

VTE Prophylaxis in the Stroke Patient

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Chest Guidelines

- Evidence based guidelines for anticoagulation and thrombolytic management
- Tool/resource for management

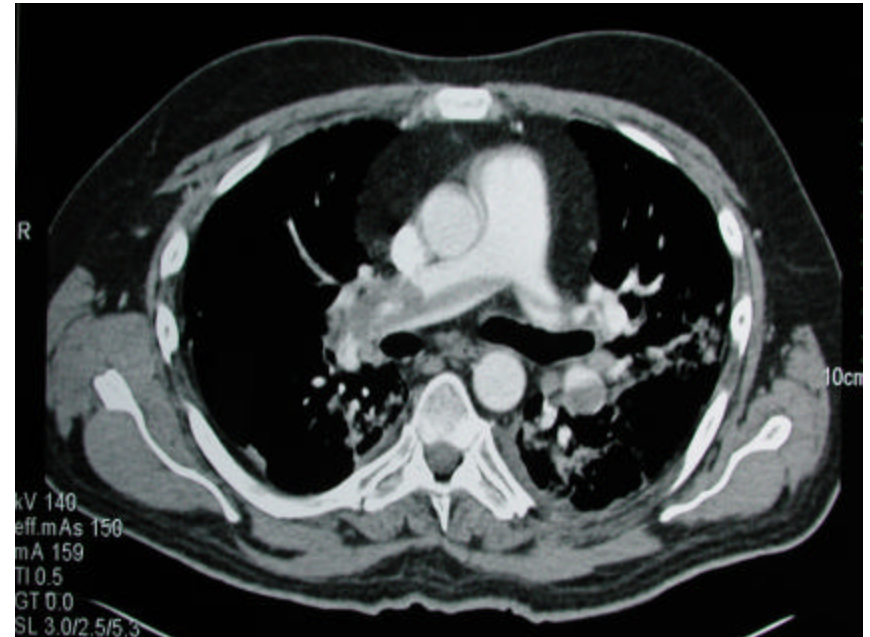
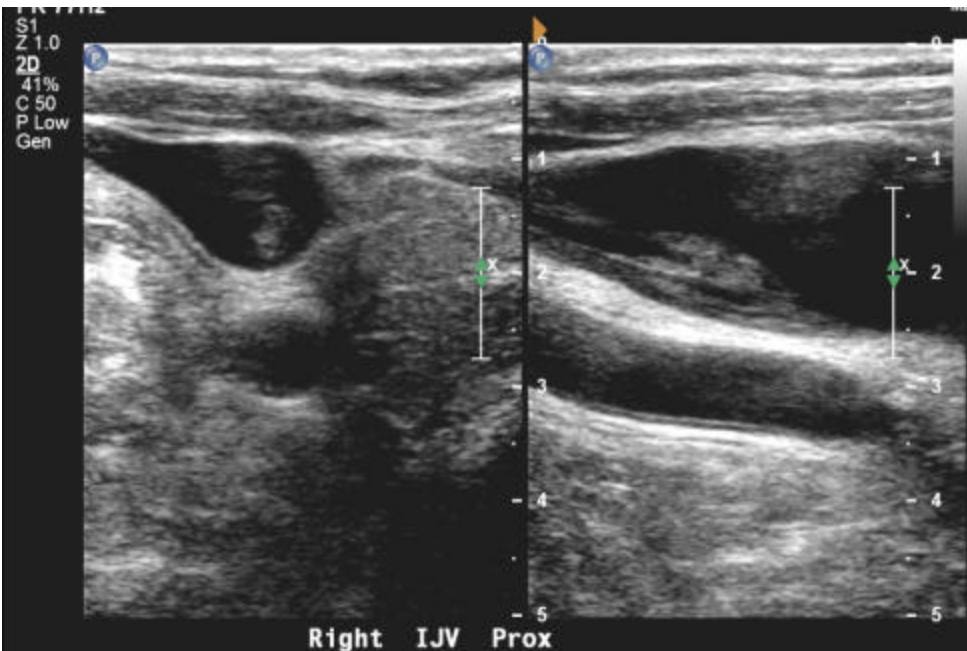


Rational for VTE Prophylaxis

- General considerations
 - Most patients have multiple risk factors
 - » Risk ranges from 10-80%
 - Many events are clinically silent
 - » Physical exam is not specific nor sensitive
 - » Screening is not advocated as cost-effective
- Adverse outcomes
 - Morbidity and mortality from VTE
 - Cost of treatment of VTE and complications
 - Post-thrombotic syndrome symptoms

Prophylaxis is effective and cost-effective

VTE is a Spectrum of Disease



Venous Thromboembolism

Location of DVT	Incidence of PE %
Proximal	45%

European multicentered, randomized, double-

DVT is PE in transit

Popliteal	47%
Femoral	49%
Iliac	38%
Caval	42%

performed baseline V/Q scans

39.5- 49.5%

Meigan et al. Arch Intern Med 2000;160:159-164.

