DVT Prophylaxis In Critically Ill and Trauma

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Why is it Important

High prevalence of VTE

- Most hospitalised patients have risk factors
- DVT is common in many patient groups
- Hospital acquired DVT and PE are usually clinically silent.
- Difficult to predict
- Screening is usually ineffective

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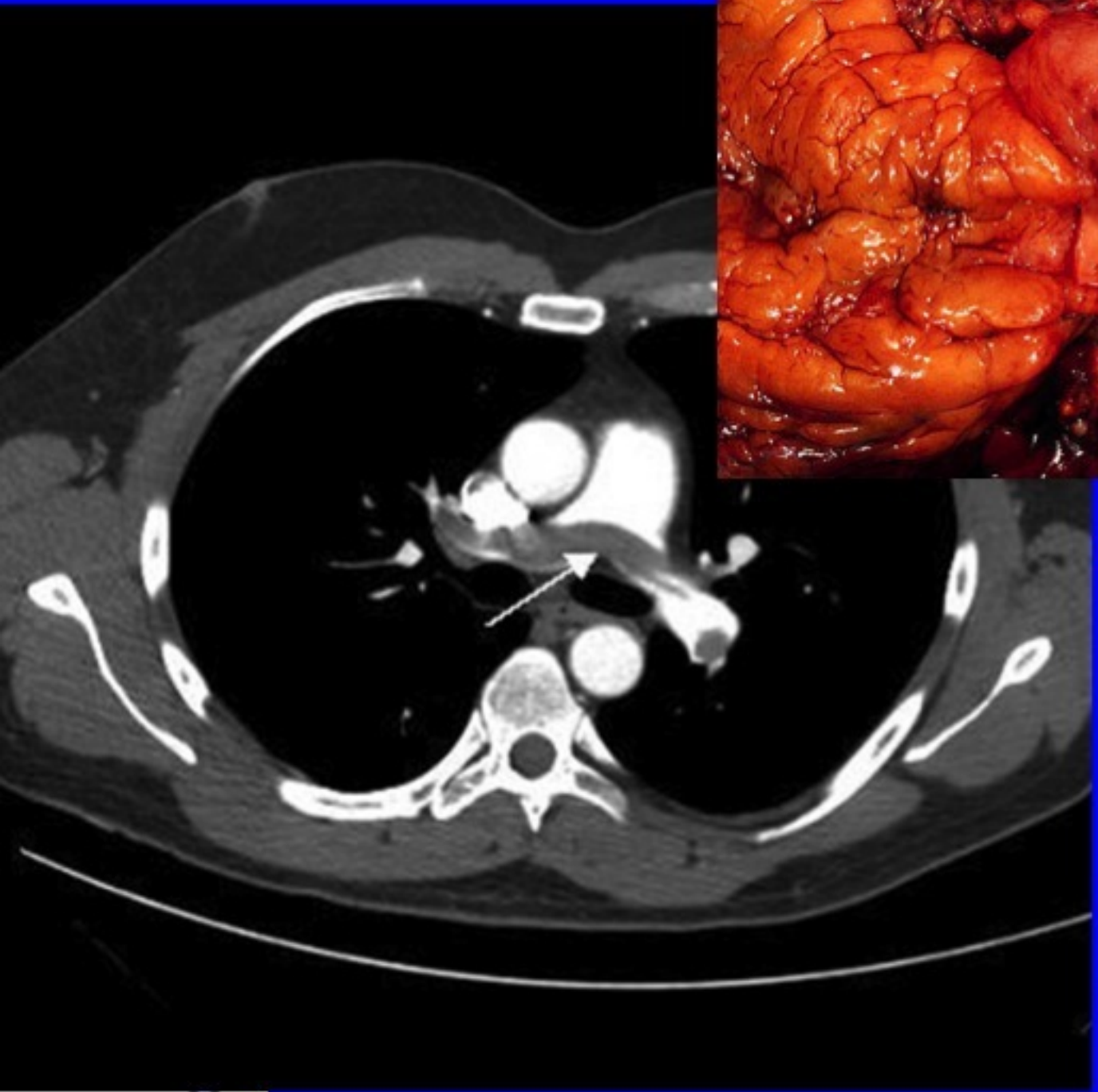
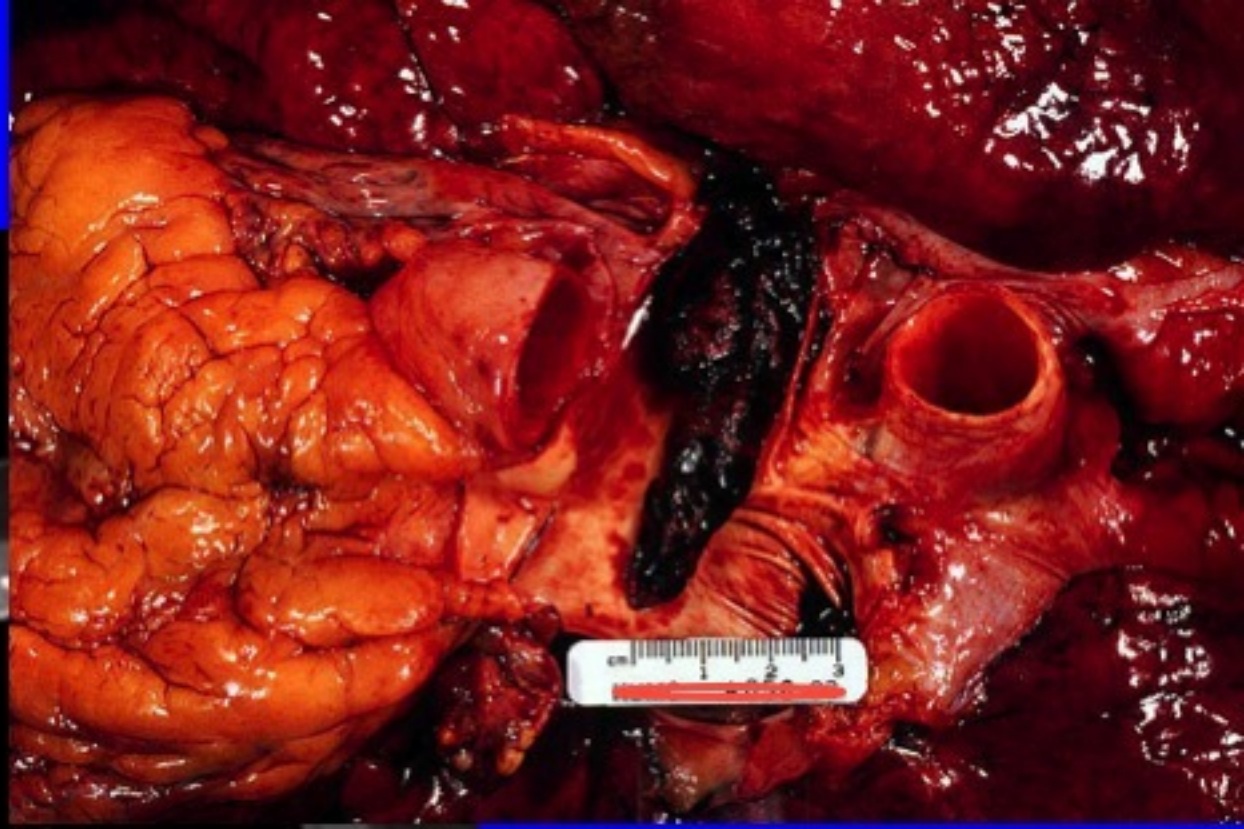
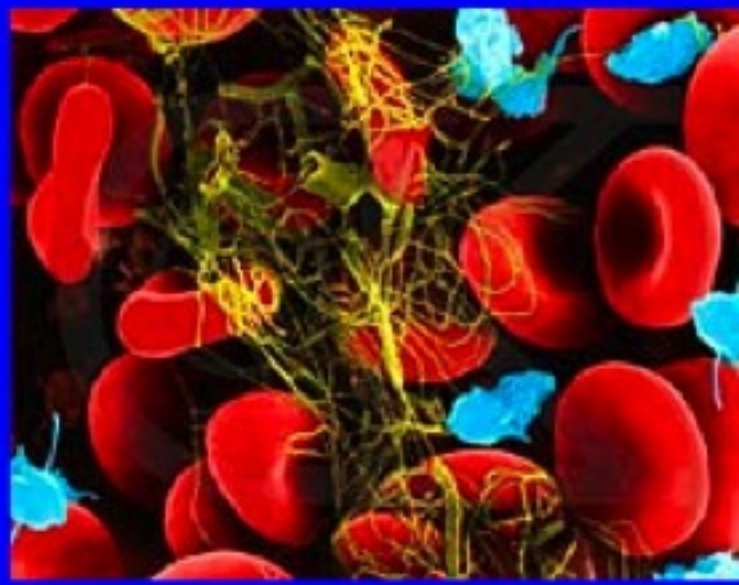
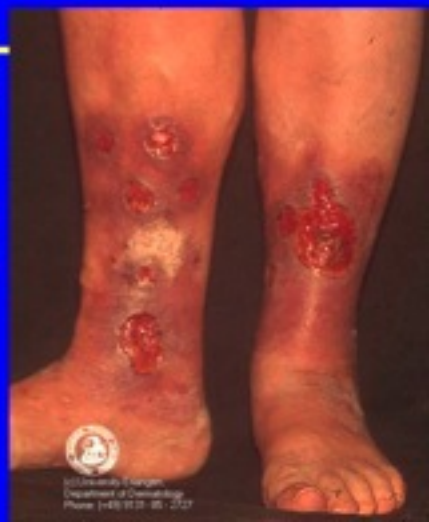






Why is it important?

