Anticoagulation in Long Term Care

- Prophylaxis of VTE
- Treatment of VTE
- Long-term oral A/C
- Bridging therapy

Anticoagulation in Long Term Care

- Simple
  - No monitoring
  - No IV
  - Oral (monitoring)
  - SC (once or twice daily)

Anticoagulation in Long Term Care

Special Considerations

- Elderly
- Renal insufficiency
- Comorbid conditions
- Multiple drugs

Prophylaxis of VTE

- Acute medical illness
- CVA
- Post orthopaedic surgery
- Post cancer surgery
- Spinal cord injury

Treatment of VTE

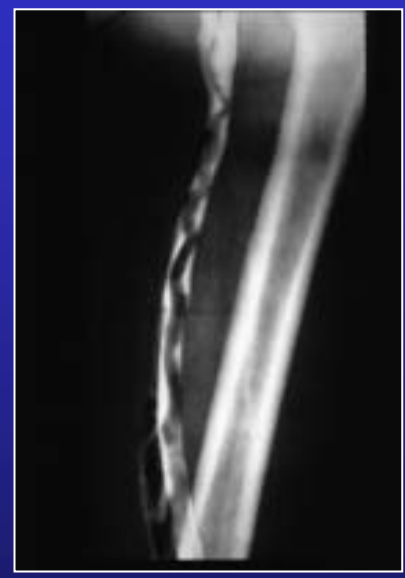
- Acute DVT
- Acute PE
- Secondary prophylaxis

Long – term oral anticoagulants

- Atrial fibrillation
- Heart valve replacement
- Post-MI
- VTE

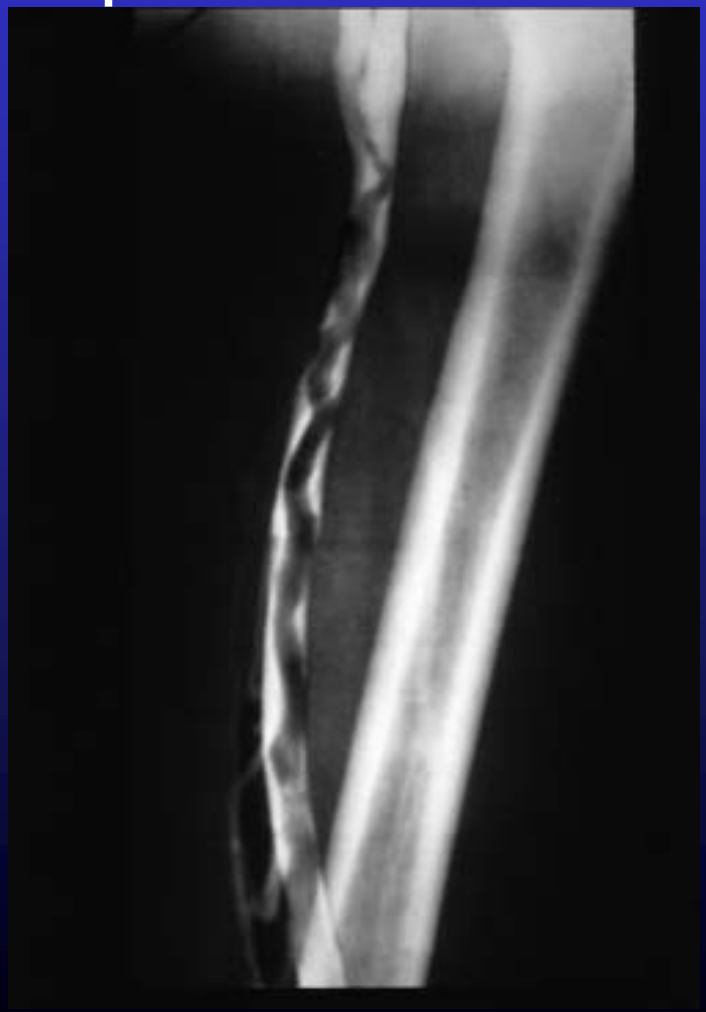
Venous Thromboembolism

- Third most common vascular disease
- PE leading preventable cause of death
- 200,000 cases of PE annually in USA

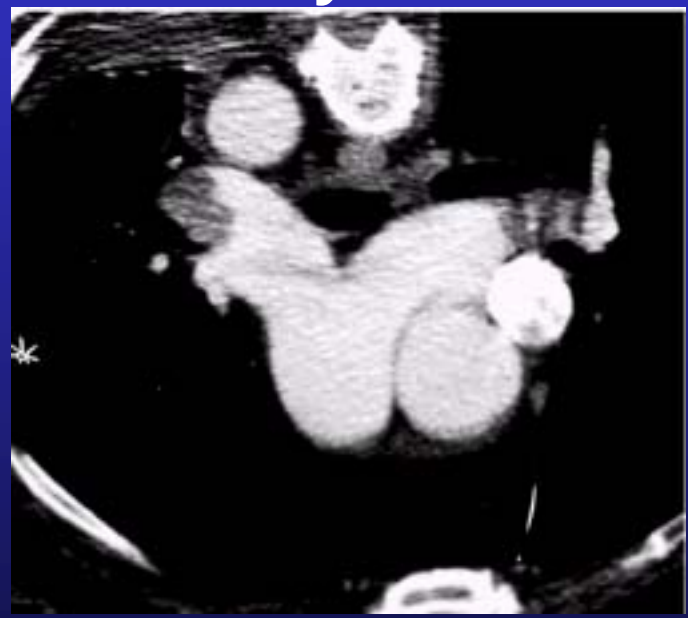


Venous Thromboembolism

Deep vein thrombosis



Pulmonary embolism



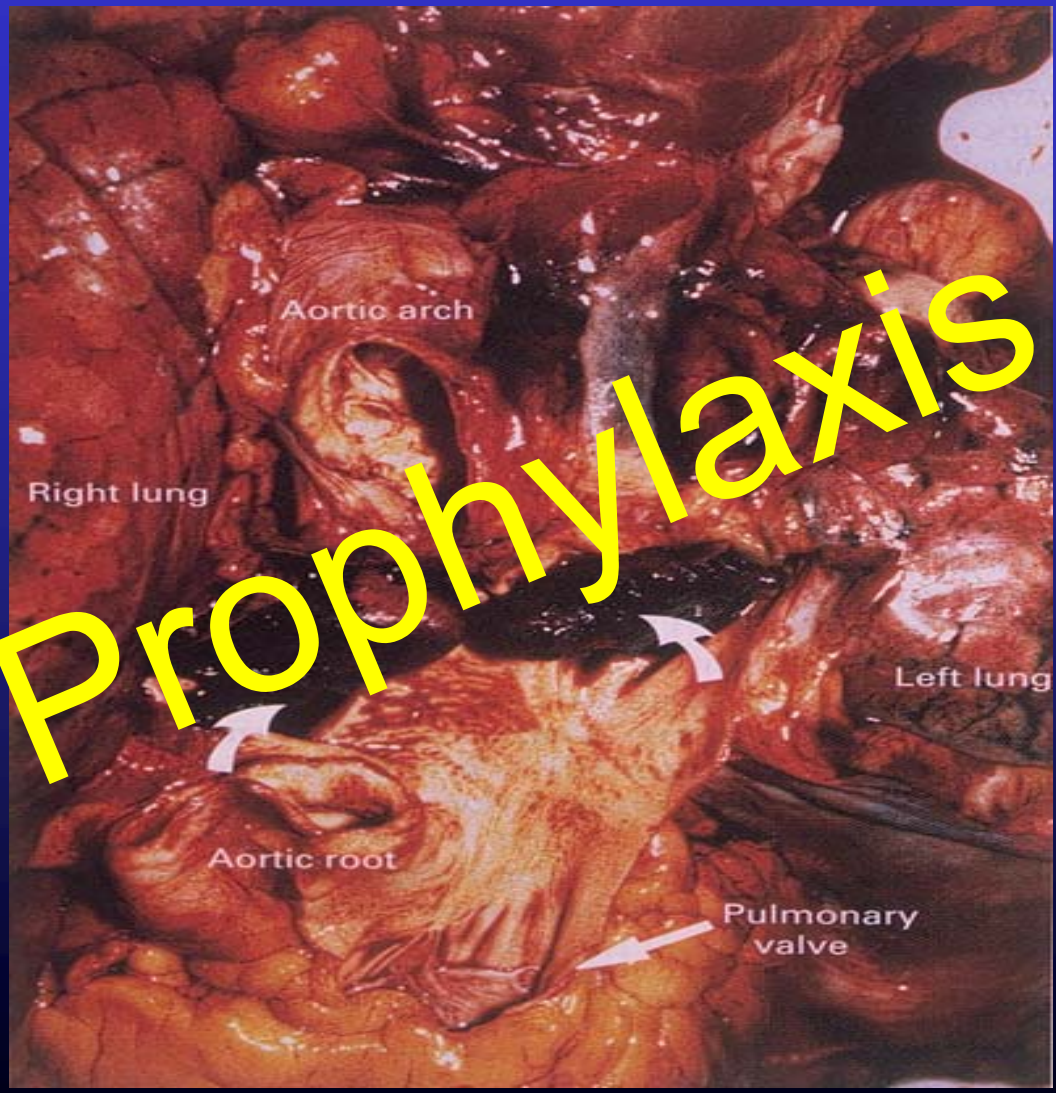
Complications of Deep Vein Thrombosis

- Permanent vascular damage
- Post-phlebitic syndrome
- Pulmonary embolism (PE)
- Pulmonary hypertension

Venous Thromboembolism

- Secondary
  - surgery
  - medical
- Idiopathic

Fatal Pulmonary Embolism



Prophylaxis

Classification of DVT risk

- **Low risk**
  - Minor surgery
  - Age <40
  - No other risk factors
- **Moderate risk**
  - Major surgery
  - Age >40
  - No other risk factors
- **High risk**
  - Major surgery
  - Age >40
  - MI
  - Additional risk factors
- **Highest risk**
  - Major surgery
  - Age >40
  - History of VTE
  - Hip fracture
  - THR or TKR
  - CVA
  - Spinal cord injury
  - Trauma
  - Malignancy
  - Congenital hypercoagulability

VTE, venous thromboembolism; THR, total hip replacement; TKR, total knee replacement; MI, myocardial infarction; CVA, cerebrovascular accident

Chest 1998;114:531S-60S

Frequency of VTE/PE according to risk level

Events	Low risk (%)	Moderate risk (%)	High risk (%)	Very high risk (%)
Calf vein thrombosis	2.0	10-20	20-40	40-80
Proximal vein thrombosis	0.4	2.4	4.8	10-20
Clinical PE	0.2	1-2	2-4	4-10
Fatal PE	0.002	0.1-0.4	0.4-1.0	1-5

PE, pulmonary embolism

Chest 1998;114:531S-60S

Methods of DVT prophylaxis

- Unfractionated heparin (UFH)
- Oral anticoagulants (warfarin)
- Dextran
- Antiplatelet therapy
- Mechanical compression and early ambulation
- Low-molecular-weight heparins (LMWHs)

