Is Interchangeability Possible? Understanding and Evaluating the Evidence-Based Implications for Quality & Safety

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Jefferson Medical College
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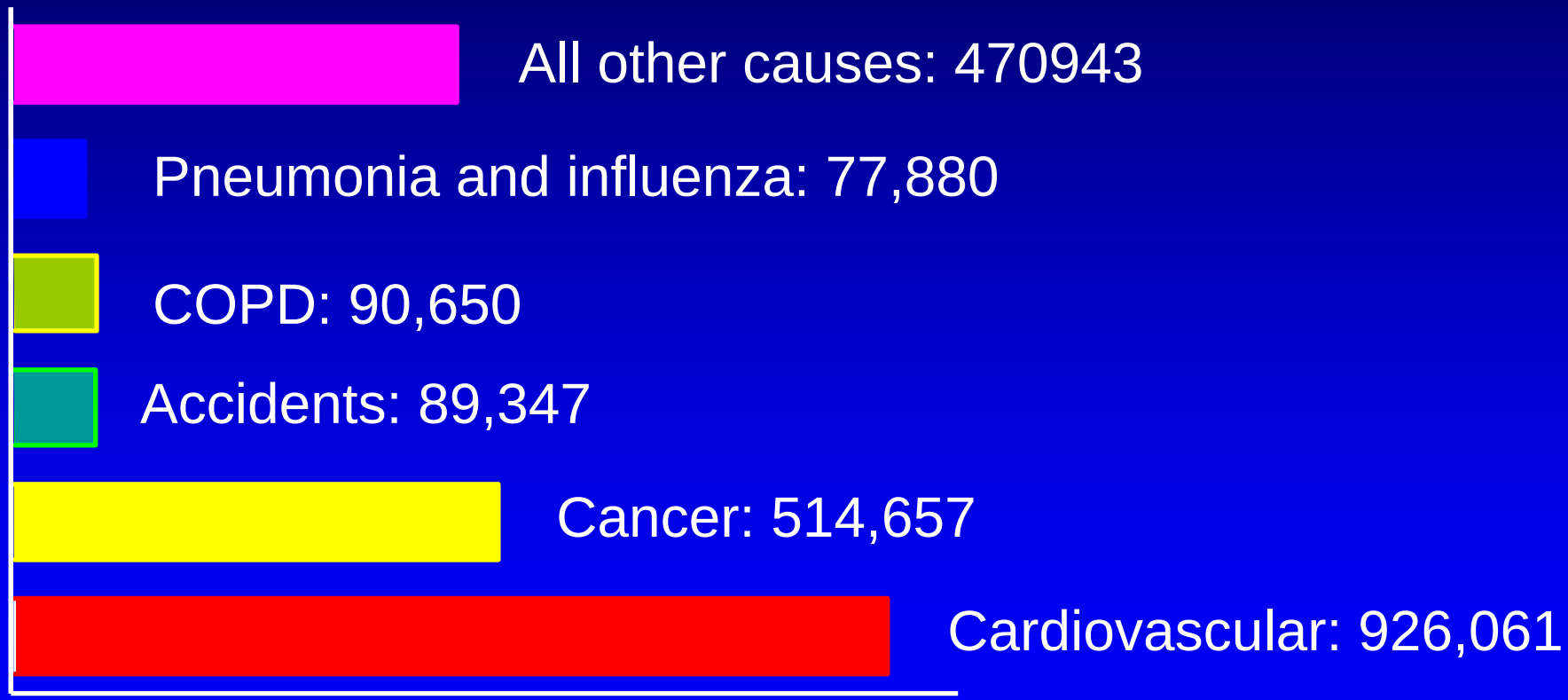
Leading Causes of Death U.S.

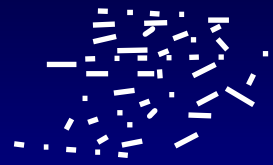


Most Cardiovascular Deaths Related to Clotting and Bleeding

Anticoagulant Drugs

TFPI

HEPARIN



Heparin-derived oligosaccharides

Organomimetics

Cyclic peptides

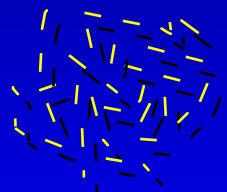
Peptidomimetics

Recombinant drugs

Fibrinolytic modulators

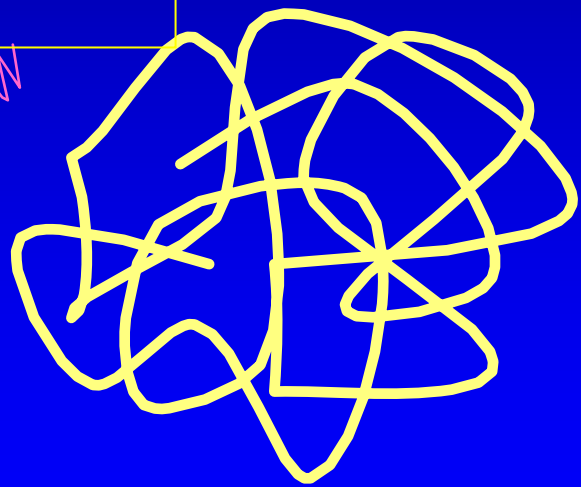
HIRUDIN

TAFI
PAI-1 inhibitor
Factor XIIIa inhibitor



LMWH

Peptidomimetics



r-Thrombomodulin

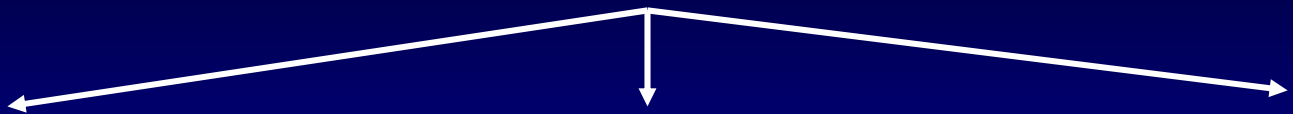
Di-, tripeptides and peptidomimetics

HIRULOG

Oligopeptides

TFPI = tissue factor pathway inhibitor; TAFI = thrombin-activatable fibrinolysis inhibitor-1; PAI-1 = plasminogen activator inhibitor-1

