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

Orthopedic and Trauma Surgery

Chapter 6

General Considerations
Timing of Prophylaxis

- **VTE prophylaxis involves a balance of risks and benefits**
- **Chemical prophylaxis dilemma:**
  - The closer to surgery for a given dose, the better the thrombo-prophylaxis but the greater is the risk of bleeding complications[1]

Hull R, et al. N Engl J Med. 1993; 329:1370-6.

General Considerations
Timing of Prophylaxis

- **Prophylaxis should be close but not too close to surgery[1,2]**
- **In Europe:**
  - LMWH is recommended at a lower dose prior to operation
  - Provides an anticoagulant effect to counteract the intra-operative activation of coagulation factors and venous stasis
  - If administered too long prior to surgery, the prophylaxis effect may be ineffective and if given too close to surgery, surgical bleeding is a threat
- **In North America:**
  - LMWH is recommended post-operatively at a higher dose and more frequently
  - Reduce the risk of surgical bleeding, but intra-operative thrombo-genesis is not prevented

1. Strebel N, et al. Arch Intern Med. 2002; 162:1451-6.
2. Hull RD, et al. Arch Intern Med. 2001; 161:1952-60.

General Considerations
Timing of Prophylaxis

- **IPC and FIT sleeves[1-3]**
  - Available in sterile packages
  - Can be used intra-operatively
  - Reduces the risk of bleeding
  - Reduces the duration the patient is not prophylaxis via chemical methods

1. Bradley JG, et al. J Arthroplasty. 1993; 8:57-61.
2. Hooker JA, et al. J Bone Joint Surg Am. 1999; 81:690-6.
3. Woolson ST, et al. Am J Orthop. 1998; 27:299-304.

General Considerations
Spinal and Epidural Anesthesia

- **Meta-analyses demonstrate spinal and epidural anesthesia reduce thromboembolism and potentially mortality in hip fractures surgery[1,2] and total knee replacement (TKR)[3-5] when used with prophylaxis**
  - Does not reduce risk sufficiently alone
- **Neuraxial anesthesia can be safely used with LMWH[6]**
  - Recent concerns that spinal hematoma may develop on rare occasions[7,8]

1. Urwin SC, et al. Br J Anaesth. 2000; 84:450-5.
2. Parker MJ, et al. Cochrane Database Syst Rev. 2000; CD000521.
3. Williams-Russo P, et al. Clin Orthop Relat Res. 1996; 199-208.
4. Sharrock NE, et al. J Bone Joint Surg Am. 1991; 73:502-6.
5. Nielsen PT, et al. Acta Orthop Scand. 1990; 61:29-31.
6. Matzsch T, et al. Lakartidningen. 1992; 89:4028-30.
7. Tryba M, et al. Acta Anaesthesiol Scand Suppl. 1997; 111:100-4.
8. Wysowski DK, et al. N Engl J Med. 1998; 338:1774-5.

General Considerations
Spinal and Epidural Anesthesia

- **Guidelines for anesthesia and prophylactic methods have been suggested[1,2]**
- **LMWH (or pentasaccharide) can be given safely four hours after removal of the epidural catheter**
- **LMWH or pentasaccharide should be avoided when using continuous postoperative neuraxial block**
  - Catheter should not be inserted until serum levels of the chemical prophylactic agent used are at their lowest level
- **Post-operative administration is generally safer and more predictable than pre-operative administration when epidural analgesia is required**

1. Horlocker TT, et al. Reg Anesth Pain Med. 1998; 23:164-77.
2. Horlocker TT. Thromb Res. 2001; 101:V141-54.

General Considerations
Duration of Prophylaxis

- **Elective orthopedic surgery**
  - Studies in patients having THR demonstrate prolonged VTE risk[1-10]
    - 45-80% of all symptomatic VTE events occur after discharge[4, 11-14]
  - Prolonged LMWH thromboprophylaxis for up to 35 days is safe and decreases venographically detected total DVT, proximal DVT and symptomatic VTE after the 7th day by >50% whether in-hospital prophylaxis was with LMWH or warfarin in THR patients[10,14-18]
    - One RCT examining warfarin prophylaxis (INR 2-3) for 9 days to warfarin extended for one month after hospital discharge reduced the incidence of VTE from 5.1% (in-hospital only) to 0.5% (extended prophylaxis)[19]
    - Extended prophylaxis with warfarin is associated with more hemorrhagic complications than with LMWH[20]

