Prevention of venous thromboembolism*

International Consensus Statement
Guidelines compiled in accordance with the scientific evidence

Under the auspices of the Cardiovascular Disease Educational and Research Trust, and the International Union of Angiology.

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Dedicated to the memory of Ernest Cooke

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Disclaimer

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Glossary

DVT: Deep vein thrombosis
FUT: Fibrinogen uptake test
GEC: Graduated elastic compression
HIT: Heparin-induced thrombocytopenia
IPC: Intermittent pneumatic compression
LMWH: Low molecular weight heparin
PE: Pulmonary embolism
Proximal DVT: DVT in popliteal or more proximal veins
VTE: Venous thromboembolism

Rules of evidence

Prevention of VTE has been traditionally undertaken subjectively among physicians, often resulting in less than optimal strategies. In this document a systematic approach has been developed with detailed grades of recommendations, based upon cumulative evidence from the literature. Levels of evidence and grades of recommendation range from Level I and Grade A to Level III and Grade C. Level I evidence and Grade A recommendations derive from scientifically sound clinical trials in which the results are clear-cut. Level II evidence

and Grade B recommendations derive from clinical studies in which the results among trials often point to inconsistencies. Level III evidence and Grade C recommendations result from poorly designed trials or from small case series.[1]

Meta-analysis

Meta-analyses are included in the present document but one should be cautious about their potential abuse. Some studies are included carelessly, by failing to adequately understand substantive issues, ignoring relevant variables, being too heterogenous; or by introducing bias in interpretation.[2]

For example, it has been demonstrated that the outcomes of 12 large randomized controlled trials were not predicted accurately 35% of the time by meta-analyses published previously on the same topics.[3]

The problem and the need for prevention

Venous thromboembolism (VTE) due to deep vein thrombosis (DVT) or pulmonary embolism (PE) is a major international health problem. At one extreme, PE can be fatal. Often overlooked is the fact that DVT can lead to post-thrombotic venous insufficiency and ulceration which adversely impacts on the quality of life and escalates health care costs. In North America and Europe, the annual incidence is approximately 160 per 100,000 for DVT, 20 per 100,000 for symptomatic non-fatal PE, and 50 per 100,000 for fatal autopsy-detected PE.[4-8] Venous ulcers develop in at least 300 per 100,000 of the population and the proportion due to DVT is approximately 25%.[9-10] The annual cost of treating venous ulcers has been estimated to be 400 million pounds for the UK[11] and more than one billion dollars for the USA.[12]

Most venous thromboembolic events are not detected clinically because the diagnosis is difficult and elusive. Therefore, it is important for the medical profession to know the epidemiology and definition of high risk groups, and to be familiar with the diagnostic methodology (Tables I-VII[13-112]) in order to apply appropriate prophylaxis and early treatment. Although VTE should be an appealing target for maximal preventive efforts, consensus on its prevention has been difficult to achieve because of considerable differences in attitudes toward prophylaxis, definition of high risk groups, and prophylactic methods chosen.[105,113-118] The aim of this document is to provide guidelines in accordance with the available scientific evidence.

Risk categories

The known clinical risk factors allow for the classification of patients into high, medium or low risk of developing thromboembolism (Tables VI and VII).

The risk in surgical patients

Patients who undergo operative procedures are at risk of developing venous thromboembolic disease (Tables I-IV).[74,105,119-122] The risk is increased by age, obesity, malignancy, prior history of venous thrombosis, varicose veins, and thrombophilic states. It is also affected by the nature and duration of the operation, type of anaesthesia, immobility, dehydration and sepsis.[123-129]

Studies in patients having general surgery[130-132] demonstrate that the risk continues after discharge from hospital. Further studies are needed before recommendations can be made on the duration of prophylaxis necessary.

The risk in gynaecology and obstetrics

The reported overall frequency of thromboembolic complications after gynaecological surgery is of the same magnitude as for general surgery. However, for benign gynaecological surgery and vaginal procedures the incidence appears to be much lower (Table I). Pulmonary embolism is a leading cause of death following gynaecological cancer surgery[133] and accounts for approximately 20% of perioperative hysterectomy deaths.[134] Risk factors for DVT include those listed for general surgery.[26,135,136] In addition, combined oral contraceptive preparations containing 50 micrograms or more of oestrogen have been shown to be associated with an increased risk of idiopathic,[137] and postoperative thromboembolism.[138-140] Recent data regarding the current low dose oestrogen oral contraceptives containing 35 micrograms of oestrogen or less, also show that the risk of VTE with these compounds is increased at least threefold.[141,142]

There is evidence that oral contraceptives containing a third generation progestagen have a higher risk (relative risk 2.5, 95% CI 1.2-5.2) than other oral contraceptive types combined.[143-145]

In pregnancy, DVT generally occurs in only 0.13-0.5 per 1000 in the antepartum period and 0.61-1.5 per 1000 postpartum.[46-148] However, PE is still a leading cause of maternal mortality.[149] Factors associated with an increased risk of VTE in pregnancy include caesarean section, obesity, advanced maternal age and thrombophilic states (see below).[149-150]

Table I - The frequency of all DVT in trauma, surgery and medical patients in the absence of prophylaxis (diagnosed by surveillance with objective methods: Phlebography or FUT). The listed frequency is true for the total groups of patients. The presence of additional risk factors indicated in the text is likely to increase the risk of thromboembolism for individual patients.

Patient groups	Number of studies	Patients number	DVT incidence (weighted mean)	95% CI
Stroke				
Czechanoswki & Heinrich 1981[13]		41	23	
Dahan et al., 1986[14]		27	3	
McCarthy et al., 1977[15]		16	12	
McCarthy & Turner 1986[16]		161	117	
Prins et al., 1989[17]		30	15	
Sandset et al., 1990[18]		50	17	
Turpie et al., 1987[19]		25	7	
Warlow et al., 1972[20]		30	18	
Total	8	380	212 (56%)	51% to 61%
Elective hip replacement				
Belch et al., 1982[21]		36	20	
Bergqvist et al., 1979[22]		71	45	
Dechavanne et al., 1974[23]		27	13	
Dechavanne et al., 1975[24]		20	8	
Evarts et al., 1971[25]		56	30	
Gallus et al., 1983[26]		47	25	
Hampson et al., 1974[27]		52	28	
Harris et al., 1977[28]		51	23	
Hoek et al., 1992[29]		99	56	
Hull et al., 1990[30]		158	77	
Ishak & Morley, 1981[31]		41	22	
Kalodiki et al., 1996[32]		14	13	
Mannucci et al., 1976[33]		51	22	
Morris et al., 1974[34]		32	16	
Turpie et al., 1986[35]		50	21	
VTCSG, 1975[36]		30	11	
Welin-Berger et al., 1982[37]		16	5	
Total	17	851	435 (51%)	48% to 54%
Multiple trauma				
Freeark et al., 1967[38]		124	44	
Geerts et al., 1994[39]		349	201	
Kudsk et al., 1989[40]		38	24	
Shackford et al., 1990[41]		25	1	
Total	4	536	270 (50%)	46% to 55%
Total knee replacement				
Hull et al., 1979[42]		29	19	
Kim, 1990[43]		244	80	
Leclerc et al., 1996[44]		57	31	
Lynch et al., 1988[45]		75	28	
Stringer et al., 1989[46]		55	31	
Stulberg et al., 1984[47]		49	41	
Wilson et al., 1991[48]		32	22	
Total	7	541	252 (47%)	42% to 51%
Hip fracture				
Ahlberg et al., 1968[49]		45	16	
Checketts & Bradley, 1974[50]		26	13	

(continues)

Table I - (continued)

Patient groups	Number of studies	Patients number	DVT incidence (weighted mean)	95% CI
Hip fracture				
Darke, 1972[51]		66	11	
Daniel et al., 1972[52]		31	19	
Galasko et al., 1976[53]		50	23	
Gallus et al., 1973[54]		23	11	
Kakkar et al., 1972[55]		50	20	
Lahnborg, 1980[56]		69	28	
Montrey et al., 1985[57]		81	22	
Morris & Mitchell, 1976[58]		74	50	
Morris & Mitchell, 1977[59]		76	49	
Myhre and Holen, 1969[60]		55	22	
Powers et al., 1989[61]		63	29	
Rogers et al., 1978[62]		37	19	
Svend-Hansen et al., 198[63]		65	28	
Xabregas et al., 1978[64]		25	12	
Total	16	836	372 (45%)	41% to 48%
Retropubic prostatectomy				
Becker et al., 1970[65]		187	39	
Coe et al., 1978[66]		8	1	
Hedlund & Blomback, 1981[67]		28	13	
Kutnowski et al., 1977[68]		12	5	
Mayo et al., 1971[69]		41	21	
Nicolaides et al., 1972[70]		21	10	
Vandendris et al., 1980[71]		33	13	
Williams, 1971[72]		5	4	
Total	8	335	106 (32%)	27% to 37%
Transurethral prostatectomy				
Hedlund, 1975[73]		101	10	
Mayo et al., 1971[69]		20	2	
Nicolaides et al., 1972[70]		29	2	
Total	3	150	14 (9%)	5% to 15%
General Surgery				
Clagett & Reisch, 1988[74]				
Total	54	4310	1084 (25%)	24% to 26%
Spinal cord injury				
Bors et al., 1954[75]		99	58	
Brach et al., 1977[76]		10	9	
Rossi et al., 1980[77]		18	13	
Silver, 1974[78]		32	8	
Watson, 1974[79]		234	42	
Frisbie & Sasahara, 1981[80]		17	1	
Merli et al., 1988[81]		17	8	
Myllynen et al., 1985[82]		9	9	
Yelnik et al., 1991[83]		22	12	
Total	9	458	160 (35%)	31% to 39%
Neurosurgery				
Skillman et al., 1978[84]		48	11	
Turpie et al., 1977[85]		63	12	
Turpie et al., 1985[86]		68	12	
Turpie et al., 1989[87]		81	16	
Zelikovski et al., 1981[88]		20	10	
Total	5	280	61 (22%)	17% to 27%