Disease Treated



Infection

- Bacterial
- Viral
- Fungal

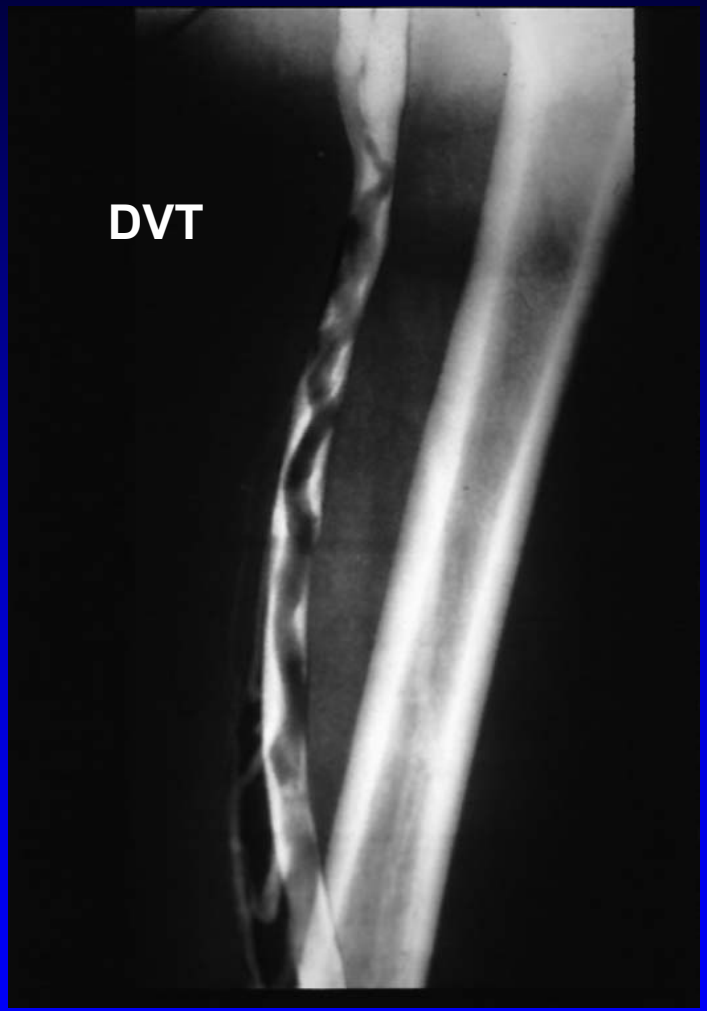
Cardiovascular

- HBP
- Cholesterol
- Arrhythmias

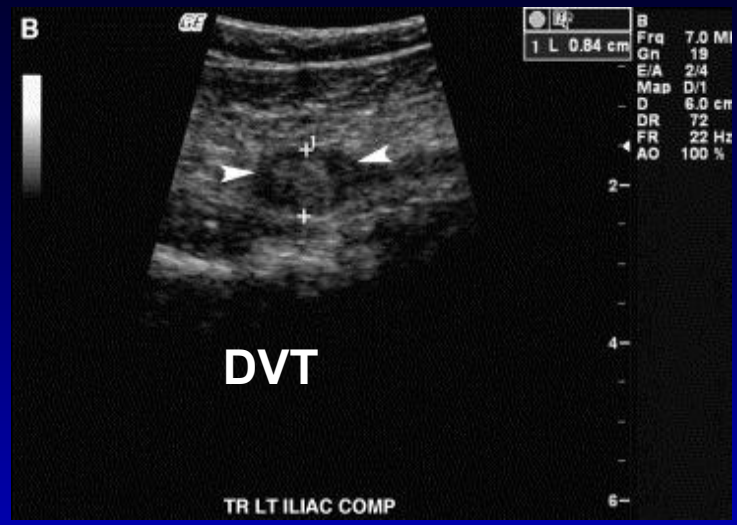
Thrombosis

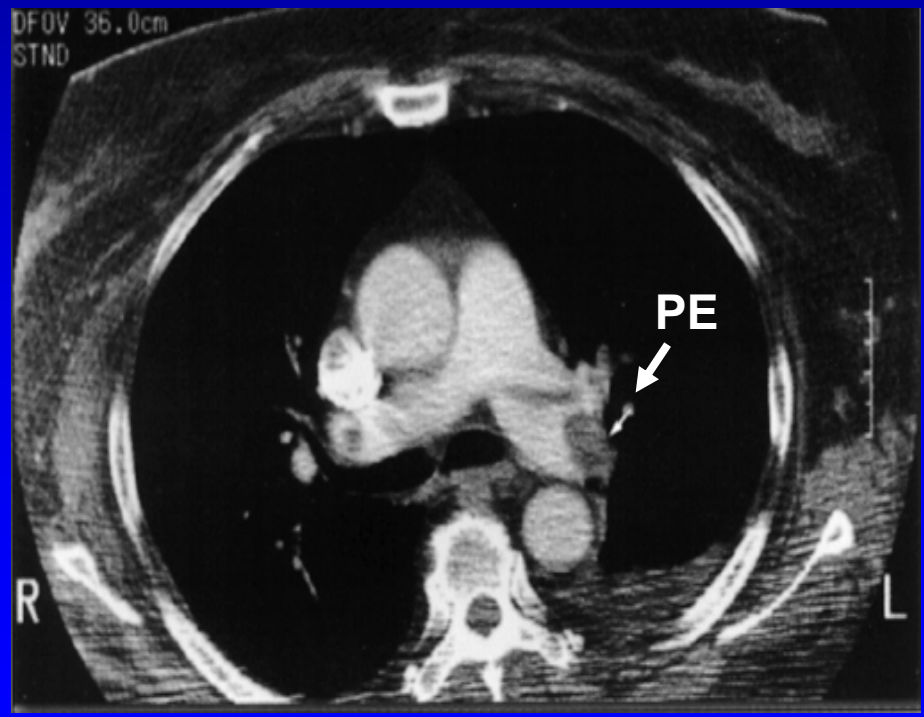
- DVT
- PE
- ACS
- Stroke
- AFIB

Venogram



Compression Ultrasound

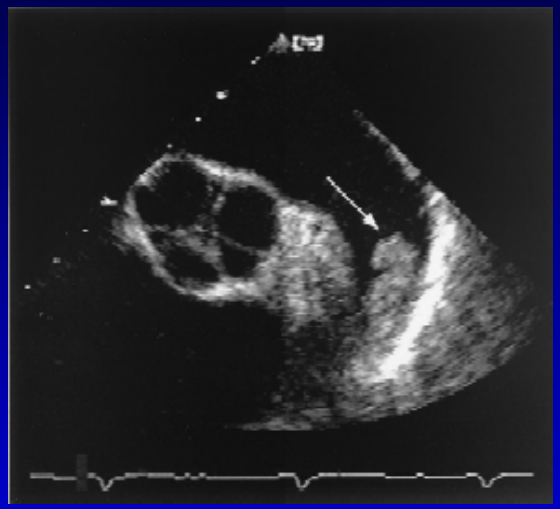


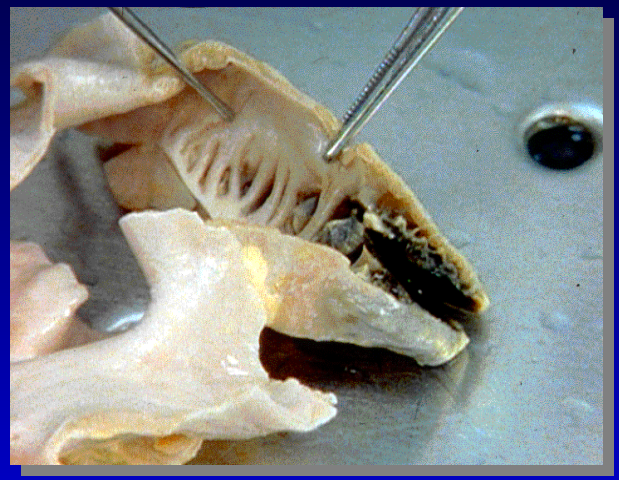


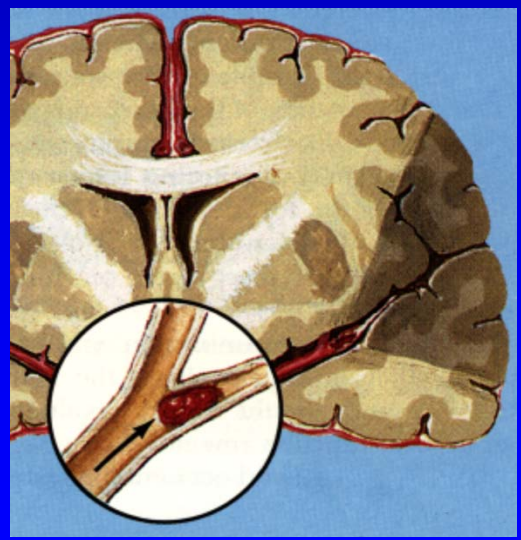
Spiral CT

Left Atrial Thrombus

Atrial Fibrillation

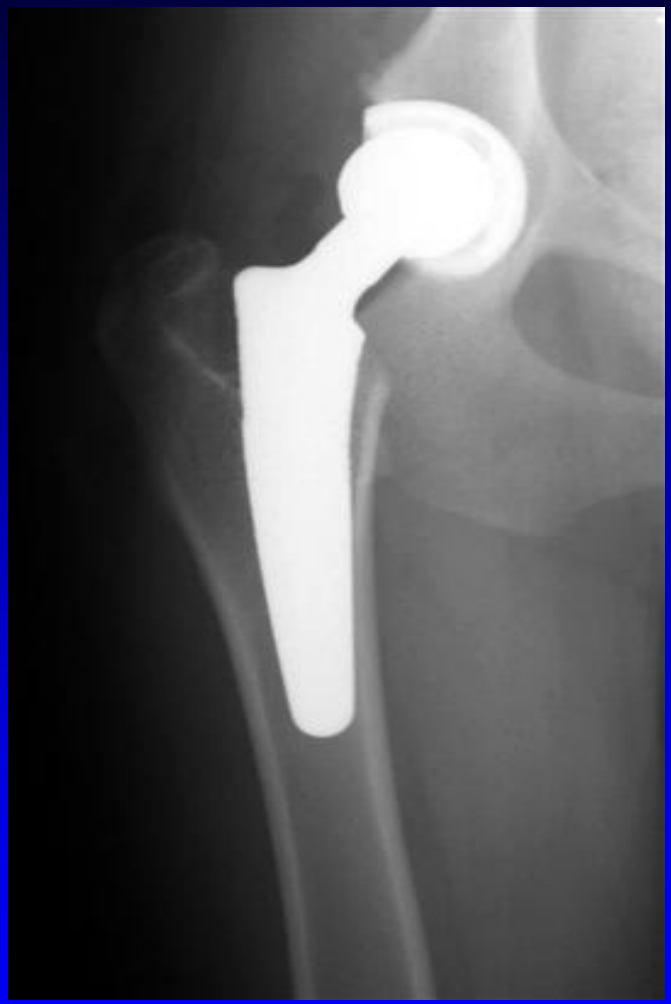




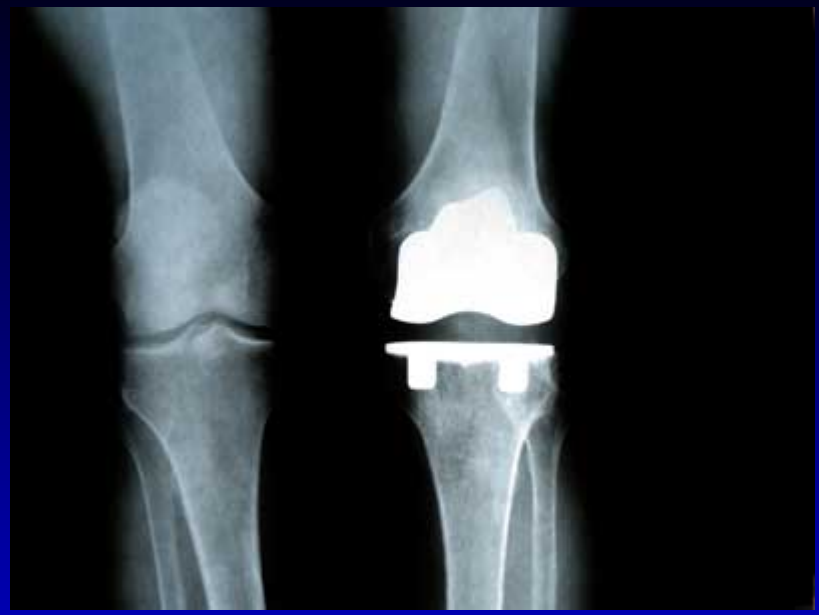


Caplan. *Stroke.* Ciba-Geigy Clinical Symposia. 1988;40(4):6.

J Am Coll ***Cardiol.*** 2001;37:691.



Total Hip Replacement

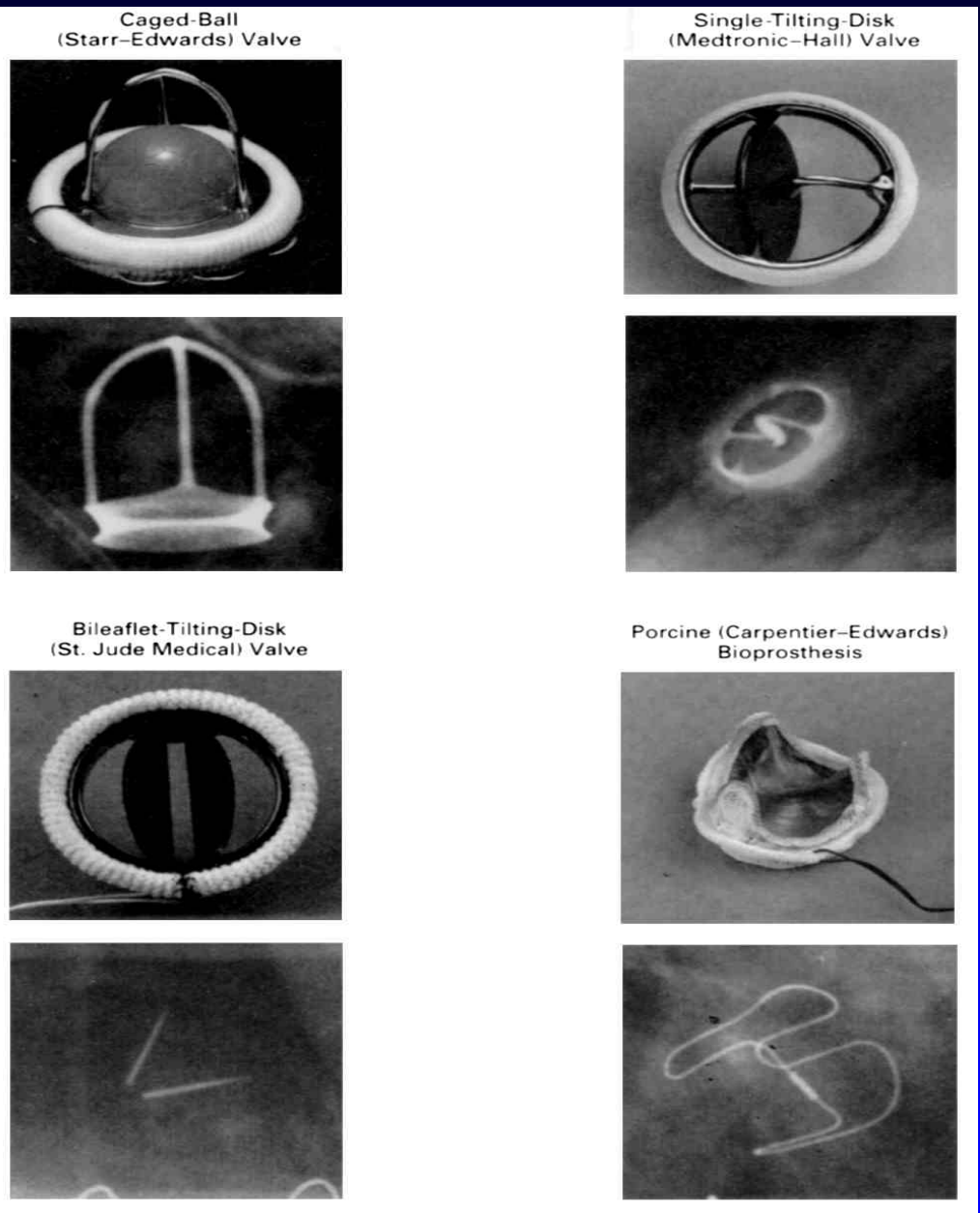


Total Hip Replacement

Fractured Hip

Thrombogenicity of Prosthetic Cardiac Valves

Caged Ball
Starr-Edwards
++++



Single Tilting Disc
+++

Bileaflet
Tilting Disc
++

Porcine
Heterograft
Carpentier-Edwards
+

Heit JA. *J Thromb Thrombolysis.* 2001;12:81-87.

Safety Considerations

Anticoagulant Drugs

- Bleeding
- Allergic Reactions
- Thrombocytopenia
- Skin Necrosis
- Liver Toxicity
- Vascular Reactions
- Rebound Thrombosis
- Anticoagulant Resistance
- Drug Interactions
- Population Variations (gender, age, ethnicity)

Generic Drug

- A generic drug is identical, or bioequivalent to a brand name drug in
  - Dosage form
  - Safety
  - Strength
  - Route of administration
  - Quality
  - Performance characteristics
  - Intended use

Traditional Generics

- Similar efficacy is assumed
- Safety is not monitored after introduction
- Interchangeable
- Economic advantages
- Clinicians thought to have a preference not necessarily based on medical literature
- Mandatory changes made by Pharmacy Benefit Managers *(ie, Blue Cross, Humana, Aetna, etc)*

Genazzani A. *Biodrugs.* 2007

Declerck P. *Drug Safety*. 2007

Oral Anticoagulants

- Warfarin (Coumadin®) and its derivatives [phenprocoumon (Sintrom®); acenocoumarol (Marcumar®)] have been used for over 50 years.
- Generics warfarins available since 1997
- 6 generic warfarins FDA rated bioequivalent to warfarin:
  - Barr Laboratories
  - Apothecon
  - Genpharm
  - Sandoz
  - USL Pharm
  - Taro Pharmaceuticals

Oral Anticoagulants

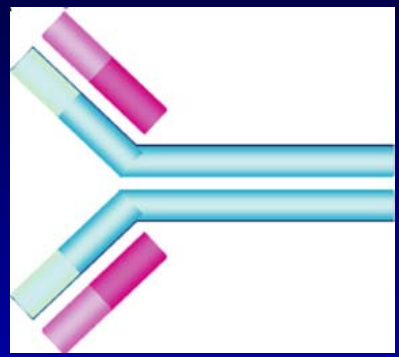
- A narrow therapeutic index (range between effective and toxic doses)
- Non-linear pharmacokinetics
- Small changes in dose can result in considerable changes in the anticoagulant response

Key Points Generic Warfarin

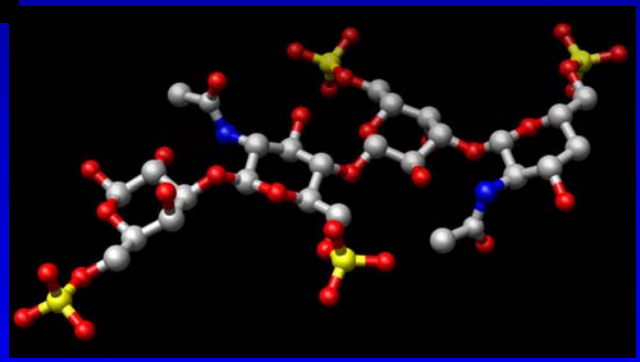
- Warfarin has a narrow therapeutic index and a varying pharmacodynamic response.
- Close monitoring is needed when patients are switched from brand name to generic product, or *vice versa*, or from one generic to another generic to avoid under-dosing or over-dosing.
- The generic interchange of warfarin should be avoided in elderly patients, and patients with liver disease and gastric resection.
- All anticoagulants are critical drugs. In the case of warfarin, small changes can result in large pharmacodynamic variations.