1. Hull R, et al. N Engl J Med. 1993; 329:1370-6.
2. Arcelus JI, et al. Semin Thromb Hemost. 1993; 19 Suppl 1:142-6.
3. Warwick D, et al. J Bone Joint Surg Br. 1995; 77:6-10.
4. White RH, et al. Arch Intern Med. 1998; 158:1525-31.
5. Dahl OE, et al. Acta Orthop Scand. 2000; 71:47-50.
6. Pellegrini VD, et al. J Arthroplasty. 1993; 8:449-57.
7. Trowbridge A, et al. Clin Orthop Relat Res. 1994; 203-8.
8. Bjorgell O, et al. Thromb Res. 2000; 99:429-38.
9. Amstutz HC, et al. J Bone Joint Surg Am. 1989; 71:321-6.
10. Planes A, et al. Lancet. 1996; 348:224-8.
11. Sandler DA, et al. J R Soc Med. 1989; 82:203-5.
12. Colwell CW, et al. J Bone Joint Surg Am. 1999; 81:932-40.
13. Lieberman JR, et al. J Bone Joint Surg Am. 1997; 79:319-25.
14. Hull RD, et al. Arch Intern Med. 2000; 160:2208-15.
15. Dahl OE, et al. Thromb Haemost. 1997; 77:26-31.
16. Lassen MR, et al. Thromb Res. 1998; 89:281-7.
17. Bergqvist D, et al. N Engl J Med. 1996; 335:696-700.
18. Comp PC, et al. J Bone Joint Surg Am. 2001; 83-A:336-45.
19. Prandoni P, et al. Arch Intern Med. 2002; 162:1966-71.
20. Samama CM, et al. Arch Intern Med. 2002; 162:2191-6.

General Considerations
Duration of Prophylaxis

- **Elective orthopedic surgery**
  - RECORD-2[1] compared extended thrombophylaxis (35 days) using rivaroxaban with short term enoxaparin (10-14 days) followed by placebo further confirmed the benefits of extended prophylaxis after THR suggested by the RECORD1 study[2]
  - Further studies are required before recommendations can be made for prophylaxis beyond 35 days[3,4]
  - Epidemiological data on postoperative death rates indicate a longer duration of risk in subgroups
    - Emergency patients (e.g. hip fracture)
    - Patients with co-morbidity (e.g. rheumatoid arthritis)

1. Kakkar AK, et al. Lancet. 2008; 372:31-9.
2. Eriksson BI, et al. N Engl J Med. 2008; 358:2765-75.
3. Lie SA, et al. Acta Orthop Scand. 2000; 71:19-27.
4. Dahl OE, et al. Thromb Haemost. 2005; 93:860-6.

Total Hip Replacement (THR) Surgery

The Risk of VTE
Orthopedic THR Surgery

- **Patients undergoing elective major joint replacement or hip fracture surgery have a DVT risk of ~50%[1-3]**
  - Similar rates of VTE were found in placebo groups of recent studies for enoxaparin and fondaparinux performed in Japan[4,5]
- **The frequencies of proximal DVT and PE are also high, and symptomatic events range from 2-5%[6]**
- **The incidence of VTE including fatal PE was 2.27% following primary hip arthroplasty and 1.79% for total knee arthroplasty[7]**
- **Risk of DVT, PE and death continues post-hospitalisation for ~3 months[1,8-11]**

1. White RH, et al. Arch Intern Med. 1998; 158:1525-31.
2. Hirsh J. Acta Chir Scand Suppl. 1990; 556:30-5.
3. Turner RS, et al. J Bone Joint Surg Br. 1993; 75:942-4.
4. Fuji T, et al. Int Orthop. 2008; 32:443-51.
5. Fuji T, et al. J Orthop Sci. 2008; 13:442-51.
6. Dahl OE, et al. Acta Orthop Scand. 2003; 74:299-304.
7. Howie C, et al. J Bone Joint Surg Br. 2005; 87:1675-80.
8. Dahl OE, et al. Acta Orthop Scand. 2000; 71:47-50.
9. Warwick D, et al. J Bone Joint Surg Br. 2007; 89:799-807.
10. Lie SA, et al. Acta Orthop Scand. 2000; 71:19-27.
11. Lie SA, et al. Acta Orthop Scand. 2002; 73:392-9.