(continues)

Table I - (continued)

Patient groups	Number of studies	Patients number	DVT incidence (weighted mean)	95% CI
Gynaecological surgery				
Malignancy				
Clarke-Pearson et al., 1983[89]		97	12	
Clarke-Pearson et al., 1984[90]		52	17	
Clarke-Pearson et al., 1990[91]		103	19	
Walsh et al, 1974[92]		45	16	
Total	4	297	64 (22%)	17% to 26%
Gynaecological surgery				
Benign disease				
Ballard et al, 1973[93]		55	16	
Bonnar & Walsh, 1972[94]		140	15	
Taberner et al., 1978[95]		48	11	
Walsh et al., 1974[92]		217	21	
Total	4	460	63 (14%)	11% to 17%
Myocardial infarction				
Emerson & Marks, 1977[96]		41	14	
Handley, 1972[97]		24	7	
Nicolaides et al., 1971[98]		51	8	
Warlow et al., 1973[99]		64	11	
Total	4	180	0 (22%)	16% to 28%
General Medical				
Belch et al., 1981[100]		50	13	
Cade, 1982[101]		60	6	
Total	2	110	19 (17%)	10% to 24%
Geriatric (>65 years)				
Dahan et al., 1986[14]				
Total	1	131	12 (9%)	5% to 15%

The risk in orthopaedic surgery and trauma

Certain patients who have suffered trauma or have undergone elective orthopaedic surgery are at moderate or high risk for VTE. Patients undergoing elective hip replacement and those with hip fracture without prophylaxis have been associated with a DVT frequency of approximately 50%, and one half of these involve the popliteal and more proximal veins (Tables I-IV).[151-153]

With modern practice, even without routine chemical prophylaxis, the fatal PE rate is much lower than previously assumed, with rates after hip replacement of <0.5%[109,111], knee replacement < 0.4%,[154] hip fracture <1%.[155] The venographic DVT rate is about 50%, although after hip replacement many of the proximal DVTs are small isolated femoral thrombi, the significance of which is unknown. Most venographic DVTs after knee replacement are calf thrombi, again the significance of which is uncertain.[156] The frequency of chronic venous insufficiency after joint replacement is not known, but this complication is probably associated with larger thrombi.[157] Symptomatic thromboembolism rates after hip replacement 3%,[109] knee replacement 10%,[158] and hip fracture 2%[155] have been reported. About 2% of hip replacement patients develop symptomatic thromboembolism beyond the tenth day after hip replacement,[159] although the risk of delayed thrombosis is less after knee replacement.[153,158,160]

The risk in medical patients

Medical conditions such as stroke, cancer, congestive heart failure, chronic respiratory disease, chest infections and myocardial infarction are associated with a high risk of VTE.[161-164] The patients' overall risk is affected by

Table II - The frequency of proximal DVT in the absence of prophylaxis diagnosed by surveillance with objective methods (fibrinogen uptake test or phlebography).

Patient group	Number of studies	Number of patients	Incidence of DVT	95% CI
General surgery (Clagett & Reisch, 1988)[74]	16	1206	83 (6.9%)	5.5 to 8.3%[4]
Elective hip replacement (Imperiale & Speroff, 1994)[102]	25	1436	330* (23%)	20.8 to 25.2%
Total knee replacement Hull et al., 1979[42] Kim, 1990[43] Leclerc et al., 1996[44] Mckenna et al., 1976[103] Stringer et al., 1989[46] Stulberg et al., 1984[47] Wilson et al., 1991[48]	7	536	41 (7.6%)	5.5 to 10.1%

* This number is an estimate from the percentage given in the paper.

Table III - The frequency of clinical pulmonary embolism* in the absence of prophylaxis.

Patient group	Number of studies	Number of patients	Clinical PE	95% CI
General surgery (Clagett & Reisch, 1988) [74]	32	5091	82 (1.6%)	1.3 to 2.0%
Elective hip replacement (Imperiale & Speroff, 1994) [102]	25	1436	57** (4%)	3.0 to 5.1%
Traumatic orthopaedic surgery (APTC,1994) [104]	11	494	34 (6.9%)	4.8 to 9.5%

* In most of the studies using an objective method of screening for DVT, patients found to have proximal thrombosis were treated with anticoagulants; the true incidence of clinical pulmonary embolism in series without such screening and intervention is unknown.

** This number is an estimate from the percentage given in the paper.

Table IV - The frequency of fatal pulmonary embolism without prophylaxis.*

Patient group	Number of studies	Number of patients	Incidence of fatal PE	95% CI
General surgery (Clagett & Reisch, 1988) [74]	33	5547	48 (0.87%)	0.62% to 1.1%
Elective hip replacement (Collins et al., 1988) [105]	12	485	8 (1.65%)	0.38% to 2.7%
Fractured neck of femur (Lassen & Borris, 1994) [106]	23	1195	48 (4.0%)	3.0% to 5.3%

* In most of the studies using an objective method of screening for DVT, patients found to have proximal thrombosis were treated with anticoagulants; the true incidence of fatal pulmonary embolism in the absence of intervention is unknown.

Table V - Mortality after elective hip replacement in the absence of routine pharmacological prophylaxis.

Author	Number of patients	Follow-up	Total deaths	95% CI	Fatal PE	95% CI	Anticoagulant use
Seagroatt et al., 1991[107]	11600	90 days	93 (1.10%)	0.87 to 1.31%	–	–	Very low
Sheppeard et al., 1981[108]	3016	Inpatient	19 (0.63%)	0.38 to 0.98%	12 (0.40%)	0.20 to 0.70%	20%*
Warwick et al., 1995[109]	1162**	90 days	15 (1.30%)	0.73 to 2.10%	4 (0.34%)	0.09 to 0.90%	11%*
Wroblewski et al., 1992[110]	18104	1 year	362 (2.0%)	1.80 to 2.20%	1.27 (0.70%)	0.58 to 0.82%	–
Fender et al., 1997[111]	2111	42 days	19 (0.91%)	0.05 to 1.42%	4 (0.19%)	0.05 to 0.49	65%

* High risk patients received anticoagulation ** All patients wore thigh-length elastic stockings –: Information not available.

chemotherapy, mechanical interventions (e.g. indwelling catheters), and by patient related risk factors such as age and coagulation disorders which can be either inherited or acquired.[165-168] A high prevalence of DVT (28% and 33%) has been detected in medical intensive care patients in two studies.[169,170]

Necropsy studies show that only 25% of patients dying from PE in general hospitals had had recent surgery. The rest were immobilised patients with medical illnesses.[171] Overall mortality in medical patients admitted to general hospitals is about 10%, and about 1 in 10 hospital deaths (1% of all admissions) is due to PE.[5,171]

The risk in acute stroke

Patients with acute stroke causing paralysis have a high risk of DVT usually occurring in the paralysed limb, and of PE, as well as a high mortality which is partly due to the latter (Table I).

Predisposing haematological changes

Congenital predisposition to thrombosis (thrombophilia) should be considered in patients with a documented unexplained thrombotic episode or positive family history.[172] The frequency of congenital thrombophilia in consecutive patients with confirmed idiopathic thrombosis occurring outside the clinical setting of surgery, trauma, or cancer is approximately 25 %. The most common genetic predisposition in Caucasians is activated protein C resistance (APC). Others include: antithrombin, protein C or protein S deficiencies, hyperhomocysteinaemia, or prothrombin G20210A gene mutation, high plasma level of factor VIII and to a lesser extend heparin cofactor-II.[150,173-184] Abnormalities in the fibrinolytic system may contribute to increase the risk of VTE, but their clinical relevance has not been well established.

Acquired haematological abnormalities such as lupus anticoagulant,[185,186] and anticardiolipin antibodies,[187] are associated with a predisposition to VTE and have the most adverse outcomes due to a high rate of recurrence and a high mortality rate if anticoagulation is discontinued.

Screening for thromboembolism

Screening for VTE is technically possible but remains highly controversial. It can take three forms: (1) laboratory evaluation for common and if necessary uncommon hereditary or acquired haemostatic defects (see above), (2) exclusion of ongoing PE or proximal DVT by ELISA D-Dimer,[188] or (3) imaging tests such as duplex scanning to detect anatomical evidence of DVT.[189]

Overt thrombosis will often not occur in patients with thrombophilia, unless these "predisposed " patients are exposed to precipitating risk factors[190] such as surgery, trauma, cancer, prior VTE, obesity, immobility, increasing age, oral contraceptives, pregnancy, hormone replacement therapy or varicosities.

Although a high incidence of asymptomatic pulmonary embolism detected by lung scans occurs in patients with DVT at the time of diagnosis, routine lung scanning for these patients is not recommended.[191]

Table VI - The definition of risk categories (modified from Salzman and Hirsh, 1982).[112]

Category	Frequency of calf vein thrombosis	Frequency of proximal vein thrombosis	Frequency of Fatal PE
High risk	40-80%	10-30%	>1%
Moderate risk	10-40%	1-10%	0.1-1%
Low risk	<10%	<1%	<0.1%

Table VII - Risk categories according to clinical risk factors in non-orthopaedic patients.

