PREVENTION AND TREATMENT OF VENOUS THROMBOEMBOLISM

International Consensus Statement 2013
Guidelines According to Scientific Evidence

Developed under the auspices of the:

Cardiovascular Disease Educational and Research Trust (UK)
European Venous Forum
North American Thrombosis Forum
International Union of Angiology and
Union Internationale du Phlebologie

General, Vascular, Bariatric and Plastic Surgical Patients

Chapter 3

The Risk of VTE in General and Vascular Surgical Patients

- **Patients who undergo general and vascular surgical procedures are at risk of developing VTE.[1-6]**
- **In the absence of prophylaxis, the risk of silent DVT:**
  - 25% (95% CI 24% to 26%) in general surgery
  - 19% (95% CI 15% to 25%) in abdominal vascular surgery
  - 15% (95% CI 9% to 23%) in peripheral vascular reconstruction

1. Bergentz SE. World J Surg. 1978; 2:19-25.
2. Colditz GA, et al. Lancet. 1986; 2:143-6.
3. Clagett GP, et al. Ann Surg. 1988; 208:227-40.
4. Collins R, et al. N Engl J Med. 1988; 318:1162-73.
5. Gallus AS. Baillieres Clin Haematol. 1990; 3:651-84.
6. Bergqvist D, et al. In: Bergqvist D, Comerota A, Nicolaides A, et al., eds. Prevention of venous thromboembolism. London: Med-Orion Publ Comp; 1994:3-15.

Frequency of DVT in General and Vascular Surgery in Absence of Prophylaxis

Patient Groups	Number of Studies	Patients (N)	DVT Incidence (weighted mean)	95% CI
General Surgery				
Clagett & Reisch, 1988[1]				
Total	**54**	**4310**	**1084 (255)**	**24% to 26%**
General Surgery (Asian studies with FUT)				
Cunningham et al, 1974[2]		68	8	
Nandi et al, 1980[3]		150	4	
Shead et al, 1980[4]		50	14	
Inada et al, 1983[5]		256	39	
Phornphibulaya et al, 1984[6]		74	9	
Total	**4**	**598**	**74 (12.4%)**	**10% to 15%**

* Diagnosed by surveillance with objective methods: Phlebography, FUT or DUS

1. Clagett GP, et al. Ann Surg. 1988; 208:227-40.
2. Cunningham IG, et al. Br J Surg. 1974; 61:482-3.
3. Nandi P, et al. Br J Surg. 1980; 67:251-3.
4. Shead GV, et al. Br J Surg. 1980; 67:813-4.
5. Inada K, et al. Am J Surg. 1983; 145:775-9.
6. Phornphibulaya P, et al. J Med Assoc Thai. 1984; 67:377-81.

Frequency of DVT in General and Vascular Surgery in Absence of Prophylaxis

Patient Groups	Number of Studies	Patients (N)	DVT Incidence (weighted mean)	95% CI
Abdominal Vascular Surgery				
Hartsuck & Greenfield,1973[1]		26	7	
Angelides et al, 1977[2]		88	18	
Belch et al, 1980[3]		25	6	
Olin et al, 1993[4]		50	9	
Killewich et al, 1997[5]		48	1	
Hollyoak et al, 2001[6]		21	9	
Total	**6**	**258**	**50 (19%)**	**15% to 25%**

* Diagnosed by surveillance with objective methods: Phlebography, FUT or DUS

1. Hartsuck JM, et al. Arch Surg. 1973; 107:733-9.
2. Angelides NS, et al. Br J Surg. 1977; 64:517-8.
3. Belch JJ, et al. Thromb Haemost. 1980; 42:1429-33.
4. Olin JW, et al. J Vasc Surg. 1993; 18:1037-41.
5. Killewich LA, et al Arch Surg. 1997; 132:499-504.
6. Hollyoak M, et al. J Vasc Surg. 2001; 34:656-60.

Frequency of DVT in General and Vascular Surgery in Absence of Prophylaxis

Patient Groups	Number of Studies	Patients (N)	DVT Incidence (weighted mean)	95% CI
Peripheral Vascular Reconstruction				
Hamer et al, 1972[1]		21	9	
Passman et al, 2000[2]		53	1	
Hollyoak et al, 2001[3]		28	5	
Total	**3**	**102**	**15 (15%)**	**9% to 23%**

* Diagnosed by surveillance with objective methods: Phlebography, FUT or DUS

1. Hamer JD. Br J Surg. 1972; 59:979-82.
2. Passman MA, et al. J Vasc Surg. 2000; 32:669-75.
3. Hollyoak M, et al. J Vasc Surg. 2001; 34:656-60.

Risk of DVT in General and Vascular Surgery in Absence of Prophylaxis

- **Meta-analysis of 32 studies involving 5,091 general surgical patients without prophylaxis, the frequency of clinical PE was 1.6% (95% CI 1.3% to 2.0%) and fatal PE 0.8% (95% CI 0.62% to 1.1%)[1]**
- **Contrary to the belief that postoperative DVT is rare in Asians, recent studies have demonstrated risk**
  - DVT incidence was 12.4% (95% CI 10% to 15%) in Asians using the fibrinogen uptake test in five studies[2-6]
  - Meta-analysis (4 studies) showed the adjusted incidence of PE and fatal PE was 1.0% (95% CI 0.0 to 2.0) and 0.4% (95% CI 0.0% to 1.0%) respectively[7]
  - Multi-centre study in Japan using venography demonstrated without prophylaxis, the incidence of postoperative DVT was similar to Caucasians (24%)[8]

1. Clagett GP, et al. Ann Surg. 1988; 208:227-40.
2. Nandi P, et al. Br J Surg. 1980; 67:251-3.
3. Shead GV, et al. Br J Surg. 1980; 67:813-4.
4. Inada K, et al. Am J Surg. 1983; 145:775-9.
5. Phornphibulaya P, et al. J Med Assoc Thai. 1984; 67:377-81.
6. Cunningham IG, et al. Br J Surg. 1974; 61:482-3.
7. Leizorovicz A, et al. Int J Angiol 2004; 13:101-8.
8. Sakon M, et al. J Thromb Haemost. 2006; 4:581-6.