Biosimilar or Follow-On Biologics

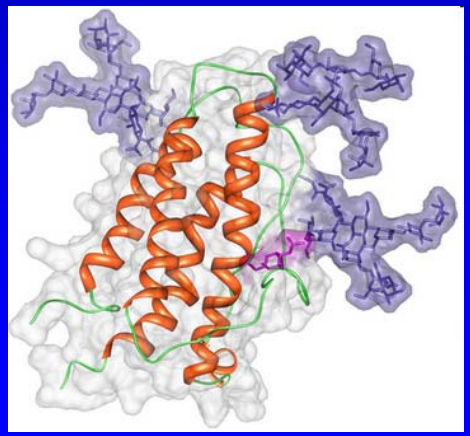
Proteins



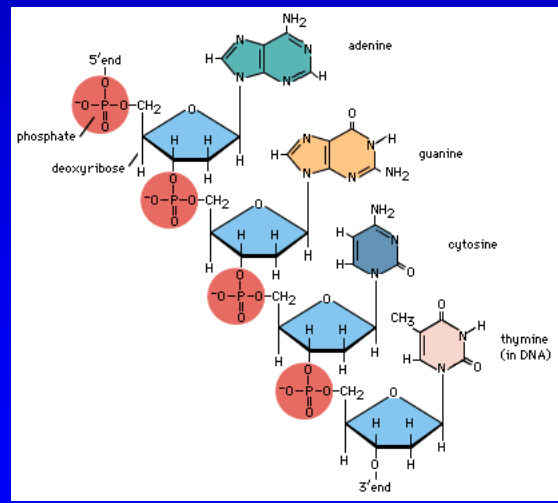
Antibodies



Polysaccharides



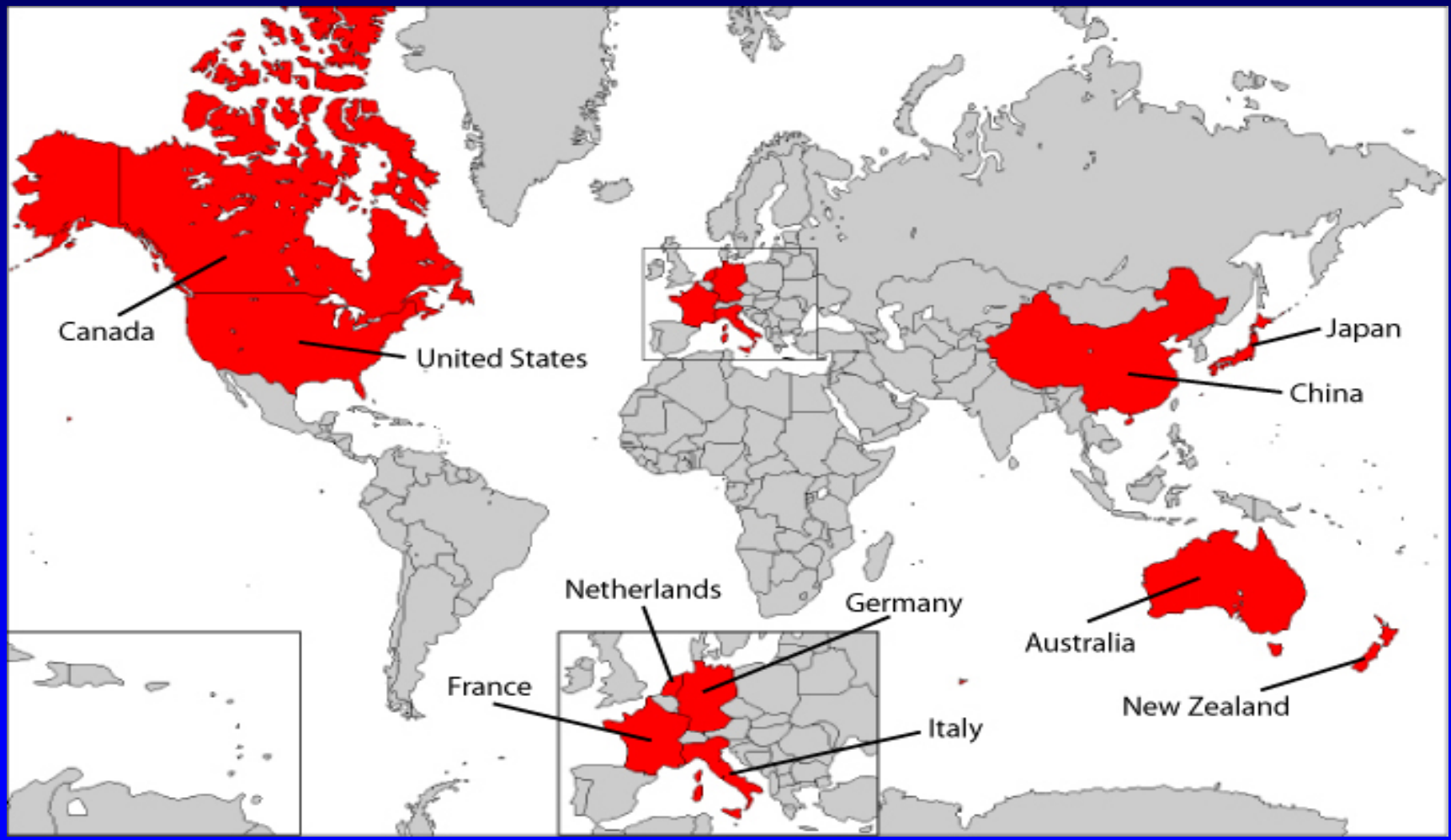
Glycosylated Proteins



Polynucleotides

Unfractionated Heparin (UFH)

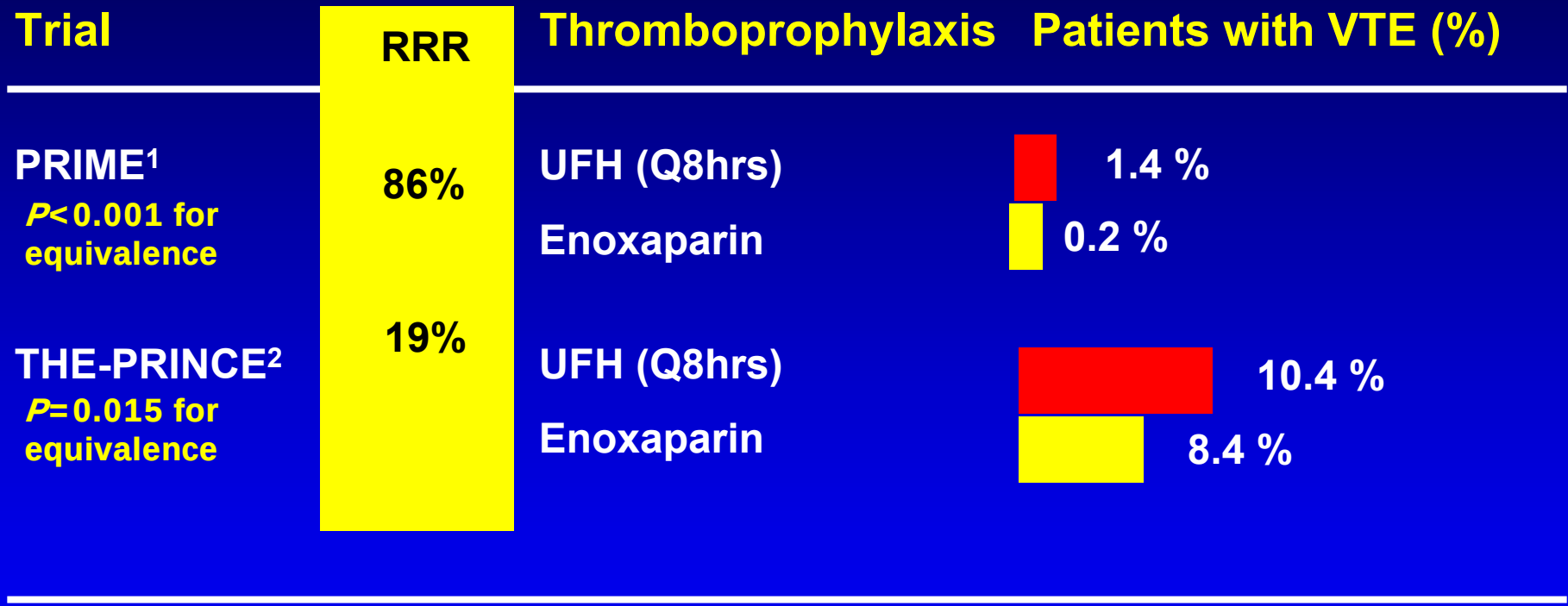
Contaminated Unfractionated Heparin



Low Molecular Weight Heparins

Agent	*Method of Preparation*
Dalteparin	Nitrous acid depolymerization
Enoxaparin	Benzylation followed by alkaline depolymerization
Tinzaparin	Enzymatic depolymerization with heparinase
Pentasaccharide	Synthetic analog

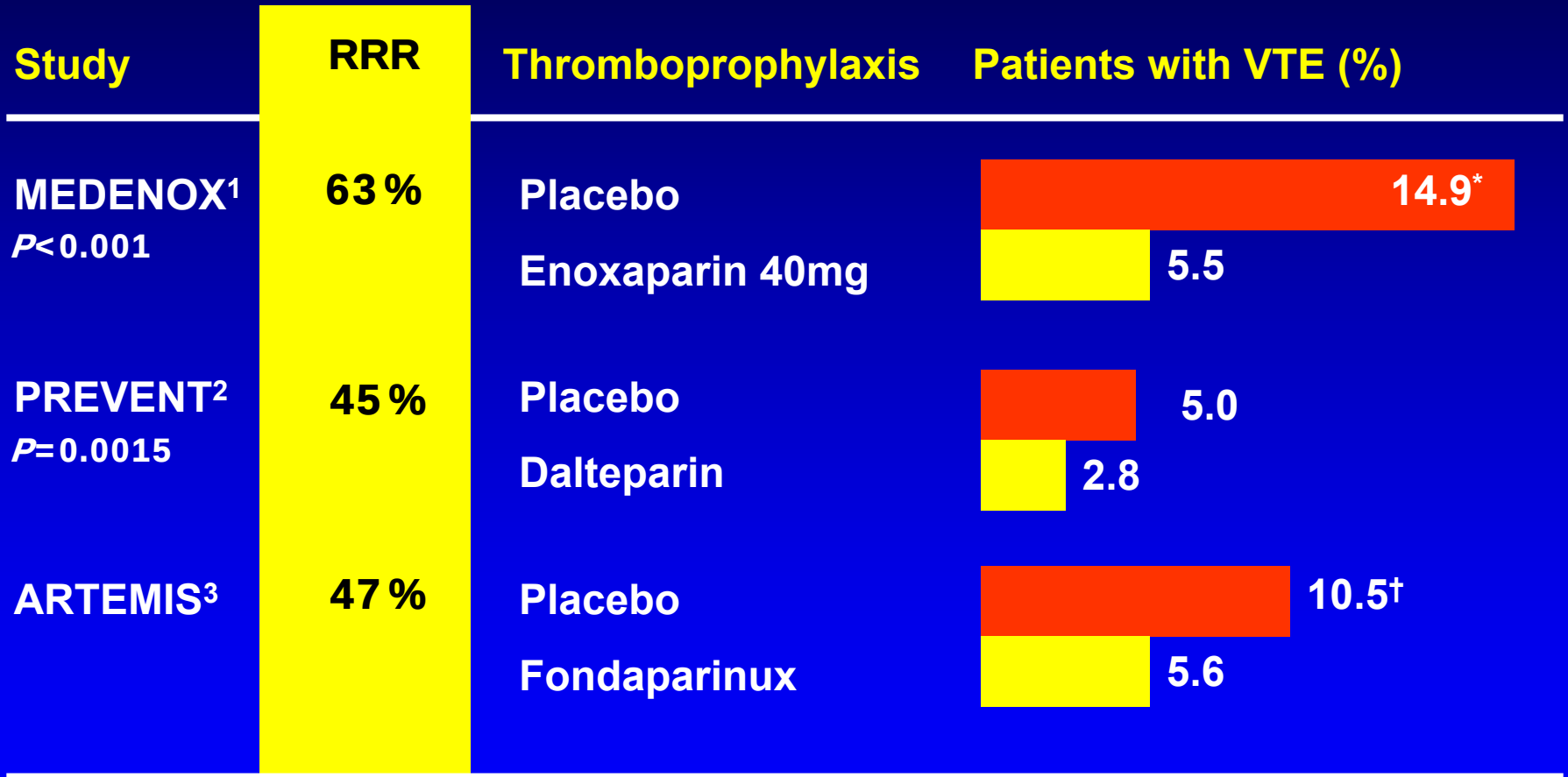
VTE Medically-ill



[1]Lechler E, et al. Haemostasis 1996;26 Suppl 2:49-56.
[2]Kleber FX, et al. Am Heart J 2003;145:614-21.

Low-Molecular-Weight Heparin (LMWH)

Clear Benefits over Placebo



[1]Samama MM, et al. N Engl J Med 1999;341:793-800

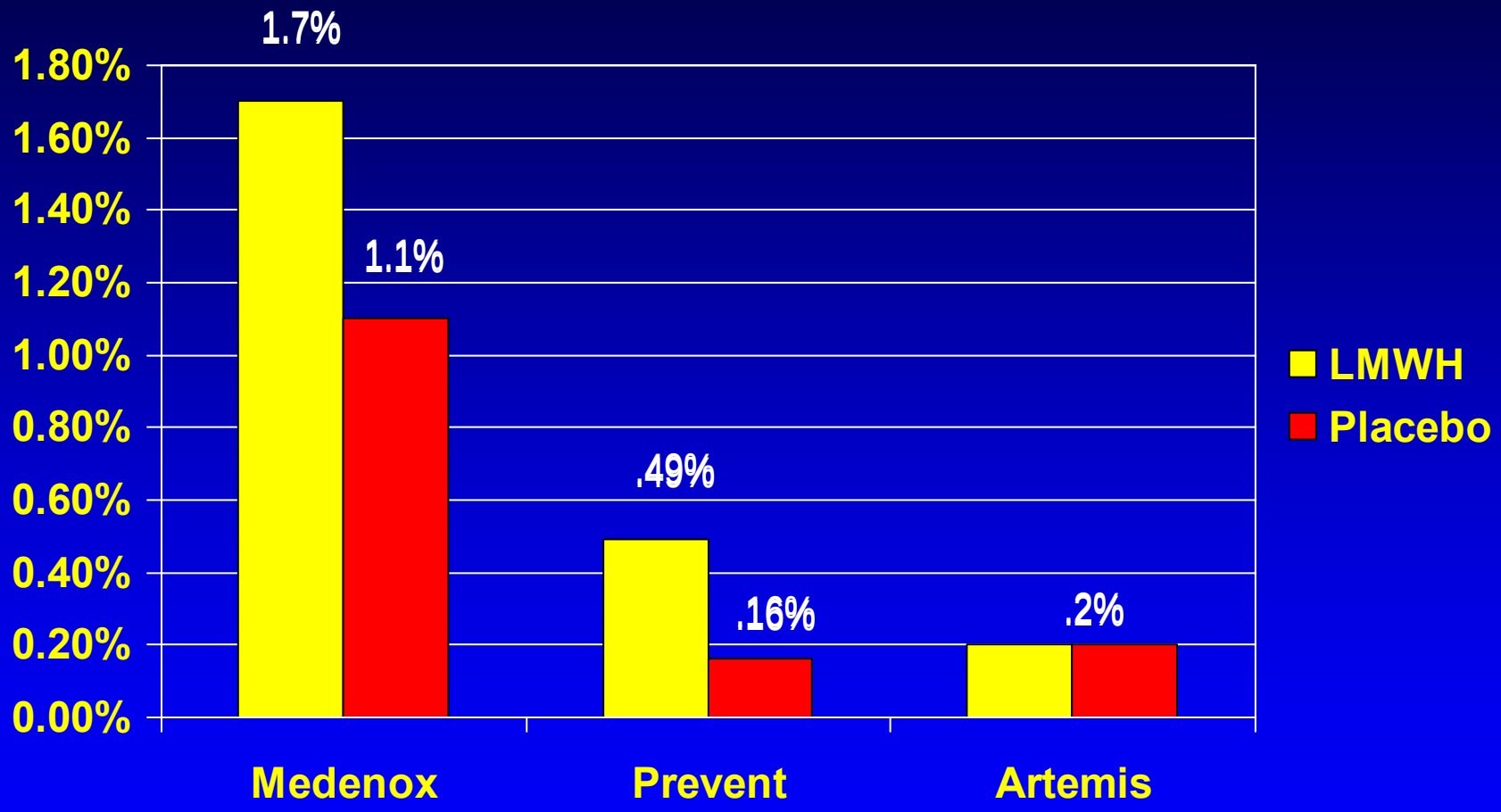
[2] Leizorovicz A, et al. Circulation 2004;110:874-879