Risk category	General surgery	Gynaecology	Obstetrics*	Medical patients
High	Major general surgery, age >60 Major general surgery, age 40-60 & cancer or history of DVT/PE Thrombophilia	Major gynaecological surgery, age >60 Major gynaecological surgery, age 40-60 & cancer or history of DVT/PE Thrombophilia	History of DVT/PE Thrombophilia	Stroke Age >70 Congestive cardiac failure Shock History of DVT/PE Thrombophilia
Moderate	Major general surgery, age 40-60 without other risk factors** Minor surgery, age > 60 Minor surgery, age 40-60 with history of DVT/PE or on oestrogen therapy	Major gynaecological surgery, age 40-60 Major gynaecological surgery, age < 40 on oestrogen therapy Minor surgery, age > 60	Age > 40 years	Immobilised patient with active disease Cardiac failure
Low	Major general surgery, age < 40 No other risk factors** Minor surgery, age 40-60 No other risk factors**	Minor gynaecological surgery, age < 40 without any other risk factors** Minor gynaecological surgery, age 40-60 without any other risk factors**	Age <40 without any risk factors	Minor medical illness

* The risk of DVT in obstetric patients with pre-eclampsia and the other factors is unknown but prophylaxis should be considered.
** The risk is increased by infectious disease, presence of varicose veins, general immobility.
Minor surgery: operations other than abdominal lasting less than 45 minutes. Major surgery: any intra-abdominal operation and all other operations lasting more than 45 minutes.

Lower limb duplex scanning is not sufficiently sensitive to determine whether a patient is likely to have a pulmonary embolus.[192] In patients referred with possible pulmonary embolism duplex scanning of the legs was positive for DVT in 40% or more if the pulmonary isotope scan was clearly positive, less than 15% if the lung scan was equivocal and less than 10% if the lung scan was normal.[193,194] Duplex scanning showed that pulmonary embolism was twice as likely for floating compared to fixed thrombi.[195]

Although B-mode ultrasound using compression appears insensitive for diagnosing asymptomatic post-operative DVT[196-198] the combination of compression plus color-Doppler imaging (duplex ultrasonography) which assists anatomical orientation, accelerates the examination and improves accuracy.[199-201] Accurate duplex scanning with colour flow imaging requires different diagnostic criteria from those for conventional B-mode scanning and a great deal of training, and it can be technically demanding, particularly in hip and knee arthroplasty patients because of postoperative oedema and limited ability to flex and position the limbs. However, in selected institutions which perform their own validation series[202], duplex scanning with colour flow imaging appears to be useful for DVT screening in high risk patients.[169,200,203]

Prophylactic methods and recommendations

Only directly randomized comparisons for each prophylactic method should be used to determine the risk reduction (Tables VIII-XIX)[204-271]. Non-randomized comparisons of outcome in different trials such as those reported by Colditz et al.,[120] Clagett and Reisch,[74] Mohr et al.,[272] and Imperiale and Speroff,[102] are potentially biased.

General surgery and urology

General considerations

Low dose unfractionated heparin (5000 IU 8 or 12 hourly subcutaneously) reduces both DVT (Table VIII) (Level I evidence) and fatal PE[105,214,273] (Level I evidence).

Table VIII - Effect of low dose subcutaneous heparin (LDH) in the prevention of DVT diagnosed by surveillance with objective methods in non-orthopaedic randomised controlled studies (fibrinogen uptake tests and/or phlebography).

Authors	Control groups		Heparin groups	
	Number of patients	DVT (%)	Number of patients	DVT(%)
Abernathy & Hartsuck, 1974[204]	62	3 (4.8)	63	4 (6.3)
Belch et al., 1979[205]	25	8 (32)	24	0
Bergqvist & Hallbook, 1980[206]	58	14 (24.1)	53	6 (11.3)
Caloghera et al., 1984[207]	40	3 (7.5)	40	2 (5)
Clarke-Pearson et al., 1983[89]	105	12 (11.4)	95	9 (9.5)
Coe et al., 1978[66]	24	7 (29.2)	28	8 (28.6)
Covey et al., 1975[208]	52	5 (9.6)	53	4 (7.5)
Gallus et al., 1973[54]	109	16 (14.7)	100	1(1)
Gallus et al., 1976[209]	412	49 (11.9)	408	9 (2.2)
Gordon-Smith et al., 1972[210]	51	21 (41.2)	105	17 (16.2)
Groote-Schuur Study, 1979[211]	323	54 (16.7)	323	30 (9.3)
Gruber et al., 1977[212]	113	36 (31.9)	119	12 (10.1)
Hedlund et al., 1979[67] & 1981[213]	29	11 (37.9)	30	2 (6.7)
IMT, 1975[214]	724	187 (25.8)	673	55 (8.2)
Kakkar et al., 1972[55]	39	17 (43.6)	39	3 (7.7)
Kettunen et al., 1974[215]	117	48 (41)	83	7 (8.4)
Koppenhagen and Matthes, 1982[216]	50	15 (30)	162	32 (19.8)
Kraytman et al., 1976[217] & 1977[218]	27	17 (63)	23	6 (26.1)
Kutnowski et al., 1977[68]	4 (30.8)	6	(16.7)	
Lahnborg et al., 1974[219] & 1975[220]	54	11 (20.4)	58	3 (5.2)
Lawrence et al., 1977[221]	129	20(15.5)	133	8 (6)
Multicentre Trial, 1984[222]	108	22 (20.4)	222	32 (14.4)
Multiunit Trial 1974[223]	128	47 (36.7)	128	15 (11.7)
Nicolaides et al., 1972[224]	122	29 (23.8)	128	1 (0.8)
Plante et al., 1979[225]	66	14 (21.2)	42	3 (7.1)
Roberts & Cotton, 1975[226]	45	8 (17.8)	39	10 (25.6)
Sebeseri et al., 1975[227]	31	18 (58.1)	34	4 (11.8)
Spebar et al., 1981[228]	19	2 (10.5)	24	3 (12.5)
Strand et al., 1975[229]	55	10 (18.2)	55	3 (5.5)
Taberner et al., 1978[95]	50	11 (22)	50	3 (6)
Torngren et al., 1978[230] & 1979[231]	62	18 (29)	66	6 (9.1)
Vandendris et al., 1980[71]	33	13 (39.4)	32	3 (9.4)
Wu et al., 1977[232]	44	6 (13.6)	44	0
Ziemski et al., 1979[233]	20	8 (40)	30	0
Overall	3339	864 (25.9%)	3512	302 (8.6%)

Relative risk: 0.33 (95% CI 0.29 to 0.37)

Low molecular weight heparin (LMWH) has been found to reduce not only the incidence of fatal PE but also the overall surgical mortality as compared to controls without prophylaxis in a multicentre study.[274]

Dextran has been shown to reduce fatal PE. In a compilation of 29 studies in which patients were randomized into dextran prophylaxis (n=2964) or controls (n=2981) the incidence of fatal PE was 0.34% in the dextran and 1.5% in the control groups (Relative Risk 0.22; 95% CI 0.11 to 0.44) although the effect of dextran on DVT was relatively small (Relative Risk 0.76; 95% CI 0.64 to 0.91).[275] It is now believed that fibrin formed in the presence of dextran is not cross-linked, so that it is easily lysed by the body's natural fibrinolytic activity.[276,277] Dextran has inherent risks of fluid overload and anaphylactoid reactions, but a pre-infusion hapten injection reduces the risk of such reactions.[74,278] The use of dextran for the prevention of PE is based on the above meta-analysis but its limited efficacy in DVT prevention and serious side-effects have limited its use in recent years.

Antiplatelet therapy. In an overview of all randomized trials in which DVT was assessed by systematic objective tests (predominantly the fibrinogen uptake test) in a wide range of surgical patients[104] antiplatelet therapy (i.e. aspirin in doses of 1000 to 1500 mg per day) appeared to reduce both the incidence of DVT (Table IX) and PE (Table X). Most trials assessed the thromboprophylactic efficacy of antiplatelet therapy in the absence of subcutaneous heparin, so that information on adding antiplatelet therapy to heparin is limited although at least for PE the results did suggest that the effects might be additive.

Heparinoids, including dermatan sulfate,[279,282] are effective in general surgery and elective total hip replacement.

Oral anticoagulants for primary thromboembolism prophylaxis have some support in general but not in urological surgery.[283] The recommended range for the INR is 2.0-2.5.[284]

Intermittent pneumatic compression (IPC) (Table XI) and *graduated elastic compression (GEC) stockings*,[285,286] (Table XII) reduce the incidence of DVT (Level I evidence), but the numbers studied have been too small to assess their effects on PE. The data concerning other methods of mechanical prophylaxis are insufficient to assess efficacy.

There is evidence from randomized controlled studies that combinations of prophylactic methods are more effective than when each agent is used singly.[287] These include low dose heparin and dihydroergotamine,[222,288-295] low dose heparin and antiplatelet agents,[104] low dose heparin and IPC,[224,234,247,248,250-252,296] (Tables XIII and XIV), LMWH and GEC,[32,297-299] dextran and GEC,[300] heparin and IPC,[247] GEC and IPC.[301] However, for some combinations the number of studies is relatively small and more are needed, particularly in hhgh risk patients.

