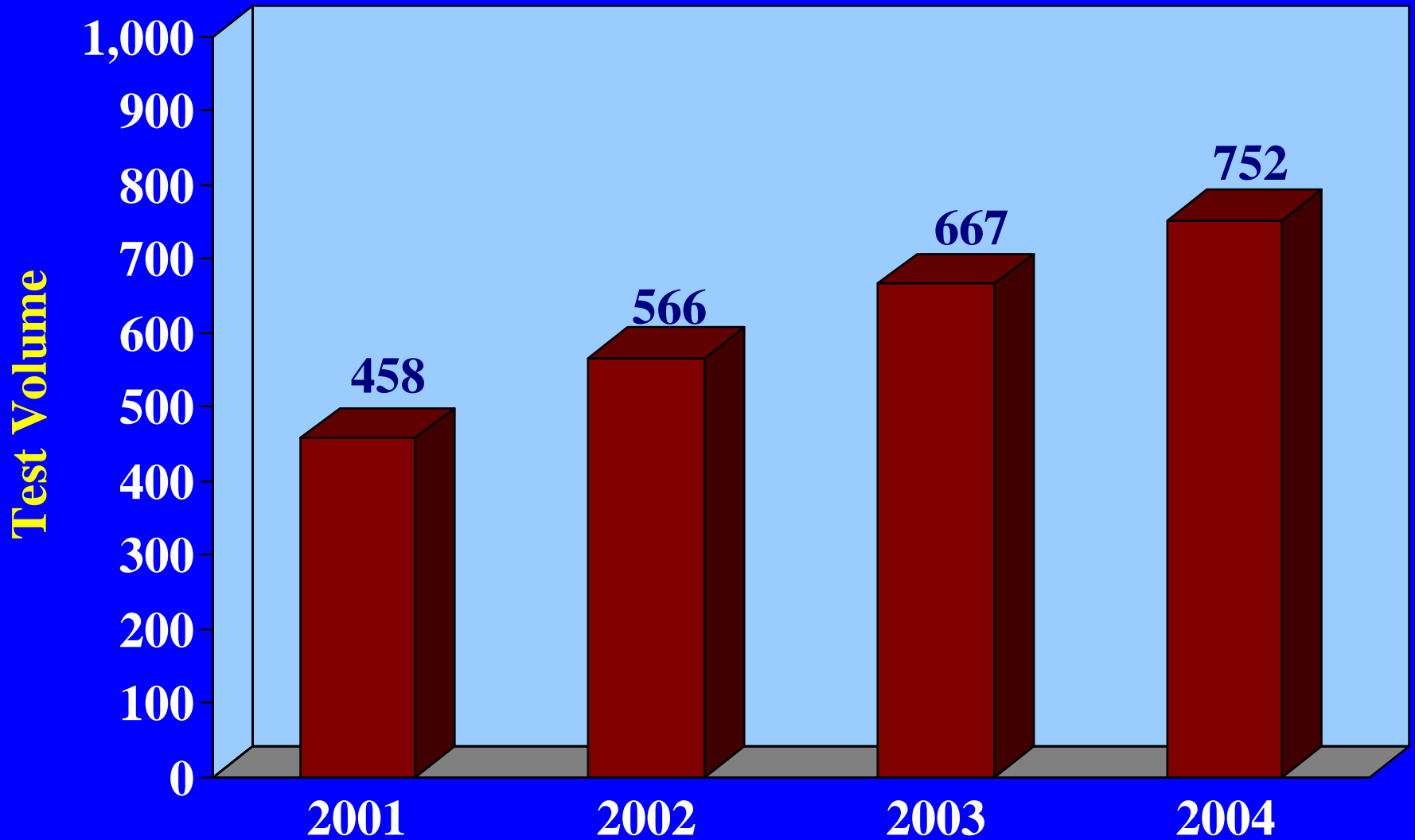
PTT volume at MGH



LMWH and Fondaparinux Inhibition of the Coagulation Cascade—Anti-Factor Xa to monitor



ANTI-FACTOR Xa volume at MGH



**Overlapping heparin,
low molecular weight
heparin, or fondaparinux
with warfarin does not
influence the INR
measurement used to
monitor coumadin**