Risk of DVT in General and Vascular Surgery Patients[1-5]

- **Risk of DVT is increased by age, obesity, malignancy, history of VTE, and hereditary or acquired thrombophilia**
- **Affected by the nature and duration of the operation, type of anaesthesia, immobility, dehydration, sepsis, varicose veins, hormone therapy and pregnancy**

1. Kakkar VV, et al. Am J Surg. 1970; 120:527-30.
2. Clayton JK, et al. Br Med J. 1976; 2:910-2.
3. Havig O. Acta Chir Scand Suppl. 1977; 478:1-120.
4. Lowe GD, et al. Lancet. 1982; 1:1474.
5. Sue-Ling HM, et al. Lancet. 1986; 1:1173-6

Risk Stratification of Patients

- **Known clinical risk factors allow for classification of patients into high, moderate and low risk of developing VTE**

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%

The definition of risk categories in general surgical patients using FUT and in hospital pulmonary embolism (modified from Salzman EW, Hirsh J. Prevention of venous thromboembolism. In: Colman RW, Hirsh J, Marder VJ, et al., eds. *Hemostasis and thrombosis, basic principles and clinical practice.* New York: Lippincott; 1982:986). Although based on old studies the percentages shown in this table are still used to define the category of risk.

Risk Categories According to Clinical Risk Factors in General Surgical Patients

- **High Risk**
  - Major General Surgery, age >60
  - Major General Surgery, age 40-60 & cancer or history of DVT/PE or other risk factors including thrombophilia
- **Moderate Risk**
  - 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 other risk factors
- **Low Risk**
  - Major General Surgery, age <40; No other risk factors*
  - Minor surgery, age 40-60; No other risk factors*

* 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.

Alternative Method of DVT Risk Stratification of Patients

- **Another approach is to use a scoring system based on weighting risk factors according to their tendency to be associated with a thrombotic event[1-5]**
  - Studies in nearly 10,000 patients demonstrate a linear association between the risk score and development of symptomatic thrombosis up to 60 days after operation
  - Scores > 8 were associated with 6.5% incidence of clinical events at 30 days and 11.3% incidence at 60 days

1. Hatef DA, et al. Plast Reconstr Surg. 2008; 122:269-79.
2. Bahl V, et al.. Ann Surg. 2010; 251:344-50.
3. Seruya M, et al. Plast Reconstr Surg. 2008; 122:1701-8.
4. Passman MA, et al. J Vasc Surg. 2011; 54:2S-9S.
5. Pannucci CJ, et al. J Am Coll Surg. 2011; 212:105-12.

Risk of DVT Continues Post-Discharge

- **Studies in abdominal or pelvic surgery patients demonstrate the DVT risk continues after discharge from hospital[1-3]**
- **Has implications for duration of thromboprophylaxis**
  - Patients having operations for cancer have been shown to benefit from 30 days of LMWH (for evidence, see section on cancer).

1. Scurr JH, et al. BMJ. 1988; 297:28.
2. Huber O, et al. Arch Surg. 1992; 127:310-3.
3. Arcelus JI, et al. Semin Thromb Hemost. 1993; 19 Suppl 1:142-6.

Risk of VTE in Laparoscopic Surgery Patients

- **Risk of DVT following laparoscopic surgery is low**
- **Two small prospective studies with no prophylaxis demonstrated an incidence of DVT detected by duplex ultrasound or venography of ~0-2%.[1,2]**
- **Large series from surveys,[3-5] registries,[6-9] literature review,[10] and a population study [11] indicate that the risk for clinical post-operative VTE after laparoscopic procedures is less than 1%.**
- **Prospective studies with some form of prophylaxis was used confirmed the low incidence[12-16]**
  - There was one exception in which 11/20 patients developed DVT[17]

1. Bounameaux H, et al. Thromb Res. 1997; 86:271-3.
2. Wazz G, et al. JSLS. 2000; 4:291-5.
3. Bradbury AW, et al. Br J Surg. 1997; 84:962-4.
4. Blake AM, et al. JSLS. 2001; 5:215-9.
5. Filtenborg Tvedskov T, et al. Br J Surg. 2001; 88:1413-6.
6. Catheline JM, et al. Surg Laparosc Endosc Percutan Tech. 1999; 9:135-9.
7. Chamberlain G. Br Med J. 1978; 2:563.
8. Hjelmqvist B. Eur J Surg Suppl. 2000; 18-21.
9. Scott TR, et al. Surg Laparosc Endosc. 1992; 2:191-8.
10. Lindberg F, et al. Surg Laparosc Endosc. 1997; 7:324-31.
11. White RH, et al. Thromb Haemost. 2003; 90:446-55.
12. Caprini JA, et al. Surg Endosc. 1995; 9:304-9.
13. Baca I, et al. Chirurg. 1997; 68:1275-80.
14. Healey MG, et al. Med J Aust. 1998; 168:524.
15. Lord RV, et al. Arch Surg. 1998; 133:967-73.
16. Mall JW, et al. Br J Surg. 2001; 88:99-100.
17. Patel MI, et al. Med J Aust. 1996; 164:652-4, 6.