A randomized study involving 2551 patients undergoing cardiac surgery has demonstrated a reduction

Table IX - Effect of antiplatelet therapy (e.g. aspirin) in the prevention of DVT diagnosed by surveillance with objective methods (fibrinogen uptake in general surgery and phlebography in orthopaedic surgery) in randomised controlled studies (Antiplatelet Trialists' Collaboration, 1994).[104]

	Control Groups*			Antiplatelet Groups			
Type of patients	Number of trials with data	Number of patients	DVT(%)	Number of patients	DVT(%)	RR	95%CI
General surgery	22	1459	396 (27)	1434	278 (19)	0.71	0.62 to 0.82
Orthopaedic traumatic	10	444	186 (42)	454	163 (36)	0.86	0.73 to 1.0
Orthopaedic elective	13	436	232 (53)	427	160 (37)	0.70	0.61 to 0.82
All surgical	45	2339	814 (35)	2315	601 (26)	0.74	0.68 to 0.81
High risk medical	8	266	61 (23)	261	39 (15)	0.65	0.45 to 0.94
All trials	53	2605	875 (34)	2576	640 (25)	0.74	0.68 to 0.81

* In most trials patients were allocated evenly to antiplatelet therapy or control, but in some more were deliberately allocated to active treatment. To allow direct comparison between percentages adjusted control totals were calculated, (actual DVT incidence in surgical controls 700/2050; all medical trials evenly balanced).

Table X - Effect of antiplatelet therapy (e.g. aspirin) in the prevention of PE in randomised controlled studies (Antiplatelet Trialists' Collaboration, 1994). [104]

	Control Groups*			Antiplatelet Groups			
Type of patients	Number of trials with data	Number of patients	PE (%)	Number of patients	PE (%)	RR	95%CI
General surgery	26	3419	58 (1.7%)	3408	16 (0.5%)	0.28	0.16 to 0.48
Orthopaedic Traumatic	11	494	34 (6.9%)	504	14 (2.8%)	0.40	0.22 to 0.71
Orthopaedic Elective	16	537	29 (5.4%)	529	14 (2.6%)	0.49	0.26 to 0.92
All surgical	53	4450	121 (2.7%)	4441	44 (1.0%)	0.36	0.26 to 0.51
High risk medical	9	280	8 (2.9%)	275	3 (1.1%)	0.38	0.10 to 1.42
All trials	62	4730	129 (2.7%)	4716	47 (1.0%)	0.36	0.26 to 0.51

Table XI - Effect of intermittent pneumatic compression (IPC) in the prevention of DVT diagnosed by surveillance with objective methods in non-orthopaedic randomised controlled studies (fibrinogen uptake test or phlebography).

Authors	Control groups		Intermittent pneumatic compression	
	Number of patients	DVT (%)	Number of patients	DVT (%)
Borow & Goldson, 1981[234]	89	32 (36)	79	9 (11)
Butson, 1981[235]	4 (7)	62	6 (10)	
Caprini et al., 1983[236]	96	20 (21)	38	1 (3)
Clark et al., 1974[237]	36	7 (19)	37	1 (3)
Clarke-Pearson et al., 1984[90]	52	18 (35)	55	7 (13)
Coe et al., 1978[66]	24	6 (25)	29	2 (7)
Hills et al., 1972[238]	50	15 (30)	50	6 (12)
Roberts & Cotton, 1974[239]	104	27 (26)	94	6 (6)
Sabri et al., 1971[240]	39	12 (31)	39	2 (5)
Skillman et al., 1978[84]	48	12 (25)	47	4 (9)
Turpie et al., 1977[85]	96	20 (21)	103	8 (8)
Turpie et al., 1979[241]	63	12 (19)	65	1 (2)
Turpie et al., 1989[87]	81	16 (20)	78	7 (9)
Overall	835	201 (24)	776	60 (7.7)

Relative risk: 0.32 (95% CI 0.24 to 0.42)

Table XII - Effect of graduated elastic compression stockings (GEC) in the prevention of DVT diagnosed by surveillance with objective methods in non-orthopaedic randomised controlled studies (fibrinogen uptake and/or phlebography)

Author	Control groups		Graduated compression stockings	
	Number of patients	DVT (%)	Number of patients	DVT (%)
Allan et al., 1983[242] General surgery	103	37 (36)	97	15 (15)
Borow & Goldson, 1981[234] Various surgical	89	32 (36)	91	14 (15)
Holford, 1976[243] Major surgery	48	23 (48)	47	11 (23)
Scurr et al., 1977[244] General surgery	70	26 (37)	70	8 (11)
Tsapogas et al., 1971[245] General surgery	44	6 (14)	54	2 (4)
Turner et al., 1984[246] Gynaecological surgery	92	4 (4)	104	0 (0)
Overall	446	128 (29)	463	50 (11)

Relative risk: 0.38 (95% CI 0.28 to 0.51)

in the incidence of PE from 4% in the low dose heparin group to 1.5% in the group receiving low dose subcutaneous heparin combined with IPC.[302]

Recommendations

Low risk patients (i.e. those without risk factors undergoing minor surgery). The data is insufficient to make any recommendations. On the basis of risk/benefit ratio and extrapolation from studies in moderate risk patients, it is the practice in some countries to use GEC stockings in addition to early ambulation and adequate hydration.

Moderate risk patients (i.e. those undergoing major surgery, age over 40 years, without any additional risk

factors). The use of low dose heparin or LMWH are Grade A recommendations for all moderate risk patients.

Alternative Grade A recommendations are IPC used continuously until the patient is ambulant, GEC stockings, or a combination of both.[286]

Further studies are needed to assess the effect of GEC stockings and/or IPC in addition to pharmacological methods and to assess the combined effects of different pharmacological methods such as heparin plus aspirin versus heparin alone.

The use of dextran or aspirin is based on meta-analysis. However, dextran and aspirin are not the methods of choice in moderate risk patients because of their limited efficacy on DVT prevention, the anaphylactoid reactions and danger of cardiac overload associated with the former, the high dose of aspirin (1000-1500 mg per day) required and the fact that oral medications are not possible for several days in patients having abdominal surgery.

High risk patients (i.e. those undergoing major surgery, aged over 60 years or with additional risk factors). All should receive prophylaxis as for moderate risk patients (Grade A recommendation). In addition to single modalities such as low dose heparin or LMWH, combined modalities of pharmacological and mechanical methods should be considered as they may be more effective (Tables XIII, XIV) (Grade B recommendation).

Table XIII - Effect of graduated elastic compression (GEC) stockings versus low dose heparin (LDH) and graduated elastic compression (GEC) in the prevention of DVT diagnosed by surveillance with objective methods (fibrinogen uptake test and/or phlebography).

Authors	GEC		LDH & GEC		Surgical procedure
	Number of patients	DVT	Number of patients	DVT	
Borow & Goldson, 1983[247]	106	15 (14%)	63	2 (3%)	General surgery & orthopaedics
Moser & Froidevaux, 1976[248]	20	5 (25%)	20	2 (10%)	General surgery
Nicolaides et al., 1972[224]	122	29 (24%)	122	1 (1%)	General surgery
Rasmussen et al., 1988[249]	74	22 (30%)	89	23 (26%)	General surgery
Overall	322	71 (22%)	294	28 (9.5%)	

Relative risk: 0.43 (95% CI 0.29 to 0.65)

Table XIV - Effect of low dose heparin (LDH) versus low dose heparin (LDH) and graduated elastic compression (GEC) in the prevention of DVT diagnosed by surveillance with objective methods (fibrinogen uptake test and/or phlebography).

Authors	LDH		LDH & GEC	
	Number of patients	DVT	Number of patients	DVT
Borow & Goldson, 1983[247]	86	23 (26%)	63	2 (3%)
Moser & Froidevaux, 1976[248]	15	0	20	2 (10%)
Rasmussen et al., 1988[249]	85	25 (29%)	89	23 (26%)
Torngren 1980[250]	98	12 (12%)	98	4 (4%)
Wille-Jorgensen et al., 1985[251]	86	11 (13%)	90	2 (2%)
Wille-Jorgensen et al., 1991[252]	81	12 (15%)	79	2 (3%)
Overall	451	83 (18%)	439	35 (8%)

Relative risk: 0.47 (95% CI 0.33 to 0.69)

Neurosurgery

General considerations

In three randomized controlled studies involving a total of 422 patients, the incidence of DVT was reduced from 21.3% in controls to 6.0% in the prophylactic groups using pneumatic compression (relative risk 0.28; 95% CI 0.16 to 0.51) (Table XI).[84,85,241]

Recommendations

Neurosurgical patients should be considered for mechanical methods of prophylaxis (Grade A recommendation). A combination of LMWH with compression stockings is more effective than compression stockings alone and does not cause excessive bleeding.[303]

Orthopaedic surgery and trauma

Elective hip replacement

General considerations

The majority of studies with elective orthopaedic surgery have been carried out on elective hip replacement patients. Prophylactic methods which have been investigated include aspirin, dextran, fixed low dose unfractionated heparin, adjusted dose unfractionated heparin, fixed low dose unfractionated heparin with dihydroergotamine, LMWH, heparinoid, recombinant hirudin, fixed mini-dose and adjusted dose of oral anticoagulant therapy, GEC stockings, IPC and foot impulse technology. To determine the risk reduction for each prophylactic method, only randomized studies with systematic screening tests for DVT were used (Tables IX, X, XV-XVIII).

Fixed low dose unfractionated heparin (5000 IU 8 or 12 hourly) is effective for reducing DVT (Table XVII) (Level I evidence) and PE,[105] (meta-analysis) in patients having elective hip replacement. Increasing the dose leads to a greater risk of bleeding.[304] Adjusting the dose against a coagulation assay may enhance efficacy but is more difficult to manage.[298,305] The addition of dihydroergotamine did increase efficacy but it is no longer used because of the risk of vasospasm.[294,306,307]

Low molecular weight heparin is superior to unfractionated heparin in reducing DVT for hip replacement surgery.[299,308-315]

Recombinant hirudin as shown by two level I studies could be another alternative.[316,317]

Fixed minidose oral anticoagulant therapy is not effective. Adjusted dose oral anticoagulants to a desired INR (2.0-3.0) improves efficacy but is difficult to manage[269,270,318,319] (Level I evidence).