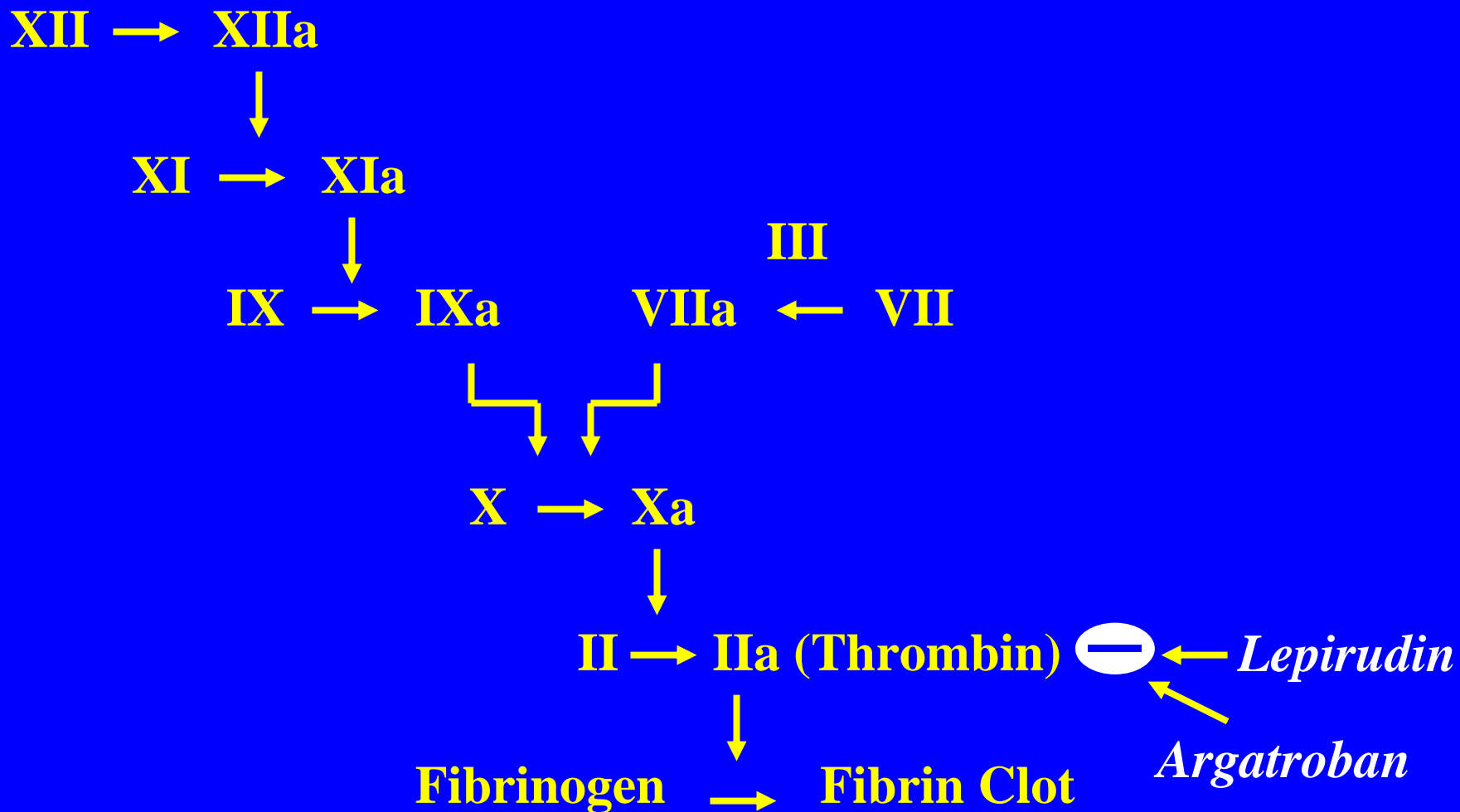
**LEPIRUDIN or
ARGATROBAN – WARFARIN
OVERLAP**

Lepirudin / Argatroban



Warfarin

Lepirudin and Argatroban Inhibition of the Coagulation Cascade – PTT to monitor



LEPIRUDIN or ARGATROBAN – WARFARIN OVERLAP

- **Decrease lepirudin dose to one that elevates PTT to approximately 1.5 x control - reduces the interference of lepirudin on INR and INR results are interpretable**
- **Argatroban interferes greatly with the International Normalized Ratio (INR)**