- Adverse consequences of VTE
  - Fatal Pulmonary Embolus
  - Costs of investigating and treating symptomatic patients
  - Increased future risk of recurrent V
  - Chronic post thrombotic syndrome



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Risk Factors in ICU

Baseline Factors	Odds Ratio
Trauma	4.6 (0.6 – 38.3)
Past VTE	4.6 (0.9 – 29.4)
Cancer	3.7 (0.7 – 18.8)
Immobilisation	2.1 (0.1 – 4.9)

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Absolute risk of DVT

PATIENT GROUP	DVT PREVALENCE
MEDICAL PATIENTS	10-20%
GENERAL SURGERY	15-40%
MAJOR GYNAEC SURGERY	15-40%
MAJOR URO SURGERY	15-40%
NEUROSURGERY	15-40%
STROKE	20-50%
HIP OR KNEE ARTHROPLASTY	40-60%
MAJOR TRAUMA	40-80%
SPINAL CORD INJURY	60-80%
CRITICAL CARE PATIENTS	10-80%

Risk factors and OR for VTE among Trauma patients

RISK FACTOR	ODDS RATIO (95% CI)
Age >40 years	2.29 (2.07-2.55)
Pelvic Fracture	2.93 (2.01-4.27)
Lower extremity fracture	3.16 (2.85-3.51)
Spinal cord injury +paralysis	3.39 (2.41-4.77)
Head Injury AIS>3	2.59 (2.31-2.90)
Ventilator days>3	10.62 (9.32-12.11)
Venous injury	7.93 (5.83-10.78)
Shock @admission	1.95 (1.62-2.34)
Major surgical procedure	4.32 (3.91-4.77)

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Why is it important?

- Efficacy and Effectiveness of Thromboprophylaxis
  - Highly efficacious in preventing DVT
  - DVT prevention prevents VTE
  - Prophylaxis is cost-effective
  - **Prophylaxis often omitted**

What are the options?

- Mechanical Devices
  - Elastic stockings
  - Compression devices – Pneumatic (IPD), Sequential pneumatic (SCD), Foot Pumps
- Chemical Prophylaxis
  - Heparins
  - Oral anticoagulants???
  - Newer agents?

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What are the options?

- Currently available data is unequivocally in favour of Heparin - LDUH or LMWH.
- No evidence for aspirin or other platelet agents
- Some evidence for mechanical devices, especially as adjuncts

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Mechanical Devices

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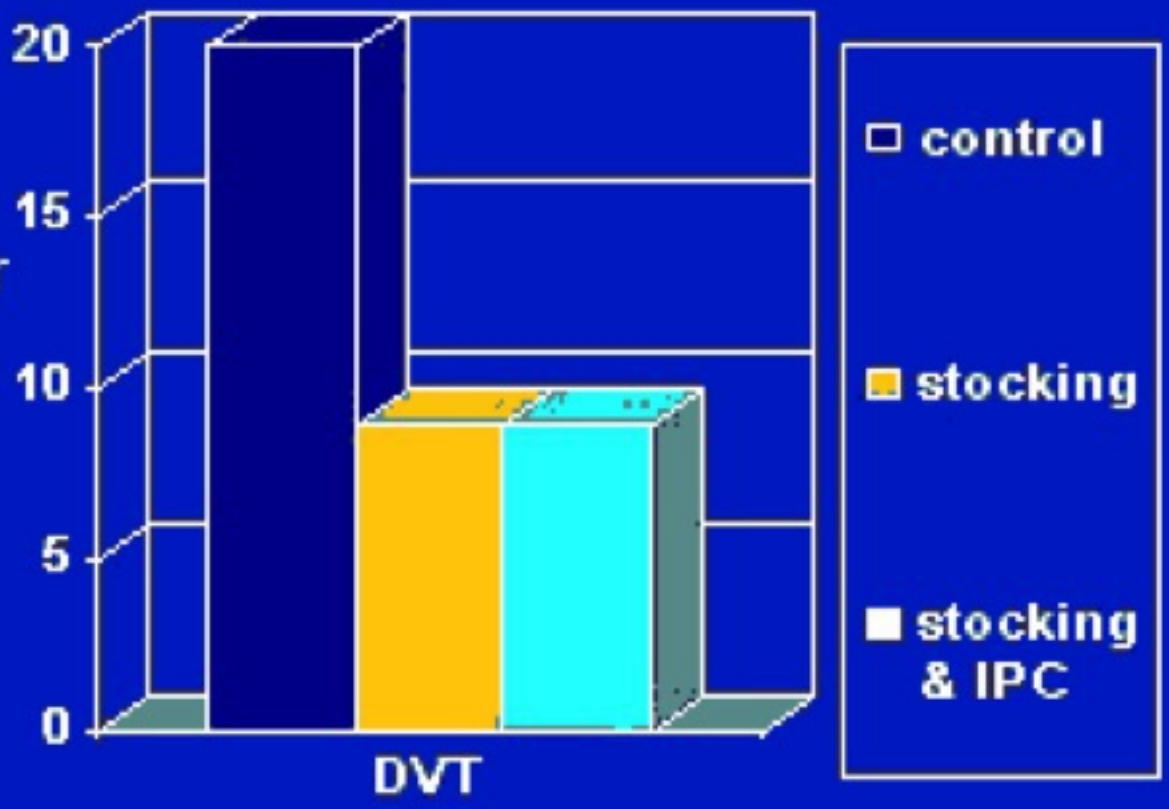
RCT of Stockings ± Pneumatic Compression in Neurosurgery