[3]Cohen AT, et al. J Thromb Haemost 2003;1 Suppl 1:P2046

***VTE at day 14; †VTE at day 15**

RRR = relative risk reduction

Major Bleeding

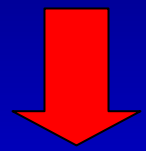


Samama MM, et al. N Engl J Med 1999;341:793-800.
Leizorovicz A, et al. Circulation 2004;110:874-879
Cohen AT, et al. J Thromb Haemost 2003;1 Suppl 1:P2046.

Is VTE Prophylaxis Effective?

Meta-Analysis

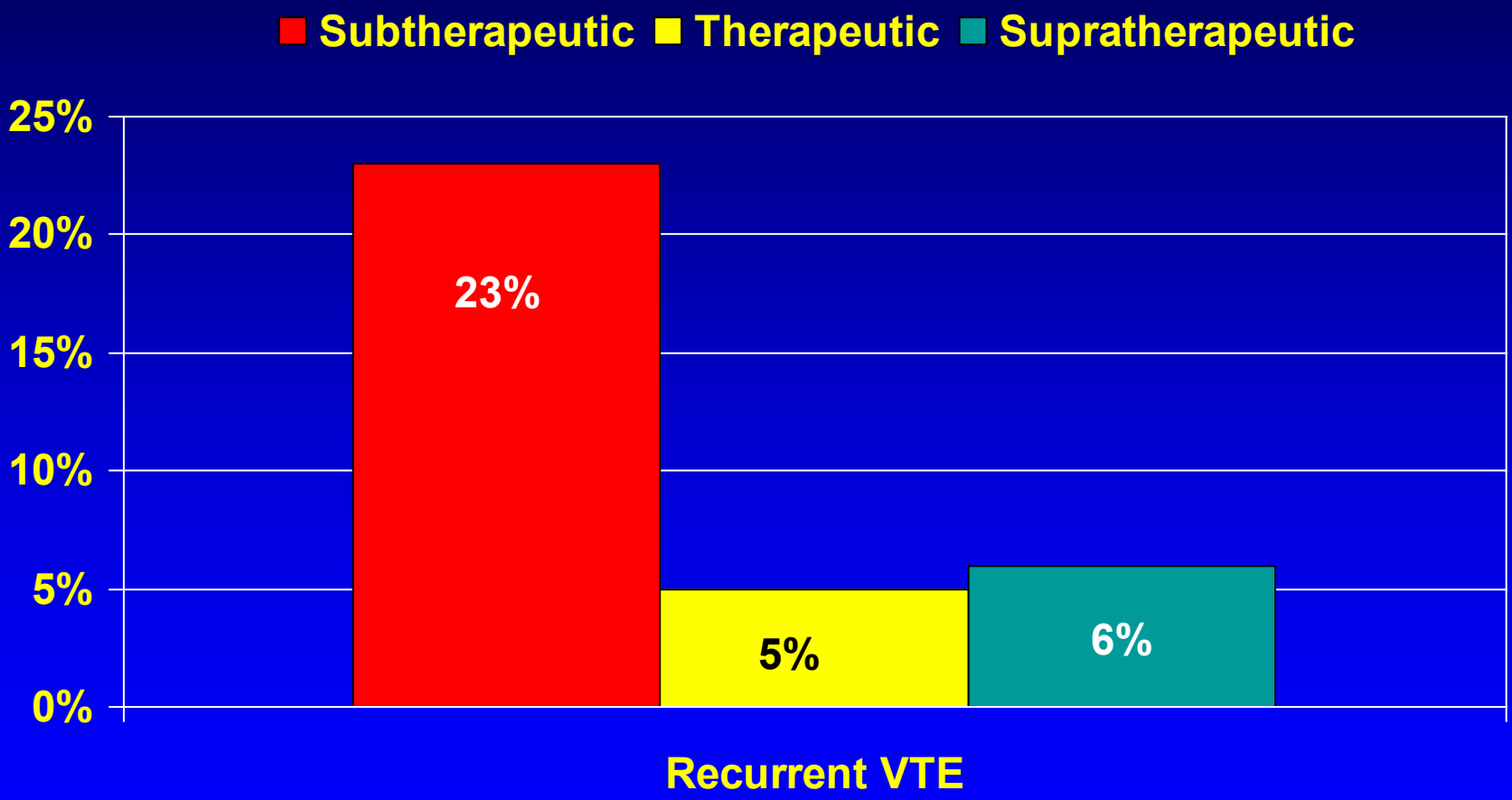
Anticoagulant VTE prophylaxis in 19,958 at-risk hospitalized medical patients in 9 studies



- **62% reduction in fatal PE [RR 0.38; CI 0.21-0.69]**
- **57% reduction in fatal or nonfatal PE [RR 0.43; CI 0.26-0.71]**
- **53% reduction in DVT [RR 0.47; CI 0.22-1.00]**
- **Nonsignificant increase in bleeding [RR 1.32; CI 0.73-2.37]**

Dentali F, et al. *Ann Intern Med*. 2007;146:278-88.

Recurrent VTE: 1st 24 Hours



Hull RD, et al. *Arch Intern Med.* 1997;157:2562-2568.

Outcomes UFH

Standard vs Weight-Based Dosing

Outcomes	Standard UFH	Weight-based UFH	*P* Value
1st aPTT > 1.5*	32%	86%	< 0.001
aPTT > 1.5 in 24 hrs	77%	97%	0.002
aPTT therapeutic in 24 hrs	75%	89%	0.08
Minor bleeding	2/52	2/63	1
Major bleeding	1/52	0	0.45
RVTE	8/32 (25%)	2/41 (5%)	0.02

*aPTT > 1.5 times control

Raschke RA, et al. *Ann Intern Med.* 1993;119:874-881.

Standard and Weight-Based UFH

- Bolus 5000 units then
- Infusion 1300 units per hour
- Target aPTT therapeutic range of the hospital
- Check aPTT in 6 hours and adjust upward or downward by 200 units
- ***aPTT should be checked every 6 hours for the first 24 hours then***
- Daily or more frequently as indicated by the need to achieve the therapeutic range
- Check platelet count baseline then every 2 to 3 days from day 4 thru 14
- Initiate warfarin 5 mg on day 1
- Continue unfractionated heparin until the INR is between 2 and 3 for 2 consecutive days

- Bolus 80 IU/kg then
- Infusion 18 IU/kg/hr
- Target aPTT therapeutic range of the hospital
- ***Check aPTT in 6 hours and adjust via the schedule***
- Check platelet count baseline then every 2 to 3 days from day 4 thru 14
- Initiate warfarin 5 mg on day 1
- Continue unfractionated heparin until the INR is between 2 and 3 for 2 consecutive days

Raschke RA, et al. *Ann Intern Med*. 1993;119:874-881
Kearon C, et al Chest 2008;133:454S-545S

Unfractionated Heparin

Subcutaneous Dosing

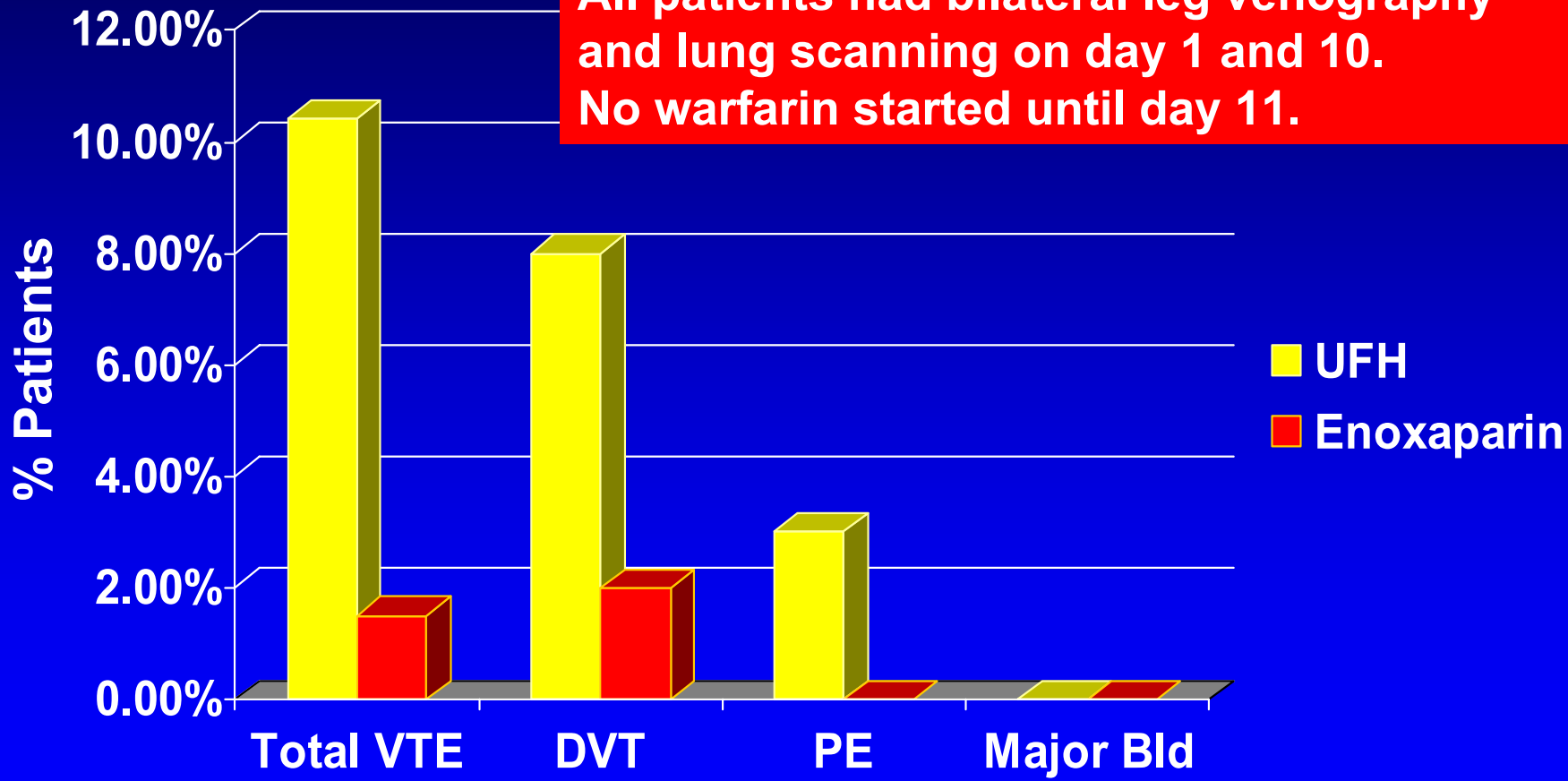
- FIDO Investigators [1C]
  - Initial Dose 333 U/kg, SC
  - Maintenance 250 U/kg, SC, Q12hrs
  - No monitoring

- Pini Method [1C]
  - 250 u / kg, Q12hrs
  - Adjust dose 6 hours after the AM dose and adjust upward or downward based on aPTT of 1.5 x baseline aPTT