Antiplatelet therapy as demonstrated by a meta-analysis,[104] is only moderately effective for protection against DVT in elective hip surgery (relative risk 0.74; 95% CI 0.68 to 0.81) (Table IX) but the observed reduction in the risk of PE is substantial (relative risk 0.36; 95% CI 0.26 to 0.51) (Table X). The effect of aspirin on PE has been confirmed in a large randomized controlled trial[155] (Level I evidence).

Table XV - Effect of intermittent pneumatic compression (IPC) in the prevention of DVT diagnosed by surveillance with phlebography in randomised controlled studies of orthopaedic patients

Authors	Control groups (no prophylaxis)		IPC		Procedure
	Number of patients	DVT (%)	Number of patients	DVT (%)	
Gallus et al., 1983[26]	47	25 (53.2)	43	15 (34.9)	Hip (elective)
Haas et al., 1990[253]	36 (Aspirin)	17 (47)	36	8 (22)	Knee
Hartman et al., 1982[254]	52	19 (36.5)	53	1 (1.9)	Hip (elective & fracture)
Hull et al., 1979[42]	29	19 (65.5)	32	2 (6.3)	Knee
Hull et al., 1990[30]	158	49 (31)	152	24 (15.8)	Hip (elective)
Overall	286	112 (39.2)	280	42 (15)	

Relative risk: 0.46 (95% CI 0.34 to 0.64)

Table XVI - Effect of prophylaxis using the combination of foot impulse technology (FIT) with graduated elastic compression (GEC) on proximal DVT, in orthopaedic patients.

	Control			Foot impulse technology plus		
Authors	Method Diagnostic of prophylaxis method	No.	Proximal DVT (%)	Additional method of prophylaxis	No.	Proximal DVT (%)
Hip replacement						
Bradley et al., 1993[255]	VG GEC	44	11 (25)	FIT+GEC	30	2 (6.7)
Fordyce & Ling 1992[256]	VG GEC	40	13 (32)	FIT+GEC	39	2 (5)
Santori et al., 1994[257]	US Heparin	65	13 (20)	FIT+GEC	67	2 (3.0)
Warwick et al.,1998[258]	VG LMWH+ GEC	138	27 (13)	FIT+GEC	136	12 (9)
Knee surgery						
Blanchard et al., 1999[259]	VG LMWH	60	2 (3)	FIT only	48	4 (6)
Wilson et al., 1992[260]	VG Nil	32	6 (19)	FIT only	28	0
Westrich et al., 1996[261]	VG Aspirin	83	49 (59)	FIT+Aspirin	81	22 (27)
Hip fracture						
Stranks et al., 1992[262]	US GEC	39	9 (32%)	FIT+GEC	10	0

Table XVII - Effect of low dose subcutaneous heparin (LDH) in the prevention of DVT diagnosed by surveillance with objective methods (fibrinogen uptake test confirmed by phlebography or routine phlebography) in randomised controlled studies of orthopaedic patients.

	Control groups		Heparin groups	
Authors	Number of patients	DVT (%)	Number of patients	DVT (%)
Elective orthopaedic surgery (hip arthroplasty)				
Abraham-Inpijn & Vreeken, 1975[263]	13	5 (38.5)	12	1 (83)
Bergqvist et al., 1979[22]	23	20 (87)	32	18 (56)
Dechavanne et al., 1974[23]	29	13 (45)	29	2 (7)
Dechavanne et al., 1975[24]	21	8 (38)	20	1 (5)
Gallus et al., 1973[54]	9	3 (33)	8	1 (12)
Hampson et al., 1974[27]	52	25 (48)	48	15 (31)
Lowe, 1979[264] & 1981[265]	49	16 (33)	51	7 (14)
Mannuci et al., 1976[33]	24	10 (42)	23	3 (13)
Morris et al., 1974[34]	36	16 (44)	36	3 (8)
Moskovitz et al., 1978[266]	23	8 (35)	29	10 (34)
VTCSG, 1975[36]	30	11 (37)	34	2 (6)
Welin-Berger et al., 1982[37]	20	6 (30)	20	8 (40)
Total	329	141 (43)	342	71 (21)
Relative risk:	0.48 (95% CI 0.38 to 0.62)			
Traumatic orthopaedic surgery				
Bergqvist et al., 1979[22]	77	45 (58)	84	35 (42)
Galasko et al., 1976[53]	50	25 (50)	50	9 (18)
Gallus et al., 1973[54]	23	11 (48)	23	3 (13)
Lahnborg, 1980[56]	69	28 (41)	70	15 (21)
Morris & Mitchell, 1977[59]	24	16 (67)	24	12 (50)
Moskovitz et al., 1978[266]	32	19 (59)	35	8 (23)
Svend-Hansen et al., 1981[63]	65	28 (43)	65	15 (23)
Xabregas et al., 1978[64]	26	12 (46)	27	0
Total	366	184 (50)	378	97 (26)
Relative risk:	0.51 (95% CI 0.42 to 0.62)			

Table XVIII - Effect of warfarin versus low molecular weight heparin (LMWH) in the prevention of DVT diagnosed by surveillance with phlebography in patients having knee surgery.

	Warfarin		LMWH	
Authors	Number of patients	DVT (%)	Number of patients	DVT (%)
Heit et al., 1997[267]	222	85 (38)	232	63 (27)
Hamulyak et al., 1994[268]	61	23 (38)	65	16 (25)
Hull et al., 1993[269]	277	152 (55)	258	116 (45)
Leclerc et al., 1996 58/44	211	109 (52)	206	76 (37)
RDHAG 1994[270]	147	60 (41)	299	78 (26)
Spiro et al., 1994[271]	176	80 (45)	173	44 (25)
Overall	1094	509 (46.5)	1233	393 (32)

Dextran is only moderately effective in preventing DVT (Level I evidence) and has inherent risks such as fluid overload and anaphylactoid reactions. The latter can be minimised by hapten inhibition (Grade A recommendation).

Graduated elastic compression on its own after hip replacement is supported by limited data as to its efficacy,[31,32,297,320] but its use in orthopaedic surgery would be supported by data extrapolated from general surgery[286] (Grade C recommendation).

Intermittent pneumatic leg compression is effective (Table XV) (Level I evidence). In addition, there is data that combined foot impulse technology with GEC is effective in reducing the incidence of proximal DVT in patients having hip and knee surgery [255-257,260-262] (Table XVI). In contrast to pharmacological agents, mechanical methods are not associated with haemorrhagic complications.

Regional anaesthesia (spinal or epidural) reduces the frequency of DVT in patients having hip surgery, although its benefit is less than that of other methods and may not be additive in the presence of other techniques for prophylaxis.[321]

Although the combined use of LMWH and neuraxial anaesthesia (spinal or epidural) may be safe,[322,323] more recently an FDA advisory recommends caution when these two methods are used together because of a risk of spinal haematoma.[324]

Recommendations

Adjusted dose warfarin, LMWH, foot impulse technology and recombinant hirudin are Grade A recommendations.

Elective knee replacement

General considerations

There are fewer studies on prophylaxis after knee replacement than hip replacement. Data from hip replacement studies should not be extrapolated to knee replacement because of the different epidemiology and pathogenesis.

Low molecular weight heparin is more effective than either unfractionated heparin or adjusted dose warfarin.[325] Mechanical methods offer an alternative, particularly for those surgeons concerned about the risk of haemorrhagic complications within the thin soft tissue envelope of the knee. There are some data to support the use of IPC,[42,253] and Foot Impulse Technology (Table XVI).

Despite thromboprophylaxis, the absolute risk of DVT remains high. The safety, efficacy and cost effectiveness of other strategies needs to be documented further.

Recommendations

Low molecular weight heparin is a grade A recommendation, superior to warfarin and unfractionated heparin, although the residual DVT frequency remains high.[269] Further studies are required for mechanical methods.

Duration of prophylaxis in elective hip and knee replacement surgery

Since intra-operative risk factors are important, prophylaxis should be started before surgery.[327] Earlier papers reported the use of thromboprophylaxis for seven to fourteen days after surgery, which was the usual hospital

stay. However, hospital stays are now falling (often three to four days only, after knee or hip replacement) so that prophylaxis confined to the in-hospital phase may be inadequate. Furthermore, recent studies show that the risk of venographic DVT after hip replacement extends to at least four weeks after surgery,[269,313,314,326,328-333] and that this risk can be reduced by extending the use of LMWH beyond discharge. Further studies on risk-benefit and cost-benefit of extended prophylaxis are needed. The epidemiology after knee replacement is different and the risk period is much closer to the immediate post-operative phase.[158] The present evidence for recommending extended prophylaxis after knee replacement is weak.

Emergency orthopaedic surgery

General considerations – Trauma surgery

Trauma patients belong to a very heterogenous group. The risk of symptomatic thromboembolic events is largely unknown and so the need for thromboprophylaxis is uncertain. In patients with multiple injuries, the risk of venographic thrombosis is high (Table 1) and can be reduced with LMWH.[334] The risk of venographic thrombosis for patients in plaster casts can be reduced with LMWH,[335] although the clinical relevance and cost effectiveness of this strategy is not known.

Hip fracture surgery

The risks of DVT and PE are high in this group of (usually) elderly patients. There are few studies to guide us on the most effective and safe methods of prophylaxis. Fragile soft tissues and intercurrent pathology means that care should be taken with chemical prophylaxis. Low molecular weight heparin,[106] warfarin,[336] dextran,[278] danaparoid, [337] IPC (Table XV) and Foot Impulse Technology (Table XVI) may all confer some benefit. Overviews of unfractionated heparin (Table XVII, Collins et al.,[105]) and aspirin (Table X),[104] show a reduction in non-fatal and fatal PE.