Risk of VTE Following Bariatric Surgery

- **Obesity is an independent risk factor for sudden post-operative fatal PE[1,2]**
- **Bariatric surgery is associated with clinical DVT in 1.2% to 1.6% of cases and with PE in 0.8% to 3.2% depending on the objective method used for the diagnosis[3-9]**
- **Risk factors in patients having bariatric surgery include:**
  - BMI > 55, venous stasis syndrome, past history of VTE, obesity hypoventilation syndrome, pulmonary hypertension, cardiomyopathy and obstructive sleep apnea[10]

1. Blaszyk H, et al. Virchows Arch. 1999; 434:529-32.
2. Blaszyk H, et al. Arch Surg. 2000; 135:1410-3.
3. Maggard MA, et al. Ann Intern Med. 2005; 142:547-59.
4. Bajardi G, et al. Minerva Chir. 1993; 48:539-42.
5. Westling A, et al. World J Surg. 2002; 26:470-3.
6. Printen KJ, et al. Surg Gynecol Obstet. 1978; 147:63-4.
7. Podnos YD, et al. Arch Surg. 2003; 138:957-61.
8. Eriksson S, et al. Obes Surg. 1997; 7:332-5; discussion 6.
9. Gonzalez R, et al. Surg Obes Relat Dis. 2006; 2:30-5; discussion 5-6.
10. Carmody BJ, et al. J Am Coll Surg. 2006; 203:831-7.

Risk of VTE Following Plastic Surgery

- **Reported incidence of VTE in patients undergoing plastic surgery[1]**
  - 0.3% for abdominoplasty
  - 0.8% for abdominoplasty and concomitant plastic surgery
  - 2.2% for abdominoplasty combined with intra-abdominal surgery
  - 3.4% for circumferential abdominoplasty
- **In a survey involving 10,000 abdominoplasties without prophylaxis, the incidence of symptomatic PE was 1%[2]**
- **In a large plastic surgery cohort, the 60 day clinically relevant VTE incidence was related to the Caprini score**
  - patients with a score of 5-6 had a 1.3% rate, a score of 7-8 had a 2.7% rate and a score of > 8 had an 11.3% rate by 60 days

1. Hatef DA, et al. Plast Reconstr Surg. 2010; 125:352-62.
2. Grazer FM, et al. Plast Reconstr Surg. 1977; 59:513-7.

General Considerations of Therapy
Low Dose Unfractionated Heparin

- **In the 1970s, LDUH (5,000 IU every 8 or 12 h subcutaneously) reduced the incidence of both DVT and fatal PE[1-3]**
  - The International Multi-centre Trial that included 4,121 patients randomised to LDUH or no prophylaxis, reported a reduction in fibrinogen uptake test detected DVT, clinical DVT, clinical PE, and fatal PE.[2,3]
- **Two meta-analyses comparing LDUH with no prophylaxis showed the incidence of asymptomatic DVT was reduced from 22% to 9% (RR 0.41; 95% CI 0.35 to 0.47) and fatal PE from 0.8% to 0.3% (RR 0.39; 95% CI 0.17 to 0.87)[4,5]**
  - The price was a small increase in bleeding complications from 3.8% to 5.9% (RR 1.56; 95% CI 1.21 to 1.99)

1. Sandler DA, et al. J R Soc Med. 1989; 82:203-5.
2. Kakkar VV, et al. Lancet. 1977; 1:567-9.
3. Anon. Lancet. 1975; 2:45-51.
4. Clagett GP, et al. Ann Surg. 1988; 208:227-40.
5. Collins R, et al. N Engl J Med. 1988; 318:1162-73.

General Considerations of Therapy
Low-Molecular-Weight Heparin (LMWH)

- **A multi-center study found that LMWH reduced the incidence of fatal PE and the overall surgical mortality as compared with controls without prophylaxis[1]**
- **Two smaller randomized placebo-controlled trials in patients having major oncological abdominal surgery[2] and emergency abdominal surgery[3] demonstrated LMWH reduced the rate of asymptomatic DVT**

1. Pezzuoli G, et al. Int Surg. 1989; 74:205-10.
2. Marassi A, et al. Int Surg. 1993; 78:166-70.
3. Bergqvist D, et al. Vasa. 1996; 25:156-60.

General Considerations of Therapy
Low-Molecular-Weight Heparin (LMWH)

- **16 studies[1-16] and 9 meta-analyses[17-25] compared LMWH with LDUH**
  - Six studies compared different doses of LDUH or LMWH[7, 26-30]
  - Four of the meta-analyses reported that there was no difference in total mortality comparing LMWH with LDUH[18, 20-22]
  - Two meta-analyses reported a reduced incidence of symptomatic PE with LMWH from 0.70% to 0.31% (RR 0.43; 95% CI 0.33 to 0.54)[18,20] and one showed a decrease in symptomatic VTE[22]
- **The overall conclusion was LMWH was more effective than LDUH in reducing PE and could be administered once daily versus the 2-3 times daily for LDUH**