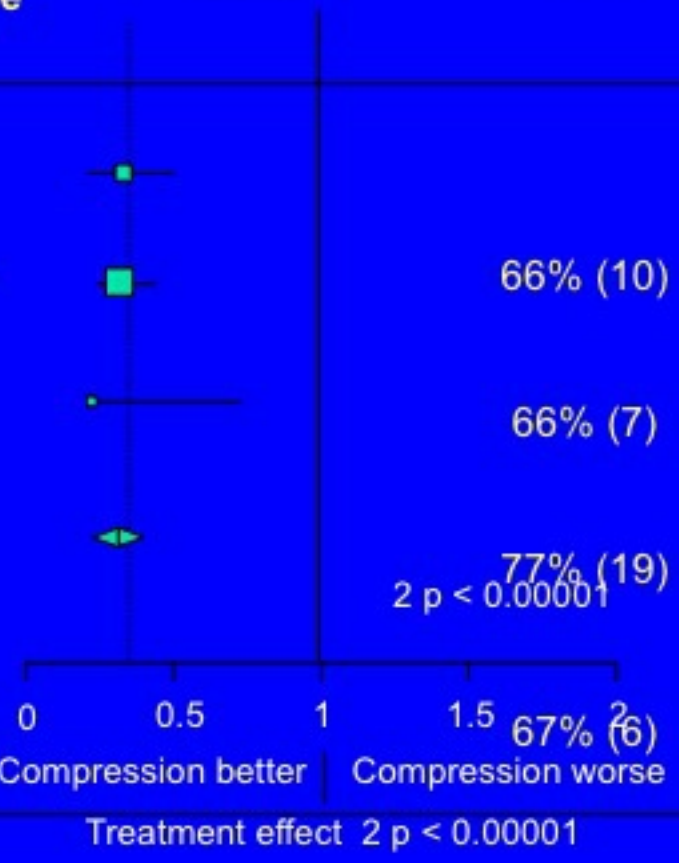
- Unblinded RCTof 239 neurosurgery patients
- DVT rates diagnosed by IPG/legscan/venogram lower when patients received stockings ± pneumatic compression than no prophylaxis
- Bleeding: none
- PE: none



Turpie et al, Arch Intern Med 1989

Effects of compression methods of thromboprophylaxis on DVT

Category	Number of trials with data	DVT		Stratified statistics		OR and CI compression: control	% OR (SE)
		Compression	Control	O–E	Variance		
Compression (monotherapy)							
GCS	9	57/665 (8.6%)	133/267 (21.2%)	– 39.7	37.2		66% (10)
IPC	19	112/1,108 (10.1%)	268/1,147 (23.4%)	– 76.3	71		66% (7)
Foot pump	2	11/61 (18%)	34/65 (52.3%)	– 10.7	7.3		77% (19)
	30	180/1,834 (8.6%)	435/1,839 (23.7%)	– 126.7	115.5		67% (6)



■ 99% or ◄► 95% CI

IPC = intermittent pneumatic compression;
GCS = graduated compression stockings.

Roderick P, et al. Health Technol Assess. 2005;9:iii-iv,ix-x,1-78.

Chemical DVT Prophylaxis

- Vitamin K antagonists
  - Warfarin
- Antithrombin agonists
  - Unfractionated heparin
  - Low molecular weight heparin
- "Factor Xa" inhibitors*
  - Fondaparinux
- Direct thrombin antagonists
  - Hirudin, argatroban, ximelgatran, etc.
- Anti-platelet agents
  - Aspirin, dipyrimadole, clopidogrel, etc.