VTE Epidemiology

- 600,000 cases diagnosed annually
- 4th leading cause of death in western populations
- 20% (1/5) die suddenly from pulmonary embolism
- > 50% of cases are clinically silent
- Up to 150,000 deaths/year
- 30% incidence of recurrent VTE
- 20-30% risk of post-thrombotic syndrome

Absolute Risk of VTE

Illness	DVT prevalence (%)
Medical patients	10-20%
General surgery	15-40%
Major GYN surgery	15-40%
Major Urologic Surgery	15-40%
Neurosurgery	15-40%
THA/TKA/HFS	40-60%
Major Trauma	40-80%
SCI	60-80%
Critical Care	10-80%
Stroke	20-50%

Acquired Risk Factors for VTE

Risk	OR	95% C.I.
Surgery	21.7	9.4-79.0
Trauma	12.7	4.1-39.7
Hospital/NH	8	4.5-14.2
Malignancy	6.5	2.1-20.2
CVP line/PPM	5.6	1.6-19.6
Superficial Phlebitis	4.3	1.8-10.6
Paralysis	3	1.3-7.4
Liver Disease	0.1	0.0-0.7

Age and VTE

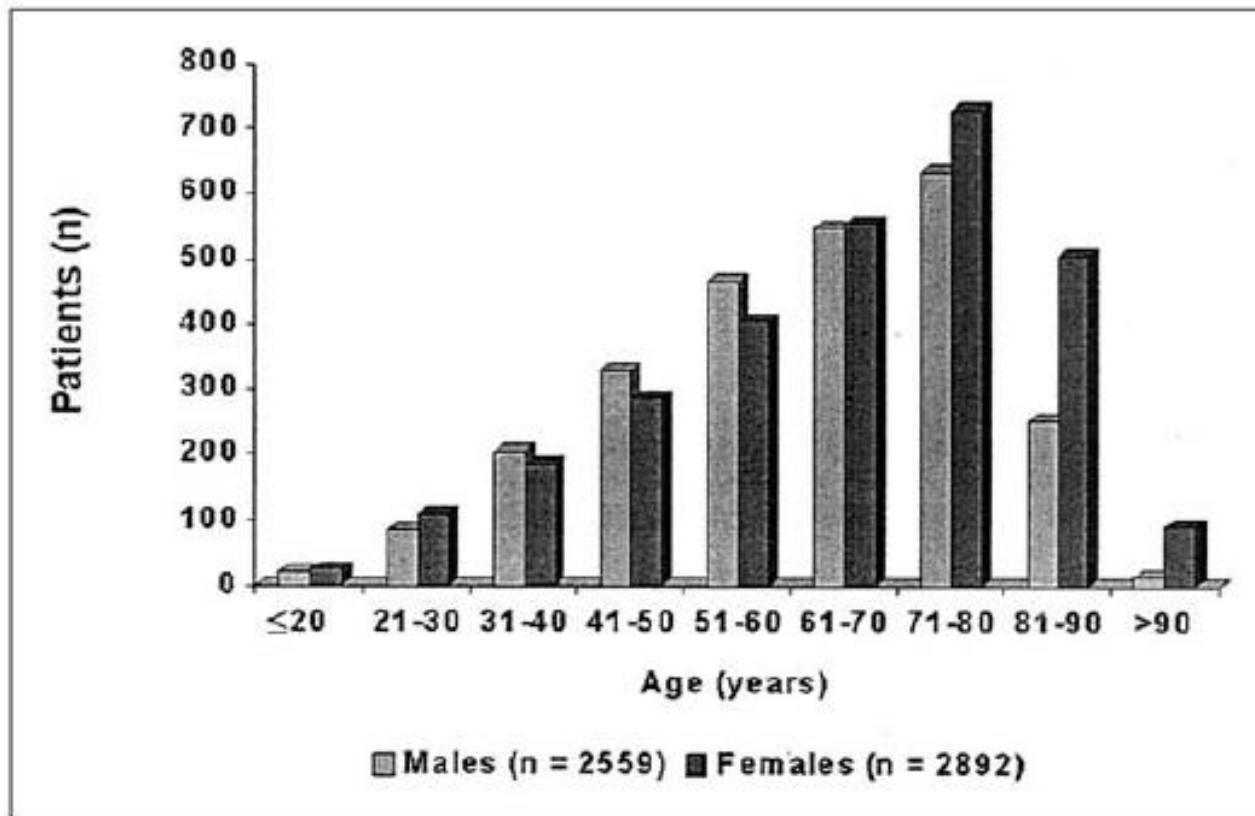
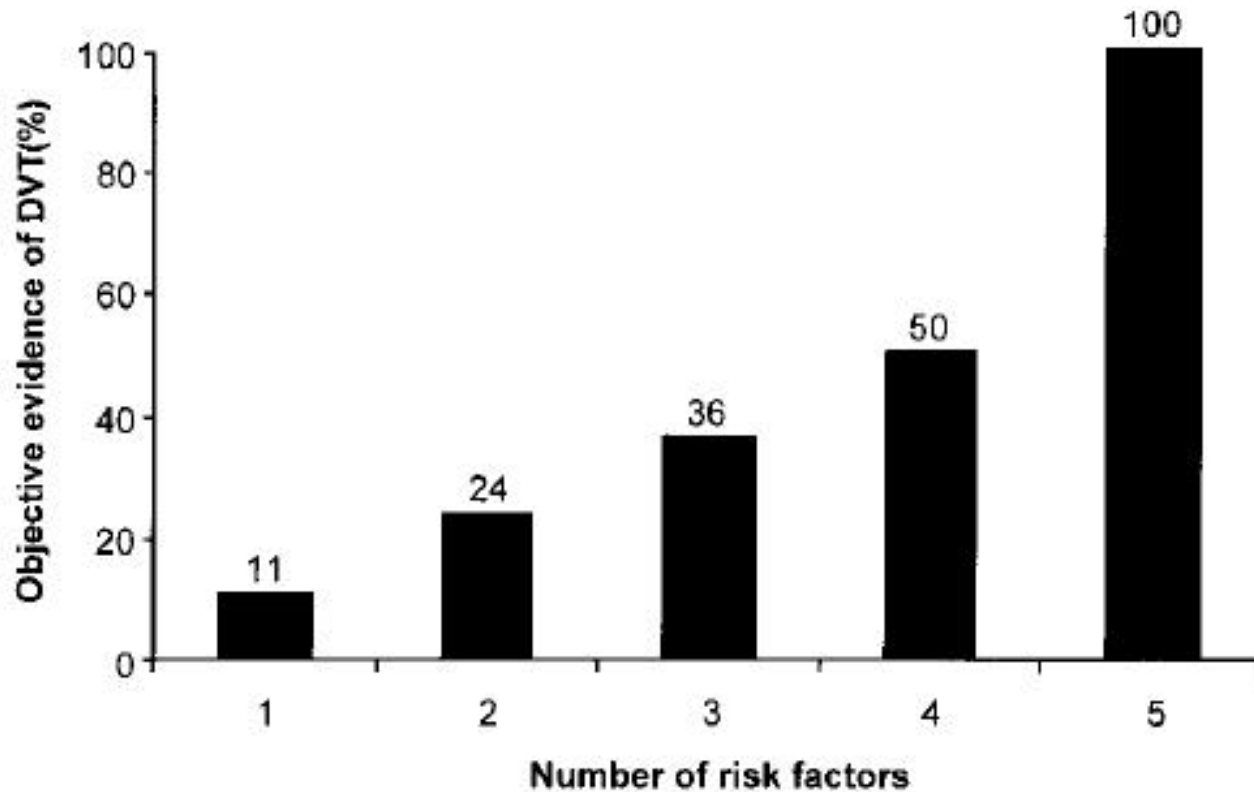


FIGURE 1. Distribution of patients by age and gender.