1. Kakkar VV, et al. World J Surg. 1997; 21:2-8; discussion-9.
2. ENOXACAN investigators. Br J Surg. 1997; 84:1099-103.
3. Creperio G, et al. Minerva Chir. 1990; 45:1101-6.
4. Garcea D, et al. Curr Med Res Opin. 1992; 12:572-83.
5. Gazzaniga GM, et al. Int Surg. 1993; 78:271-5.
6. Haas S. Semin Thromb Hemost. 1999; 25 Suppl 3:101-5.
7. Hartl P, et al. Thromb Res. 1990; 57:577-84.
8. Hoffmann R, et al. Langenbecks Arch Chir. 1992; 377:258-61.
9. Kakkar VV, et al. Lancet. 1993; 341:259-65.
10. Koppenhagen K, et al. Langenbecks Arch Chir Suppl II Verh Dtsch Ges Chir. 1990; 1163-6.
11. Koppenhagen K, et al. Thromb Haemost. 1992; 67:627-30.
12. McLeod RS, et al. Ann Surg. 2001; 233:438-44.
13. Moreno Gonzalez E, et al. Hepatogastroenterology. 1996; 43:744-7.
14. Nurmohamed MT, et al. Am J Surg. 1995; 169:567-71.
15. Wolf H, et al. Semin Thromb Hemost. 1991; 17:343-6.
16. Leizorovicz A, et al. Br J Surg. 1991; 78:412-6.
17. Breddin HK. Semin Thromb Hemost. 1999; 25 Suppl 3:83-9.
18. Jorgensen LN, et al. Br J Surg. 1993; 80:689-704.
19. Koch A, et al. Thromb Res. 2001; 102:295-309.
20. Koch A, et al. Br J Surg. 1997; 84:750-9.
21. Leizorovicz A, et al. Bmj. 1992; 305:913-20.
22. Mismetti P, et al. Br J Surg. 2001; 88:913-30.
23. Nurmohamed MT, et al. Lancet. 1992; 340:152-6.
24. Palmer AJ, et al. Haemostasis. 1997; 27:65-74.
25. Wille-Jorgensen P, et al Cochrane Data Syst Rev. 2003.
26. Bounameaux H, et al. Arch Surg. 1993; 128:326-8.
27. Bergqvist D, et al. Br J Surg. 1995; 82:496-501.
28. Bjerkeset O, et al. World J Surg. 1997; 21:584-8; discussion 8-9.
29. Egger B, et al. Dig Surg. 2000; 17:602-9.
30. Lausen I, et al. Eur J Surg. 1998; 164:657-63.

General Considerations of Therapy
Low-Molecular-Weight Heparin (LMWH)

- **Additional considerations**
  - LMWHs have a lower risk of heparin-induced thrombocytopenia (HIT) than LDUH[1,2]
  - High dose LMWH is more effective but is associated with a higher incidence of hemorrhagic complications than LDUH, whereas a low dose of LMWH has a similar efficacy with less bleeding[3]
  - Regulatory bodies in Europe and North America now consider the various LMWHs to be distinct drug products. They require clinical validation for specific indications for each drug. Therapeutic interchange among these products is not appropriate[4]

1. Warkentin TE, et al. Arch Intern Med. 2003; 163:2518-24.
2. Warkentin TE, et al. N Engl J Med. 1995; 332:1330-5.
3. Koch A, et al. Br J Surg. 1997; 84:750-9.
4. Kalodiki E, et al. Clin Appl Thromb Hemost. 2009; 15:8-11

General Considerations of Therapy
Fondaparinux

- **In a double-blind double-dummy randomized study (2,927 patients) in high risk major abdominal surgery, fondaparinux 2.5 mg once daily was found to be at least as effective as peri-operative dalteparin 5000U daily in preventing venographically detected DVT[1]**
  - Incidence of DVT was 6.1% in the dalteparin group and 4.6% in the fondaparinux group (P=0.14)
  - In the subgroup of 1,941 patients with cancer, the incidence of DVT was reduced from 7.7% in the dalteparin group to 4.7% in the fondaparinux group (RR 0.74; 95% CI 0.40 to 0.93) (P = 0.02).
  - No difference in major bleeding (2.4% vs 2.8%) provided fondaparinux was administered at least six hours after operation

1. Agnelli G, et al. Br J Surg. 2005; 92:1212-20.

General Considerations of Therapy
Antiplatelet Agents

- **Antiplatelet agents including high-dose aspirin (500-1500 mg/day) reduce DVT by 30% and PE by 50%**
  - In a meta-analysis of 22 RCTs[1] of 1,459 general surgical patients where DVT was diagnosed by surveillance with FUT, the incidence of DVT was reduced from 27% in the control group to 19% in the antiplatelet therapy group (RR 0.71; 95% CI 0.62 to 0.82).
  - In the same meta-analysis data on PE were available in 26 RCTs of 3,419 patients. The incidence of PE was reduced from 1.7% in the control group to 0.5% in the antiplatelet group (RR 0.28; 95% CI 0.16 to 0.48)
- **In view of the availability of more effective methods of prophylaxis and the hazards of high-dose aspirin, aspirin is not considered as an alternative prophylaxis**

1. Collins R, et al. BMJ. 1994; 309:1215-7.

General Considerations of Therapy
Graduated Elastic Compression

- **Graduated elastic compression (GEC) stockings reduce the incidence of asymptomatic DVT by approximately 50-60%[1-8] and three systematic reviews[9-11]**
  - However, the number of patients studied has been too small to be able to assess the effects on the development of PE
- **A Cochrane systematic review demonstrated that in four studies with 530 patients, the incidence of DVT was reduced from 35.6% in the control group to 15.9% in the compression group[12]**
- **In another five studies involving 848 patients, elastic compression added to a background of additional antithrombotics reduced the incidence of DVT from 10.5% in the control group to 1.9% in the compression group**