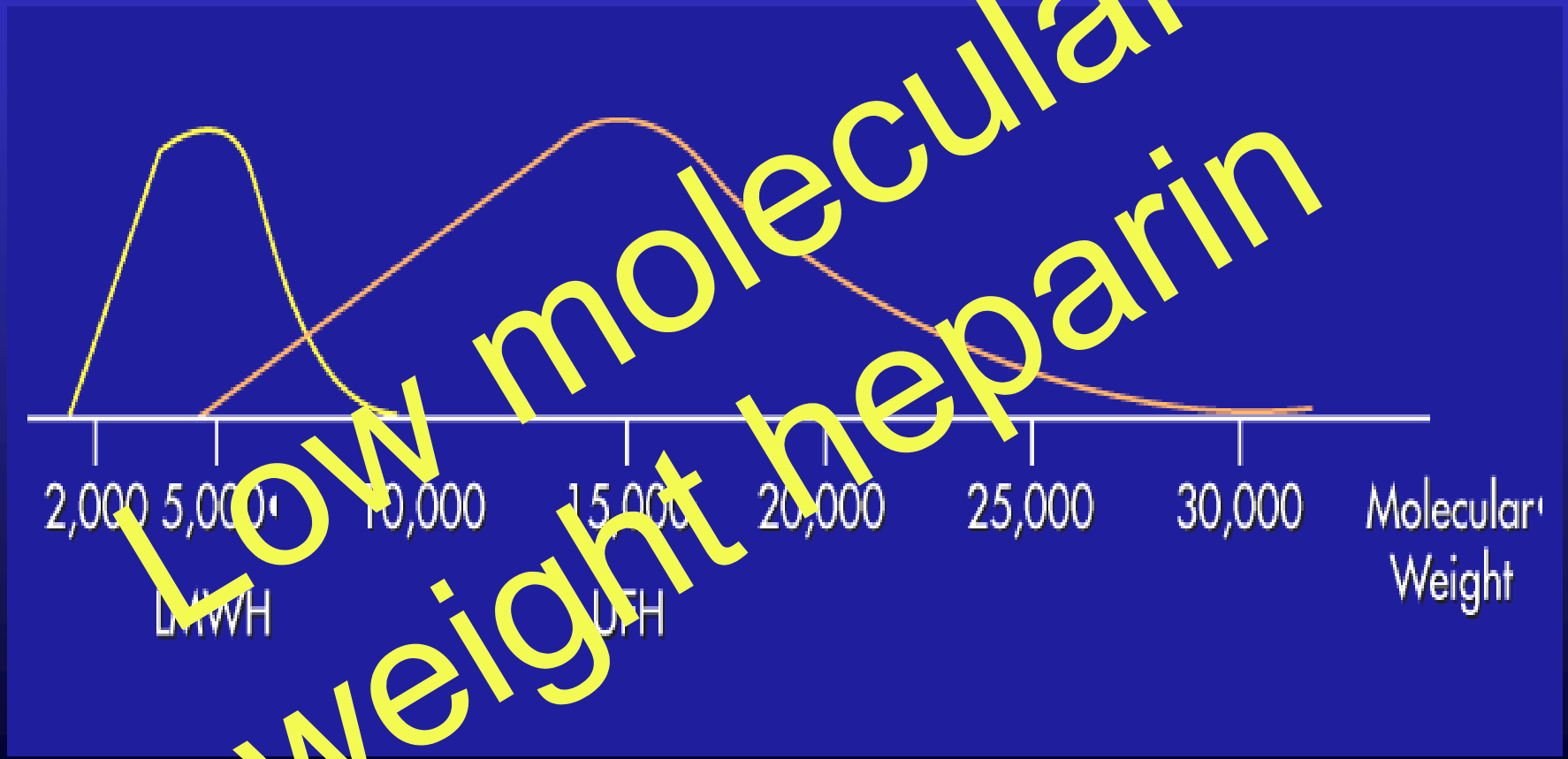
Heparin

- Venous thromboembolism
  - *prophylaxis*
  - *treatment*
- Ischaemic heart disease
  - *unstable angina*
  - *acute MI*
  - *post-thrombolysis*
- Embolic stroke
- Extracorporeal circulation
- Haemodialysis
- Peripheral arterial disease

New Anticoagulants

- Low Molecular Weight Heparins
- Low Molecular Weight Heparinoids
- Parenteral Direct Thrombin Inhibitors
- Oral Direct Thrombin Inhibitors
- Pentasaccharides

Schematic Molecular-Weight Distribution



Low-molecular-weight heparin (LMWH)

	Median molecular weight	Anti-Xa IU/mg	Anti-IIa IU/mg	Xa/IIa
Enoxaparin	4800	104	32	3.3
Dalteparin	5000	122	60	2.0
Nadroparin	4500	94	31	3.0
Tinzaparin	4500	90	50	1.8
Clivarine	3900	130	40	3.3

Low-Molecular-Weight Heparins

Potential Advantages:

- Lack of binding to plasma proteins and endothelium
- Good bioavailability
- Stable dose response
- Long half-life
- Resistance does not develop

Frequency of DVT without prophylaxis

Type of surgery	*DVT incidence*
Overall incidence in general surgery	19-29% [1]
Major abdominal surgery (over age 40)	
malignancy	30-35% [2]
benign disease	25-29% [2]
Gynaecological surgery	
malignancy	22% [3]
benign disease	14% [3]
Urological surgery	
retropubic prostatectomy	30-35% [2]
transurethral prostatectomy	10-12% [2]

1. Clagett et al. Ann Surg 1988; 2. Kakkar. Semin Hematol 1997;
3. Nicolaides et al. Int Angiol 1997.

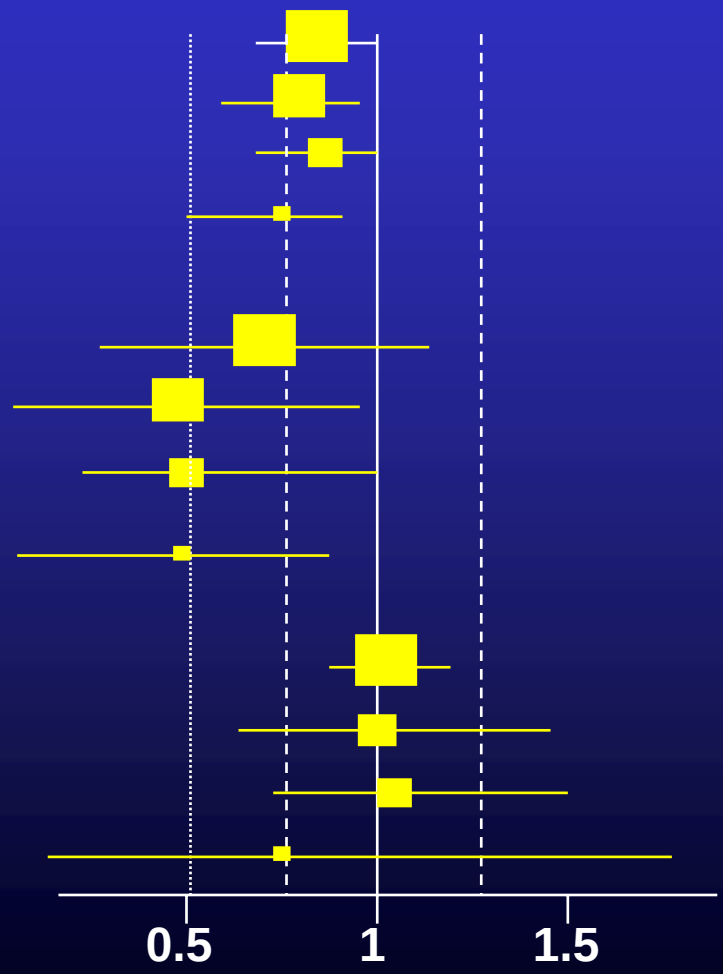
Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin

Collins et al. New England Journal of Medicine, 318 (18) 1162-1173 1988

- 68% reduction in DVT following surgery
- 67% reduction in PE following surgery

21% reduction in total mortality ($p < 0.02$)

LMWH vs UFH for VTE prophylaxis



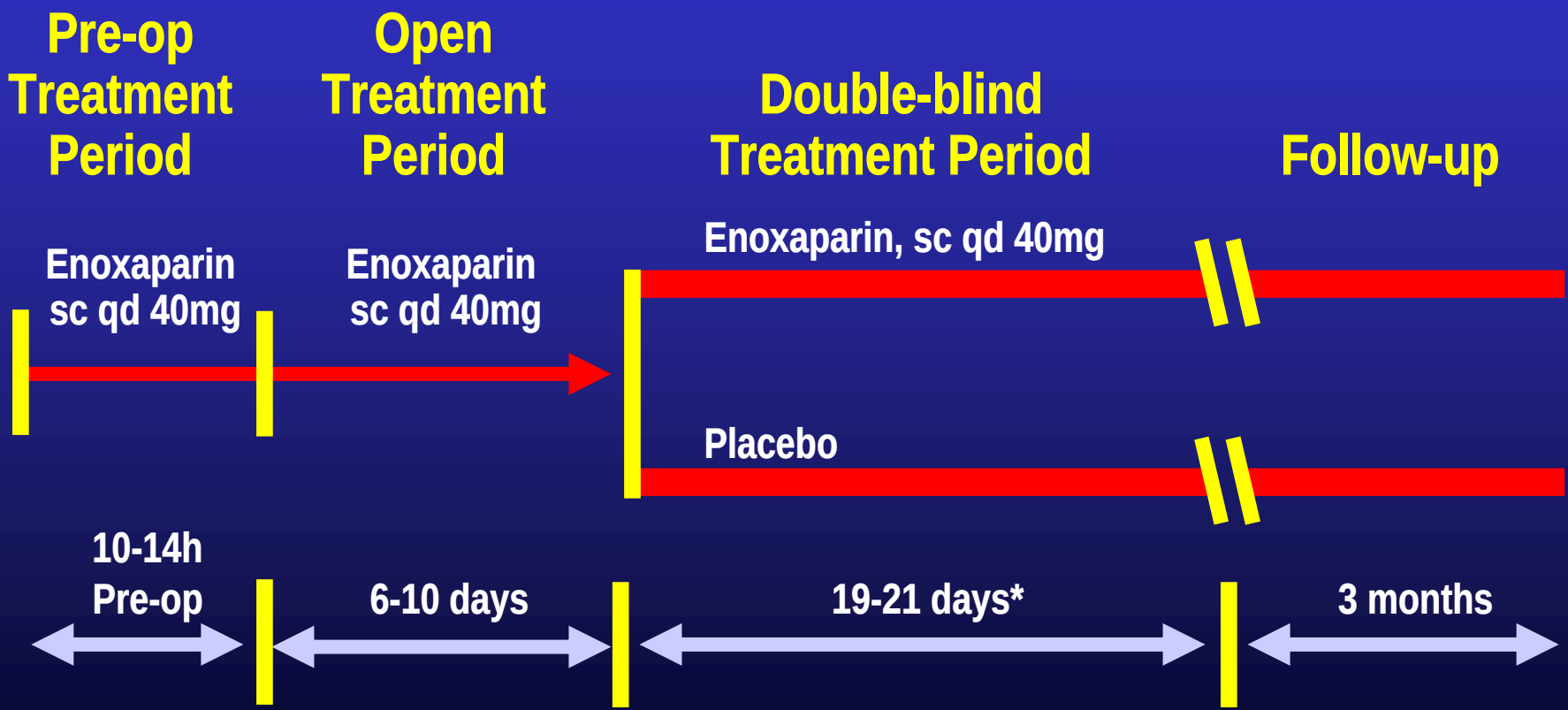
		(n)	*P*
Prevention of DVT			
General surgery	[1]	9683	0.12
	[2]	6878	<0.05
Orthopaedic surgery	[1]	2692	0.07
	[2]	1294	<0.05
Prevention of PE			
General surgery	[1]	9146	0.12
	[2]	5731	<0.05
Orthopaedic surgery	[1]	2475	0.06
	[2]	1172	<0.05
Major bleeding			
General surgery	[1]	9683	>0.6
	[2]	3943	NS
Orthopaedic surgery	[1]	2692	>0.6
	[2]	1294	NS