In the recently published randomized, placebo-controlled study of patients undergoing surgery for hip fracture (13356 patients) and knee or hip replacement (4088 patients), aspirin in a dose of 160mg daily started pre-operativeley was the primary prophylaxis for 35 days. In the patients with hip fracture, aspirin reduced the rate of symptomatic DVT by 29% (95% CI 3-48, p=0.03) and PE by 43% (95% CI 18-60, p=0.002). Among elective arthroplasty patients the proportional reductions were similar. The fatal PE rate was also reduced , although the overall death rate was unchanged.[155]

Recommendations

There are too few comparative studies in this group to make secure recommendations; the studies that exist are consistent with those from hip replacement patients from whom recommendations could be reasonably extrapolated.

Gynaecological surgery

General considerations

Low risk patients: Turner et al.,[246] reported a Level I study that demonstrated a lower DVT rate with the use of GEC (0 versus 4%; $p<0.05$). On the basis of this study, the risk-benefit ratio, and extrapolation from data from moderate risk patients, graduated compression stockings may be used in addition to early ambulation and adequate hydration.

Moderate risk patients: Low dose unfractionated heparin (5000 units 12 hourly),[93,95] and LMWH,[338] have been demonstrated to be an effective prophylaxis in medium risk gynaecological surgery patients (Grade A recommendation based on Level I data). Intermittent pneumatic compression used continuously should also be considered since it is effective in higher risk patients,[90] (Grade A recommendation).

Adjusted dose warfarin is not recommended for routine prophylaxis but may have a role when low dose heparin is contraindicated, for example where there is a history of heparin-induced thrombocytopenia,[95] (Grade A recommendation).

By extrapolation from other types of surgery, antiplatelet therapy may be considered (Grade C recommendation).

Data relating to GEC in moderate risk gynaecological surgery is not sufficient at present to make a recommendation.[246] Any use of GEC is based on extrapolation from studies in general surgery.

High risk patients: Low dose heparin (5,000 units 8 hourly),[91] or IPC used continuously for at least 5 days,[90] provide effective prophylaxis (Grade A recommendation). When these two modalities were compared in a randomized trial their efficacy appeared to be equal, but there were more bleeding complications associated with the use of low dose heparin (Clarke-Pearson et al., 1993-311/339).

Prophylaxis with combined methods such as the addition of aspirin or GEC stockings to heparin and for extended periods need to be studied further. Data evaluating the combined use of LMWH and GEC stockings in high risk gynaecological surgery patients is insufficient.

Recommendations

Low risk patients: These may receive prophylaxis. Graduated elastic compression stockings used in addition to early ambulation and adequate hydration are Grade C recommendations.

Moderate risk patients: Low dose unfractionated heparin (5000 units 12 hourly), LMWH or IPC are Grade A recommendations. The addition of GEC based on extrapolation from studies in general surgery is a Grade C recommendation.

High risk patients: Low dose heparin (5,000 units 8 hourly) or IPC used continuously for at least five days are Grade A recommendations. The use of combined modalities should be considered in high risk patients with cancer (Grade C recommendation).

Pregnancy

General considerations

Low dose heparin prophylaxis is commonly used successfully in pregnant patients at high risk for DVT and PE such as those with previous thromboembolism and certain thrombophilias (antiphospholipid antibodies, protein C deficiency, protein S deficiency),[340-348] although data from controlled trials on its efficacy is lacking (Grade C recommendation). There is insufficient data on both the optimum timing and dosing schedules for low dose heparin prophylaxis.

Oral anticoagulants are contraindicated for prophylaxis of venous thromboembolism in the first trimester due to increased risk of embryopathies, and available data indicate that they are associated with increased fetal and maternal-fetal bleeding in the second and particularly the third trimester.[349,350] There is evidence that LMWH does not cross the placenta.[351-353]

The benefits of prophylaxis have not been demonstrated in patients undergoing Caesarian section who do not have additional risk factors. Peri-operative and postpartum prophylaxis should be considered if there are risk factors, particularly those of age over 35 years, and those with obesity, previous DVT or PE, or thrombophilia (Grade C recommendation).

Dextran should be avoided in pregnancy, as an anaphylactoid reaction may precipitate acute fetal distress.[354] Dextran should be withheld during Caesarian section until after delivery of the baby. There is insufficient data on the use of LMWHs or mechanical methods in pregnancy. There is an urgent need for a multicentre trial comparing standard heparin with LMWH in high risk pregnant patients to assess efficacy, safety and possible side effects such as osteoporosis.

Recommendations

Low dose heparin or LMWH prophylaxis should be used in pregnant patients at high risk because of a history of previous DVT or PE and certain thrombophilias. (Grade C recommendation). In the presence of contraindications to heparin, oral anticoagulants can be considered for prophylaxis in the second trimester because bleeding is uncommon at this stage (Grade C recommendation).

Women who develop thromboembolism during pregnancy should be treated with therapeutic levels of adjusted dose heparin which should be continued throughout pregnancy, labour and delivery. Higher doses are required in late pregnancy but the subcutaneous dose should be reduced in labour or before Caesarean section to reduce the risk of haemorrhage at delivery. Anticoagulation is usually continued for at least six weeks postpartum but the optimal duration of this therapy has not been established (Grade C recommendation).

Patients who develop thromboembolism during pregnancy or the puerperium should be referred for haematological screening. The management of thrombophilic conditions through pregnancy usually requires adjusted dose heparin with monitoring of the heparin effect (Grade C recommendation).

Additional considerations for surgical patients

In most randomized studies in surgical patients, prophylaxis with low dose heparin or LMWH was initiated before operation, but prophylaxis starting after operation was also effective in a small number of studies.[44,269,308] There are no studies comparing the two practices. There is an urgent need for a randomized study to compare the results of pre- and postoperative commencement of pharmacological prophylaxis.

Progestagens used for oral contraception,[355] and hormone replacemnet therapy also predispose to VTE.[356-358]

For women taking the oestrogen-containing contraceptive pills, prophylaxis should be considered if the pill is not stopped 4-6 weeks before surgery. Pills with a low ethinyl content (30 mg or less) and a progestagen of the third generation (gestodene, norgestimate or desogestrel) are still associated with coagulation changes,[359-361] and also predispose to thrombosis.[363-364] Stopping oral contraceptives must be weighed against the

chance of becoming pregnant. Heparin prophylaxis is advisable where oral contraceptives have not been discontinued and additional risk factors are present. For emergency surgery, thromboprophylaxis should be provided in women taking oral contraceptives (Grade C recommendation). Patients with an increased risk of bleeding either from a coagulation disorder or from specific surgical procedures should be considered for mechanical rather than pharmacological methods of prophylaxis.

Medical patients

General considerations

Compared with surgical patients, there are fewer randomized trials of DVT prophylaxis using objective diagnostic measures in hospitalised medical patients. However, the available data show that prophylaxis with low dose unfractionated heparin prevents about two thirds of cases of DVT (Table XIX) (Collins et al.,[365]). A number of randomized controlled studies of LMWH versus unfractionated low dose heparin have demonstrated that LMWH is at least as effective as low dose heparin given for a period of 10 days.[170,366-370]

All medical patients admitted to hospital should be assessed for risk of VTE and those at moderate or high risk should receive prophylaxis.

Recommendations - Acute myocardial infarction

Several trials have provided evidence that low-dose and high-dose unfractionated heparin can significantly prevent DVT in patients with acute myocardial infarction[54,96,97,99,371] (Grade A recommendation).

In patients with acute myocardial infarction who are at high risk for DVT but in whom anticoagulants are contraindicated due to overt or high risk of bleeding, the addition of GEC stockings and/or IPC to aspirin may be considered (Grade C recommendation based on extrapolation of data from trials in surgical patients.[286]

Recommendations - Acute stroke

In patients with ischemic stroke, low dose subcutaneous unfractionated heparin, LMWH or danaparoid, are effective in reducing the incidence of DVT,[16-19,372] (Grade A recommendation). However, it is essential to exclude intracranial haemorrhage, usually by early CT scanning, prior to instituting anticoagulant prophylaxis.

In patients with suspected or proven haemorrhagic stroke, and in those with ischemic stroke in whom the risks of prophylactic anticoagulant therapy are perceived to outweigh the benefits, GEC stockings and/or IPC can be recommended. This is a grade C recommendation based on extrapolation of data from trials in neurosurgical patients,[87] and surgical patients.[286]

Table XIX - Efficacy of low dose unfractionated subcutaneous heparin (LDH) or low molecular weight heparin (LMWH) in the prevention of DVT diagnosed by surveillance with objective methods (fibrinogen uptake test and/or phlebography) in acute medical patients.

Study and type of heparin	Number of patients	Incidence of DVT (%)		p
		Control	Heparin	
Belch et al., 1981[100] (heart failure/chest infection)				
LDH	100	26%	4%	<0.05
Cade, 1982[101] (critical care)				
LDH	119	29%	13%	<0.05
Dahan et al., 1986[14] (age over 65)				
LMWH	270	9%	3%	0.03
Gallus et al., 1973[54] (heart failure)				
LDH	26	45%	9%	<0.05
Emerson and Marks, 1977[96] (acute MI)				
LDH	78	34%	5%	<0.05
Handley, 1972[97] (acute MI)				
LDH	50	29%	23%	NS
Warlow et al., 1973[99] (acute MI)				
LDH	127	17%	3.2%	<0.025

Recommendations - Patients with malignant disease

In patients with metastatic breast cancer receiving chemotherapy, very-low-dose warfarin was found to be significantly effective and safe in reducing venous thromboembolic events.[373] Warfarin given as a fixed dose of 1 mg/d or single daily doses of LMWH respectively, were also effective and safe in preventing catheter-related thromboses in cancer patients with indwelling central venous catheters[167,168] (Grade A recommendation).