1. Inada K, et al. Am J Surg. 1983; 145:775-9.
2. Tsapogas MJ, et al. *Arch Surg.* 1971; 103:561-7.
3. Holford CP. B*r Med J.* 1976; 2:969-70.
4. Scurr JH, Iet al. *Br J Surg.* 1977; 64:371-3.
5. Borow M, et al. *Am J Surg.* 1981; 141:245-51.
6. Allan A, et al. *Br J Surg.* 1983; 70:172-4.
7. Turner GM, et al. *Br J Obstet Gynaecol.* 1984; 91:588-91.
8. Turpie AG, et al. *Arch Intern Med.* 1989; 149:679-81.
9. Wells PS, et al. *Arch Intern Med.* 1994; 154:67-72.
10. Agu O, et al. *Br J Surg.* 1999; 86:992-1004.
11. Amaragiri SV, et al. *Cochrane Database Syst Rev.* 2000; CD001484.
12. Sachdeva A, et al. *Cochrane Database Syst Rev.* 2010; CD001484.

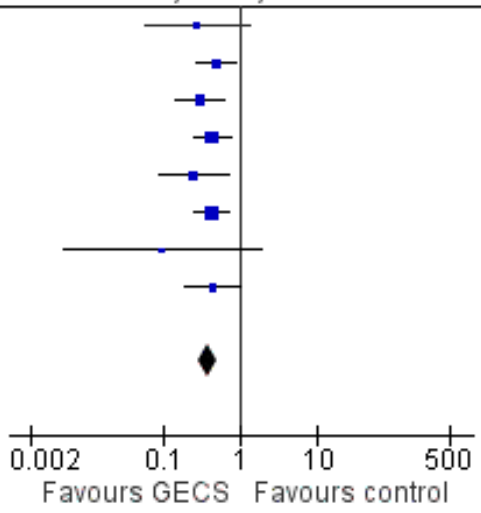
General Considerations of Therapy
Graduated Elastic Compression

- **Effect of graduated elastic compression stockings in the prevention of DVT diagnosed by objective methods (FUT or phlebography) in non-orthopedic surgical RCTs[1-7]**

Study or Subgroup	GECS Events	GECS Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Tsapogas, general surgery	2	54	6	44	4.1%	0.27 [0.06, 1.28]	1971
Holford, major surgery	11	47	23	48	14.2%	0.49 [0.27, 0.89]	1976
Scurr, general surgery	8	70	26	70	16.2%	0.31 [0.15, 0.63]	1977
Borow, various surgical	14	91	32	89	20.2%	0.43 [0.25, 0.75]	1981
Inada, abdominal surgery	4	110	16	110	10.0%	0.25 [0.09, 0.72]	1983
Allan, general surgery	15	97	37	103	22.4%	0.43 [0.25, 0.73]	1983
Turner, gynaecol surgery	0	104	4	92	3.0%	0.10 [0.01, 1.80]	1984
Turpie, neurosurgery	7	80	16	81	9.9%	0.44 [0.19, 1.02]	1989
Total (95% CI)		**653**		**637**	**100.0%**	**0.39 [0.30, 0.50]**	
Total events	61		160				

Heterogeneity: $Chi^2 = 3.08$, $df = 7$ ($P = 0.88$); $I^2 = 0\%$

Test for overall effect: $Z = 7.08$ ($P < 0.00001$)



1. Tsapogas MJ, et al. *Arch Surg.* 1971; 103:561-7.
2. Holford CP. B*r Med J.* 1976; 2:969-70.
3. Scurr JH, let al. *Br J Surg.* 1977; 64:371-3.
4. Borow M, et al. *Am J Surg.* 1981; 141:245-51.
5. Allan A, et al. *Br J Surg.* 1983; 70:172-4.
6. Turner GM, et al. *Br J Obstet Gynaecol.* 1984; 91:588-91.
7. Turpie AG, et al. *Arch Intern Med.* 1989; 149:679-81.

General Considerations of Therapy
Intermittent Pneumatic Compression (IPC)

- **IPC tested in 11 RCTs (1,318 patients)[1-11] was found to reduce the incidence of asymptomatic DVT from 25% in the control group to 7.9% in the IPC group (RR 0.32; 95% CI 0.24 to 0.42)**

1. Borow M, et al. Am J Surg. 1981; 141:245-51.
2. Sabri S, et al. Br Med J. 1971; 4:394-6.
3. Hills NH, et al. Br Med J. 1972; 1:131-5.
4. Roberts VC, et al. Br Med J. 1974; 1:358-60.
5. Clark WB, et al. Lancet. 1974; 2:5-7.
6. Turpie AG, et al. Neurology. 1977; 27:435-8.
7. Coe NP, et al. Surgery. 1978; 83:230-4.
8. Skillman JJ, et al. Surgery. 1978; 83:354-8.
9. Turpie AG, et al. Thromb Res. 1979; 15:611-6.
10. Butson AR. Am J Surg. 1981; 142:525-7.
11. Clarke-Pearson DL, et al. Obstet Gynecol. 1984; 63:92-8.