[1] *Lancet*, 1992;340:152-6
[2] *Br Med J*, 1992;305:913-20

ENOXACAN II

Study Design

332 Patients undergoing abdominal or pelvic surgery for cancer

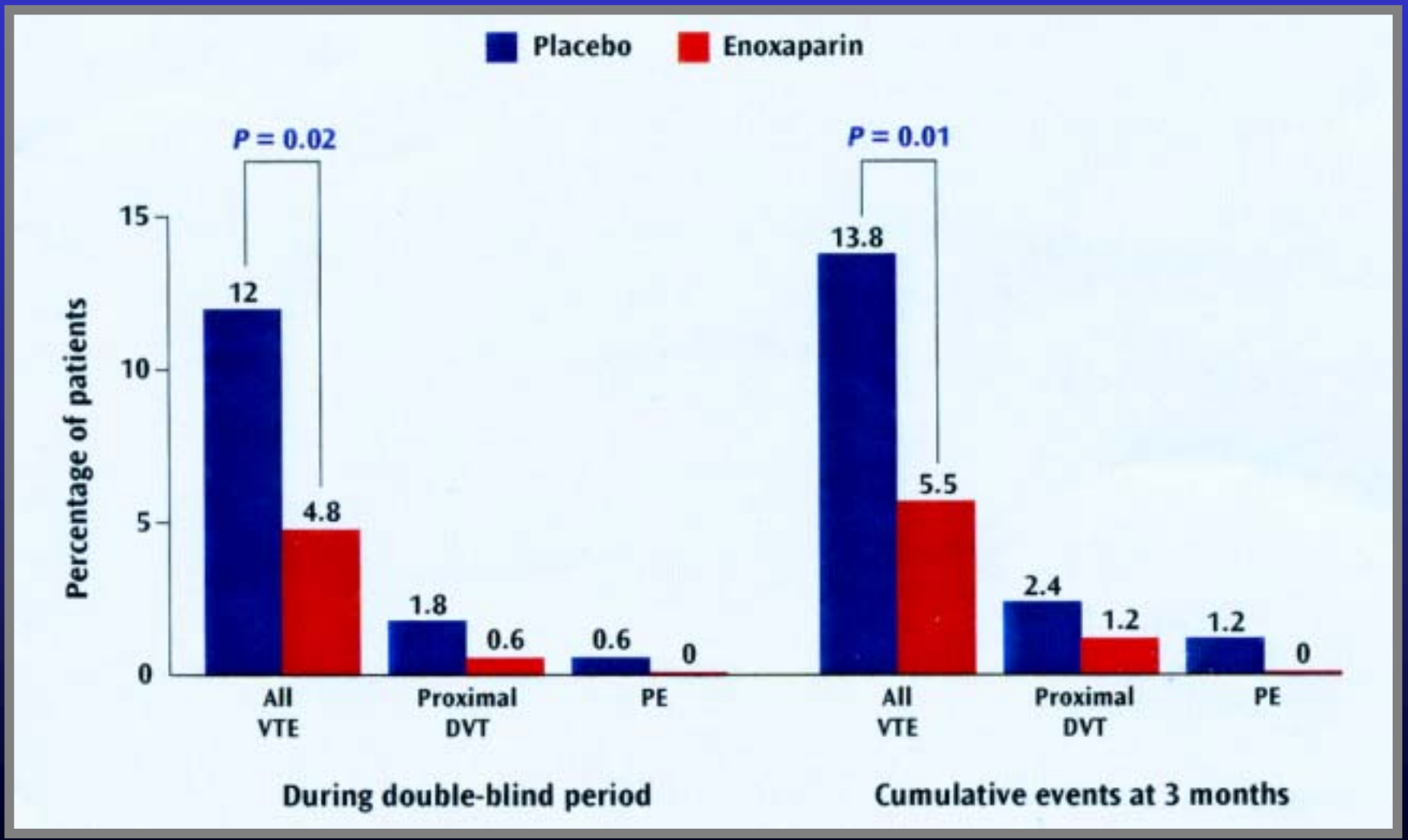


*** Venography between days 25-31**

Bergqvist D, et al. N Engl J Med 2002;346:975-980.

ENOXACAN II

Results



Bergqvist D, et al. N Engl J Med 2002;346:975-980.

ENOXACAN II
Conclusions

- Prolonged post-operative prophylaxis with enoxaparin significantly reduced VTE incidence by 60%
- Number needed to treat to avoid one VTE is 14
- Benefit maintained at 3 months

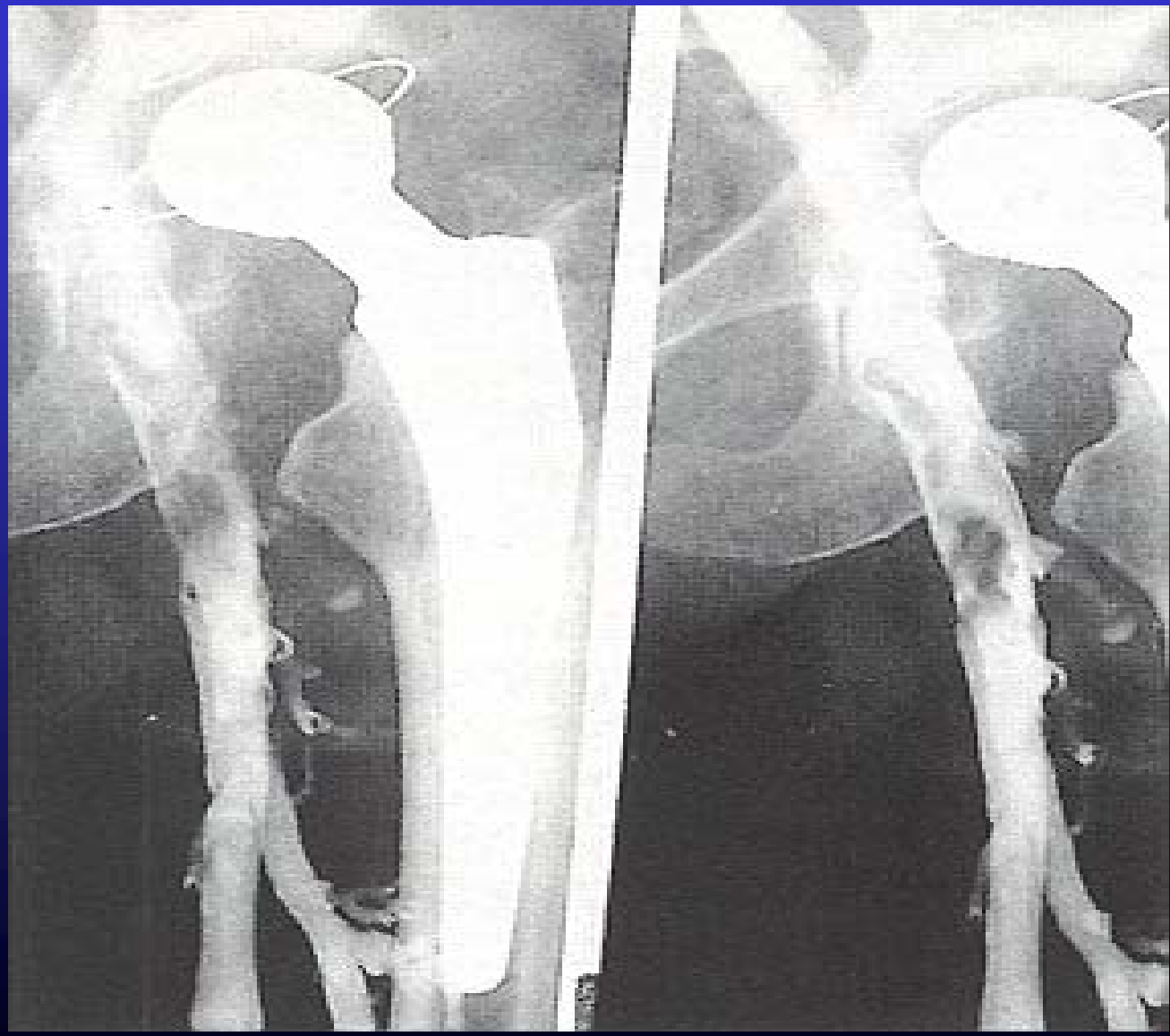
Bergqvist D, et al. N Engl J Med 2002;346:975-980.

General Surgery

RISK CATEGORY	RECOMMENDATION	LEVEL
Low risk	**Early ambulation**	C1
Moderate risk	**LDUH, LMWH, IPC, ES**	A1
High risk	**LDUH** **or** **Higher dose LMWH (40mg/day)** **or** **IPC if high risk of bleeding**	A1 A1 A1
Very high risk	**LDUH or higher dose LMWH combined with IPC** **or** **warfarin (INR 2.0-3.0)**	B1

ACCP Guidelines - Paris99
Chest 1998, Volume 114

Deep Vein Thrombosis



Major Orthopaedic Surgery

Increasing numbers - currently 2.2 million procedures per year

- Marked growth in the number of major orthopedic surgery procedures:
  - Technical advances
  - Patient aging
- Age is NOT a contraindication to surgery
- Cultural differences exist in patient management
- Despite major advances in patient care, the risk of VTE remains high.

Frequency of VTE in orthopaedic patients no prophylaxis

	DVT (%)	Prox VT (%)	PE (%)	Fatal PE (%)
THR	45–55	25–35	7–30	3–6
TKR	40–85	9–20	2–7	0.5
Hip #	35–60	15–35	4–24	4–13
Leg #	60–80			
Trauma	20–65		2–22	
Arthroscopy	18			

Clagett *et al. Chest* 1995; Lassen *et al. Orthopedics* 1997.

Geerts *et* al. *N Engl J Med* 1996 Demers *et al. Arch Int Med* 1998.

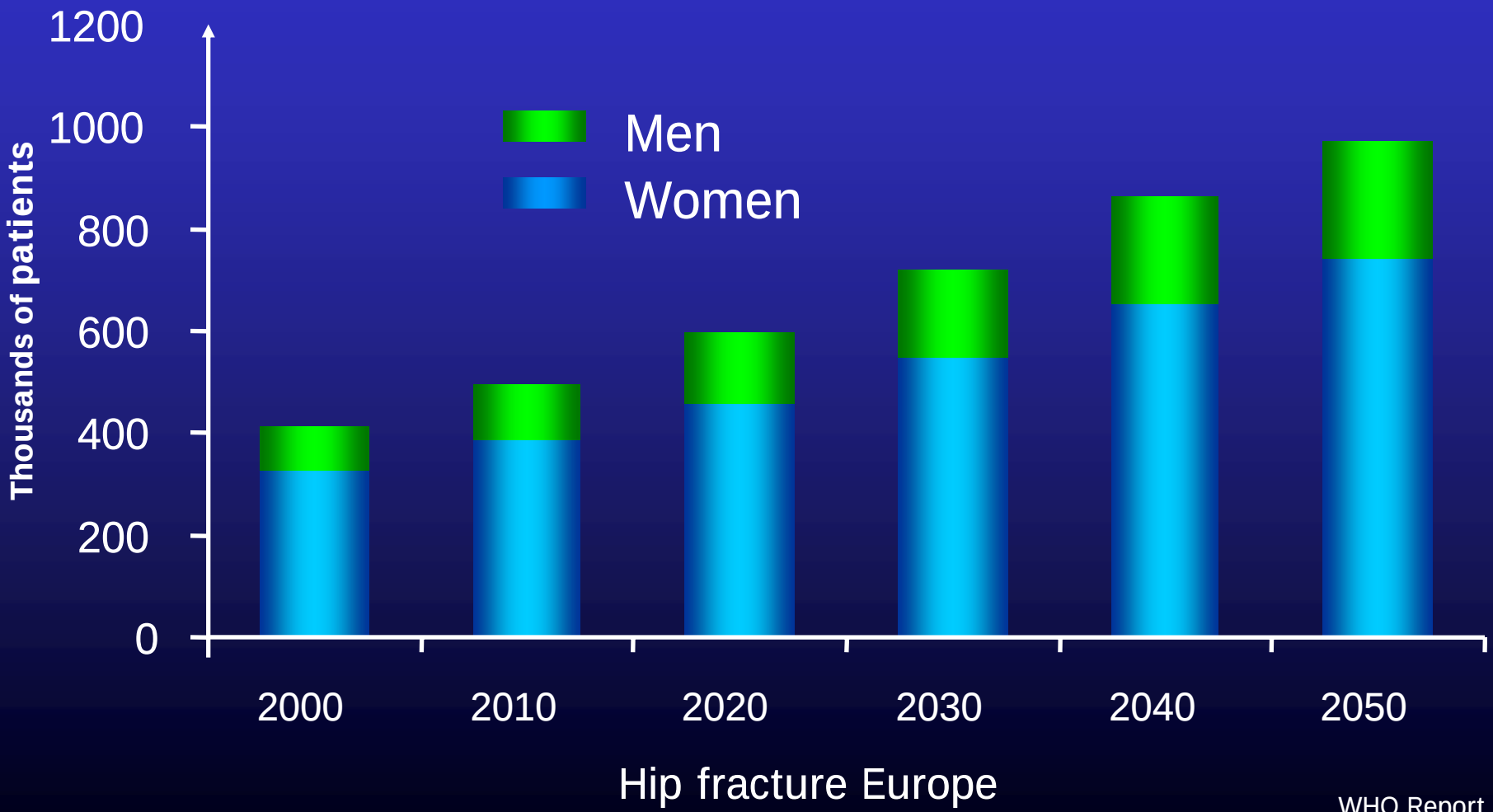
Prevention of Venous Thromboembolism

Geerts et al, Chest 2001; 119:132

Total Hip Replacement

Regimens	Trials	Patients	DVT Prevalence% 95% CI	RRR%	Prox DVT Prevalence% 95% CI	RRR%
Control	12	626	54.2 (50-58)	---	26.6 (23-31)	---
Comp Stock.	4	290	41.7 (36-48)	23	25.5 (21-31)	4
Aspirin	6	473	40.2 (35-45)	26	11.4 (8-16)	57
LDH	11	1016	30.1 (27-33)	45	19.3 (17-22)	27
Warfarin	13	1828	21.1 (20-24)	59	5.2 (4-6)	80
IPC	7	423	20.3 (17-24)	63	13.7 (11-17)	48
Hirudin	3	1172	16.3 (14-19)	70	4.1 (3-5)	85
LMWH	30	6216	16.1 (15-17)	70	5.9 (5-7)	78
Danaparoid	3	441	15.6 (12-19)	71	4.1 (2-6)	85
Adjusted Hep	4	293	14.0 (10-19)	74	10.2 (7-14)	62

Hip fracture:
An increasing problem



WHO Report 2000.