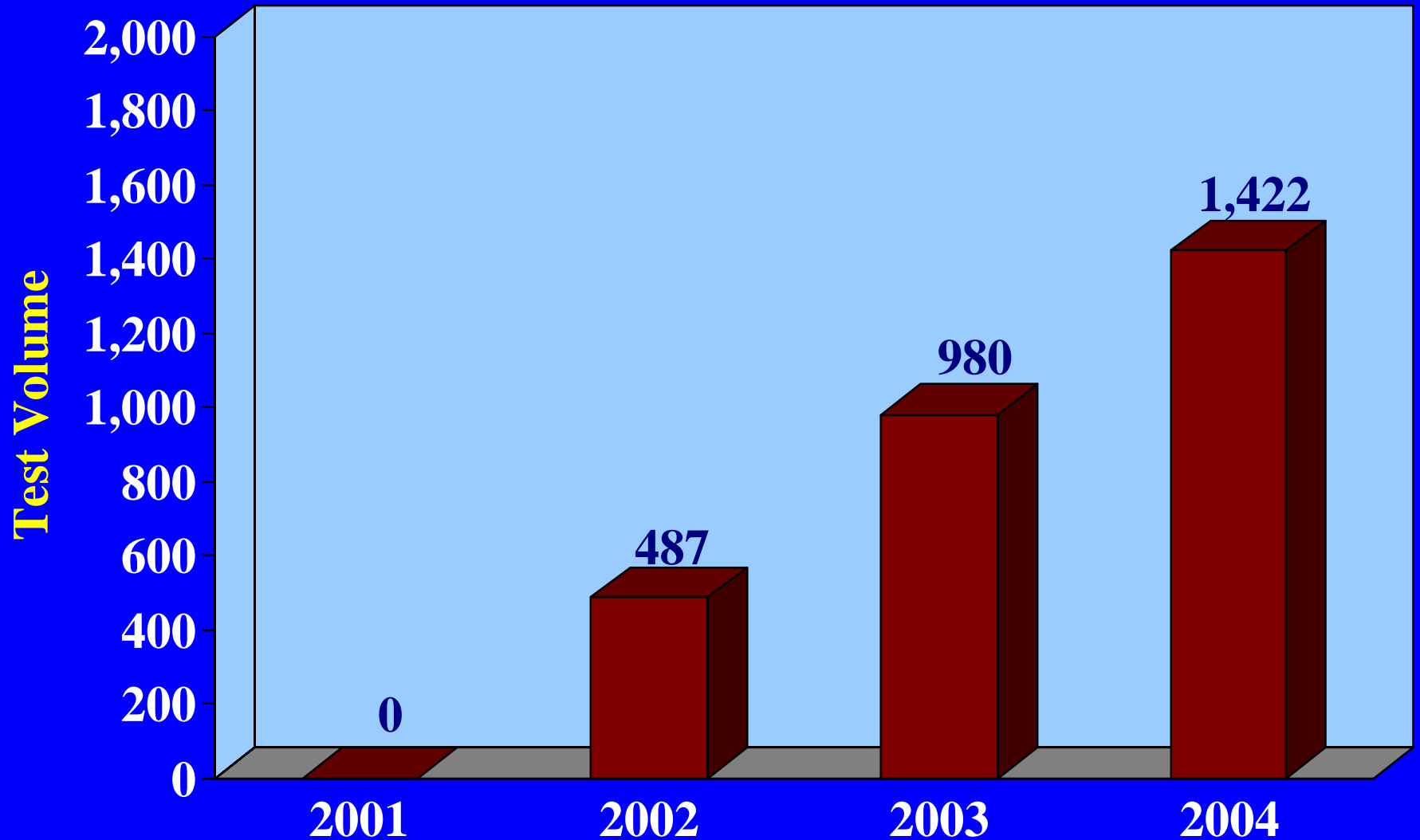
**Overlapping lepirudin
does not necessarily influence
the INR measurement used to
monitor coumadin – but
overlapping with argatroban
definitely interferes with the
INR measurement**

HOW TO MONITOR WARFARIN EFFECT WHEN ARGATROBAN AND WARFARIN ARE CO-ADMINISTERED

- Use Chromogenic Factor X instead of INR
- **INR 3 hours after discontinuation of argatroban**
- Use of manufacturer nomogram to extrapolate to INR without argatroban

CHROMOGENIC FACTOR X

volume at MGH



SUMMARY OF THE PRESENTATION

- **Clot formation**
- **Coumadin action**
- **Coumadin monitoring**
- **Coumadin prophylaxis**
- **Coumadin in treatment of existing thrombosis**
- **Other anticoagulants – Monitoring each alone and monitoring coumadin in their presence**