Recommendations for other general medical patients

These include patients with acute medical illnesses such as heart failure, chronic respiratory disease, or severe chest infection as well as critically ill patients.

Prophylactic low dose subcutaneous unfractionated heparin or high-dose LMWH prophylaxis are Grade A recommendations in these general medical patients with disease-related risk factors and/or additional patient related risk factors [54,100,101,164] (Grade A recommendation).

Two large randomized and double-blind controlled studies have provided strong evidence that chronic respiratory disease and congestive heart failure significantly increase predisposition to DVT. Single daily doses of high-dose LMWH have proven to be most effective for prophylaxis in these patients and is a Grade A recommendation.[164]

There are no reported trials of mechanical methods of prophylaxis such as GEC or IPC in medical patients. Although there is no reason to believe that such methods would be less effective than in surgical patients, further studies are needed before evidence based recommendations can be made.

While the risk of VTE increases with age, age of more than 65 years does not in itself constitute sufficient risk to merit routine prophylaxis in medical geriatric patients in the absence of other risk factors.[14]

Thrombophilia

Among asymptomatic patients with congenital thrombophilia, the value of primary prophylaxis is not yet known, but patients should be protected during surgery or in the presence of any medical condition associated with an increased risk of thrombosis. Pregnant women with congenital thrombophilia are at risk throughout pregnancy,[374] and should be considered for prophylaxis. The period of risk may begin early in the first trimester,[375-377] particularly in those with antithrombin deficiency.[375,378-380] In patients with acquired haematological abnormalities, the decision regarding prophylaxis should be made on an individual basis.

The oestrogen-containing oral contraceptive pill is contraindicated in women with thrombophilia since there is epidemiological evidence to suggest a relationship between estrogen containing oral contraceptives and VTE,[137,138,140,150,381] at least in the presence of antithrombin III or protein C deficiencies, or APC-resistance.[382,383] Pills with a low ethinyl content (30 mg or less) and a progestagen of the third generation (gestodene, norgestimate or desogestrel) are still associated with coagulation changes,[359-361] and also predispose to thrombosis.[362-364]

Progestagens used for oral contraception,[355] and hormone replacement therapy which predisposes to VTE[356-358] are also contraindicated in women with thrombophilia.

In symptomatic patients with thrombophilia, the optimal duration of anticoagulation is unknown. Ongoing trials are addressing this controversial issue.

Secondary prevention: methods and recommendations

General considerations

The objectives of treatment are to prevent death and disability from PE, pulmonary hypertension, and peripheral venous disease. Extension of a DVT and progressive swelling of the leg can result in increased compartmental pressure, possibly leading to phlegmasia cerulea dolens, venous gangrene, and limb loss. More common problems, however, are recurrence of VTE and the post-thrombotic syndrome due to dysfunction of the venous valves.[384]

Anticoagulants

In patients with DVT, initial therapy with oral anticoagulants alone is associated with an unacceptably high rate of recurrent VTE. Initial heparin and long term oral anticoagulation are both necessary[384,385] (Grade A recommendation). Ordinarily, anticoagulation should be started with LMWH. Alternatives include intravenous adjusted dose unfractionated heparin by continuous infusion or subcutaneous adjusted dose unfractionated heparin.[384]

The findings of randomized clinical trials have indicated that LMWHs given subcutaneously should replace continuous intravenous unfractionated heparin in treating DVT,[386-402] and PE.[402-405] Low molecular

weight heparins have a predictable dose response with a high absorption rate when given subcutaneously so that they may not require pharmacological measurement apart from the platelet count.[406] Some of them may be administered once a day.[407] These properties have made them the preferred method of treating uncomplicated patients with DVT at home.[397,398] Low molecular weight heparin may also be used for secondary prophylaxis as an alternative,[408] when oral anticoagulants are contraindicated.[396,409,410]

Low molecular weight heparin administration is based upon weight, only requiring blood test monitoring in patients with massive obesity or renal insufficiency. In these patients, the ideal weight-based dose is uncertain. However, a mid-interval anti-Xa level target of 0.5-1.0 Units/ml is usually considered therapeutic. With unfractionated heparin, it is mandatory to rapidly achieve an activated partial thromboplastin time (APTT) within the therapeutic range of 1.5 to 2.5 times the control in order to avoid an unacceptable rate of recurrent venous thrombosis,[384,411-414] (Grade B recommendation). There is a need to standardise the APTT assay. In patients treated with subcutaneous heparin it should be measured in the mid-interval between two injections.

Warfarin therapy should be adjusted to maintain the INR between 2.0 to 3.0 (Grade A recommendation). An INR greater than 3.0 is associated with an increased frequency of haemorrhagic complications.[384,415,416]

Oral anticoagulants may be started on the first day of heparin therapy, except when patients require thrombolysis, surgery, or have comorbidities that predispose to major bleeding.[417,418] Heparin should be administered for at least five days,[417,418] and should be discontinued when the patient's INR is stable within the therapeutic range of 2.0 to 3.0 for two days. Oral anticoagulants should generally be continued for about six months in patients with a first episode of VTE and no continuing risk factors.[419,420] Those with continuing risk factors may require more prolonged prophylaxis. The optimal duration for anticoagulation is under intense investigation.

Patients presenting with recurrent venous thrombosis should be treated with a more prolonged anticoagulation regimen compared with those having a first episode. Again, the optimal duration of oral anticoagulant therapy is not known.[384]

Adjusted doses of subcutaneous heparin may be used as secondary prophylaxis in special conditions such as pregnancy where oral anticoagulant therapy is contraindicated.[384,416]

When calf DVT is diagnosed by duplex scanning, with or without venography, it is recommended that patients should be treated with LMWH followed by warfarin for 6-12 weeks. Idiopathic calf DVT should be treated for a longer period.[123,421,422]

Immediate mobilisation with elastic compression of the legs leads to a faster reduction of pain and swelling than bed-rest.[423]

Thrombolytic therapy

General considerations

Thrombolytic therapy was initially approved for PE in 1977 but its adoption has been impeded by the small number and size of clinical trials, lack of effect on overall mortality and a relative high risk of bleeding complications. As a result, the standard treatment for PE has remained heparin anticoagulation. Nevertheless, the significant advantages for thrombolysis for treating VTE have led to further studies into its efficacy and safety.

Thrombolytic therapy, as an adjunct to anticoagulation, may reduce the rate of recurrent PE in a subset of patients.[424] Thrombolysis in patients with massive PE has now been shown to decrease mortality.[425] Right ventricular dilatation and hypokinesis on echocardiography, identifies patients at increased risk for recurrence in spite of adequate anticoagulation.[426] It had long been suspected that sudden easing of the haemodynamic burden on the right ventricle should decrease the relatively high mortality rate of massive PE, but previous studies with mortality as an endpoint had been lacking.

Thrombolysis acts as a "medical embolectomy". Rapid reduction of the haemodynamic insult by dissolving a pulmonary embolus reverses right heart failure. In the long-term, thrombolysis may help to improve pulmonary vascular reserve, more complete resolution of pulmonary emboli, prevent or attenuate pulmonary hypertension and improve functional and symptomatic clinical status.[427]

Haemorrhagic complications: newer regimens

Potential benefits from thrombolysis must be balanced against the risk of haemorrhage.[428] Contraindications such as intracranial disease, recent surgery or trauma preclude its use in some patients who can safely receive heparin alone. There is about a 1.6-3% risk of intracranial haemorrhage,[429] but careful screening should minimise the risk.[430]. In ICOPER the intracranial haemorrhage was 3% [431] The risk of haemorrhage increases with prolonged infusions of thrombolytic agents. Consequently,

investigators have studied the efficacy and safety of shorter duration therapy with higher concentrations of thrombolytic agents and shown that the efficacy is similar to that for the older, longer duration studies, with significantly less haemorrhagic complications.[432]

Thrombolysis of deep vein thrombosis

Thrombolysis of DVT may reduce the rates of recurrent DVT and the post-thrombotic syndrome. In three randomized trials of systemically administered streptokinase, long-term venous valvular function was better preserved than with heparin alone.[433,435] In a pooled analysis of 13 randomized studies, only 4% of patients treated with heparin had substantial or complete lysis, compared with 45% of patients receiving systemic streptokinase.[436] In an overview of data from six trials, systemic thrombolysis was 3.7 times more effective in producing some degree of lysis than was heparin.[437] However, prolonged streptokinase infusions are often unsatisfactory because of frequent allergic reactions and a haemorrhagic rate three-fold higher than that of patients managed with heparin anticoagulation alone.[437] In addition, the frequency of satisfactory lysis is not high enough to generate enthusiasm for systemic thrombolysis.