Hip Fracture surgery:

A common and increasingly frequent condition

- By 2050, numbers will increase 3 fold from 1.7 million to 6.3 million
- Unprecedented increases will occur in developing countries over next 50 years
- Life time risk of fracture will rise to an incredible 35% for women, 17% of men

A Global Health Problem

WHO Press release 1999
American Academy of Orthopedic Surgeons Bulletin. June 2001

Hip Fracture Surgery:
The highest risk of VTE

Rate of VTE without prophylaxis

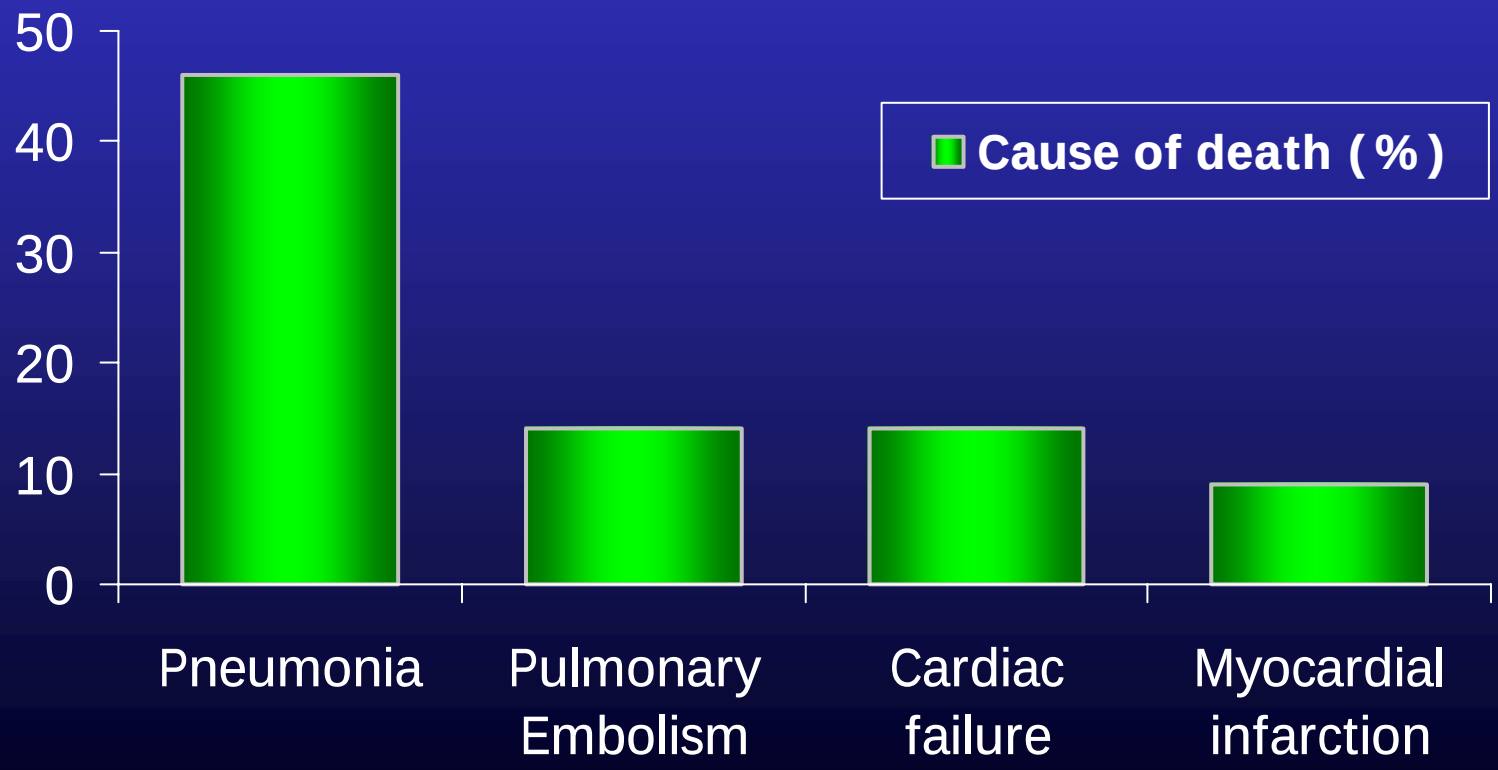
	% DVT rate	% PE rate (range)	
		Any PE	Fatal PE
Total hip replacement	45–57	0.7–30	0.1–0.4
Total knee replacement	40–84	1.8–7.0	0.2–0.7
Hip fracture	36–60	4.3–24	3.6–12.9

Geerts WH, et al. Chest 2001;119:132S–175S

Pulmonary Embolism

A leading cause of mortality following hip fracture surgery

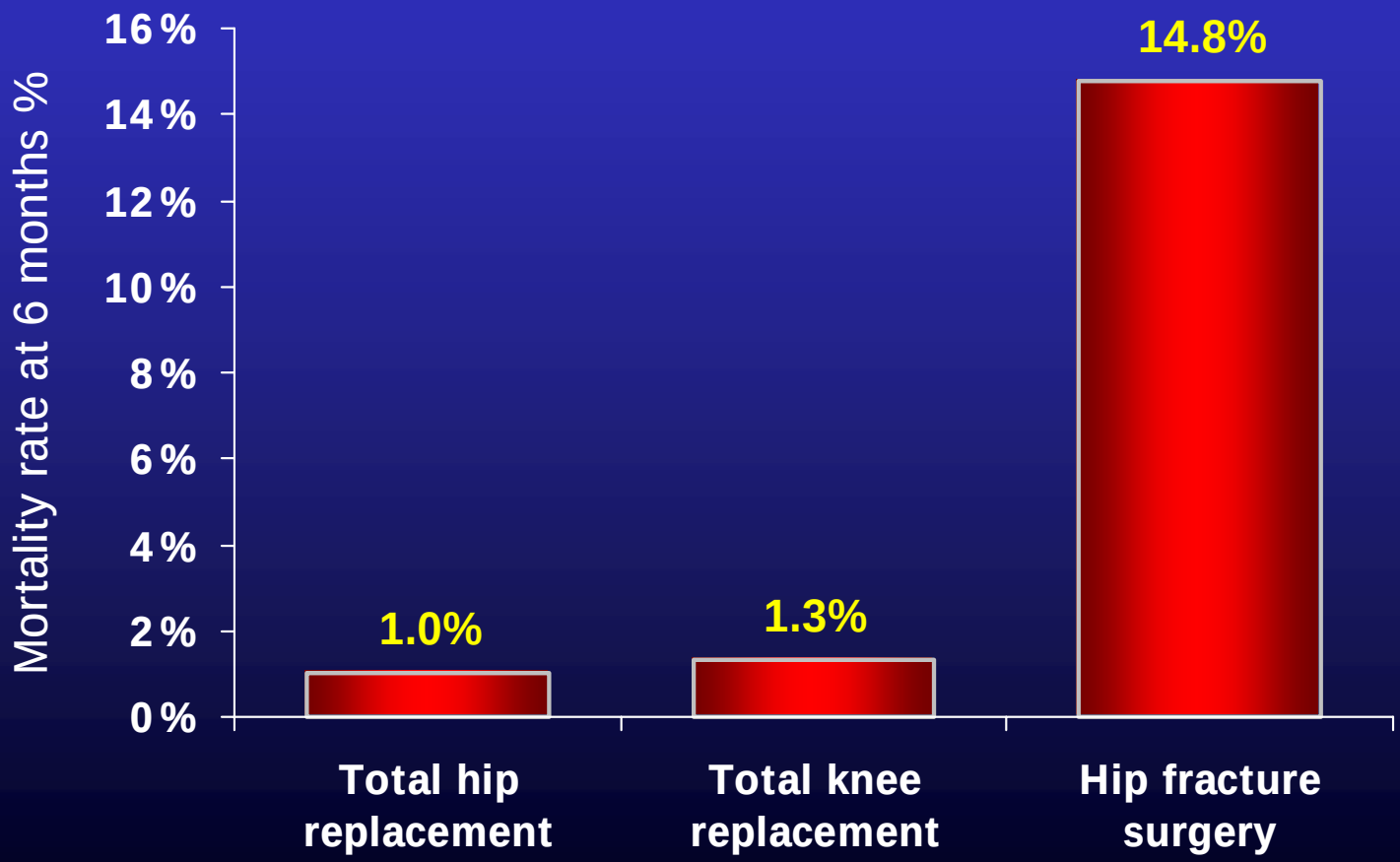
Primary causes of death in patients undergoing hip fracture surgery



Perez et al. Injury 1995;26:237-40.

Mortality following hip fracture

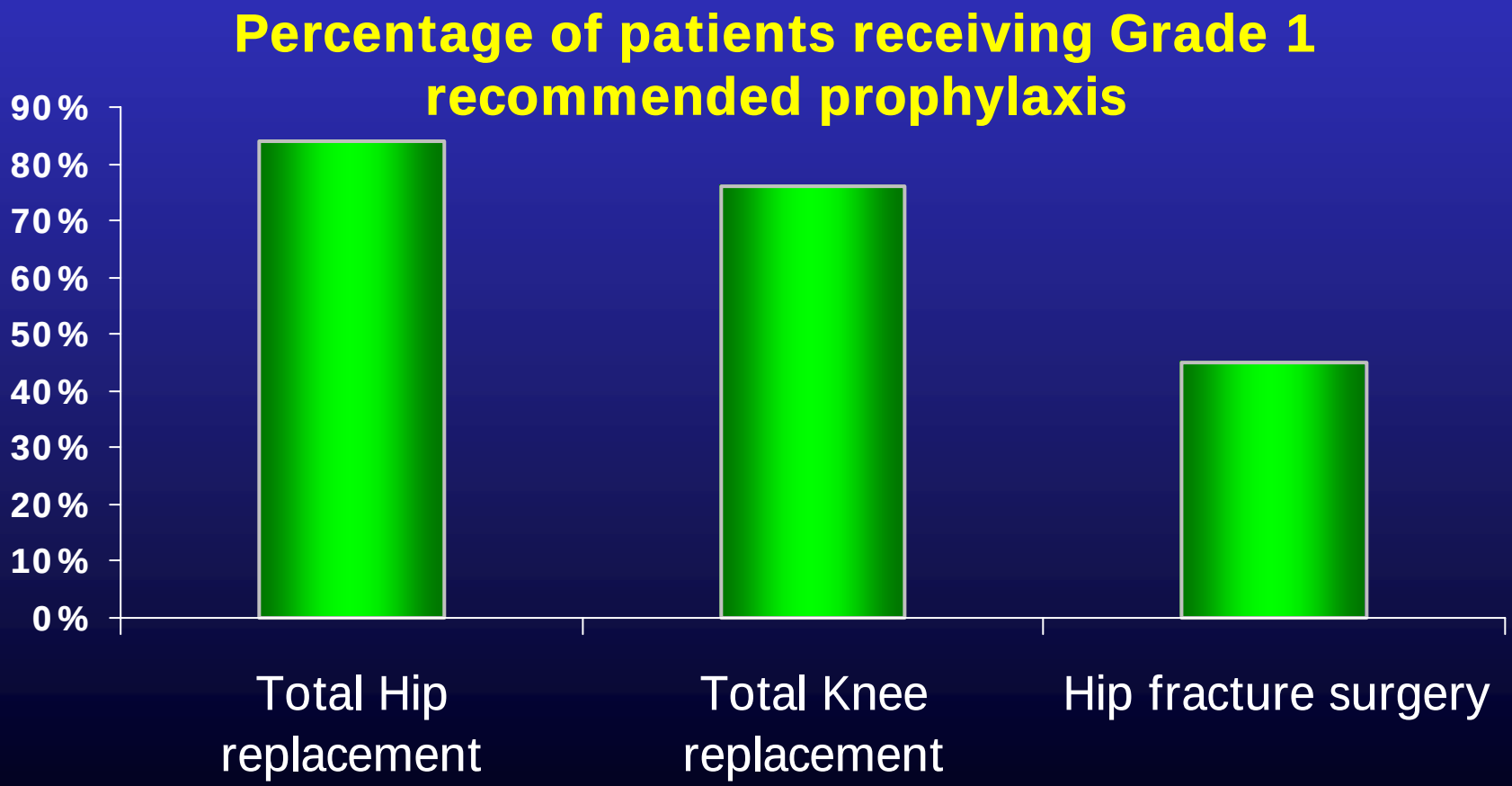
887 patients undergoing major orthopaedic surgery



Frostick SP. Haemost 2000;30(Suppl 2):84-7.