The Risk of VTE
Orthopedic THR Surgery

- **High incidence of proximal DVT following THR[1-9] and preponderance of distal thrombosis following TKR[10-14]**
- **Modern THR surgery has a reduced hospital stay (3-6 days) and discharged at risk**
- **Majority of clinical events appear after hospitalization producing the false impression of a decreasing problem[15-17]**
  - Recent meta-analysis (10 RCTs) in THR patients treated by LMWH reported for every 5 patients with asymptomatic DVT in a screening program, one patient experienced symptomatic VTE within 3 months[17]
  - The consistency of this finding strengthens the belief that asymptomatic DVT is a surrogate for symptomatic DVT

1. Gallus A, et al. Br J Surg. 1983; 70:17-9.
2. Hoek JA, et al. Thromb Haemost. 1992; 67:28-32.
3. Hull RD, et al. JAMA. 1990; 263:2313-7.
4. Kalodiki EP, et al. Int Angiol. 1996; 15:162-8.
5. Turpie AG, et al. N Engl J Med. 1986; 315:925-9.
6. Beisaw NE, et al. J Bone Joint Surg Am. 1988; 70:2-10.
7. Haake DA, et al. Clin Orthop Relat Res. 1989; 212-31.
8. Lassen MR, et al. Semin Thromb Hemost. 1991; 17 Suppl 3:284-90.
9. Freedman KB, et al. J Bone Joint Surg Am. 2000; 82-A:929-38.
10. Lynch AF, et al. J Bone Joint Surg Am. 1988; 70:11-4.
11. Stringer MD, et al. J Bone Joint Surg Br. 1989; 71:492-7.
12. Stulberg BN, et al. J Bone Joint Surg Am. 1984; 66:194-201.
13. Lotke PA, et al. Clin Orthop Relat Res. 1996; 251-8.
14. Westrich GH, et al. J Bone Joint Surg Am. 1996; 78:826-34.
15. Dahl OE, et al. Acta Orthop Scand. 2000; 71:47-50.
16. White RH, et al. Thromb Haemost. 2003; 90:446-55.
17. Warwick D, et al. J Bone Joint Surg Br. 2007; 89:799-807.

Mortality After Elective Hip Replacement in the Absence of Routine Pharmacologic Prophylaxis

Author	No. of Patients	Follow-up	Total Deaths	95% CI	Fatal PE	95% CI	Anticoagulant Use
Seagroatt et al 1991[1]	11,600	90 days	93 (1.10%)	0.87% to 1.31%	-	-	Very Low
Sheppeard et al 1981[2]	3,016	Inpatient	19 (0.63%)	0.38% to 0.98%	12 (0.40%)	0.20% to 0.70%	20%*
Warwick et al 1995[3]	1,162**	90 days	15 (1.30%)	0.73% to 2.10%	4 (0.34%)	0.09% to 0.90%	11%*
Wroblewski et al 1992[4]	18,104	1 year	362 (2.0%)	1.80% to 2.20%	1.27 (0.70%)	0.58% to 0.82%	***
Fender et al 1997[5]	2,111	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

1. Seagroatt V, Tet al. BMJ. 1991; 303:1431-5.
2. Sheppeard H, et al. Arch Orthop Trauma Surg. 1981; 99:65-71.
3. Warwick D, et al. J Bone Joint Surg Br. 1995; 77:6-10.
4. Wroblewski BM, et al. Clin Orthop Relat Res. 1992; 222-4.
5. Fender D, et al.. J Bone Joint Surg Br. 1997; 79:896-9.

Frequency of Proximal DVT in the Absence of Prophylaxis

Patient Group	No. of Studies	Patients (n)	DVT Incidence	95% CI
Elective Hip Replacement[1]	25	1436	330* (23%)	20.8% to 25.2%
Total Knee Replacement[2-8]	7	536	41 (7.6%)	5.5% to 10.1%

Diagnosed by surveillance with objective methods: phlebography or FUT

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

1. Imperiale TF, et al. JAMA. 1994; 271:1780-5.
2. Hull R, et al. Thromb Res. 1979; 16:37-45.
3. Kim YH. J Bone Joint Surg Br. 1990; 72:779-83.
4. Leclerc JR, et al. Ann Intern Med. 1996; 124:619-26.
5. McKenna R, et al. J Bone Joint Surg Am. 1976; 58:928-32.
6. Stringer MD, et al. J Bone Joint Surg Br. 1989; 71:492-7.
7. Stulberg BN, et al J Bone Joint Surg Am. 1984; 66:194-201.
8. Wilson NV, et al. J Bone Joint Surg Br. 1992; 74:50-2.