Catheter-directed thrombolysis for deep vein thrombosis

In 1994, a new catheter-directed technique using urokinase (no longer available) for proximal DVT achieved complete lysis in 72% of patients with concomitant abatement of symptoms.[438] Delivery of the thrombolytic agent within a clot achieves a high concentration of the agent that had not been possible with systemic administration. Because of simultaneous exposure of large segments of thrombus to high concentrations of the thrombolytic agent, thrombolysis can be enhanced, the duration of treatment shortened, the total amount of thrombolytic agent administered lessened and the complications associated with the longer systemic thrombolysis reduced. Once thrombi are lysed, underlying lesions such as stenosis can be managed by angioplasty with or without stenting.[438,439]

Recommendations

Catheter-directed thrombolysis should be considered for proximal DVT, especially iliofemoral thrombosis, where the risk of PE and the post-thrombotic syndrome is higher than for a more distal DVT, (Grade C recommendation). Systemic thrombolysis should be avoided because it is significantly less effective, and because the longer duration of therapeutic infusion required, increases the risk of haemorrhagic complications. For patients with PE, peripherally administered intravenous thrombolysis is approved and should be used in patients with massive PE with hypotension. A short, high concentration thrombolytic regimen should be considered in PE patients with haemodynamic impairment as demonstrated by moderate or severe right ventricular enlargement and/or hypokinesis on echocardiography, even in the absence of systemic arterial hypotension.[440]

Surgical thrombectomy

Thrombectomy, preferably with a temporary arteriovenous fistula, can occasionally be considered in patients with acute severe iliofemoral DVT.[441,442] Long-term follow-up shows significant patency of the iliac vein compared with that achieved with anticoagulation alone.[443-446] Preservation of valves with normal calf-muscle pump function is important in preventing the post-thrombotic syndrome. Early results showed significant patency and competency in thrombectomised patients.[447] Late results showed that this improvement of venous function was maintained.[444-446]

Catheter-based mechanical procedures

For acute massive DVT, percutaneous mechanical thrombectomy is now frequently used to dissolve, fragment and aspirate clot.[448] This new procedure is best suited for fresh thrombi less than 10-14 days old. Its efficacy in older thromboemboli is less predictable. Data concerning the short and long-term effects of catheter-based intervention on the vessel wall, venous valves, and pulmonary vasculature are lacking and are required before its role can be precisely definined. Its use in combination with thrombolysis may shorten the procedure and improve efficacy and safety.[449]

Inferior vena cava filters

A filter device should be inserted in the inferior vena cava of patients with proximal DVT (above the knee) when anticoagulation is contraindicated or when adequate anticoagulation fails to prevent PE.[384,450,451] For thrombosis extending to or involving the renal veins, only a proven device should be placed above the level of the renal veins.[452,453].

In recent years, increasing numbers of inferior vena cava filters have been inserted for prophylactic measures in patients at high risk of developing thromboembolic complications, predominantly after trauma.[454] A high frequency of thrombotic complications occurs with filter

placement, including insertion site thrombosis in as many as 25% and early inferior vena cava thrombosis in 12%.[454] Many of these thromboses are asymptomatic and their clinical significance is uncertain.

There have been conflicting reports regarding the rate of recurrent DVT in patients with inferior vena cava filters.[455,456] In a recent review of 1191 filter patients over a mean of nine years, recurrent DVT was seen in 12% of Greenfield filter patients receiving anticoagulants versus 15% of those who were not ($p>0.05$).[457] Anticoagulation did not affect the rate of recurrent DVT, but is recommended in order to reduce thrombus progression and subsequent late complications of DVT (Grade C recommendation).

Heparin induced thrombocytopenia

Heparin-induced thrombocytopenia (HIT) is a relatively common adverse effect of exposure to heparin that causes platelet activation and thrombosis.[458-460] Reduction of platelets to less than 100,000/ml occurs in approximately 2-3% of individuals exposed to heparin for prophylaxis or treatment of thrombosis or from exogenous sources such as a catheter flush.[460-462] There may be a lower risk of developing antibodies to LMWH than to unfractionated heparin.[460] Most patients are asymptomatic at the time low platelet counts are documented. Bleeding has been reported only rarely. Progression to overt thrombosis is the most serious complication occurring in approximately 0.5-1% of heparin-treated patients.[460,461,463,464] Thrombosis can occur anywhere throughout the venous and arterial circulation.[462]

Heparin-induced thrombocytopenia should be suspected on the basis of platelet counts less than 100,000/ml on two consecutive days or a 50% decrease from baseline in the absence of other aetiologies.[458,459,461,462,465] Laboratory assays of heparin-dependent antibodies may confirm the diagnosis, but negative assays cannot exclude the diagnosis.[440,465-467]

Awareness of the potential for heparin-induced thrombocytopenia, with frequent performance of platelet counts, is the most important preventive approach.[461] Heparin must be discontinued in patients with a suspicion or confirmation of heparin-induced thrombocytopenia.[461,462,468] Prophylactic heparin may be substituted with argatroban, danaparoid, oral anticoagulants or mechanical methods of prophylaxis.[462,468-471] Oral anticoagulants are best administered in sub-therapeutic doses (INR less than 3.0) initially, beginning only after platelet counts are on the rise.[471] Established HIT associated thrombosis can be treated with argatroban or hirudin prophylaxis.[469] Oral anticoagulants should be given with overlapping of an immediate acting anticoagulant, such as danaparoid, argatroban or hirudin.[468,470,472-477] For patients with a history of HIT requiring cardiac surgery or other intervention, it is recommended to reduce the antibody titer, perform the procedure under heparin anticoagulation when the patient is test negative for heparin antibody and use post-procedure thromboembolic prophylaxis with argatroban, hirudin or danaparoid.[478,479] In pregnancy, danaparoid should be considered during the first trimester followed by oral anticoagulants in the second and third trimesters; intravenous gammaglobulin can be used as adjunctive treatment for rapid blockade of the platelet activation process by the heparin antibody.[468,470,480]

Selective thrombolytic therapy and surgical removal of thrombus have been used in patients with extensive DVT and/or PE.[462] Plasmapheresis has resulted in an improved clinical outcome in severely affected patients.[481]

Cost-effectiveness

A number of studies have reported on the cost-effectiveness for commonly used approaches to prevent VTE.[474-477,480,482,483] In medium and high-risk patients, the cost of screening, diagnosis and treatment of VTE are so high that the currently used recommended methods of prophylaxis are cost-effective (i.e. in optimising the use of available resources). In low-risk patients, no data is available concerning the cost-effectiveness of currently used prophylactic methods.

Although the cost of LMWH is greater than unfractionated heparin, the overall cost for treating DVT or PE is less as there is no need for pharmacological monitoring (apart from platelet counts), a shorter period in hospital is required, and the complication rates are decreased.[484,485]

Key questions to be answered

The statements and recommendations made in this document are based on a review of the literature using clearly defined levels of evidence. Throughout the text the level of evidence has been stated. This process has revealed a number of key questions which require to be addressed by future studies. They are summarised as follows:

Patient populations

Patient populations at minimal risk and not requiring prophylaxis should be identified.

Patient populations at increased risk outside the hospital (i.e. travellers' thrombosis) should be identified.

The natural history of isolated proximal thrombosis after hip replacement needs further study.

A prospective audit is needed by major orthopaedic centres. Such an audit should carefully record the method of prophylaxis used in each patient. Patients should be followed up for at least three months and a high proportion of those who die should be subjected to post-mortem examination. Only then can the overall mortality and incidence of fatal PE in relation to prophylactic practice be determined.

There is a need to determine the frequency of the post- thrombotic syndrome after hip surgery.

The risk of DVT in the new minimally invasive abdominal surgical procedures needs to be established.

Treatment regimes

The effectiveness and safety of thrombolytic therapy in patients with PE and right ventricular dysfunction requires confirmation by Grade A randomized trials.

A randomized study comparing thrombectomy with catheter directed thrombolysis is required.

The cost benefit of prophylaxis continued beyond hospitalisation deserves investigation.

The hypothesis that LMWH twice daily subcutaneously is necessary if commenced postoperatively instead of the same dose once daily requires further investigations by randomized controlled trials for each individual agent separately.

A direct comparison of fixed low dose heparin with alternative strategies with respect to total mortality and confirmed fatal PE is urgently needed in moderate risk patients. Such a study would need around 20,000 patients to demonstrate a reduction of fatal PE from 1% to 0.5%.

Further cost-effectiveness studies of LMWH prophylaxis versus strategies other than unfractionated heparin such as foot impulse technology are required.

Pharmacological prophylaxis

More studies comparing the efficacy and safety of different LMWH compounds and doses are required for both prevention and treatment of DVT.

Cost-effectiveness studies of various preparations of LMWHs used for prophylaxis versus unfractionated heparin are necessary.

The role of long-term LMWH versus oral anticoagulants in the treatment of DVT should be determined by randomized trials.

Comparisons of combinations such as heparin and aspirin with heparin rather than comparisons of single modalities with each other are needed.

A multicentre trial comparing standard heparin with LMWH in high risk pregnant patients assessing efficacy, safety and side effects such as osteoporosis and thrombocytopenia is needed.

Combined regimens

The possible differences in efficacy of mechanical devices of different design need to be determined such as thigh length versus knee length stockings and pneumatic sleeves, and sequential gradient versus uniform pressure sleeves and fixed cycle versus automatic cycle adjusting devises.

Further studies to assess the additive effects on the efficacy and safety of heparin or LMWH and mechanical technology in high and medium risk patients are needed.

Other

There is an important discrepancy between incidence and prevalence in studies of thromboprophylaxis which rely on a single assessment such as venography. The natural history of thrombi is likely to be influenced by different types of prophylaxis so that the incidence of DVT at the time of a single assessment may skew the impression of efficacy or otherwise. The possible improved accuracy of ultrasonography with colour flow imaging for the diagnosis of asymptomatic venous thrombosis needs to be documented so that this repeatable modality can be confidently employed to determine the true prevalence of DVT regardless of the influence of a particular prophylactic regimen on its natural history.

Many orthopaedic surgeons are concerned about the relationship between anticoagulant-induced haemorrhage and implant infection. Such an association needs to be scientifically investigated.

The problem of stasis (a very prominent but very much neglected risk factor) being promoted by conventional bed rest versus compression and mobilisation should be addressed.

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