Heparin Mechanisms

- Anti thrombin activation
- Occurs when the penta-saccharide chain randomly distributed along the UH or LMWH chain binds to anti thrombin.
- Anti thrombin then under goes a conformational change that accelerates interaction between anti thrombin, factor X a and thrombin

Unfractionated Heparin

- Heterogenous polysaccharide chains
- MW 3,000-30,000 Daltons
- 1/3 dose contains penta-saccharide sequence
- Anti X a: anti II a ratio =1:1
- Non-specific binding to macrophages, platelets, and endothelial cells makes anticoagulation difficult to predict

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Low molecular weight heparin

- Derived from UH molecules
- MW 1000-10,000 daltons
- Penta-saccharide sequence present on roughly 15-25% of LMWH chains
- Predominant anti Xa antagonism
- Anti Xa: anti II a ratio 4:1-5:1
- Less binding to macrophages and endothelial cells- predictable, reliable, safe

Advantages of LMWH over UH

- Decreased "heparin resistance"
  - Pharmaco-kinetics of UH are influenced by its bindings to plasma protein, endothelial cell surfaces, macrophages, and other acute phase reactants
  - LMWH has decreased binding to non anticoagulant-related plasma proteins

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Advantages of LMWH over UH

- No need for laboratory monitoring
  - when given on a weight-adjusted basis, the LMWH anticoagulant response is predictable and reproducible
- Higher bioavailability - 90% vs 30%
- Longer plasma half-life
  - 4 to 6 hours vs. 0.5 to 1 hour
  - Renal (slower) vs. Hepatic clearance

Advantages of LMWH over UH

- Less inhibition of platelet function
  - potentially less bleeding risk, but not shown in clinical use
- Lower incidence of thrombocytopenia and thrombosis (HIT syndrome)
  - less interaction with platelet factor 4
  - fewer heparin-dependent IgG antibodies

WHICH HEPARIN?

HOW MUCH?

HOW OFTEN?

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Unfractionated Heparin

- Primary agent over many years.
- Data primarily from surgical patients
- 60-70% relative risk reduction in both DVT/PE
- Data supporting UH use in medical patients are more difficult to interpret.

Unfractionated heparin

- Earliest study 30 years back
- Patients with MI, HF and unspecified medical problems
- DVT rates 2.6% and 22.5% in Heparin and placebo groups.
- Similar results in a larger study in 192 patients older than 40 years with pulmonary disease

Low molecular weight heparins

- ENOXAPARIN
- DALTEPARIN
- FRAXIPARIN etc.

ENOXAPARIN

- First trial- 270 patients; 60mg s/c bd vs placebo
- Significant reduction of frequency of DVT
- More injection site hematomas.
- No clinically significant bleeding.

Enoxaparin in Medicine Study Group (EMSG)

- 5000 U UH q 12 h vs Enoxaparin 20 mg s/c bd in 442 elderly ICU patients

- No difference in DVT rates diagnosed by RFUT

Prophylaxis in Medical Patients with Enoxaparin (MEDENOX)

- Targets: Risk of VTE

  Safety and efficacy of 20mg vs. 40mg bd of Enoxaparin
- No difference in incidence of DVT/VTE between placebo and 20mg bd Enoxaparin
- 63% risk reduction with 40mg bd dose.
- Benefit maintained for 110 days.
- No major bleeding/thrombocytopenia.
- No data on 40mg bd Enoxaparin vs. UH

Thrombo-embolism prophylaxis in Internal Medicine with Enoxaparin (PRIME) Group

- Multi-center, double blind, RCT 885 pts- 40mg bd Enoxaparin vs. 5000U UH q 8h.
- No statistical difference in incidence of VTE.
- No difference in major bleeding tendencies
- Fewer injection site haematomas with Enoxaparin

Thrombo-embolism prevention in cardiopulmonary diseases with Enoxaparin (PRINCE)

- Enoxaparin 40mg bd vs UH 5000 U q8h- 665 patients.
- No difference in DVT prevention rates
- More bleeding in UH group
- Better risk reduction with Enoxaparin in those with CHF.