DVT and Risk Factors



Risk of VTE

Level of Risk	DVT, %		PE, %	
	Calf	Proximal	Clinical	Fatal
Low risk (minor surgery, <40 yo, no additional RF)	2	0.4	0.2	<0.01
Moderate risk (minor surgery w/RF; 40-60 yo no add RF)	10-20	2-4	1-2	0.1-0.4
High risk (age >60; 40-60 w/RF)	20-40	4-8	2-4	0.4-1.0
Highest risk (multiple RF; THA, TKA, HFS, major trauma, SCI)	40-80	10-20	4-10	0.2-5

VTE Prevention

Risk assessment

- Low risk
- Moderate risk
- High risk
- Highest risk

Universal application

- Mechanical prophylaxis
- Pharmacologic prophylaxis
- Combined modalities

Current Recommendations

Table 5—Levels of Thromboembolism Risk and Recommended Thromboprophylaxis in Hospital Patients (Section 1.3)*

Levels of Risk	Approximate DVT Risk Without Thromboprophylaxis, %†	Suggested Thromboprophylaxis Options‡
Low risk Minor surgery in mobile patients Medical patients who are fully mobile	< 10	No specific thromboprophylaxis Early and “aggressive” ambulation
Moderate risk Most general, open gynecologic or urologic surgery patients Medical patients, bed rest or sick	10–40	LMWH (at recommended doses), LDUH bid or tid, fondaparinux
Moderate VTE risk plus high bleeding risk		Mechanical thromboprophylaxis§
High risk Hip or knee arthroplasty, HFS Major trauma, SCI	40–80	LMWH (at recommended doses), fondaparinux, oral vitamin K antagonist (INR 2–3)
High VTE risk plus high bleeding risk		Mechanical thromboprophylaxis§

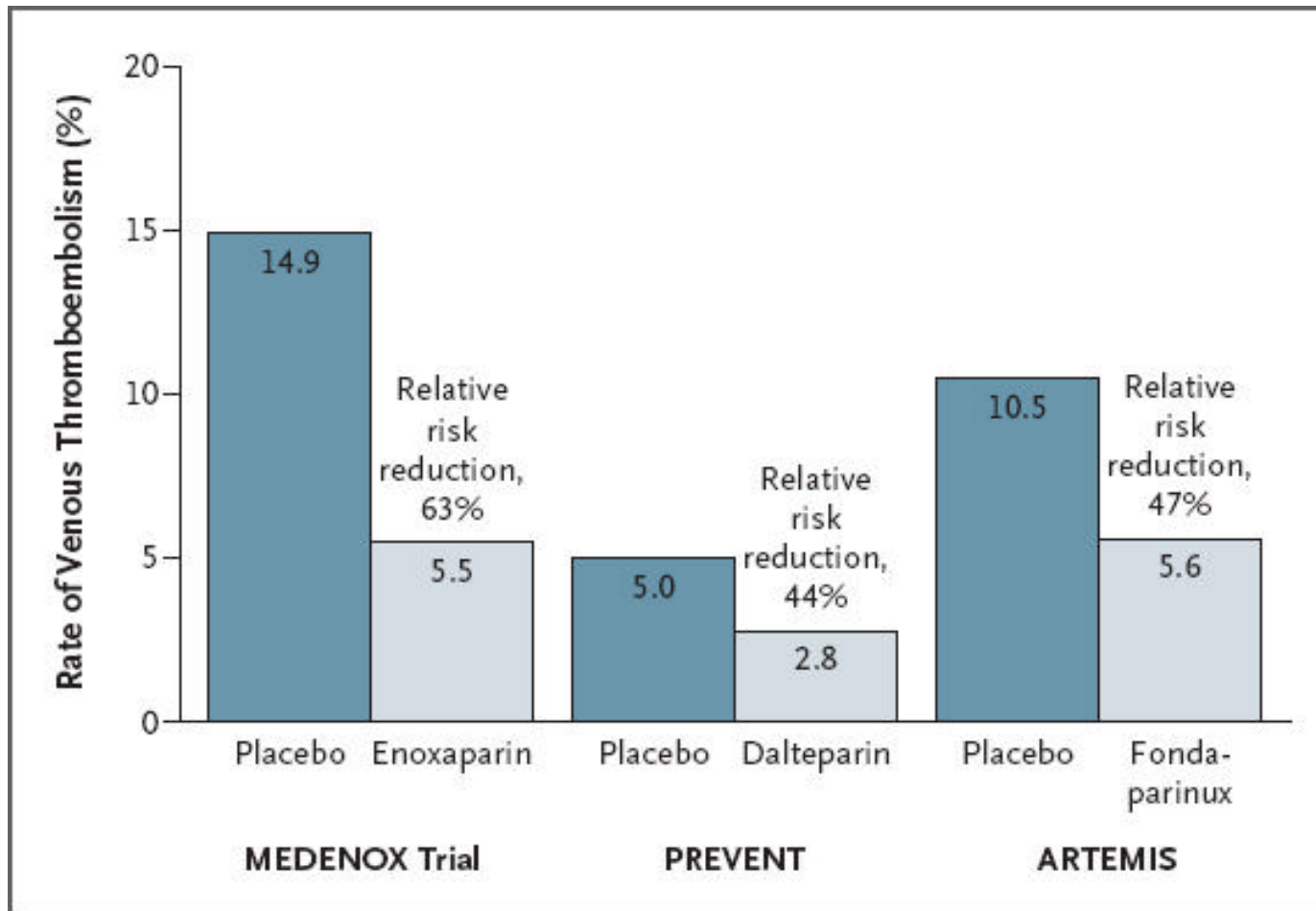
*The descriptive terms are purposely left undefined to allow individual clinician interpretation.