Frequency of Clinical Pulmonary Embolism* in the Absence of Prophylaxis

Patient Group	No. of Studies	Patients (n)	Clinical PE	95% CI
Elective Hip Replacement[1]	25	1436	57** (4%)	3.0% to 5.1%
Traumatic Orthopedic Surgery[2]	7	494	34 (6.9%)	4.8% to 9.2%

* 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.

1. Imperiale TF, et al. JAMA. 1994; 271:1780-5.
2. Collins R, et al. BMJ. 1994; 309:1215-7.

Frequency of Fatal Pulmonary Embolism* in the Absence of Prophylaxis

Patient Group	No. of Studies	Patients (n)	Clinical PE	95% CI
Elective Hip Replacement[1]	12	485	8 (1.65%)	0.38% to 2.7%
Fractured neck of femur[2]	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 clinical pulmonary embolism in series without such screening and intervention is unknown.

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

1. Collins R, et al. N Engl J Med. 1988; 318:1162-73.
2. Lassen MR, et al. London: Med-Orion; 1994:281-95.

THR Prophylaxis Recommendations
General Considerations

- **Prophylactic methods investigated THR patients include aspirin, fixed LDUH, LMWH, heparinoid, recombinant hirudin, oral direct-Xa inhibitors, oral direct thrombin inhibitors, fixed mini-dose and adjusted doses of VKA, GEC stockings, IPC and foot impulse technology (FIT)**
- **To determine the risk reduction for each prophylactic method, only RCTs with systematic screening tests for DVT have been used**

THR Prophylaxis Recommendations
General Considerations: LDUH and LMWH

- **LDUH (5 000 IU 8 or 12 h) was found to be effective in reducing DVT from 46.8% to 23.3% (RR 0.50; 95% CI 0.43 to 0.58)**
  - Meta-analysis (20 RCTs)[1]
  - Method of choice in the 1980s
- **LMWH subsequently demonstrated superior evidence to LDUH for elective THR surgery, reducing DVT from 21.2% to 13.8% (RR 0.66; 95% CI 0.52 to 0.84) and PE from 4.1% to 1.7% (RR 0.4; 95% CI 0.19 to 0.84)[2-11]**
  - LDUH is no longer recommended
  - Regulatory bodies in Europe and North America consider the LMWHs to be distinct drug products

1. Collins R, et al. N Engl J Med. 1988; 318:1162-73.
2. Bergqvist D, et al. N Engl J Med. 1996; 335:696-700.
3. Freedman KB, et al. J Bone Joint Surg Am. 2000; 82-A:929-38.
4. Leizorovicz A, et al. BMJ 1992; 305:913-20.
5. Nurmohamed MT, et al. Lancet. 1992; 340:152-6.
6. Jorgensen LN, et al. Br J Surg. 1993; 80:689-704.
7. Koch A, et al. Thromb Res. 2001; 102:295-309.
8. Levine MN, et al. Ann Intern Med. 1991; 114:545-51.
9. Colwell CW, Jr., et al. J Bone Joint Surg Am. 1994; 76:3-14.
10. Planes A, et al. Thromb Haemost. 1988; 60:407-10.
11. GHAT Group. Arch Orthop Trauma Surg. 1992; 111:110-20.

THR Prophylaxis Recommendations
General Considerations: Hirudin

- **Recombinant hirudin (Desirudin) is more effective than LDUH[1-3]**
- **Recombinant hirudin is more effective than LMWH[2]**
  - 2,079 patients studied, 1,587 were included in the primary efficacy analysis
  - DVT was reduced with hirudin 15mg twice daily compared with 40 mg enoxaparin from 25.5% to 18.45% (p=0.001; RRR 28.0%)
  - The safety profile was the same in both groups[2]

1. Eriksson BI, et al. Thromb Haemost. 1994; 72:227-31.
2. Eriksson BI, et al. N Engl J Med. 1997; 337:1329-35.
3. Eriksson BI, et al. J Bone Joint Surg Am. 1997; 79:326-33.