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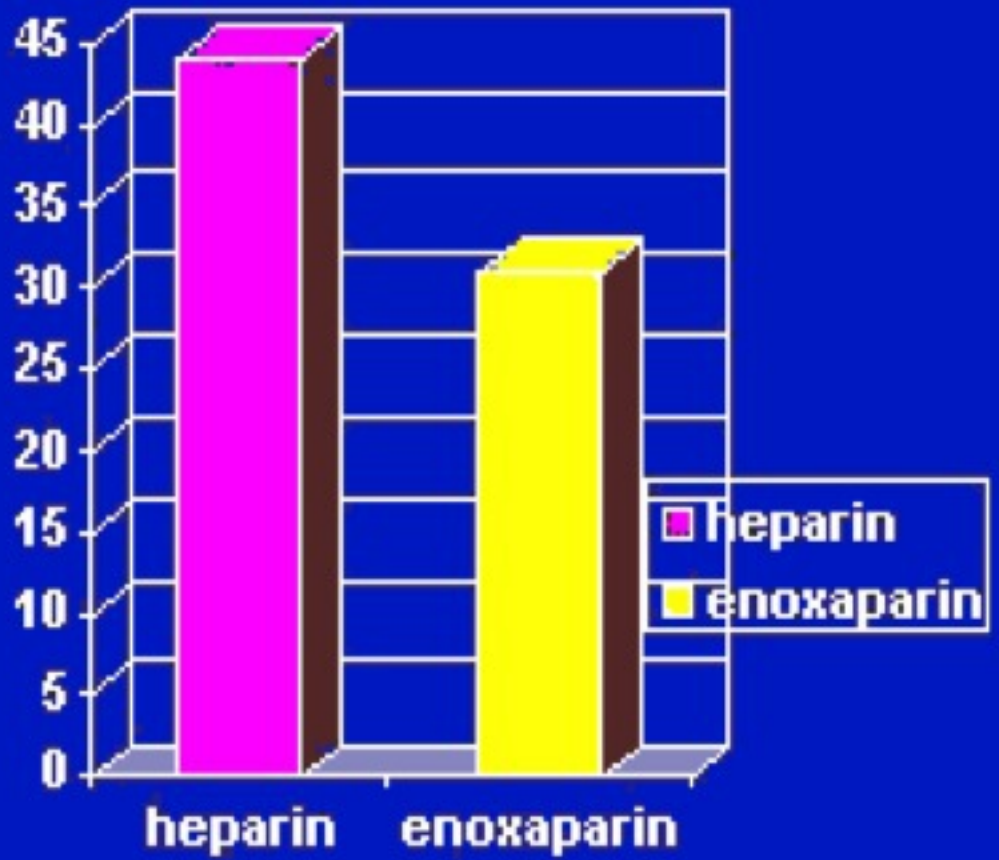
Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE in Immobilised patients (PREVENT)

- 3706, moderate risk hospitalised patients Dalteparin 5000 U vs. Placebo once daily for 14 days
- Assessed for DVT at 21 days
- 2.77% vs 4.96% in favour of Dalteparin
- 45% risk reduction with Dalteparin
- No data in exclusively ICU patients

RCT of UF Heparin vs LMWH in Trauma Patients

- Double-blind RCT of 344 trauma patients with ISS>9
- DVT rates proven by venography were lower in patients receiving LMWH than unfractionated heparin
- Bleeds: 5 with LMWH, 1 with unfractionated

Geerts et al, NEJM 1996



Prophylaxis recommendations in critically ill patients

Bleeding risk	Thrombosis risk	Prophylaxis recommendations
LOW	MODERATE	LDUH 5000 U q 12h
LOW	HIGH	LMWH qd
HIGH	MODERATE	GCS or IPC→LDUH when bleeding risk decreases
HIGH	HIGH	GCS or IPC→LMWH when bleeding risk decreases

Principles of DVT prophylaxis in critically ill patients

- Daily review – change prn
- No interruption for Sx or procedures unless risk of bleeding is high.
- Routine screening for asymptomatic patients not recommended if prophylaxis has been adequate.
- Periodic audits.

DVT Prophylaxis - Recommendations

Prevention of Venous Thromboembolism: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy

William H. Geerts, Graham F. Pineo, John A. Heit, David Bergqvist, Michael R. Lassen, Clifford W. Colwell and Joel G. Ray