†Rates based on objective diagnostic screening for asymptomatic DVT in patients not receiving thromboprophylaxis.

‡See relevant section in this chapter for specific recommendations.

§Mechanical thromboprophylaxis includes IPC or VFP and/or GCS; consider switch to anticoagulant thromboprophylaxis when high bleeding risk decreases.

Medical Prophylaxis



VTE in Stroke

- Risk factors
 - Immobility
 - Age > 75
 - Stroke severity

PREVAIL Study

- 1762 patients with acute ischemic stroke
- Patients were unable to walk unassisted
- Rx:
 - enoxaparin 40 mg daily vs. UFH 5000 U BID
 - treatment x 10 d
- Outcome: VTE at day 14

VTE in Acute Ischemic Stroke

	Enoxaparin (n=666)	Unfractionated heparin (n=669)	Relative risk (95% CI)*	p†	Difference (95% CI)
VTE	68 (10%)	121 (18%)	0.57 (0.44-0.76)	0.0001	-7.9% (-11.6 to -4.2)
PE‡	1 (<1%)	6 (1%)	0.17 (0.02-1.39)	0.059	-0.7% (-1.5 to 0)
Symptomatic VTE	2 (<1%)	7 (1%)	0.29 (0.06-1.38)	0.096	-0.7% (-1.6 to 0.1)
Symptomatic DVT	1 (<1%)	4 (1%)	0.25 (0.03-2.24)	0.18	-0.4% (-1.1 to 0.2)
Asymptomatic DVT§	66 (10%)	114 (17%)	0.57 (0.43-0.75)	<0.0001	-7.1% (-10.8 to -3.5)
All DVT	67 (10%)	118 (18%)	0.57 (0.43-0.75)	<0.0001	-7.6% (-11.3 to -3.9)
Proximal	30 (5%)	64 (10%)	0.47 (0.31-0.72)	0.0003	-5.1% (-7.8 to -2.3)
Distal	44 (7%)	85 (13%)	0.52 (0.37-0.74)	0.0002	-6.1% (-9.2 to -2.9)
Proximal and distal¶	7 (1%)	31 (5%)	0.23 (0.10-0.51)	<0.0001	-3.6% (-5.4 to -1.8)

Data are number (%) unless otherwise indicated. DVT=deep vein thrombosis. PE=pulmonary embolism. VTE=venous thromboembolism. The individual numbers of events for each endpoint do not always add up to the total number because patients might have had more than one type of event. *Enoxaparin versus unfractionated heparin. †Adjusted for National Institutes of Health Stroke Scale score stratification for VTE, but unadjusted for other criteria. ‡Three PE events were fatal (one with enoxaparin and two with unfractionated heparin). §Confirmed by ultrasound: five of 66 (8%) enoxaparin, nine of 114 (8%) unfractionated heparin; confirmed by venography: 61/66 (92%) enoxaparin, 104/114 (91%) unfractionated heparin. ¶Events also counted in proximal DVT and distal DVT.