Kearon C, et al JAMA 2006;296:935-942
Kearon C, et al Chest 2008;133:454S-545S

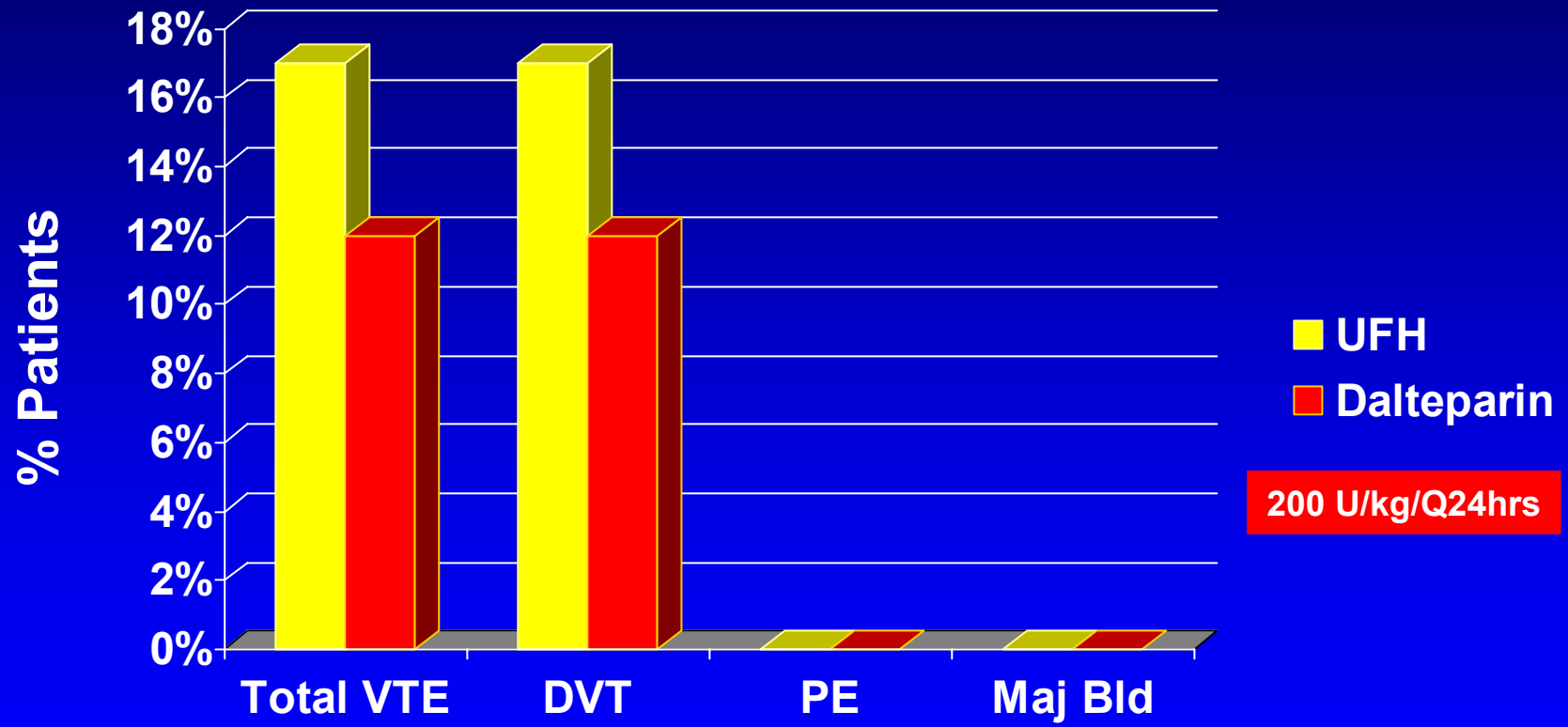
Venographic Assessment Efficacy and Safety LMWH vs UFH

All patients had bilateral leg venography and lung scanning on day 1 and 10. No warfarin started until day 11.



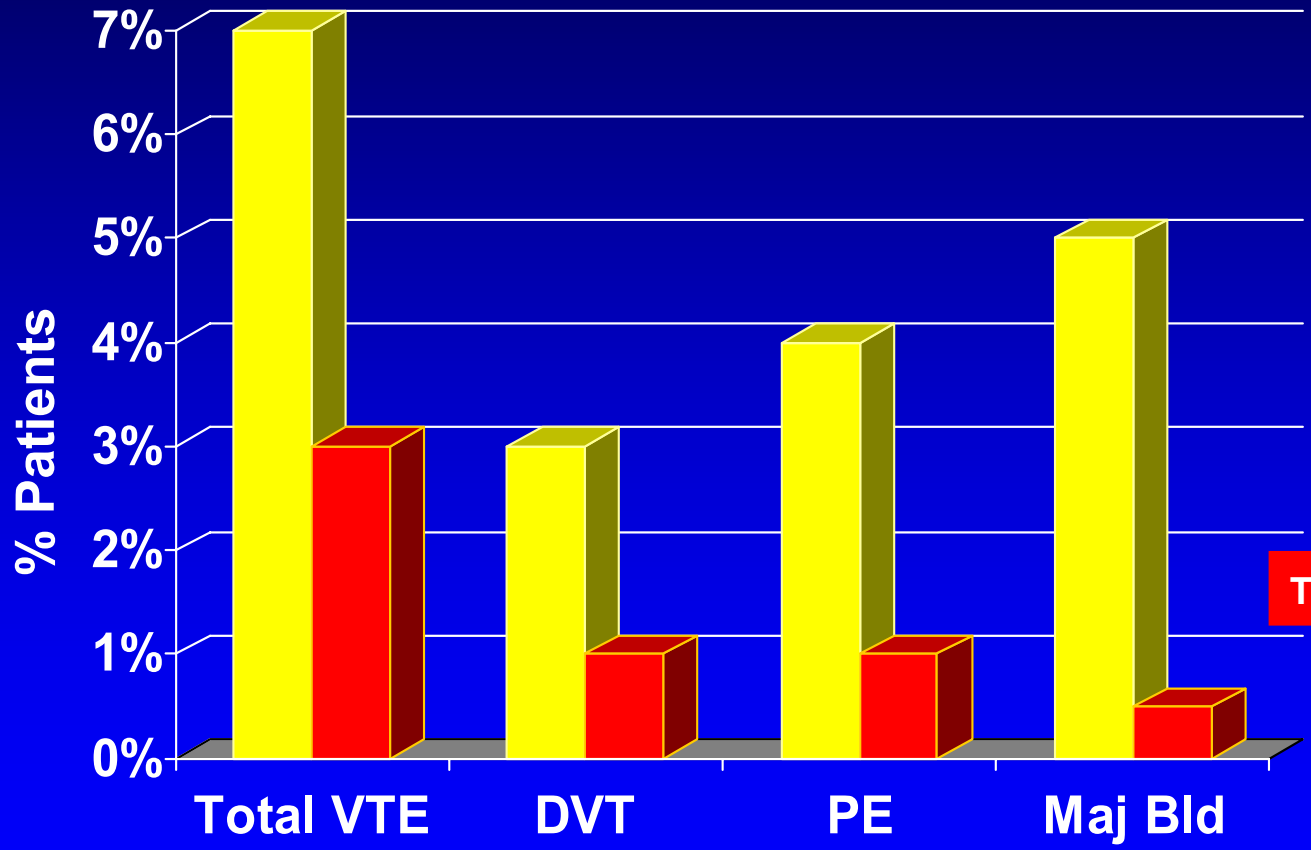
Simonneau G, et al. *Arch Intern Med.* 1993;153:1541-1546.

Venographic Assessment Efficacy and Safety LMWH vs UFH



Lindmarker P, Holmstrom M. *J Intern Med.* 1996;240:395-401.

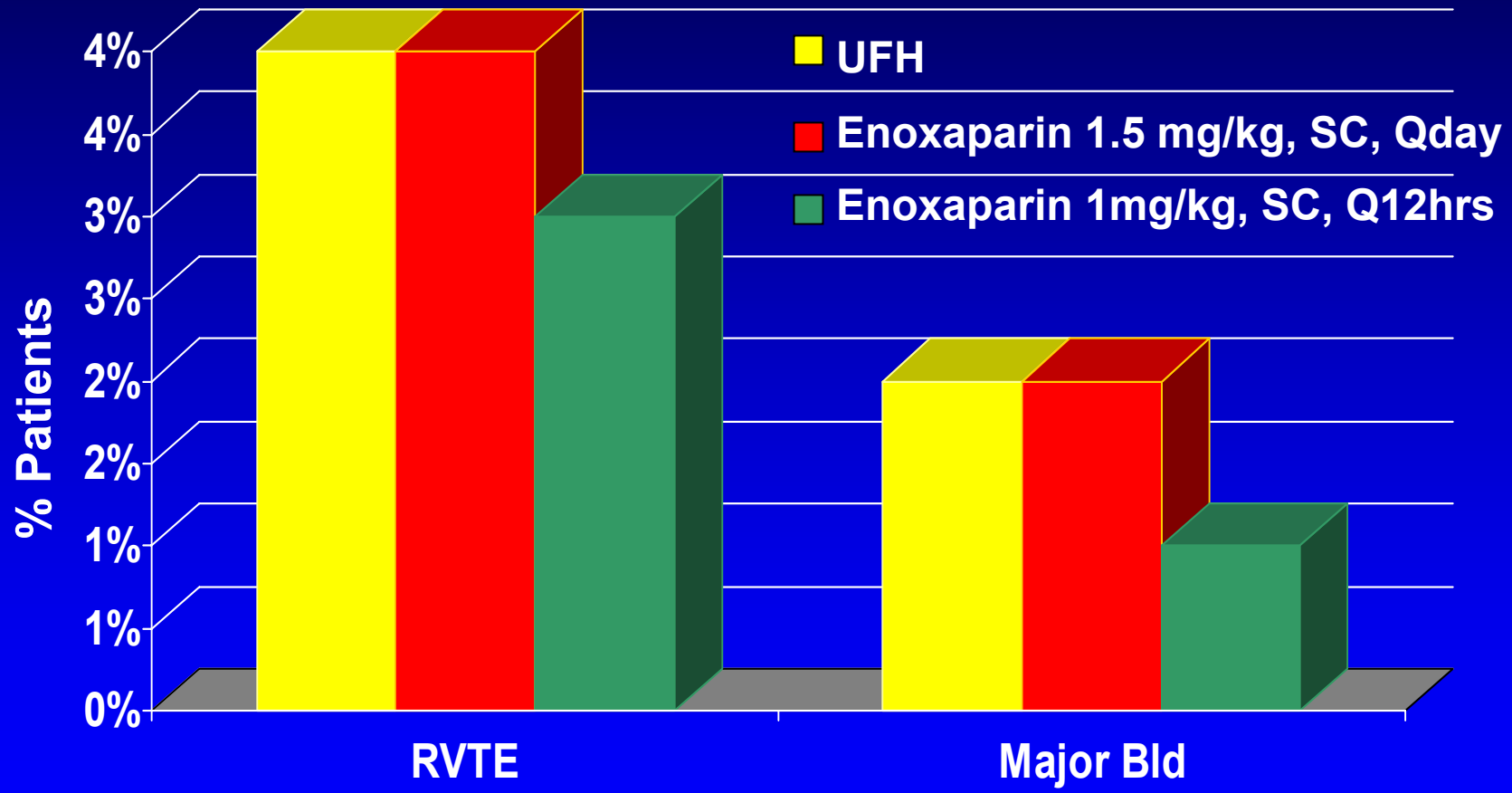
Clinical Outcomes
Efficacy and Safety LMWH vs UFH



Tinzaparin 175 U/kg, Q24hrs

Hull RD, et al. *N Engl J Med.* 1992;326:975-982.

Clinical Outcomes
Efficacy and Safety LMWH vs UFH



Merli G, et al. *Ann Intern Med.* 2001;134:191-202.

ACCP Guidelines

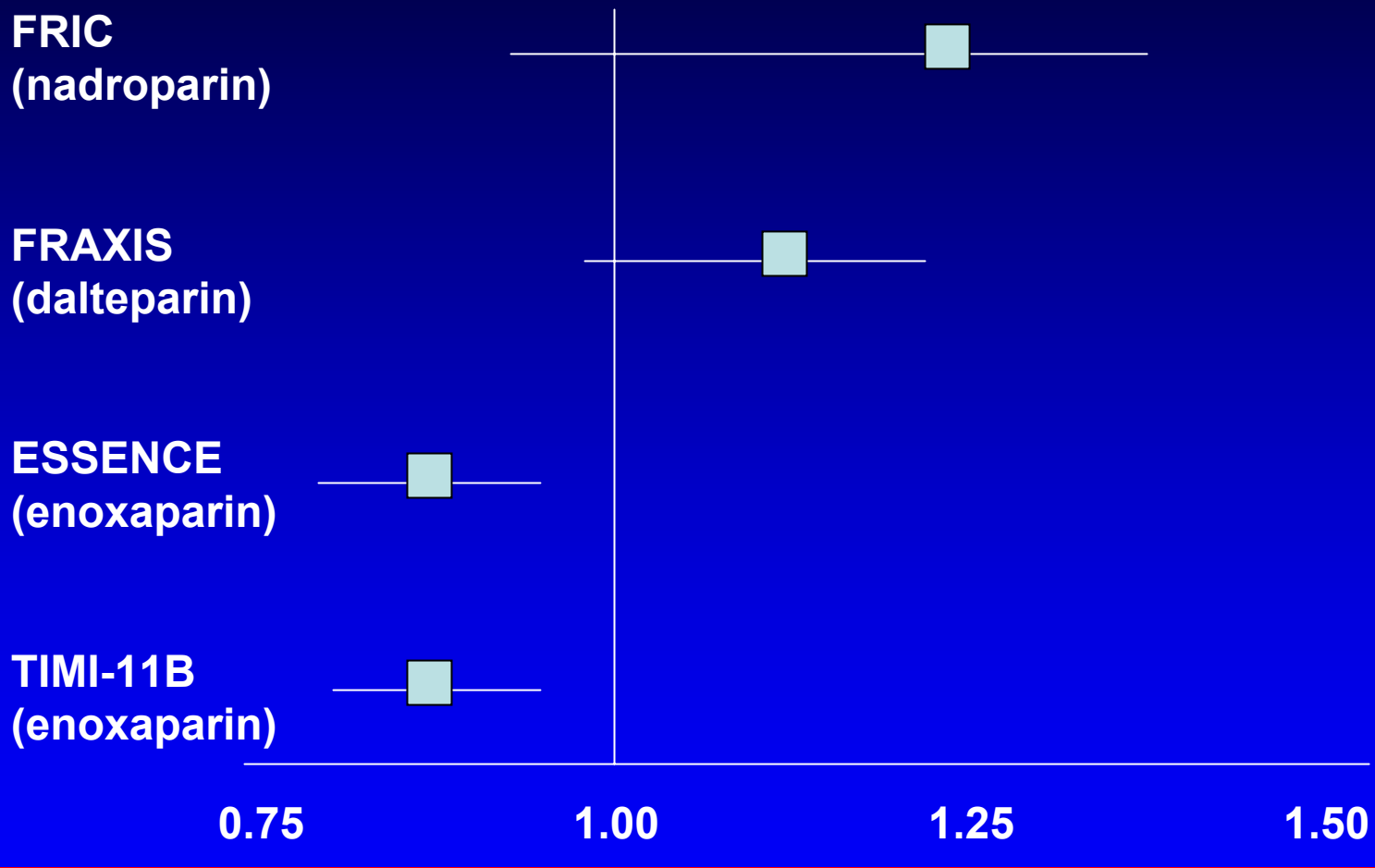
- Initial treatment with LMWH, subcutaneously once or twice daily as an outpatient [1C] or as an inpatient [1A] rather than UFH.
  - Dalteparin
    - 200 IU/kg, Qday
  - Enoxaparin
    - 1 mg/kg, Q12hrs or
    - 1.5 mg/kg, Qday
  - Tinzaparin
    - 175 IU/kg, Qday
  - Fondaparinux
    - < 50 kg – 5mg, Qday
    - 50-100 kg – 7.5 mg, Qday
    - > 100 kg – 10 mg, Qday