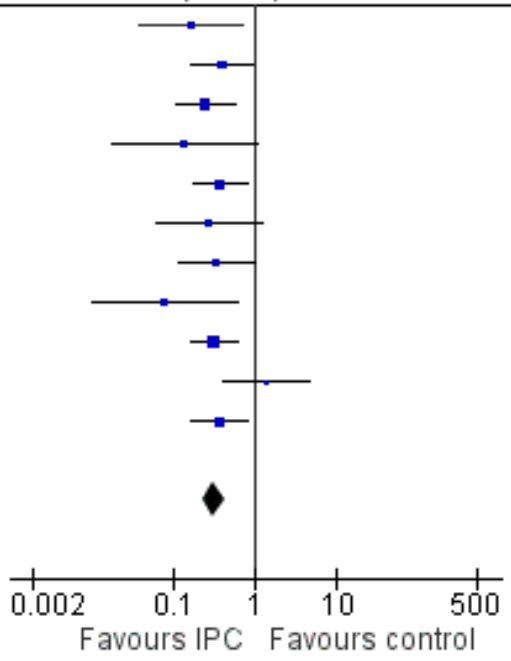
General Considerations of Therapy
Intermittent Pneumatic Compression

- **Effect of IPC in prevention of DVT diagnosed by objective methods (FUT or phlebography) in non-orthopaedic surgical RCTs[1-10]**

	IPC		Control			Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year	M-H, Fixed, 95% CI
Sabri*	2	39	12	39	7.3%	0.17 [0.04, 0.70]	1971	
Hills	6	50	15	50	9.2%	0.40 [0.17, 0.95]	1972	
Robert	6	94	27	104	15.6%	0.25 [0.11, 0.57]	1974	
Clark*	1	37	7	36	4.3%	0.14 [0.02, 1.07]	1974	
Turpie, a	8	103	20	96	12.6%	0.37 [0.17, 0.81]	1977	
Coe	2	29	6	24	4.0%	0.28 [0.06, 1.24]	1978	
Skillman	4	47	12	48	7.2%	0.34 [0.12, 0.98]	1978	
Turpie, b	1	65	12	63	7.4%	0.08 [0.01, 0.60]	1979	
Borow & Goldson	9	79	32	89	18.4%	0.32 [0.16, 0.62]	1981	
Butson	6	62	4	57	2.5%	1.38 [0.41, 4.64]	1981	
Clarke-Pearson	7	55	18	52	11.3%	0.37 [0.17, 0.81]	1984	
Total (95% CI)		**660**		**658**	**100.0%**	**0.32 [0.24, 0.42]**		
Total events	52		165					

Heterogeneity: $Chi^2 = 9.81$, $df = 10$ ($P = 0.46$); $I^2 = 0\%$

Test for overall effect: $Z = 7.70$ ($P < 0.00001$)



1. Sabri S, et al. Br Med J. 1971; 4:394-6.
2. Hills NH, et al. Br Med J. 1972; 1:131-5.
3. Roberts VC, et al. Br Med J. 1974; 1:358-60.
4. Clark WB, et al. Lancet. 1974; 2:5-7.
5. Turpie AG, et al. Neurology. 1977; 27:435-8.
6. Coe NP, et al. Surgery. 1978; 83:230-4.
7. Skillman JJ, et al. Surgery. 1978; 83:354-8.
8. Turpie AG, et al. Thromb Res. 1979; 15:611-6.
9. Butson AR. Am J Surg. 1981; 142:525-7.
10. Clarke-Pearson DL, et al. Obstet Gynecol. 1984; 63:92-8.

General Considerations of Therapy
Mechanical Compression versus LDUH or LMWH

- **A systematic review of 16 RCT of mechanical compression (MC) versus LDUH or LMWH demonstrated the pooled risk reduction for MC versus LDUH or LMWH was 1.07 (95% CI 0.72 to 1.61 for DVT and 1.03 (95% CI 0.48 to 2,22) for PE[1]**
  - MC was associated with significant reduced risk of postoperative bleeding compared with LDUH or LMWH (RR 0.47; 95% CI 0.31 to 0.70)
  - Among the studies that used LDUH, there was a non-significant trend towards a lower risk of DVT with heparin compared with MC (RR 0.71; 95% CI 0.42 to 1.19)
  - Among the studies that used LMWH, there was a significant higher risk of DVT with MC (RR 1.80; 95% CI 1.16 to 2.79) compared with heparin, but LMWH was still associated with an increased risk of bleeding

1. Eppsteiner RW, et al. World J Surg. 2010; 34:10-9.

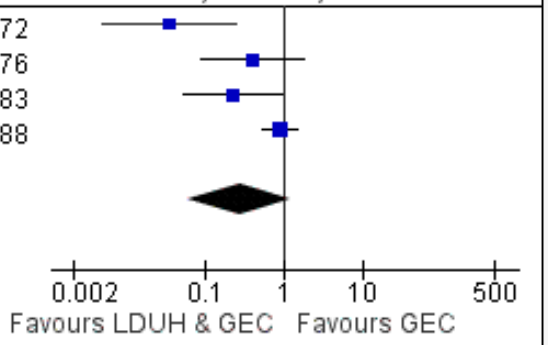
General Considerations of Therapy
Combined Modalities: GEC versus GEC plus LDUH

- **Effect of graduated elastic compression (GEC) stockings versus low dose unfractionated heparin (LDUH) plus GEC in the prevention of DVT diagnosed by objective methods (FUT or phlebography)[1-4]**

	LDUH & GEC		GEC			Risk Ratio		Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**Year**	**M-H, Random, 95% CI**
Nicolaides, prostatectomy	1	122	29	122	20.5%	0.03 [0.00, 0.25]	1972	
Moser, general surgery	2	20	5	20	24.0%	0.40 [0.09, 1.83]	1976	
Borow, gen surg & orthop	2	63	15	106	24.6%	0.22 [0.05, 0.95]	1983	
Rasmussen general surgery	23	89	22	74	30.9%	0.87 [0.53, 1.43]	1988	
Total (95% CI)		**294**		**322**	**100.0%**	**0.27 [0.06, 1.18]**		
Total events	28		71					

Heterogeneity: $Tau^2 = 1.81$; $Chi^2 = 16.77$, df = 3 (P = 0.0008); $I^2 = 82\%$

Test for overall effect: Z = 1.74 (P = 0.08)



1. Nicolaides AN, et al. Br J Surg. 1972; 59:487-8.
2. Moser G, et al. Schweiz Rundsch Med Prax. 1976; 65:1015-20.
3. Borow M, et al. Am Surg. 1983; 49:599-605.
4. Rasmussen A, et al. J Med. 1988; 19:193-201.