Hip fracture Surgery:

50% of patients don't receive adequate prophylaxis



Stratton MA, et al. Arch Intern Med 2000;160:334-340

Guidelines for Antithrombotic Therapy Major Orthopaedic Surgery

- Elective THR
  LMWH (started either 12 hours before or 12-24 hours after surgery) or adjusted dose warfarin INR target 2.5, range 2.0-3.0; started preoperatively or immediately after surgery). *Grade 1A.* Adjusted-dose heparin started preoperatively is an acceptable alternative. *Grade 2A*

- Elective TKR
  LMWH or adjusted-dose warfarin. *Grade 1A.* IPC is an alternative option. *Grade 1B*

- Hip fracture
  LMWH or adjusted-dose warfarin . *Grade 1B*

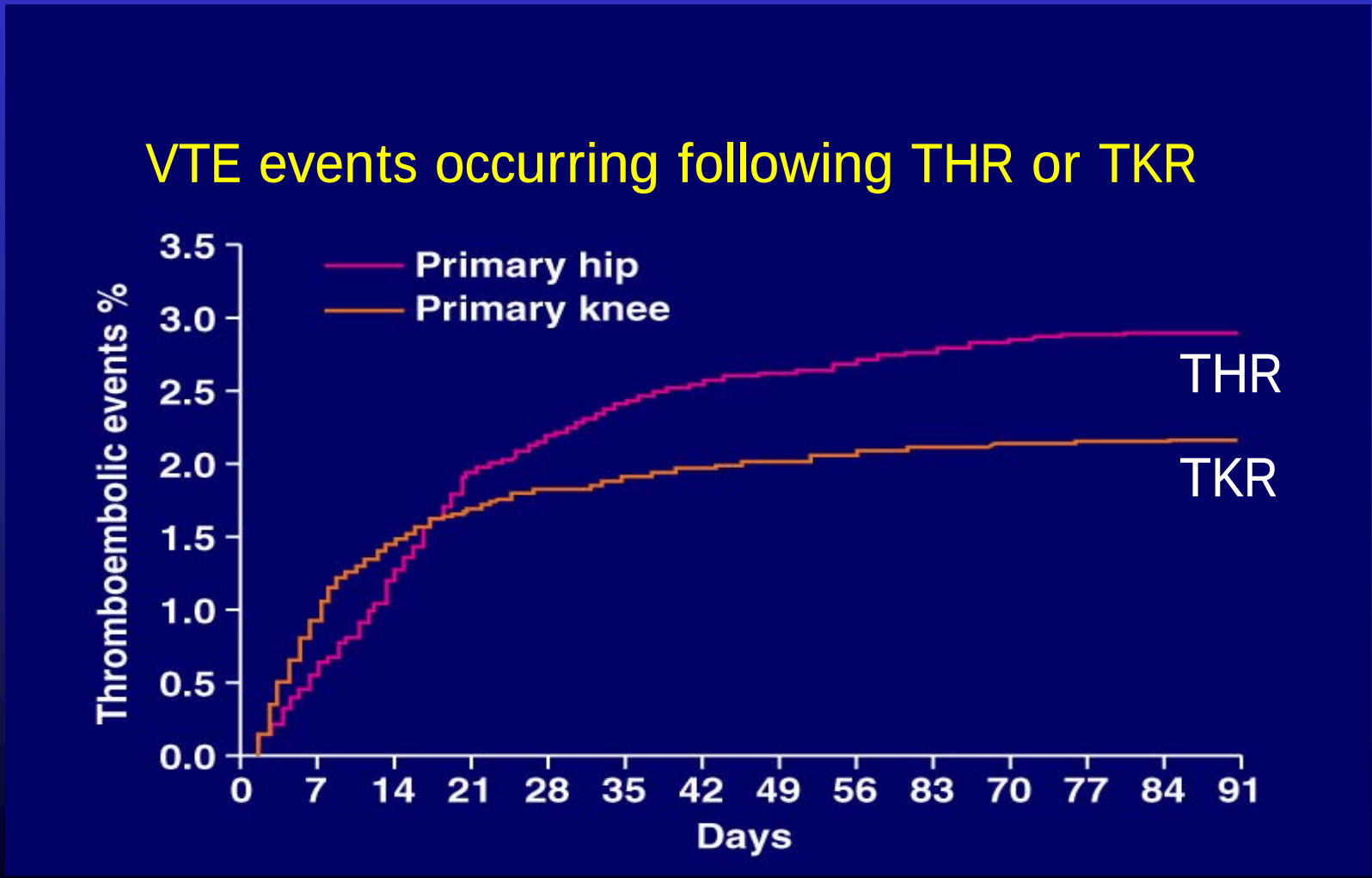
ACCP Chest 2001

Guidelines for Antithrombotic Therapy Major Orthopaedic Surgery

- Anticoagulant prophylaxis should be continued for at least 7-10 days. *Grade 1A*
- Extended out-of-hospital LMWH prophylaxis is recommended for high-risk patients. *Grade 2A*

ACCP Chest 2001

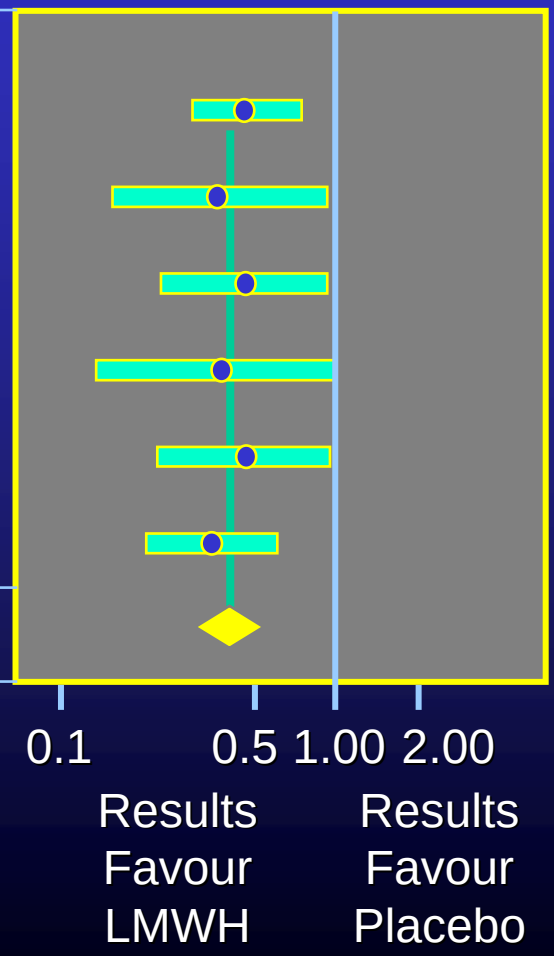
VTE events post orthopedic surgery:
2/3 occur beyond hospital discharge



White RH, et al. Arch Intern Med1998;158:1525–31.

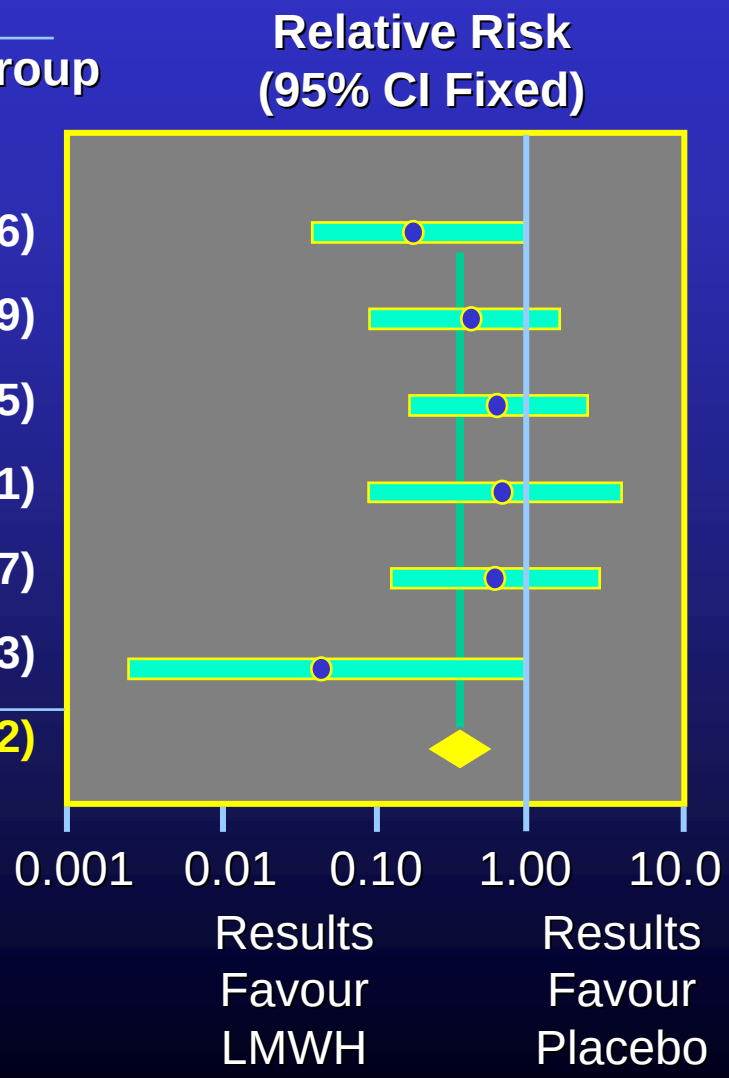
Relative Risk for All Deep Venous Thrombosis During the Out-of-hospital Time Interval

Study	Year	Patients with Events: LMWH Group n/n	(%)	Control Group n/n	(%)
Bergqvist et al.	1996	21/117	(17.9)	45/116	(38.8)
Planes et al. (30)	1996	6/85	(7.1)	17/88	(19.3)
Dahl et al. (31)	1997	11/93	(11.8)	23/89	(25.8)
Lassen et al. (32)	1998	5/113	(4.4)	12/102	(11.8)
Hull et al. (45)	2000	14/291	(4.8)	14/133	(10.5)
Comp et al. (46)	2001	15/152	(9.9)	39/138	(28.2)
Total		72/911	(7.9)	150/666	(22.5)