Kearon C, et al Chest 2008;133:454S-545S
Merli GJ. Am J Med. 2008;121:S2-S9

Acute Coronary Syndrome

- 5.3 million ER visits due to chest pain
- 1.4 million hospitalizations per year
- 15% of (UA/NSTEMI) patients die or have recurrent MI within 30 days
- 41% of UA/NSTEMI patients die, have a recurrent MI or experience severe ischemia requiring
- Hospitalization within 2 weeks of initial presentation
- 85% of patients presenting with UA/NSTEMI go to the catheterization laboratory

Acute Coronary Syndrome

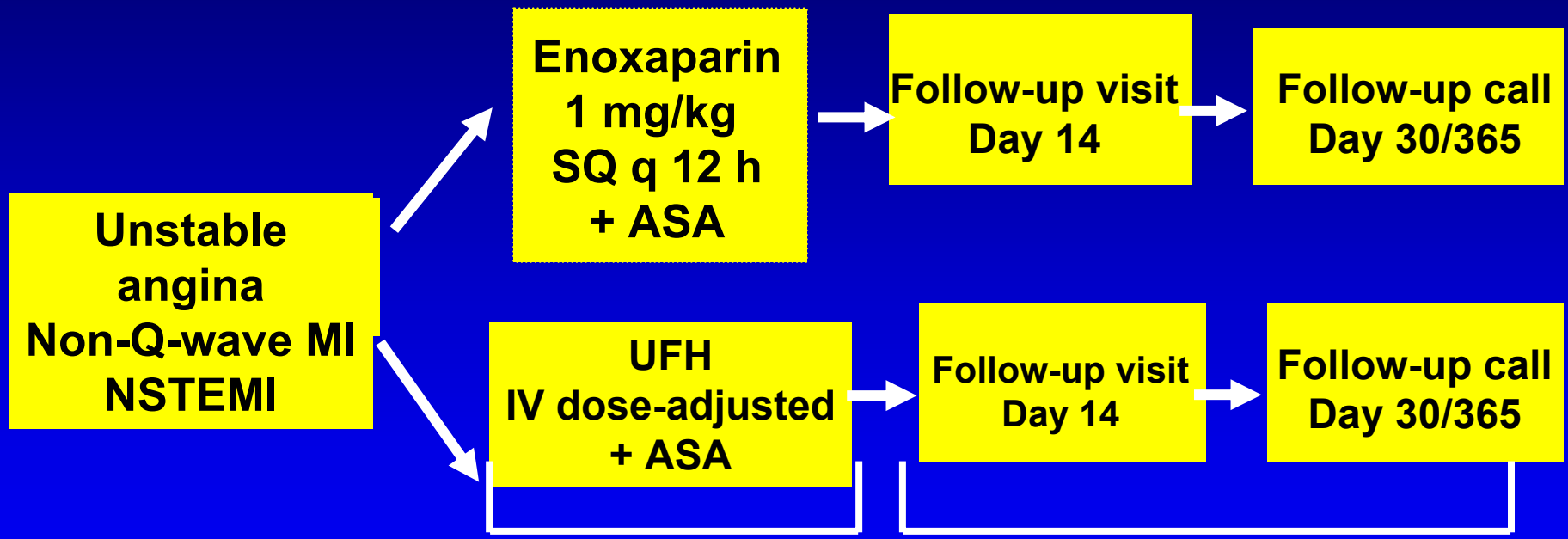


End Point: Death, MI, Recurrent Ischemia / +/- Revascularization

Brunwald E, et al JACC 2002;40:1366-1374

Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events

(ESSENCE)



min 48hrs, max 8 days

N=3,171

Double-blind, multicenter

Cohen M et al. *NEJM* 1997;337:447-52.

ESSENCE: Results up to 30 days

Endpoints	UFH (N=1,564)	Enoxaparin (N=1,607)	p
14 days			
Death, MI, recurrent angina	19.8%	16.6%	0.019
Death, MI	6.1%	4.9%	0.130
30 days			
Death, MI, recurrent angina	23.3%	19.8%	0.016
Death, MI	7.7%	6.2%	0.080
Revascularization	32.2%	27.1%	0.001

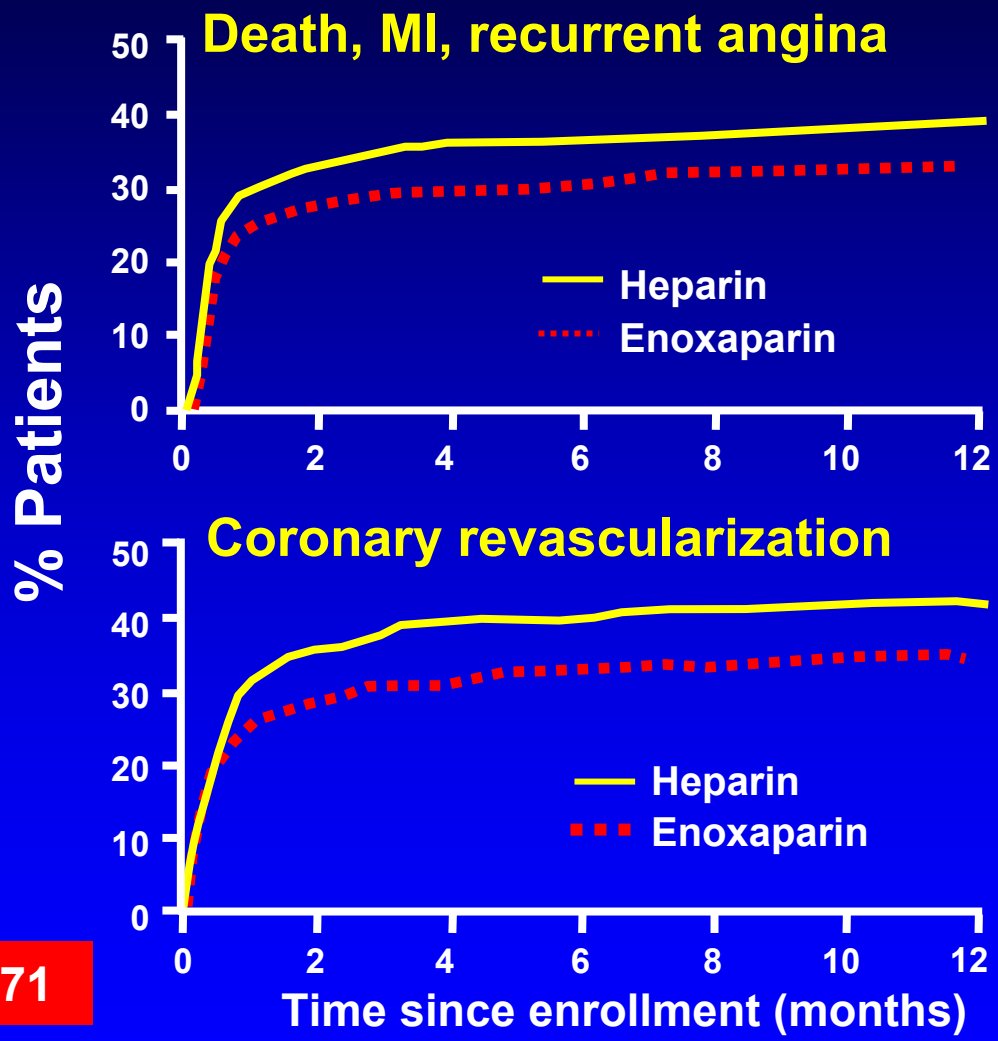
Cohen M et al. NEJM 1997;337:447-52.

ESSENCE: Results

Endpoints	UFH (N=1,564)	Enoxaparin (N=1,607)	p
30 days			
Major bleeding	7.0%	6.5%	NS
Any bleeding	14.2%	18.4%	0.001

Cohen M et al. NEJM 1997;337:447-52.

ESSENCE: One-year follow-up



p=0.022

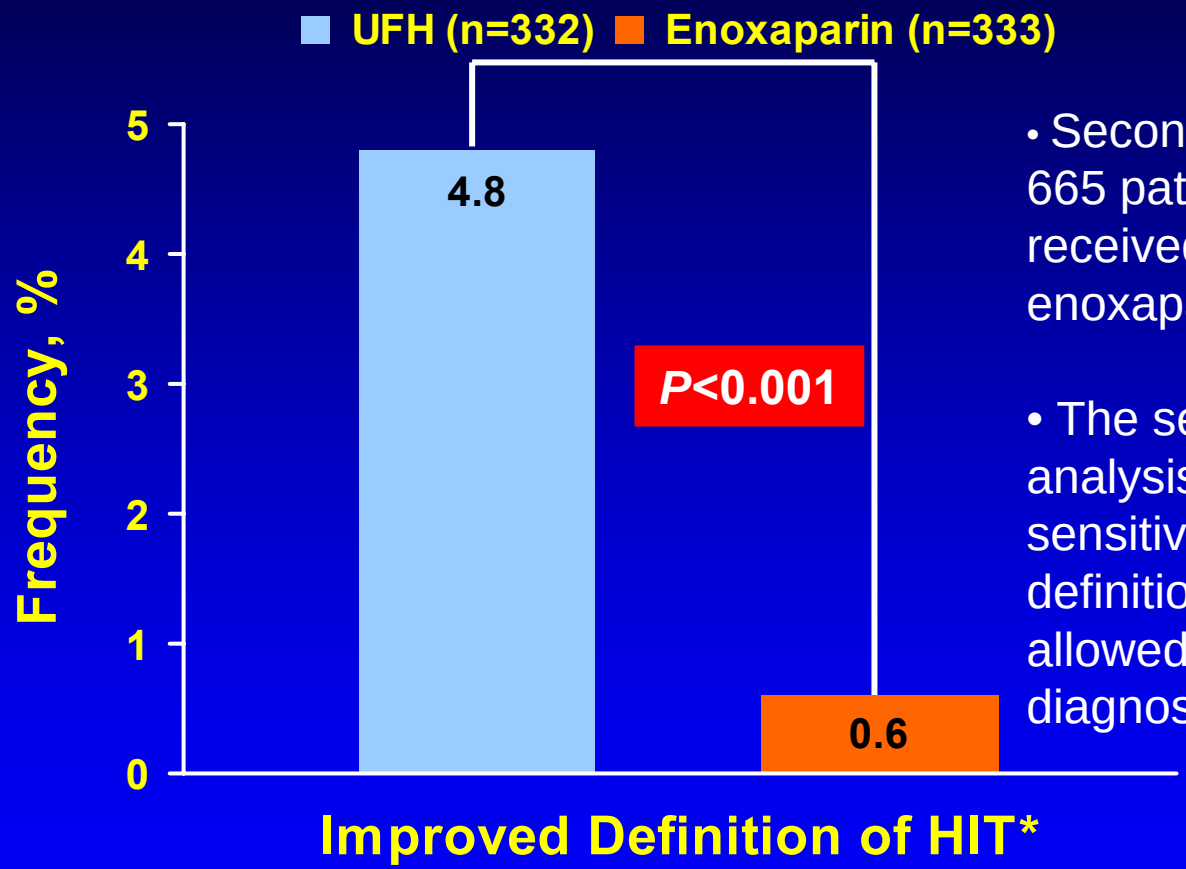
p=0.002

N=3,171

Goodman SG et al. *JACC* 2000;36:693-8.