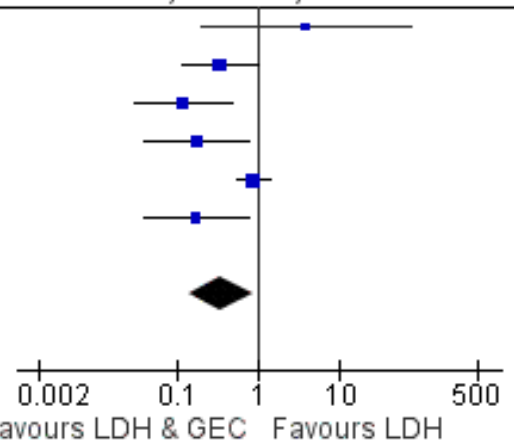
General Considerations of Therapy
Combined Modalities: DUH versus LDUH plus GEC

- **Effect of low dose unfractionated heparin (LDUH) versus LDUH plus graduated elastic compression (GEC) in the prevention of DVT in non-orthopedic surgical patients diagnosed by objective methods (FUT or phlebography)[1-6]**

Study or Subgroup	LDH & GEC Events	LDH & GEC Total	LDH Events	LDH Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Moser & Froidevaux	2	20	0	15	7.1%	3.81 [0.20, 73.95]	1976
Torngren	4	98	12	98	19.5%	0.33 [0.11, 1.00]	1980
Borow & Goldson	2	63	23	86	16.5%	0.12 [0.03, 0.49]	1983
Wille-Jorgensen, a	2	90	11	86	15.9%	0.17 [0.04, 0.76]	1985
Rasmussen	23	89	25	85	24.9%	0.88 [0.54, 1.42]	1988
Wille-Jorgensen, b	2	79	12	81	16.0%	0.17 [0.04, 0.74]	1991
Total (95% CI)		**439**		**451**	**100.0%**	**0.34 [0.14, 0.87]**	
Total events	35		83				

Heterogeneity: $Tau^2 = 0.83$; $Chi^2 = 16.83$, $df = 5$ ($P = 0.005$); $I^2 = 70\%$

Test for overall effect: $Z = 2.25$ ($P = 0.02$)



1. Moser G, et al. Schweiz Rundsch Med Prax. 1976; 65:1015-20.
2. Borow M, et al. Am Surg. 1983; 49:599-605.
3. Rasmussen A, et al. J Med. 1988; 19:193-201.
4. Torngren S. Br J Surg. 1980; 67:482-4.
5. Wille-Jorgensen P, et al. Br J Surg. 1985; 72:579-81.
6. Wille-Jorgensen P, et al. Surg Gynecol Obstet. 1991; 172:44-8.

General Considerations of Therapy
Electrical Stimulation

- **In a study of the efficacy of electrical calf stimulation during surgery using one leg as control in general surgical patients (110 patients), the incidence of asymptomatic DVT was 21% in the unstimulated leg and 8.2% in the stimulated leg (OR 0.33; 95% CI 0.15 to 0.77)[1]**
- **Another study of 60 patients reported the incidence of asymptomatic DVT was 15% in the unstimulated leg and 1.6% in the stimulated leg (OR 0.11; 95% CI 0.01 to 0.90)[2]**
- **In a RCT, electrical calf stimulation was applied to both legs of 37 patients compared to 40 controls. The incidence of asymptomatic DVT was 30% in the unstimulated group and 14% in the stimulated group (OR 0.35; 95% CI 0.90 to 1.16)[3]**
  - In this RCT, perfusion lung scanning and chest x-rays were performed the day before operation and 4-6 days after operation. The incidence of silent PE was 35% in the control group and 10% in the stimulated group (OR 0.33; 95% CI 0.11 to 0.97)

1. Browse NL, et al. Br Med J. 1970; 3:615-8.
2. Nicolaides AN, et al. Br Med J. 1972; 3:756-8.
3. Lindstrom B, et al. Br J Surg. 1982; 69:633-7.

General Considerations of Therapy
Electrical Stimulation

- **Most studies of electrical stimulation were performed prior to 1990 and the equipment used produced painful stimuli so that electrical calf muscle stimulation could be used only during general anesthesia**
- **Modern equipment now commercially available produces muscle contractions as a result of electrical impulses that are painless and can be tolerated by patients throughout the day**
- **The efficacy of such modern equipment should be determined in adequately powered RCT before any recommendations can be made**

Duration of Prophylaxis

- **Duration of prophylaxis in most studies is 5-7 days**
- **Studies suggested that the risk continues after discharge from hospital[1-8]**
  - RCT have demonstrated that extending prophylaxis from one week to one month reduces asymptomatic DVT by 50-70%[9-13]
  - 3 meta-analyses suggest the relative risk reduction for preventing VTE following extended prophylaxis is 60-70%[14-16]
- **Extended prophylaxis with bemiparin was associated with an 88% reduction in proximal DVT and a 24% reduction in the composite endpoint of DVT, nonfatal PE and death from any cause[17]**