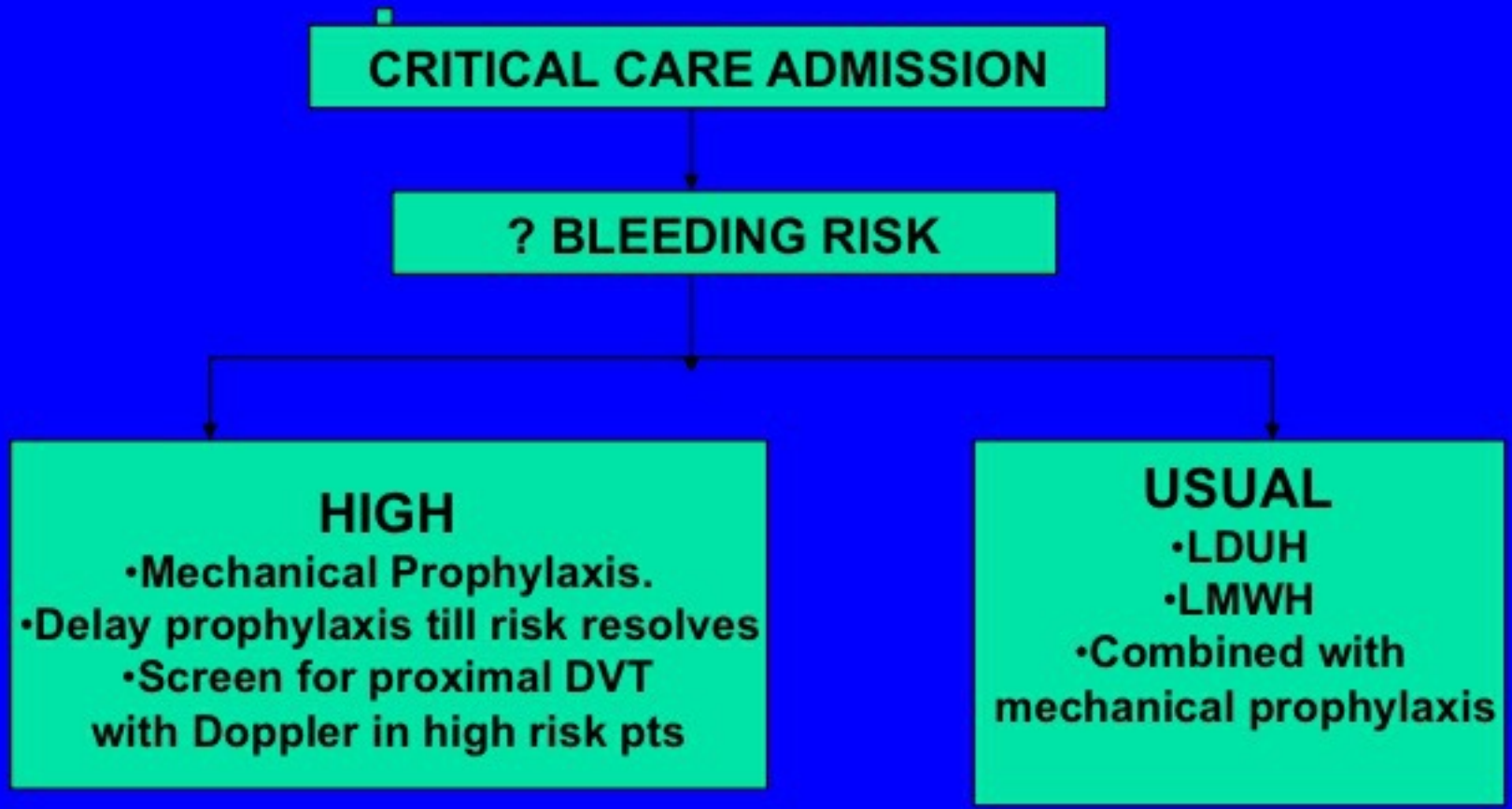
Chest 2004;126;338-400
DOI 10.1378/chest.126.3_suppl.338S

- Orthopaedic surgery sections of recommendations were formally reviewed by 16 external experts, 10 of whom were orthopaedic surgeons (including several well known orthopaedic traumatologists).
- Recommendations reviewed and supported by the AAOS.

DVT Prophylaxis Recommendations

- 5.1 Trauma
  - All trauma patients receive thromboprophylaxis, if possible (Grade 1A).
  - Unless contraindicated, use LMWH starting as soon as it is considered safe to do so (Grade 1A).
  - Recommend against the use of vena cava filters as primary prophylaxis in trauma patients (Grade 1C).
  - Recommend continuation of prophylaxis through the completion of inpatient rehab (Grade 1C+), and suggest continued prophylaxis after discharge with LMWH or VKA in patients with impaired mobility (Grade 2C).

Initial prophylaxis consideration



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To summarize……

- All ICU & Trauma patients have a combination of risk factors for VTE.
- Balanced assessment and decision making crucial.
- LMWH preferred in those with multiple risk factors vs. risk bleeding
- Adherence to guidelines and regular audits needed for better results.

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VH-CFO

PROphylaxis for ThromboEmbolism in Critical Care Trial (PROTECT)

- Effect of LMWH vs. UH on primary outcome of DVT diagnosed by USG
- LMWH vs. UH on secondary outcomes of PE, HIT and Bleeding.
- Expected enrolment 3600
- Expected completion June 2009.

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What's new?

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Synthetic oligo-saccharides

- Result of breakthrough in polysaccharide chemistry.
- Fondaparinux-selective inhibitor of factor Xa.
- Approved for use in orthopaedic surgery.
- Also found to be beneficial in ACS and in VTE.
- Efficacy at least as good as Enoxaparin; better safety profile.