Incidence of HIT

UFH vs Enoxaparin — THR Patients



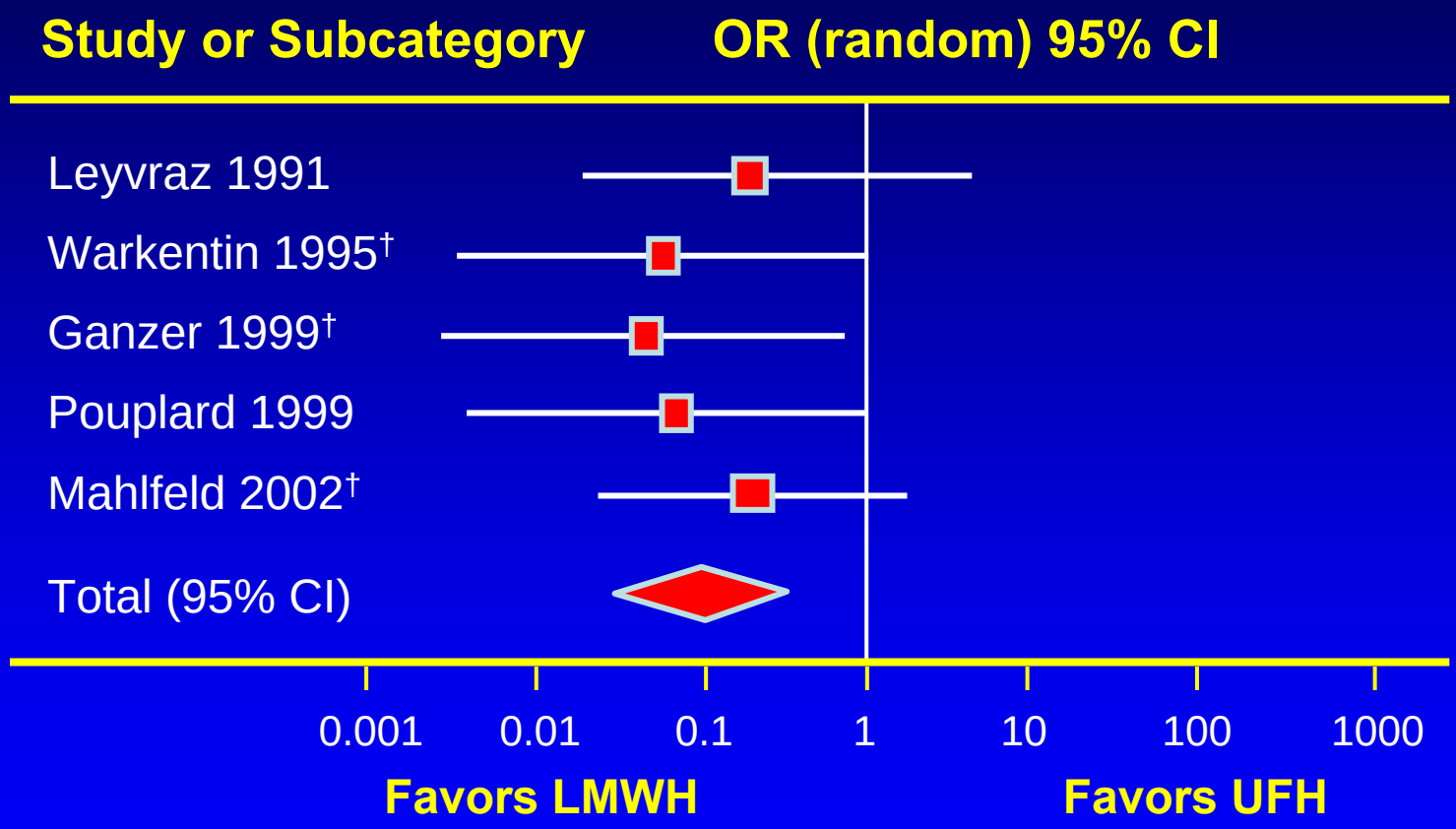
- Secondary analysis of 665 patients who received (UFH) or enoxaparin after THR
- The secondary analysis employed a sensitive laboratory definition of HIT that allowed for earlier diagnosis and treatment

***≥50% platelet count fall from the postoperative peak.**

Warkentin TE et al. *Arch Intern Med.* 2003;163:2518-2524.

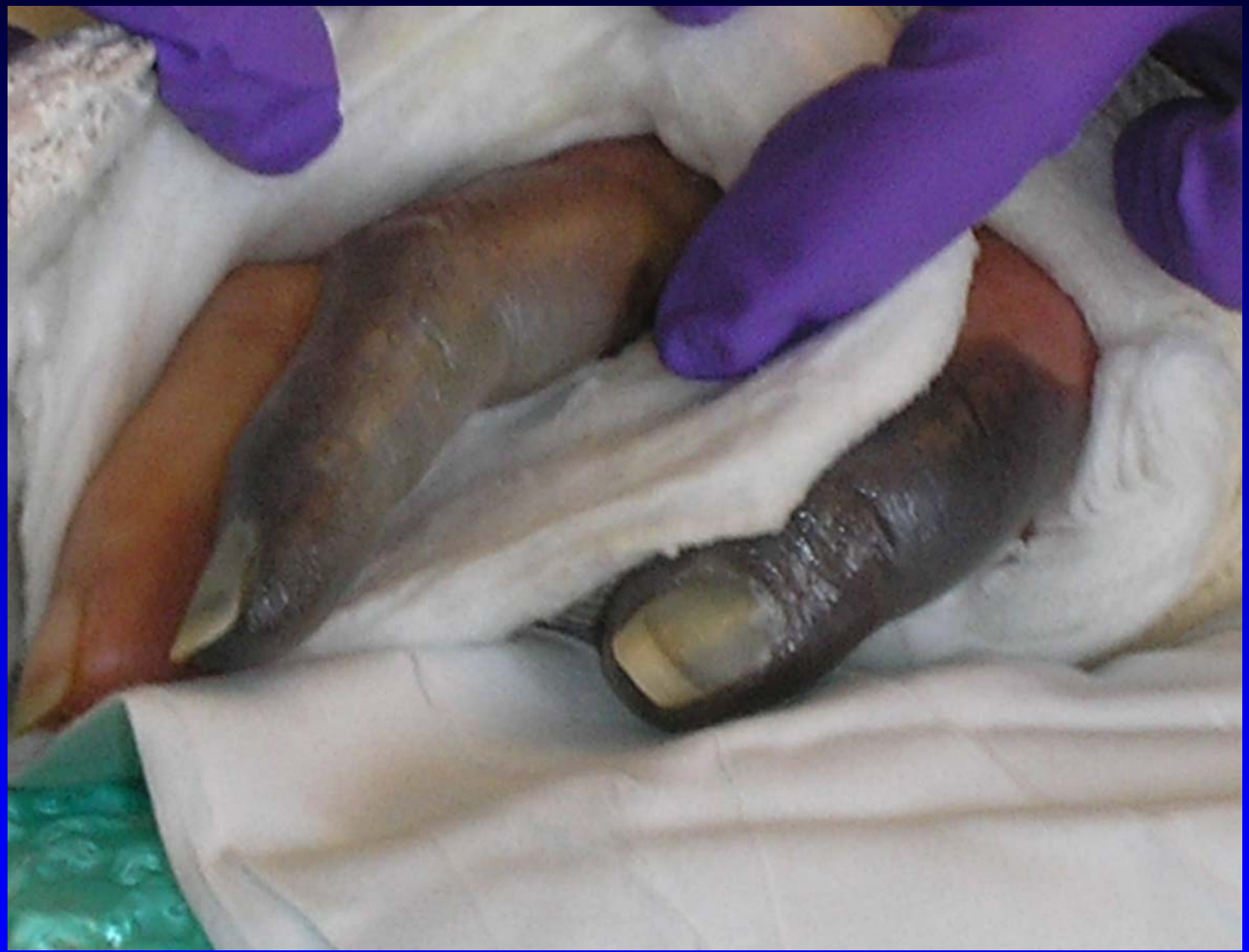
HIT: LMWH vs UFH

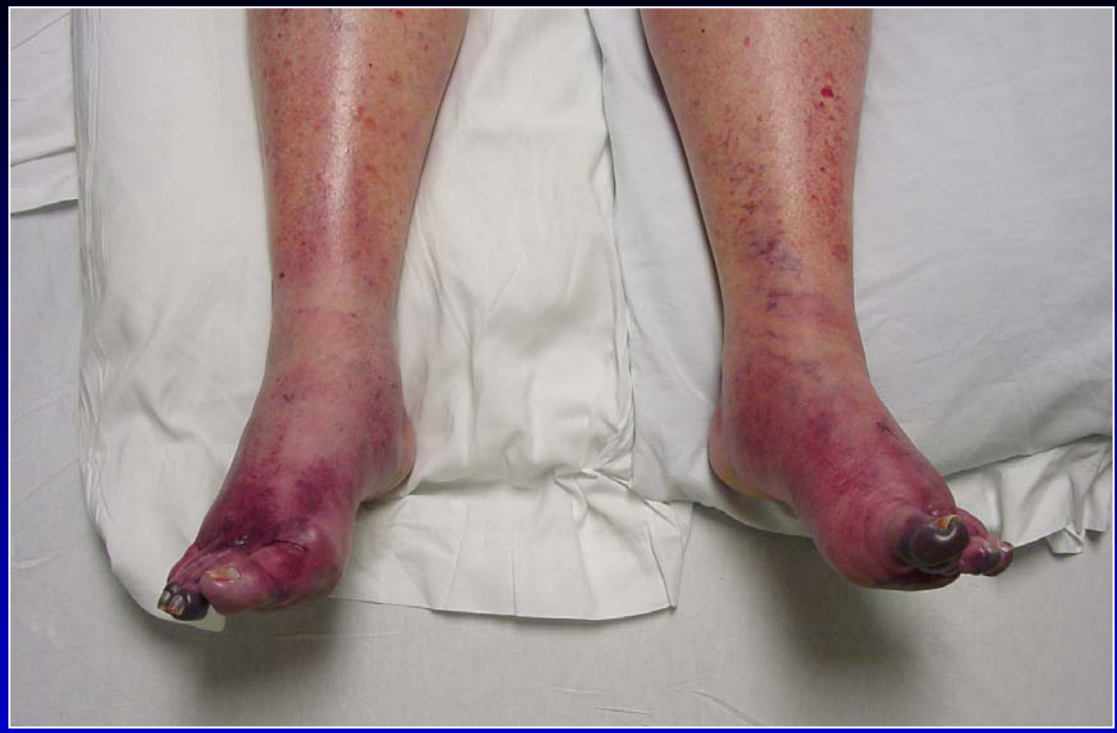
Meta-analysis of 5 Studies[1,2]*

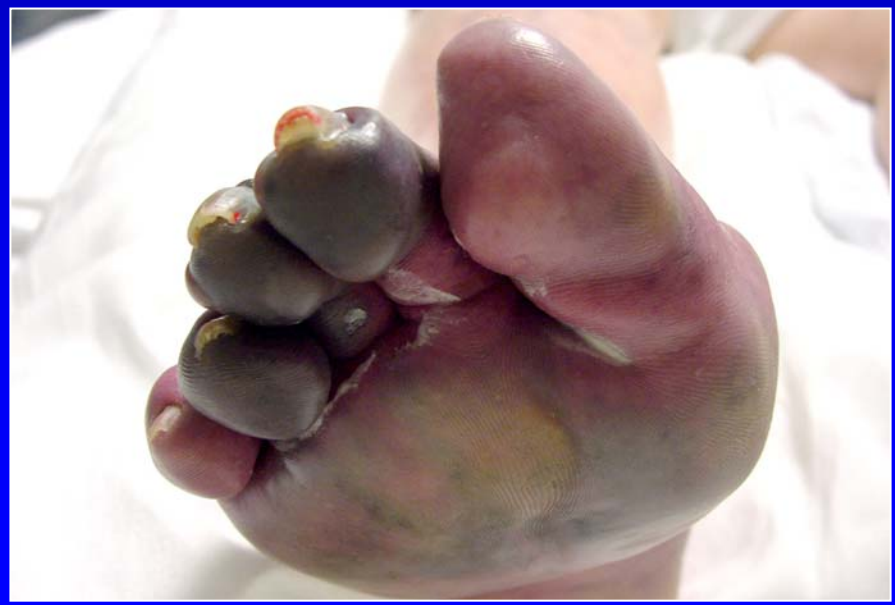


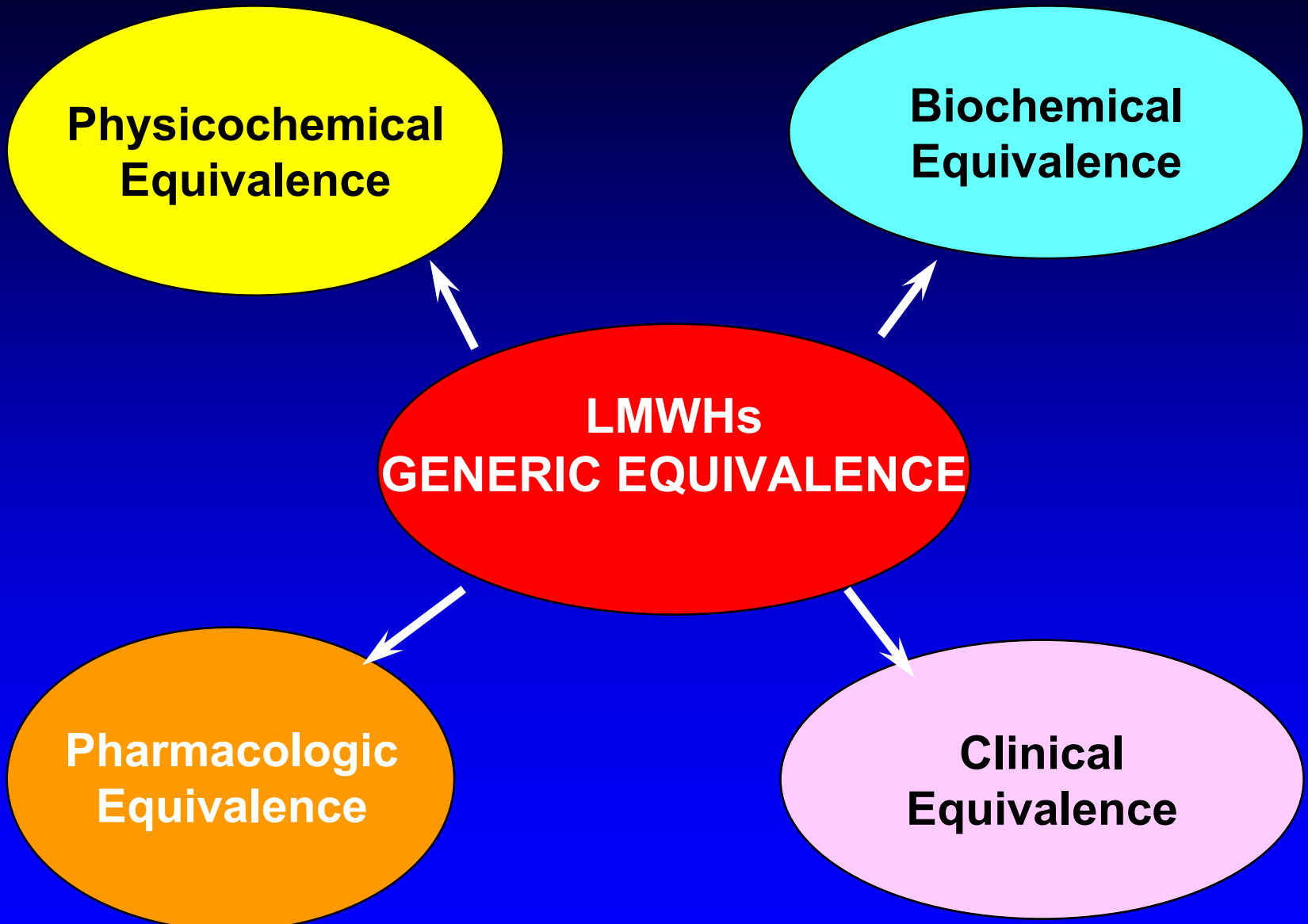
***Included surgical patients. †Three studies compared enoxaparin with UFH.**