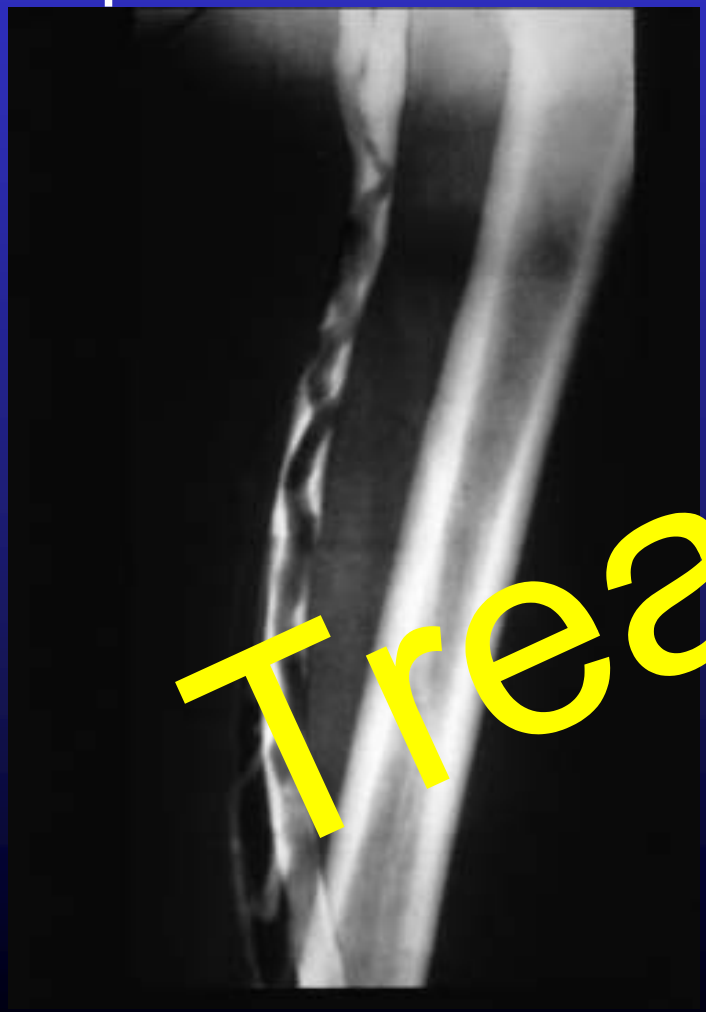
Relative Risk for Symptomatic Venous Thrombo-embolism During the Out-of-Hospital Time Interval

Study	Year	Patients with Events: LMWH Group *n/n (%)*		Patients with Events: Control Group *n/n (%)*	
Bergqvist et al.	1996	2/131	(1.5)	10/131	(7.6)
Planes et al. (30)	1996	3/90	(3.3)	7/89	(7.9)
Dahl et al. (31)	1997	4/117	(3.4)	6/110	(5.5)
Lassen et al. (32)	1998	2/140	(1.4)	3/141	(2.1)
Hull et al. (45)	2000	4/389	(1.0)	3/180	(1.7)
Comp et al.(46)	2001	0/224	(0.0)	7/211	(3.3)
Total		15/1091	(1.4)	36/862	(4.2)

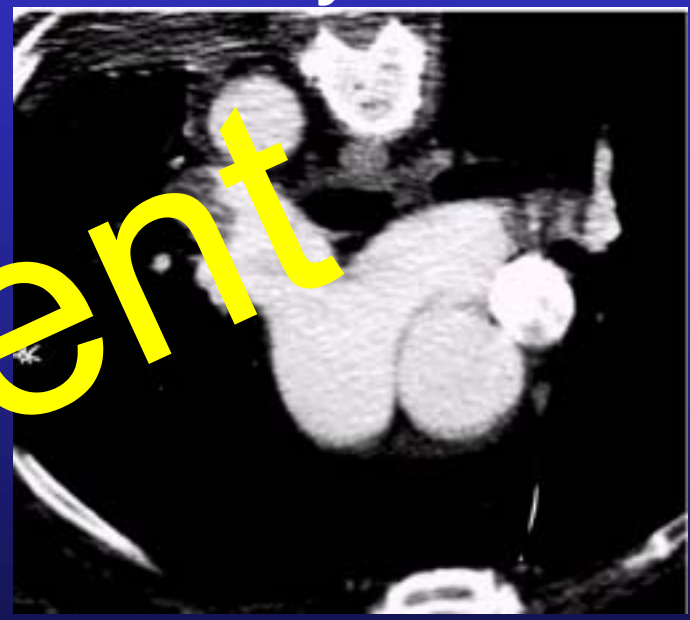


Venous Thromboembolism

Deep vein thrombosis



Pulmonary embolism



Treatment

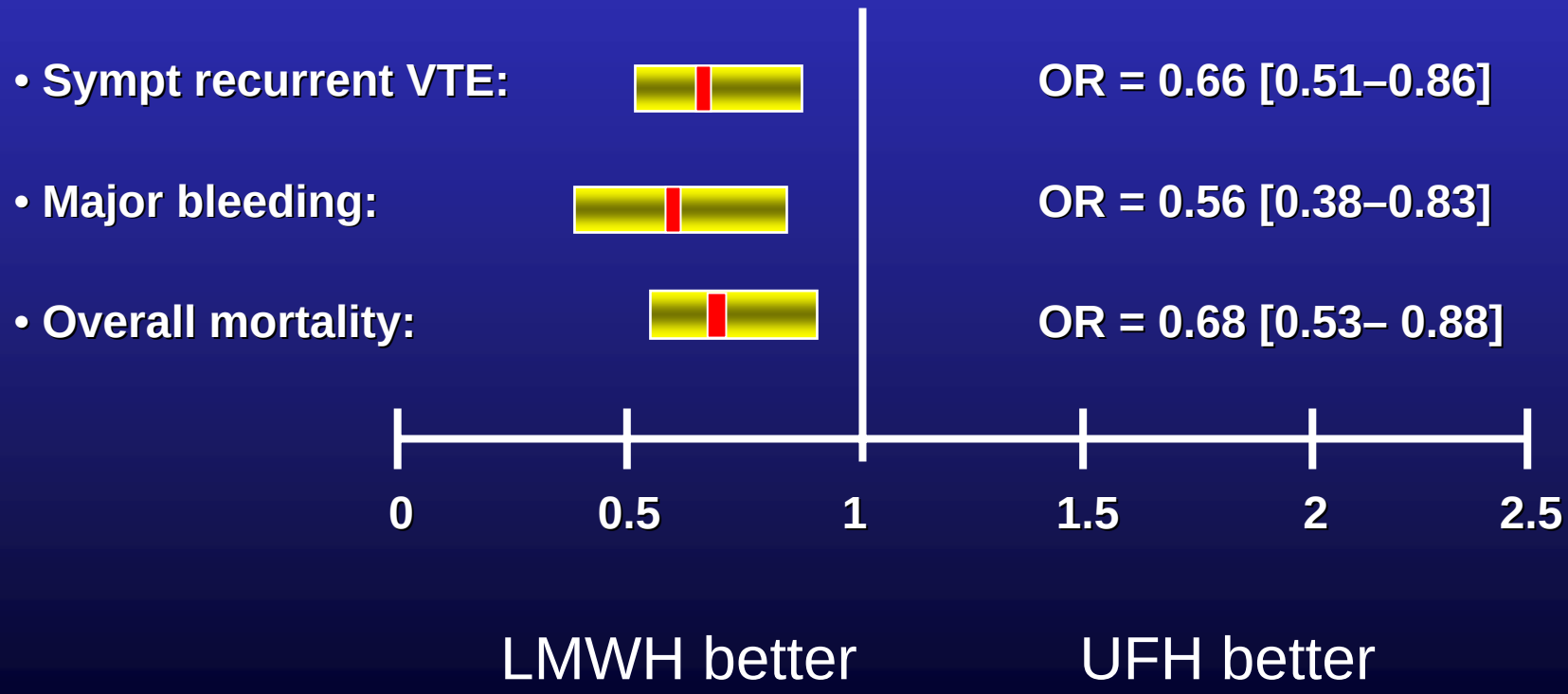
Guidelines for Antithrombotic Therapy Treatment of Venous Thromboembolism

ACCP Chest 2001

Suspected VT
SC LMWH or IV heparin bolus (5000u)
Confirm diagnosis
Confirmed VTE
Continue LMWH or UFH for 5 days
Monitor UFH with APTT and adjust dose
Start warfarin 5mg, target INR 2.5 (2.0-3.0)
Overlap minimum 4-5 days and until INR >2.0 for 2 days
Daily platelet count with UFH; x 1 for LMWH

LMWH at Least as Effective and Safe as UFH

Odds Ratio (OR, Peto), LWMH *vs* UFH with 95% confidence interval (13 comparative studies)



Van der Heijden, Cochrane 2001

Treatment of VTE : Advantages of LMWH

- Efficacy: better than UFH
- Safety: safer than UFH
- Mortality: perhaps a mortality benefit
- Patient satisfaction: outpatient treatment
- Clinical utility: once-a-day injections
- Cost savings: substantial

Guidelines for Antithrombotic Therapy Long-Term Anticoagulation

- All patients: Continue oral anticoagulation for at least 3 months at target INR of 2.5 (range 2.0-3.0). (This does not apply to patients with isolated calf-vein thrombosis). *Grade 1A*
- Oral anticoagulation contraindicated or inconvenient: LMWH or adjusted-dose s.c. heparin in therapeutic doses. *Grade 1A*

ACCP Chest 2001

Guidelines for Antithrombotic Therapy Long-Term Anticoagulation in VTE

- Patients with reversible or time-limited risk factors: treat for at least 3 months. Grade 1A
- Patients with a first episode of idiopathic VTE: treat for at least 6 months. Grade 1A
- Patients with recurrent idiopathic VTE or a continuing risk factor such as cancer, antithrombin deficiency, or anticardiolipin syndrome: treat for at least 12 months. Grade 1C
- Patients with protein C or S deficiency, multiple thrombophilic conditions, homocysteinemia, or factor V Leiden: treat for at least 6 months. Grade 1C

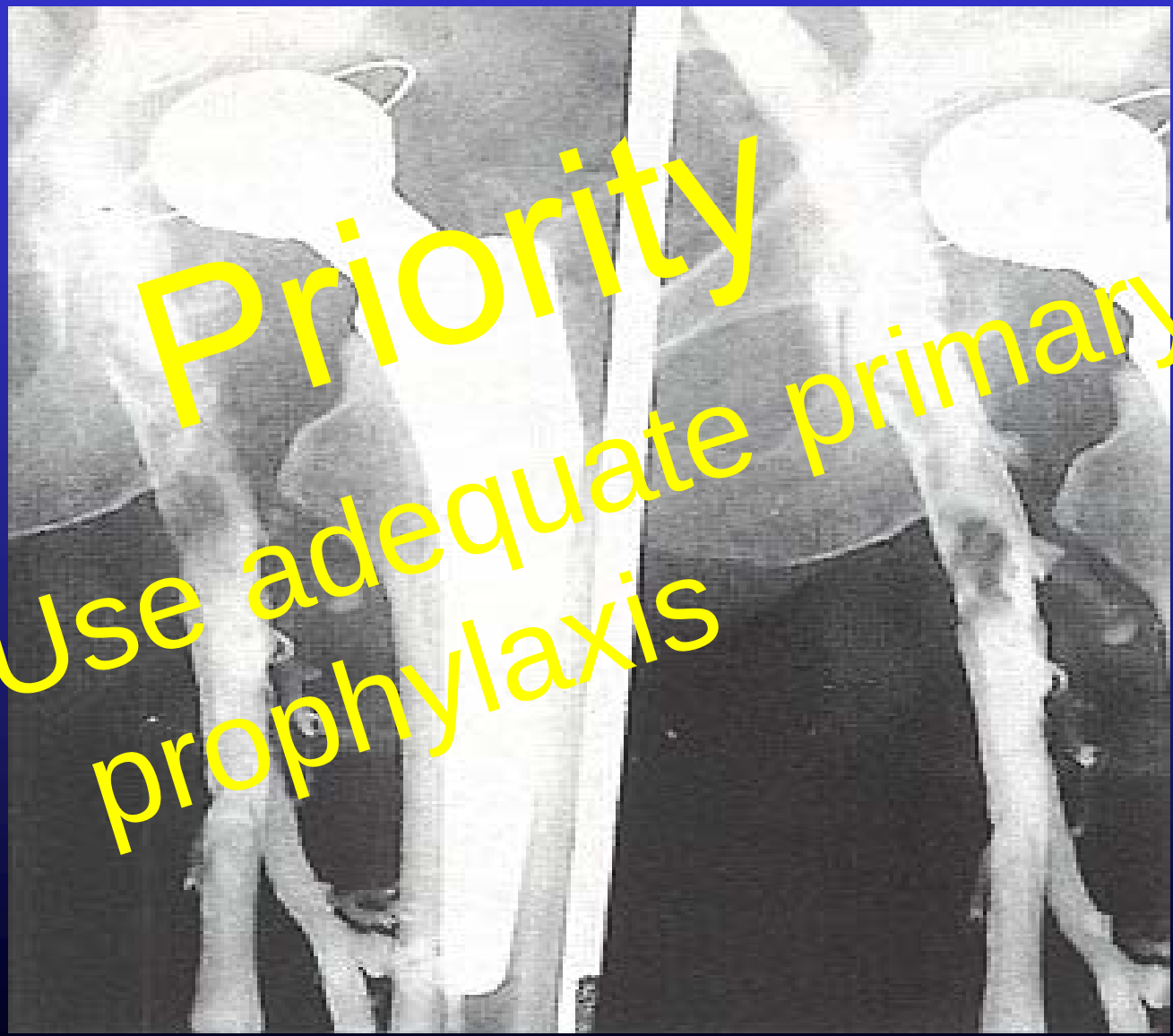
ACCP Chest 2001

Guidelines for Antithrombotic Therapy Long-Term Anticoagulation

- Symptomatic isolated calf-vein thrombosis: treat for at least 6-12 weeks. *Grade 1A*
- Alternatively, serial non-invasive studies over the next 10-14 days to assess for proximal extension of thrombus. *Grade 1C*