1. Scurr JH, et al. BMJ. 1988; 297:28.
2. Huber O, et al. Arch Surg. 1992; 127:310-3.
3. Scholten DJ, et al. Obes Surg. 2002; 12:19-24.
4. Heit JA, et al. Arch Intern Med. 2002; 162:1245-8.
5. Bergqvist D, et al. Br J Surg. 1985; 72:105-8.
6. Agnelli G, et al. Ann Surg. 2006; 243:89-95.
7. Arcelus JI, et al. Thromb Haemost. 2008; 99:546-51.
8. Merkow RP, et al. Ann Surg. 2011; 254:131-7.
9. Lausen I, et al. Eur J Surg. 1998; 164:657-63.
10. Heit JA, et al. Mayo Clin Proc. 2001; 76:1102-10.
11. Rasmussen MS. Cancer Treat Rev. 2002; 28:141-4.
12. Bergqvist D, et al. N Engl J Med. 2002; 346:975-80.
13. Rasmussen MS, et al. J Thromb Haemost. 2006; 4:2384-90.
14. Rasmussen MS, et al. Cochr Database Syst Rev. 2009; CD004318.
15. Bottaro FJ, et al. Thromb Haemost. 2008; 99:1104-11.
16. Akl EA, et al. Thromb Haemost. 2008; 100:1176-80.
17. Kakkar VV, et al. J Thromb Haemost. 2010; 8:1223-9.

Duration of Prophylaxis

- **Further studies are needed to determine the optimal duration of extended prophylaxis and whether or not mortality is influenced**
  - There are no studies on extended prophylaxis after vascular surgery
- **Extended duration of pharmacological prophylaxis (>7 days) should be considered if patients develop complications such as infection during the post-operative hospitalization period[1-2]**
- **Obese patients undergoing bariatric surgery should be evaluated for post-discharge VTE risk and considered for extended pharmacological prophylaxis[3]**

1. Kaatz S, et al. Hosp Pract (Minneap). 2011; 39:7-15.
2. Amin AN, et al. Hosp Pract (Minneap). 2011; 39:7-17.
3. Winegar DA, et al. Surg Obes Relat Dis. 2011; 7:181-8.

VTE Prophylaxis Recommendations
Low-Risk General, Vascular, Bariatric and Plastic Surgical Patients

- ***Low-risk patients*** **are those without risk factors undergoing minor surgery**
- **The data are insufficient to make any recommendations**
- **On the basis of risk/benefit ratio and extrapolation from studies in moderate-risk patients, it is common practice in some countries to use GEC stockings in addition to early ambulation and adequate hydration**
  - Level of evidence: Low

VTE Prophylaxis Recommendations
Moderate-Risk General, Vascular, Bariatric and Plastic Surgical Patients

- ***Moderate-risk patients*** **are over 40 years of age and undergoing major surgery for benign disease in the absence of additional risk factors**
- **LMWH (initiated and dosed according to labelling) or LDUH is recommended**
  - Level of evidence: High
  - LMWH is the preferred option because it is administered as one injection daily and is associated with a lower incidence of HIT
- **An alternative method, especially in patients at risk for or with active bleeding, is GEC with IPC used continuously until the patient is fully ambulant**
  - Level of evidence: High
- **LMWH may be added if risk of bleeding is minimized**

VTE Prophylaxis Recommendations
High-Risk General, Vascular, Bariatric and Plastic Surgical Patients

- ***High- risk patients*** **are over 60 years of age and undergoing major surgery for benign disease or any patient with additional risk factors**
- **LMWH or fondaparinux initiated and dosed according to labelling is recommended**
  - Level of evidence: High
- **In the absence of LMWH or fondaparinux, LDUH 5000 IU commenced pre-operatively and continued twice or 3 times daily can be used**
  - Level of evidence: High
- **Any of the above therapies may be combined with mechanical methods (GEC and/or IPC), particularly in the presence of multiple risk factors**
  - Level of evidence: High

VTE Prophylaxis Recommendations
Laparoscopic Surgery

- **Patients undergoing laparoscopic surgery who do not have any additional risk factors should receive GEC**
  - Level of evidence: Low
- **LDUH, LMWH, fondaparinux or IPC with GEC should be used in the presence of additional risk factors**
  - Level of evidence: Low

VTE Prophylaxis Recommendations
Abdominal or Pelvic Surgery

- **Patients undergoing abdominal or pelvic major surgery for cancer and do not present contraindications to extended prophylaxis should receive LMWH up to one month after operation**
  - Level of evidence: High

VTE Prophylaxis Recommendations
Bariatric Surgery

- **Patients undergoing bariatric surgical procedures should receive LMWH (higher dosage) alone or in combination with GEC and IPC**
  - Level of evidence: Moderate

VTE Prophylaxis Recommendations
Major Vascular Surgery

- **Patients undergoing major vascular procedures should receive LMWH or fondaparinux**
  - Level of evidence: Low
- **In the absence of LMWH or fondaparinux, LDUH 5000 IU commenced pre-operatively and continued twice or 3 times daily can be used**
  - Level of evidence: Low

VTE Prophylaxis Recommendations
Plastic Surgery

- **High-risk patients having plastic surgery should receive LMWH, fondaparinux starting 24 hours after surgery or a combination of LMWH with IPC and GES**
  - Level of evidence: Low
- **In the absence of LMWH or fondaparinux, LDUH 5000 IU commenced pre-operatively and continued twice or 3 times daily can be used**
  - Level of evidence: Low
- **GEC is contraindicated in patients with peripheral arterial disease because of anecdotal reports of gangrene**