Table 2: Incidence of venous thromboembolic events up to day 14 in the efficacy group

Prophylaxis and Bleeding

	Enoxaparin (n=877)	Unfractionated heparin (n=872)	Relative risk (95% CI)	p*	Difference (95% CI)
Bleeding at end of treatment + 48 h					
Total†	69 (8%)	70 (8%)	0.98 (0.71-1.35)	0.90	-0.2% (-2.7% to 2.4)
Symptomatic intracranial haemorrhage	4 (1%)	6 (1%)	0.66 (0.19-2.34)	0.55	-0.2% (-0.9% to 0.5)
Death of patient with symptomatic intracranial haemorrhage	3 (<1%)	4 (1%)	-0.1% (-0.7% to 0.5)
Major extracranial haemorrhage‡	7 (1%)	0	..	0.015	0.8% (0.2% to 1.4)
Resulting in death	2 (<1%)	0	0.2% (-0.1% to 0.5)
Drop of haemoglobin \geq 30 g/L	7 (1%)	0	0.8% (0.2% to 1.4)
Transfusion of \geq 2 units of blood	5 (1%)	0	0.6% (0.1% to 1.1)
Clinically important haemorrhage	11 (1%)	6 (1%)	1.82 (0.68-4.91)	0.23	0.6% (-0.4% to 1.5)
Death of patient with clinically important haemorrhage§	5 (1%)	4 (1%)	1.24 (0.33-4.65)	1.0	0.1% (-0.6% to 0.8)
Minor extracranial haemorrhage¶	42 (5%)	48 (6%)	0.87 (0.58-1.30)	0.50	-0.7% (-2.8% to 1.4)
All-cause mortality up to day 14	48 (6%)	45 (5%)	1.12 (0.75-1.69)	0.58**	..
All-cause mortality up to day 90	100 (12%)	103 (12%)	1.01 (0.77-1.33)	0.96**	..

Data are number (%) unless otherwise indicated. *Fisher's exact test if n<6 in one group. χ^2 test if n \geq 6 in one group. †Some patients had more than one bleeding event. ‡Three were gastrointestinal bleeding, one surgical stoma of tracheostomy, one duodenal ulcer haemorrhage, one haematuria, and one haemoglobin decrease. §Defined as the composite of major extracranial and symptomatic intracranial haemorrhages. ¶All intracranial haemorrhages were regarded as major. ||Hazard ratio. **Log-rank test.

Table 5: Safety outcomes

Prophylaxis and Stroke

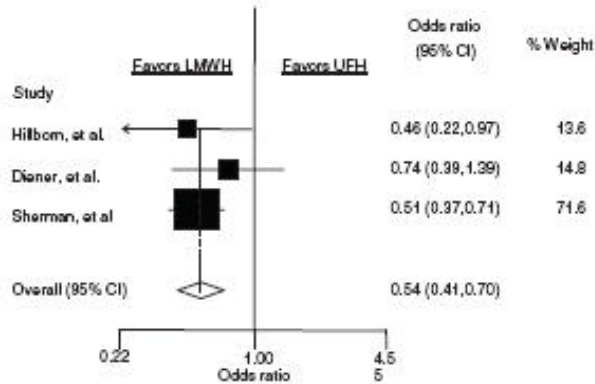


FIGURE 1. Frequency of VTE based on type of heparin used. χ^2 test for heterogeneity, 1.16 (df, 2); $p = 0.561$. Test of OR, 1; $z = 4.54$; $p < 0.001$.

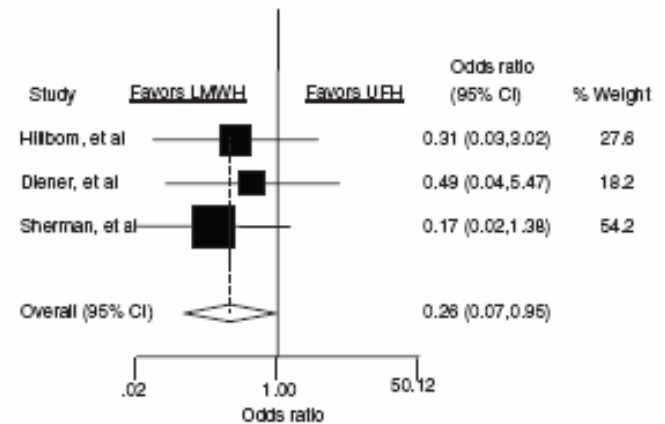


FIGURE 2. Impact of different heparin types on PE. χ^2 test for heterogeneity, 0.46 (df, 2); $p = 0.795$. Test of OR, 1; $z = 2.03$; $p = 0.042$.