ACCP Chest 2001

Deep Vein Thrombosis



Atrial Fibrillation: Antithrombotic Therapy

Laupacis et al, Chest 1998; 114 (5):579-589

- Oral Anticoagulants vs Aspirin
- Efficacy vs safety
- Risk stratification
  - -Major
  - -Intermediate
  - -Low

Atrial Fibrillation: Risk Factors for Stroke

Laupacis et al, Chest 1998; 114 (5):579-589

High Risk

- Age >75 years
- Prior TIA, stroke or systemic embolism
- Hypertension or history of hypertension
- Poor LV function (clinical or 2-D echo)
- Rheumatic mitral valve disease
- Heart valve replacement

Atrial Fibrillation: Risk Factors for Stroke

Laupacis et al, Chest 1998; 114 (5):579-589

Intermediate Risk

- Age 65-75 years
- Diabetes
- CAD
- Thyrotoxicosis

Atrial Fibrillation: Risk Factors for Stroke

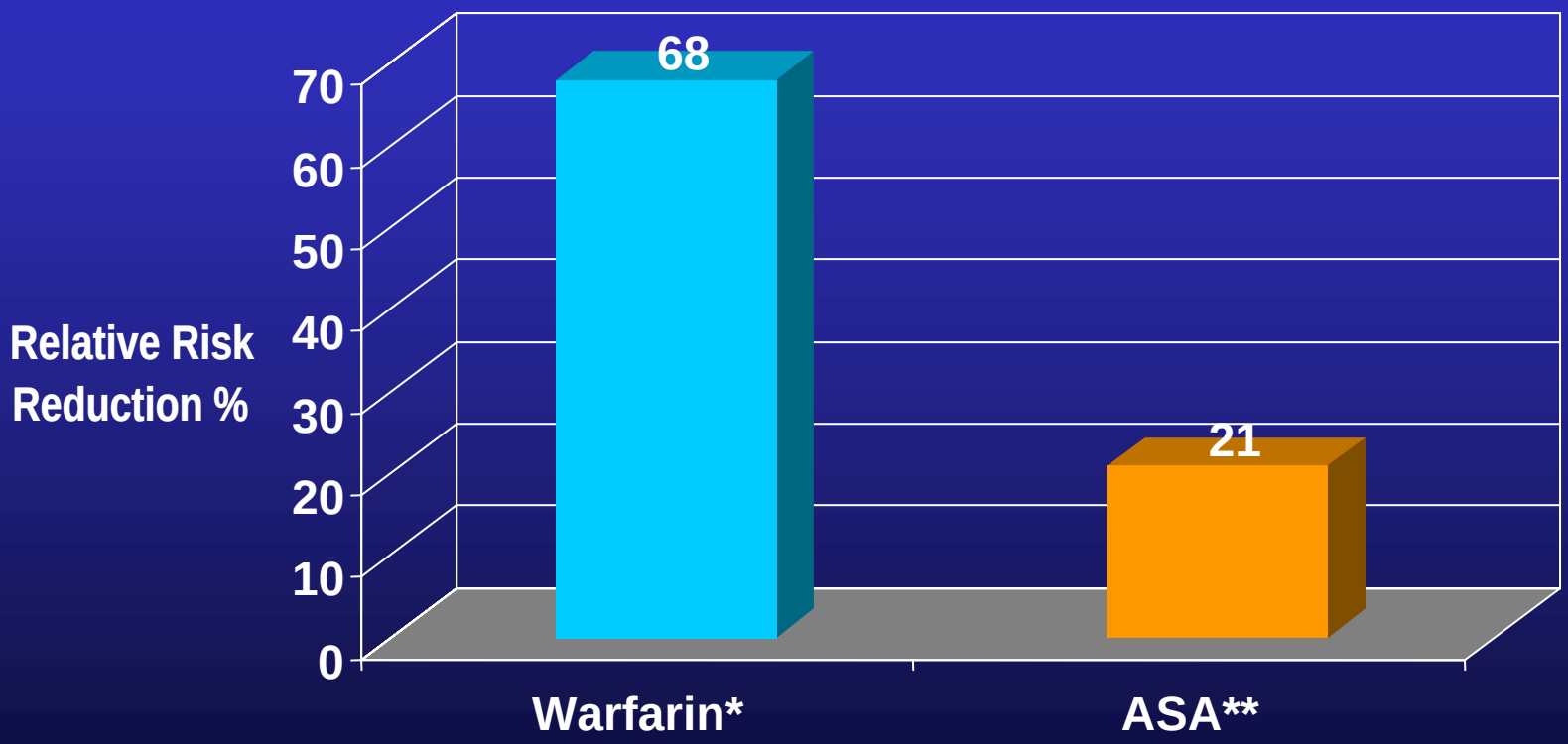
Laupacis et al, Chest; 114 (5):579-589

Low Risk

–Age <65 years

–No cardiac abnormality

Stroke Relative Risk Reduction in Atrial Fibrillation Patients



*Based on AFASAK, BAATAF, CAFA, SPAFI, SPINAF (vs control)

** Based on AFASAK, SPAFI, EAFT (vs placebo)

Adapted from AFI. *Arch Intern Med* 1994;154:1449-1457 & 1997;157:1237-1240

Risk/Benefit Analysis of Anticoagulation in Atrial Fibrillation

1,000 patients treated with warfarin for 1 year

Benefit

35 fewer thromboembolic events

Risk

1 more intracranial or major bleed

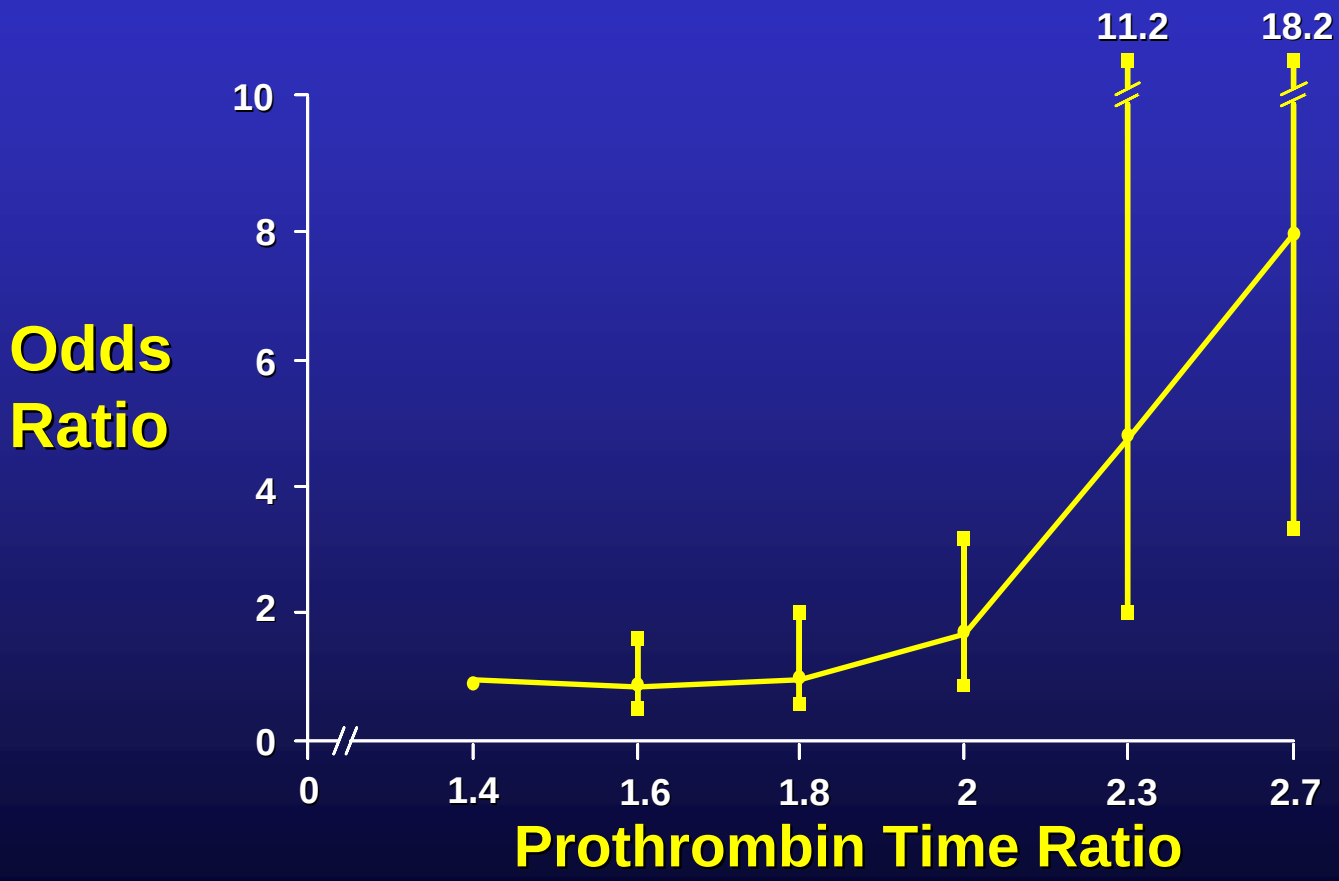
Adapted from Albers GW, et al. *Annals of Neurology* 1991;30(4):512-518.

Summary of ACCP Recommendations in Atrial Fibrillation

Age	Risk Factors	Recommendation
<65 years	Absent	ASA
	Present	Warfarin (Target INR 2.5; range 2.0-3.0)
65-75 years	Absent	ASA or warfarin
	Present	Warfarin (Target INR 2.5; range 2.0-3.0)
>75 years	All Patients	Warfarin (Target INR 2.5; range 2.0-3.0)

Laupacis A, et al. *Chest* 1998;114(Suppl):579S-589S.