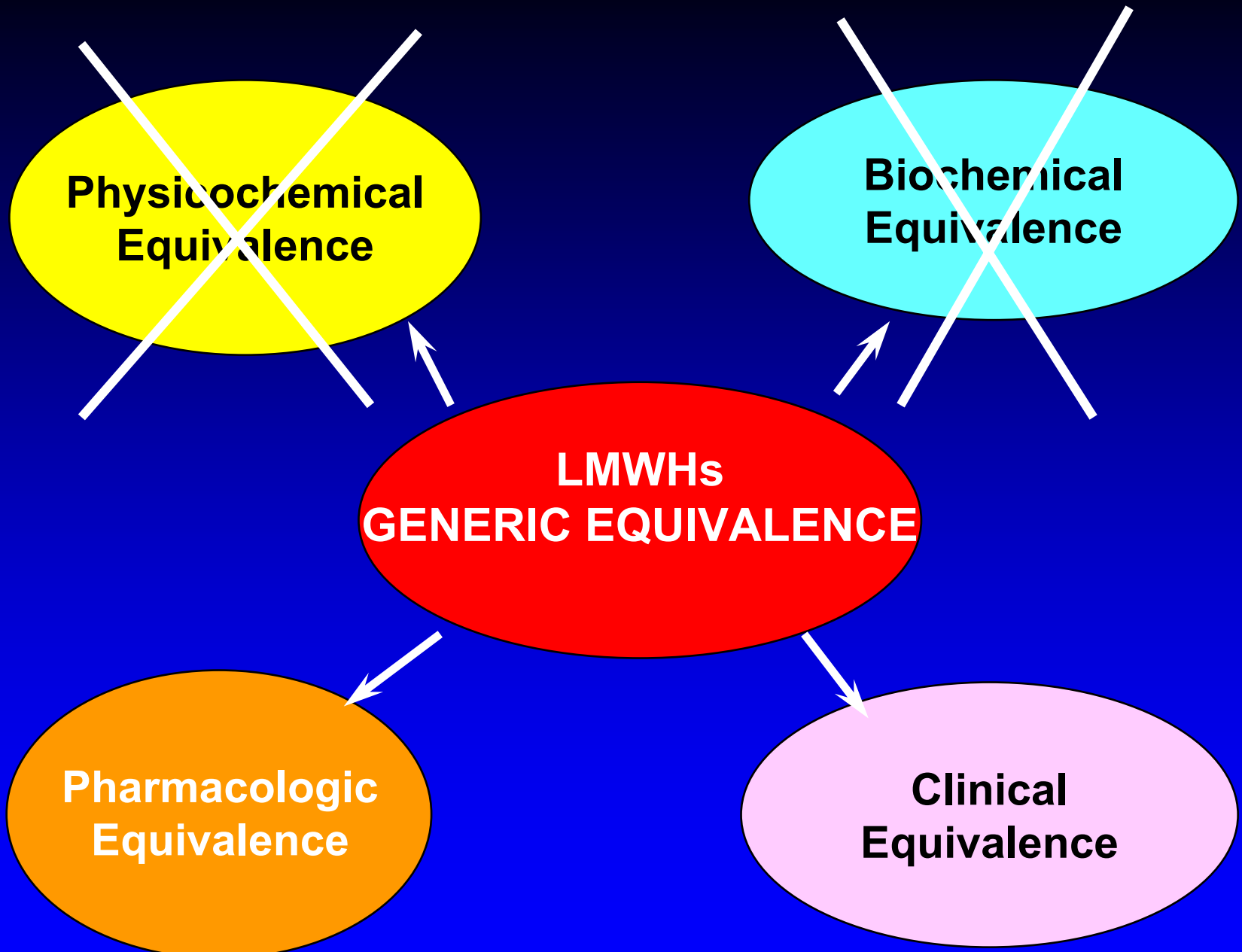
1. Warkentin TE. *Blood*. 2005;106:2600.
2. Martel N et al. *Blood*. 2005;106:2710-2715.








Physicochemical Equivalence
Biochemical Equivalence
LMWHs
GENERIC EQUIVALENCE
Pharmacologic Equivalence
Clinical Equivalence


Physicochemical Equivalence
Biochemical Equivalence
LMWHs
GENERIC EQUIVALENCE
Pharmacologic Equivalence
Clinical Equivalence

CURRENT PERSPECTIVE ON GENERIC LMWHS

- The regulatory bodies, US FDA and EMEA, may allow the generic versions of LMWHs and apply the same guidelines as for other biologicals.
- Additional requirements to provide supplementary chemical and biological data to support the filing may be needed. Some stipulations from the Citizens Petition may be considered.
- Clinical trials may or may not be required for specific products for approved indications depending upon the filing material review.

Issues with Biosimilars

- Variable potency and response
- Immunogenicty (glycosylation, contamination, changes to 3D structure)
  - Immune system is able to detect small changes in protein structure between an introduced molecule versus the original

Is Chemical Characterization of Branded LMWH Sufficient to Satisfy Assure Pharmacodynamics Equivalence?

- No: LMWHs are hybrid products of biologic origin with chemical modifications. The starting material is more important to characterize for product consistency.

BioSimilar Drugs

- Derived from living cells, therefore they can not be copied or duplicated
- Two biologics can result in significantly different immune responses
- Lack of scientific evidence to guarantee a safe interchange between biologics
- Difficulties exist in:
  - Molecular characterization
  - Depth of knowledge in regard to mechanism of action

Genazzani A. *Biodrugs.* 2007

Declerck P. *Drug Safety.* 2007

Immunogenicity of BioSimilars

- Generally proteins isolated from human tissues or serum are less immunogenic than non-human proteins
- Immune system is able to detect small changes in protein structure between an introduced molecule versus the original
- Methods used to detect formation of antibodies:
  - Difficulties with measurement
  - Inability to compare different studies

Schellekens H. *Clin Ther*. 2002

Kessler M, et al. *Nephrol Dial Transplant*. 2006

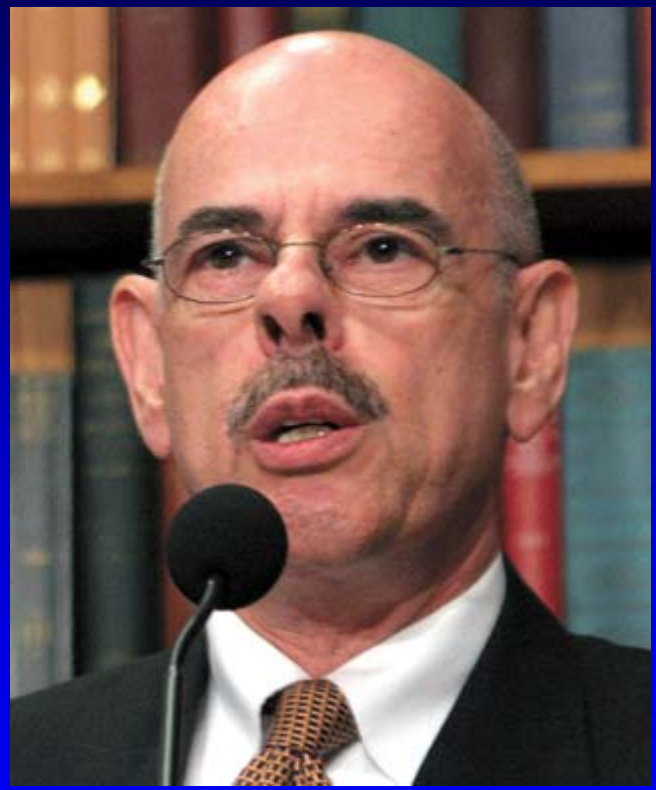
Immunogenicity of Biosimilars Clinical Consequences

- **Severe allergic or anaphylactic reaction**
- **Immune response to therapeutic protein may reduce efficacy**
- **Immune response leading to autoimmunity to patients own endogenous proteins**
- **Main focus is the questionable efficacy of protein and non-protein products that are being manufactured**
- **Manufacturing process in some cases have been able to address these concerns**

Schellekens H. *Clin Ther*. 2002

Kessler M, et al. *Nephrol Dial Transplant*. 2006

Political Statement	*Scientific Fact*
Biosimilar designed to be identical to parent product	Biosimilars may be similar but not identical
Parent product composition varies batch or lot	Batch-to-batch variability is a characteristic of all biologics Variability is unique to each product Limits of acceptable variability defined by clinical experience
Laboratory data predicts biosimilar efficacy and safety in clinical settings	Laboratory testing not sufficient Clinical data on efficacy, safety, and immunogenicity needed
MFG process changes frequently for parent product without supporting studies	FDA requires clinical data on MFG MFG changes are supported by data



Henry Waxman

Waxman Biosimilars Bill

- **Biosimilarity based on chemical, physical, biologic and other non-clinical laboratory studies.**
- **One or more clinical studies are required to demonstrate safety, purity and potency.**
- **Demonstration on similarity in one indication can be used to support claims of similarity in other indications.**
- **Requested indications must be approved for the reference product.**
- **Route, dosage and strength must be the same as that of the reference product.**

Waxman Biosimilars Bill

- Designation of interchangeability is possible, though not a requirement for biosimilarity.
- The official name of the biosimilar agent will be the same as that of the reference product.
- Innovator biologic products will receive marketing exclusivity for 5 years from the date of approval.
  - Period may be extended 6 months if supplement application for new indication is approved (excluding use in pediatric subpopulation).
  - Period may be reduced by 3 months is annual gross sales in US exceed $1 billion.

Rep. Anna Eshoo
14th Congressional District of California

Eshoo Biosimilars Bill

- Biosimilarity based on analytical studies to show product is highly similar to reference product notwithstanding minor differences in clinically inactive components.
- Clinical studies are required to demonstrate safety, purity and potency in each condition of use approved for the reference product.
- Requested indications must be approved for the reference product.
- Route, dosage and strength must be the same as that of the reference product.

Eshoo Biosimilars Bill

- **Designation of interchangeability is possible, though not a requirement for biosimilarity.**
- **The official name of the biosimilar shall be unique so that it is distinguished from the reference product an any subsequent biosimilars.**
- **Guidance for licensure must be provided by the FDA.**
  - **FDA has the ability to not approve a given product or product class if the current science or experience precludes it.**

Eshoo Biosimilars Bill

- Innovator biologic products will receive marketing exclusivity for 12 years from the date of approval.
  - Period may be extended to 14 years if supplement application for new indication is approved
  - Period may be increased by an additional 6 months if use in pediatric populations is approved.

Comparison of the Biosimilars Legislation Proposed by Representatives Waxman and Eshoo

	Waxman Bill	Eshoo Bill
Biosimilarity based on:	Chemical, physical, biologic and other non-clinical laboratory studies	Analytical studies to show that product is highly similar to the reference **notwithstanding minor differences in clinically inactive components**
Animal studies	Not specifically mentioned	Yes; including assessment of toxicity
Clinical studies	Yes; one or more studies sufficient to demonstrate safety, purity and potency. Applicant may use demonstration of similarity or interchangeability in one indication to support claims in other indications provided the same mechanism of action is involved in all conditions	Yes; one or more studies (including immunogenicity and PK/PD) to demonstrate safety, purity and **potency in each condition of use approved for the reference product.**
Mechanism of action	Must be the same as that of the reference product	Same as Waxman bill
Requested indications	Must be approved for the reference product	Same as Waxman bill
PK/PD	Route, dosage, strength must be the same as the reference product	Same as Waxman bill
Production	Appropriate facility must be used	Same as Waxman bill
Waiver of requirements		FDA Secretary has the discretion to waive any analytical, animal or immunogenicity requirements determined to be unnecessary.
Interchangeability	Possible to get such a designation, though not required for biosimilarity	Same as Waxman bill
Product name	FDA Secretary shall designate the same official name for the biosimilar as for the reference drug	FDA Secretary shall ensure that each biologic product approved under the bill bears a unique name that distinguishes it fro the reference product and any subsequent biosimilars approved.

Comparison of the Biosimilars Legislation Proposed by Representatives Waxman and Eshoo

	Waxman Bill	Eshoo Bill
Guidance on requirements		FDA Secretary must issue guidance on requirements for licensure following a period of public comment/input. No products can be approved until such a time that final guidance has been issued. FDA Secretary may indicate in guidance that certain products or product classes will not be licensed because current science or experience does not allow it.
Marketing exclusivity for innovator products	5 years from date of approval May be extended by 6 months if a supplement application is approved for a new indication other than use in a pediatric subpopulation May be reduced by 3 months is annual gross sales in the US exceed $1 billion.	12 years from the date of approval If a supplement application for a new indication is approved during the initial 8 years following approval, the period of exclusivity is increased to 14 years. An additional 6 months is granted if use in pediatric or neonatal subpopulations is approved at any time during the period of exclusivity.