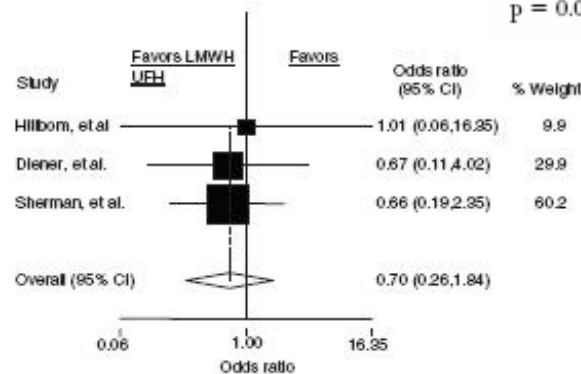


FIGURE 3. Intracerebral hemorrhage based on type of heparin exposure. χ^2 test for heterogeneity, 0.08 (df, 2); $p = 0.962$. Test of OR, 1; $z = 0.73$; $p = 0.466$ (random-effects model). OR with LMWH, 0.75; 95% CI, 0.21 to 1.91; $p = 0.567$ (fixed-effects model).

Mechanical Prophylaxis Considerations

Table 6—Advantages and Limitations of Mechanical Thromboprophylaxis Modalities (Section 1.4.3)

Advantages

- Do not increase the risk of bleeding
- Can be used in patients at high bleeding risk
- Efficacy has been demonstrated in a number of patient groups
- May enhance the effectiveness of anticoagulant thromboprophylaxis
- May reduce leg swelling

Limitations

- Not as intensively studied as pharmacologic thromboprophylaxis (fewer studies and smaller)
- No established standards for size, pressure, or physiologic features
- Many specific mechanical devices have never been assessed in any clinical trial
- Almost all mechanical thromboprophylaxis trials were unblinded and therefore have a potential for bias
- In high-risk groups are less effective than anticoagulant thromboprophylaxis
- Greater effect in reducing calf DVT than proximal DVT
- Effect on PE and death unknown
- May reduce or delay the use of more effective anticoagulant thromboprophylaxis
- Compliance by patients and staff often poor
- Trials may overestimate the protection compared with routine use
- Cost: associated with purchase, storage, dispensing, and cleaning of the devices, as well as ensuring optimal compliance

Intermittent Pneumatic Compression

- Augments blood return 180-240%
- Activated urokinase and t-PA mediated fibrinolysis, releases endothelial nitric oxide stores
- Mechanical prophylaxis decreases the incidence of DVT and may be appropriate as sole prophylaxis in patients with increased bleeding risks
- Use as an adjunct to pharmacologic prophylaxis in patients with increased risk
- Compliance with application may be problematic
- **No evidence that it mechanical prophylaxis decreases the incidence of fatal PE**

DO NOT rely on TED hose
alone!!!

VTE and Acute Intracerebral Hemorrhage

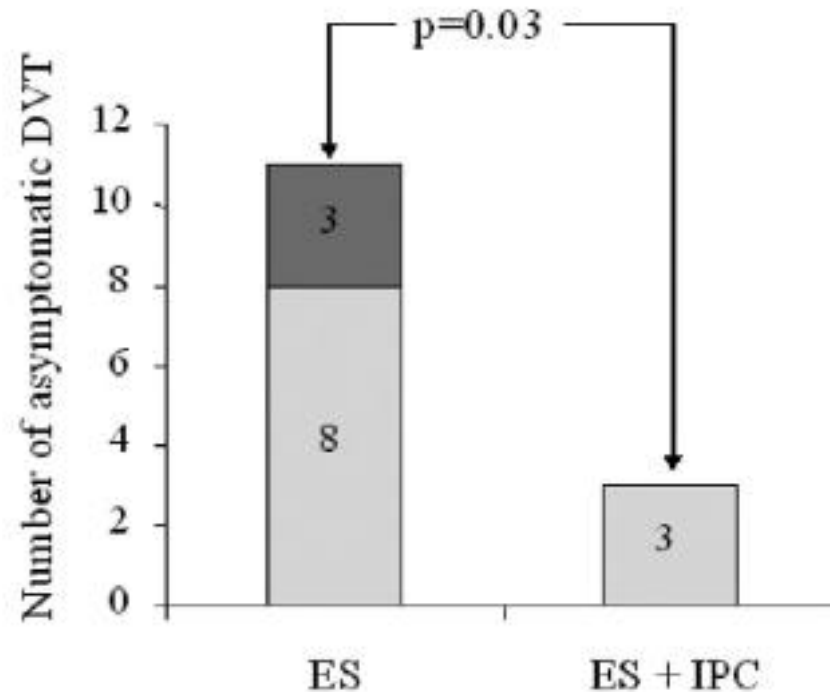


Figure 2. Description of events. Proximal DVT is represented by dark gray shading. Distal DVT is represented by light gray shading.