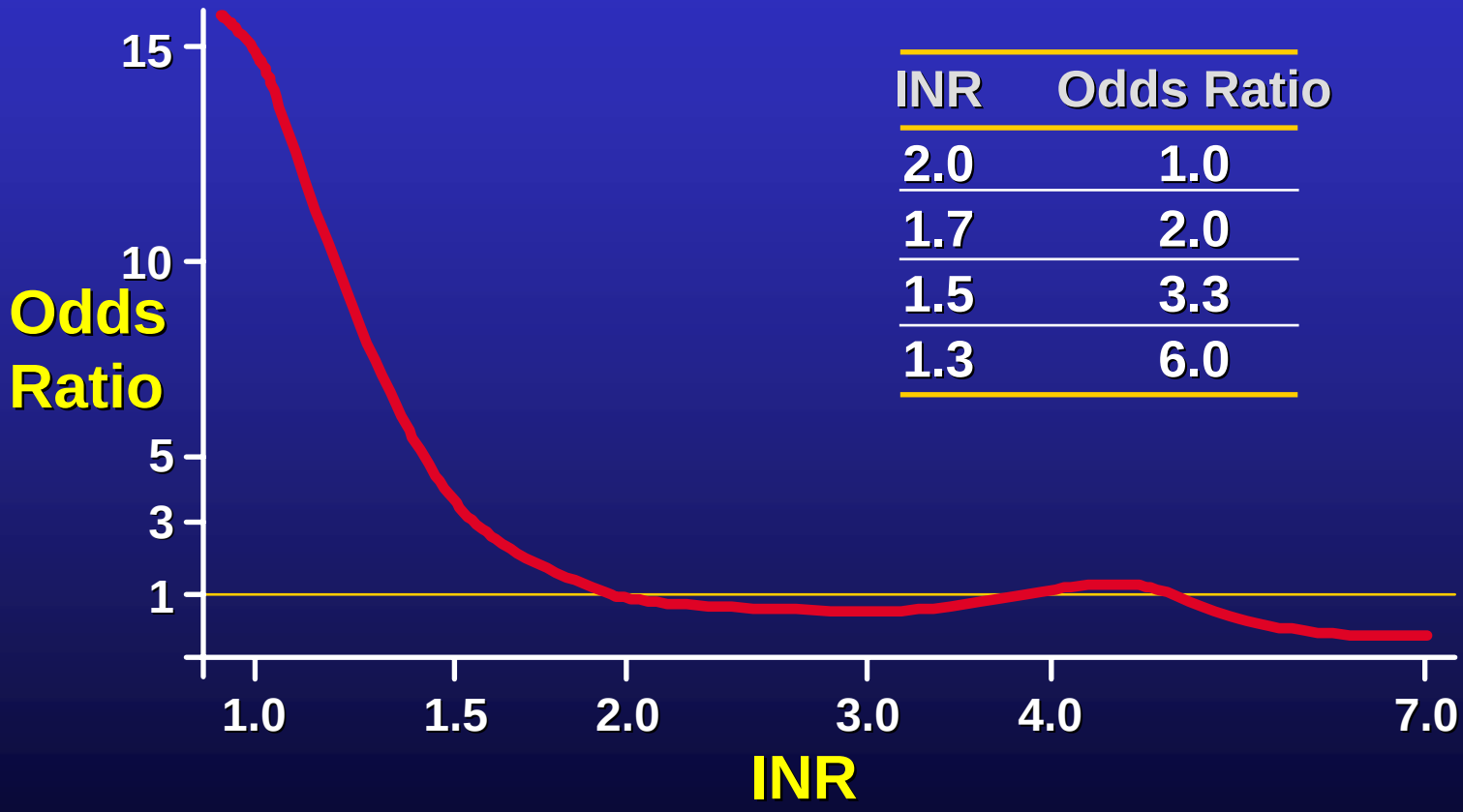
Odds Ratios of Intracranial Hemorrhage



PTR above 2.0 (INR of 3.7 to 4.3) dramatically increased the risk of bleeding

Adapted from Hylek EM, Singer DE. *Ann Intern Med* 1994;120:897-902.

Odds Ratios for Stroke



INR	Odds Ratio
2.0	1.0
1.7	2.0
1.5	3.3
1.3	6.0

INR below 2.0 results in a higher risk of stroke

Adapted from Hylek EM, et al. *NEJM* 1996;335:540-546.

Antithrombotic Therapy in Heart Valve Replacement

ACCP, 2000

Aortic

- St. Jude bileaflet INR 2.5 (2.0-3.0)
- Carbomedics bileaflet INR 2.5 (2.0-3.0)
- Medtronic Hall tilting disk INR 2.5 (2.0-3.0)
- Atrial fibrillation (any) INR 3.0 (2.5-3.5)

Antithrombotic Therapy in Heart Valve Replacement

ACCP, 2000

Mitral

- Bileaflet INR 3.0 (2.5-3.5)
- Tilting disk INR 3.0 (2.5-3.5)
- Any (atrial fib) INR 3.0 (2.5-3.5)
- Caged ball/disk INR 3.0 (2.5-3.5)

+

Aspirin 80 mg/day

Antithrombotic Therapy in Heart Valve Replacement

ACCP 2000

Mechanical Valves

- Previous embolism INR 3.0 (2.5-3.5) + Aspirin 80mg/day

Bridging Therapy

Bridging Therapy - Options

- D/C oral A/C
- Reduce INR
- D/C oral A/C: IV heparin
- D/C oral A/C: LMWH

Background

- Most clinicians opt for anticoagulant cover with intravenous heparin. However, there are a number of limitations to this approach including a requirement for hospitalization.
  - *Costs of hospitalization*
  - *Limited availability of hospital beds*
- Low molecular weight heparins have pharmacological and pharmacokinetic advantages over heparin that allow outpatient treatment by self-administered subcutaneous injection.

Methods

- Prospective cohort
- Patients on long-term oral anticoagulants
- Temporary discontinuation
- Low molecular weight heparin
- Out-patient management

Patients

Number of patients = 1082

Male/Female = 618/464

Average age (yrs) = 65.6

Anticoagulant Management

- Discontinue oral A/C day 5 pre-procedure
- INR day 4/5 pre-procedure
- If INR <2.0 start LMWH (enoxaparin or dalteparin)
- If INR >2.0 repeat above next day
- Continue LMWH until evening prior to procedure

Dalteparin Regimen

- 100 antifactor Xa units/kg subcutaneously twice daily
- Last injection administered 12 hours prior to procedure
- First injection after the procedure 8-12 hours post and after haemostasis secure
- Oral anticoagulants resumed evening of procedure or next day
- Dalteparin continued until INR therapeutic

Enoxaparin Regimen

- 1mg/kg subcutaneously twice daily
- Last injection administered 12 hours prior to procedure
- First injection after the procedure 8-12 hours post and after haemostasis secure
- Oral anticoagulants resumed evening of procedure or next day
- Enoxaparin continued until INR therapeutic

Indications for Long-term Anticoagulants

Mechanical MVR (sinus)	65
Mechanical MVR (AF)	61
Mechanical AVR (Sinus)	170
Mechanical AVR (AF)	29
Bioprosthetic MVR (Sinus)	2
Bioprosthetic MVR (AF)	12
Bioprosthetic AVR (Sinus)	6
Bioprosthetic AVR (AF)	9
Other valve	47

Indications for Long-term Anticoagulants

Lone AF	392
Recurrent VTE	87
Embolic CVA/TIA/VTE	116
Lupus with VTE	7
CAD +/- LV thrombus	62
Thrombophilia	15
PVD	2

Reasons for Interruption of Anticoagulants

General surgery	227
Major	95
Minor	132
Urological surgery	36
Major	22
Minor	14
Invasive diagnostic procedures	346
Cardiac surgery	230
Major	77
Minor	153
Orthopaedic surgery	51
Vascular surgery	35
Dental surgery	116
Eye surgery	40
Neurosurgery	1

Peri-operative Regimens

Days off oral anticoagulants	6.00
LMWH doses pre-procedure	5.60
LMWH doses post-procedure	5.38

Peri-operative Regimens

No pre-procedure LMWH	25
Pre-procedure Vit K	13
No post-procedure LMWH	196

- cardiac surgery
- epidural catheter
- major urological surgery
- IV heparin

Adverse Events

Minor bleeding	28 (7.6%)
Major bleeding	3 (0.27%)
Bruising at injection site	38 (3.5%)
Thromboembolic events	0 (0.0%)
Deaths	2

Average Nursing Time

Teach self-injection

Arrange drug supply

Give specific written instructions

30-45 minutes

Patients given a contact telephone number in case of problems with injections

Injections

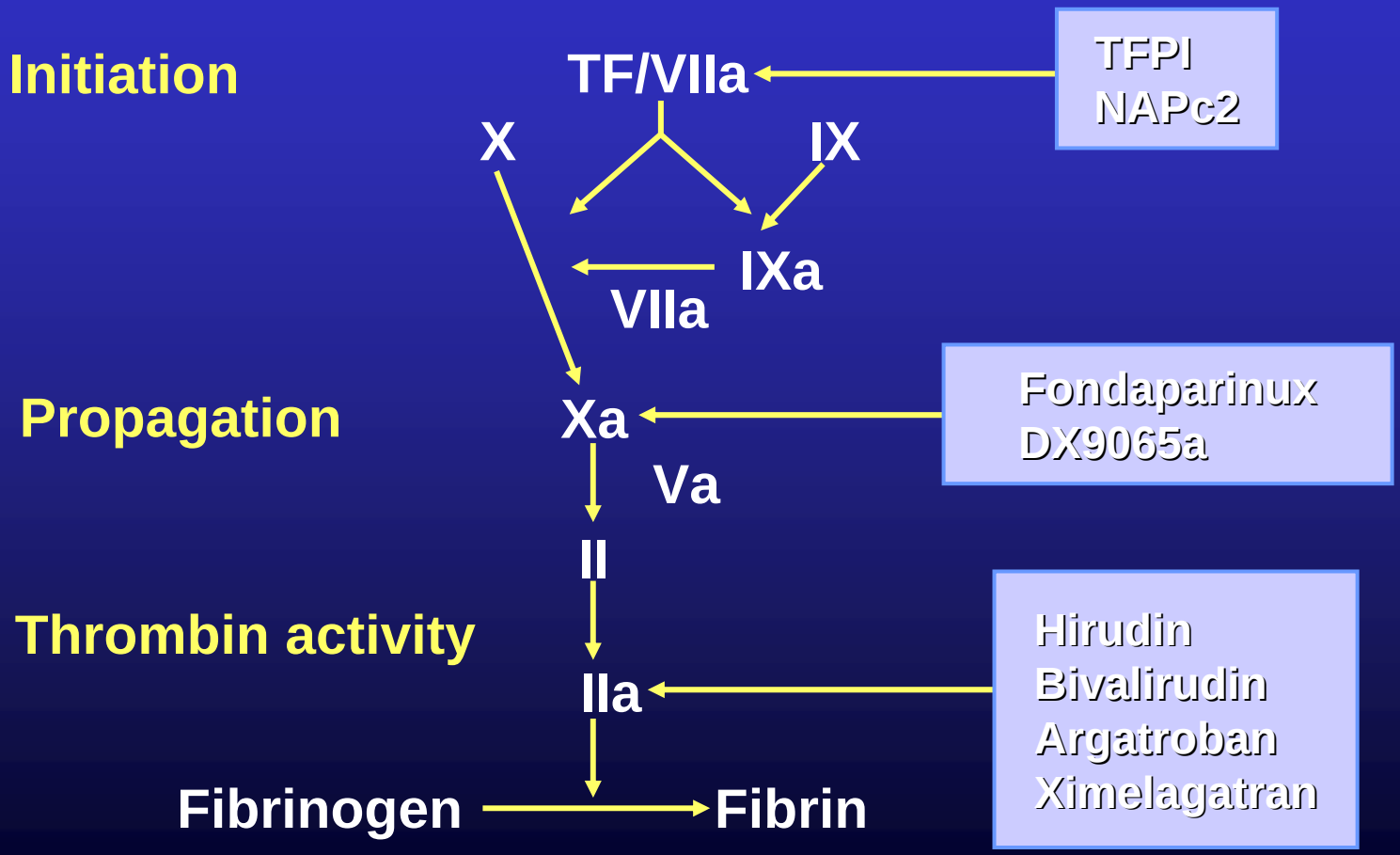
Self	956 (88.3%)
Family	77 (7.1%)
Nurse	49 (4.6%)

Conclusion

- Low molecular weight heparin administered sc on an outpatient basis is a practical alternative to iv heparin to cover temporary interruption of oral anticoagulants for operative, dental or invasive diagnostic procedures in patients who are at a high risk for recurrent thrombosis or systemic embolic events.
- Low molecular weight heparin can be self-administered subcutaneously by most patients for this indication

New Anticoagulants

Coagulation cascade



Adapted with permission from Weitz J, Hirsh J. Chest. 2001;119:95S.