Arixtra for Thromboembolism Prevention in a Medical Indications Study (ARTEMIS)

- 849 acutely ill medical patients bedridden for >4 days
- Multinational, double blind
- 2.5mg Fondparinux vs placebo once daily.
- Venography at 6 and 14 days
- 5.6 vs 10.6% with OR 49.5% for DVT
- No PTE in fondparinux group vs 1.2% in placebo group
- Similar bleeding rates

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Properties of conventional anticoagulants

Property	Vit..K antagonism	UH	LMWH	Fondaparinux
Source	Synthetic	Animal	Animal	Synthetic
Structure	Homogenous	Heterogenous	Heterogenous	Homogenous
Target	Multiple	Multiple	Multiple	Single
Prot.binding	Albumin	AT III +pl.prot	AT III +pl.prot	AT III
Administration	Daily	Q 8h	Q12h	Daily
Monitor coagulation	Frequent	Frequent	No	No
Interactions	Many	None known	None known	None known
HIT Ab cross reactivity		100%	80%	0%

Direct Thrombin Inhibitors (DTI)

- Parenteral
  - Hirudin
  - Bivalirudin
  - Argatroban
- Oral
  - Ximelagatran- studied in DVT

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	30	180/1,834 (8.6%)	435/1,839 (23.7%)	– 126.7	115.5		67% (6)

2 p < 0.00001

■ 99% or ◄► 95% CI.

0 0.5 1 1.5 2

Compression better | Compression worse

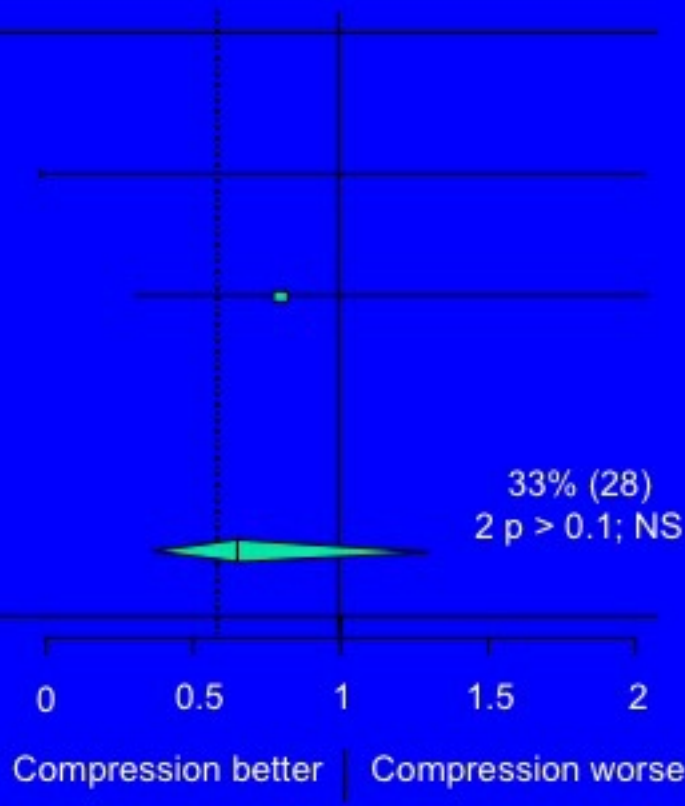
Treatment effect 2 p < 0.00001

pneumatic compression;
compression stockings.

Roderick P, et al. Health Technol Assess. 2005;9:iii-iv,ix-x,1-78.

Effects of compression methods of thromboprophylaxis on PE

Category	Number of trials with data	PE		Stratified statistics		OR and CI compression: control	% OR (SE)
		Compression	Control	O–E	Variance		
Compression (mono-therapy)							
GCS	3	0/123 (0%)	4/90 (4.4%)	– 1.8	0.9		
IPC	8	14/590 (2.4%)	18/618 (2.9%)	– 1.6	7.6		
Foot pump	1	0/28 (0%)	0/32 (0%)				
	12	14/741 (1.9%)	22/740 (3%)	– 3.4	8.5		



99% or 95% confidence intervals

Roderick P, et al. Health Technol Assess. 2005;9:iii-iv,ix-x,1-78.

DVT & Trauma – Risk Factors

Risk factor (number at risk)	Odds ratio (95% CI)
Age ≥ 40 y (n = 178,851)	2.29 (2.07–2.55)
Pelvic fracture (n = 2707)	2.93 (2.01–4.27)
Lower extremity fracture (n = 63,508)	3.16 (2.85–3.51)
Spinal cord injury with paralysis (n = 2852)	3.39 (2.41–4.77)
Head injury (AIS score ≥ 3) (n = 52,197)	2.59 (2.31–2.90)
Ventilator days > 3 (n = 13,037)	10.62 (9.32–12.11)
Venous injury (n = 1450)	7.93 (5.83–10.78)
Shock on admission (BP < 90 mm Hg) (n = 18,510)	1.95 (1.62–2.34)
Major surgical procedure (n = 73,974)	4.32 (3.91–4.77)

$P < 0.001$ for all factors.

AIS, Abbreviated Injury Scale; BP, blood pressure.

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Current Opinion Crit Care Volume 10(6), December 2004, pp 539-548

Why Is Prophylaxis Omitted?

- Lack of awareness
- Diversion of attention
- Concerns regarding safety of regimens
  - Neurosurgical – Brain, Spinal
- More daily injections
- Cost

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