ES Prophylaxis in Neurosurgery

TABLE 3. RATES OF DEEP-VEIN THROMBOSIS AND PULMONARY EMBOLISM IN PATIENTS RECEIVING PLACEBO OR ENOXAPARIN.*

EVENT	PLACEBO (N=130)	ENOXAPARIN (N=130)	P VALUE†	RELATIVE RISK (95% CI)
	no. of patients (%)			
PE or DVT	43 (33)	22 (17)	0.004	0.51 (0.33–0.80)
PE or proximal DVT	18 (14)	7 (5)	0.04	0.39 (0.17–0.90)
Overall DVT	42 (32)	22 (17)	0.004	0.52 (0.33–0.82)
Proximal DVT	17 (13)	7 (5)	0.04	0.41 (0.17–0.95)
PE	1 (1)	0		

*CI denotes confidence interval, PE pulmonary embolism, and DVT deep-vein thrombosis. The placebo group included 129 patients with adequate venographic studies and 1 who died of pulmonary embolism, confirmed at autopsy, before venography could be performed.

†P values were calculated with use of Fisher's exact test.

TABLE 4. MAJOR AND MINOR BLEEDING IN STUDY PATIENTS.

EVENT	PLACEBO (N=154)	ENOXAPARIN (N=153)	P VALUE*
	no. of patients (%)		
Major and minor bleeding	11 (7)	18 (12)	0.18
Major bleeding	4 (3)	4 (3)	
Intracranial bleeding	4	3	
Melena with anemia	0	1	
Minor bleeding	7 (5)	14 (9)	
Surgical-wound hematoma	2	8	
Hematuria	3	1	
Injection-site hematoma	0	2	
Anemia without clinically overt bleeding	2	3†	

*The P value was calculated with use of Fisher's exact test.

†Treatment was discontinued in two patients.

ES in Stroke

	Thigh-length GCS (n=1256)	Avoid GCS (n=1262)	Odds ratio (95% CI)
Primary outcome			
Proximal DVT	126 (10.0%)	133 (10.5%)	..
Alive and free of primary outcome	974 (77.5%)	1000 (79.2%)	..
Dead before any primary outcome	115 (9.2%)	101 (8.0%)	..
Missing	41 (3.3%)	28 (2.2%)	..
Unadjusted (dead and missing excluded)	0.97 (0.75-1.26)
Adjusted* (dead and missing excluded)	0.98 (0.76-1.27)
Secondary outcomes by 30 days or later second compression Doppler ultrasound			
Dead by 30 days	122 (9.7%)	110 (8.7%)	1.13 (0.86-1.48)
Symptomatic proximal DVT	36 (2.9%)	43 (3.4%)	0.84 (0.53-1.31)
Asymptomatic proximal DVT	90 (7.2%)	90 (7.1%)	1.01 (0.74-1.36)
Symptomatic DVT (proximal or distal)	55 (4.4%)	61 (4.8%)	0.90 (0.62-1.31)
Any DVT (proximal or distal)	205 (16.3%)	224 (17.7%)	0.90 (0.73-1.11)
PE confirmed on imaging or autopsy	13 (1.0%)	20 (1.6%)	0.65 (0.32-1.31)
PE on autopsy	1 (0.1%)	1 (0.1%)	1.00 (0.06-16.08)
Any DVT or PE	213 (17.0%)	232 (18.4%)	0.91 (0.74-1.11)
Skin breaks/ulcers/blisters/skin necrosis	64 (5.1%)	16 (1.3%)	4.18 (2.40-7.27)
Lower limb ischaemia/amputation	7 (0.6%)	2 (0.2%)	3.53 (0.73-17.03)

Current Recommendations for Stroke

- Medically ill patients with CHF, respiratory disease, cancer, previous VTE, sepsis, acute neurologic disease, or IBD
 - LMWH (grade 1A); LDUH (Grade 1A); fondaparinux (Grade 1A)
 - With a contraindication to anticoagulation – IPC (Grade 1)

VTE Prophylaxis

- All patients should be assessed for VTE risk
- ES alone are not useful
- Pharmacologic or mechanical prophylaxis should be instituted
- Be as aggressive as indicated and as possible

Conclusions

- Assess and administer appropriate VTE prophylaxis to all hospitalized patients
- VTE is common despite adequate prophylaxis
- Ambulate patients ASAP
- Management strategies for VTE should fit the clinical risk
- AC is preferred however, surveillance or filter placement may be the most practical/optimal choice