THR Prophylaxis Recommendations
General Considerations: LMWH and VKA

- **LMWH more effective than VKA[1-4] or at least as effective[5] for preventing asymptomatic DVT**
  - LMWH has a slight increase in hemorrhagic complications.
- **LMWH started before or immediately after surgery produced a marked reduction of proximal DVT from 3% to 0.8% (RR 0.28; 95% CI 0.1 to 0.74)[6]**
  - Symptomatic DVT was reduced from 4.4% in the VKA to 1.5% in the LMWH group (RR 0.32; 95% CI 0.12 to 0.88)
- **Meta-analysis of VKA showed a RR of 0.56 (95% CI 0.37 to 0.84) for DVT and 0.23 for PE (95% CI 0.09 to 0.59) compared with placebo[7]**
  - LMWH more effective than VKA in preventing total DVT (RR 1.51; 95% CI 1.27 to 1.79) and proximal DVT (RR 1.51; 95% CI 1.04 to 2.17)
  - Risk of wound hematoma increased to 5.3% with LMWH versus 3.3% with VKA (RR 2.29; 95% CI 1.09 to 7.75)

1. Hull R, et al. N Engl J Med. 1993; 329:1370-6.
2. RD Heparin Arthroplasty Group. J Bone Joint Surg Am. 1994; 76:1174-85.
3. Francis CW, et al. J Bone Joint Surg Am. 1997; 79:1365-72.
4. Hull RD, et al. Arch Intern Med. 2000; 160:2199-207.
5. Hamulyak K, et al. Thromb Haemost. 1995; 74:1428-31.
6. Hull RD, et al. Arch Intern Med. 2001; 161:1952-60.
7. Mismetti P, et al. J Thromb Haemost. 2004; 2:1058-70.

THR Prophylaxis Recommendations
General Considerations: LMWH and VKA

- **1,279 THR patients were randomized on the third post-operative day to LMWH or warfarin for 6 weeks[1]**
- **Primary endpoint was overall failure rate (radiologically confirmed symptomatic VTE, major hemorrhage or deaths**
  - Failure rate was 3.7% in the LMWH group and 8.3% in the warfarin group (p=0.01)
  - Major bleeding occurred in 1.4% in the LMWH group and 5.5% in the warfarin group
  - Reduced bleeding seen initially after surgery due to the slow onset of action for warfarin was offset by long-term increased bleeding
- **Drug registries have shown warfarin to be a major cause of readmission and fatal bleeding[2-3]**
- **With these data, need for monitoring, small therapeutic window, and risk for drug interactions, some surgeons find it difficult to see an advantage for VKA over LMWH**

1. Samama CM, et al. Arch Intern Med. 2002; 162:2191-6.
2. Pirmohamed M, et al. BMJ. 2004; 329:15-9.
3. Budnitz DS, et al.. Ann Emerg Med. 2005; 45:197-206.

THR Prophylaxis Recommendations
General Considerations: Fondaparinux

- **Fondaparinux is a pure synthetic pentasaccharide compound**
- **Potent indirect inhibitor of factor Xa facilitating antithrombin binding to activated factor X**
- **Administered by subcutaneous injection once daily**
  - May accumulate and increase bleeding risk with impaired renal function
- **Two RCT compared fondaparinux to enoxaparin[1,2]**
  - Reduction of asymptomatic DVT was 26% (RR 0.74; 95% CI 0.47 to 0.89) and symptomatic PE was 56% (RR 0.44; 95% CI 0.27 to 0.66) with fondaparinux.
  - Combined incidence of major bleeding was 3% in the fondaparinux and 2.1% in the enoxaparin patients ($p > 0.05$)

1. Lassen MR, et al. Lancet. 2002; 359:1715-20.
2. Turpie AG, et al. Lancet. 2002; 359:1721-6.

THR Prophylaxis Recommendations
General Considerations: Antiplatelet Agents

- **Meta-analysis in early 1990s[1] demonstrated antiplatelet therapy in THA is only moderately effective for protection against DVT (RR 0.7; 95% CI 0.61 to 0.82) even though the reduction in the risk of PE was substantial (RR 0.49; 95% CI 0.26 to 0.92)**
- **Subsequent PEP study[2,3] demonstrated aspirin is not as valuable as the meta-analysis suggested**
  - >13,000 hip fracture patients randomized to either aspirin or placebo
  - Overall death rate was identical in each group
  - Risk reduction for symptomatic VTE was 1.6% with aspirin versus 2.5% with placebo which was only one-half of that expected from LMWH and one- third from pentasaccharide
  - Increased risk of blood transfusion, gastrointestinal and wound bleeding
  - Study in supplementary 4,000 elective THR and TKR patients demonstrated an insignificant difference in symptomatic VTE[3]
- **Relative weak thromboprophylactic effect of aspirin and associated complication rate may deprive patients of safer or more effective prophylaxis**

1. Collins R, et al. BMJ. 1994; 309:1215-7.
2. PEP trial. Lancet. 2000; 355:1295-302.
3. Cohen A, et al. Lancet. 2000; 356:247; author reply 50-1.

Effect of Antiplatelet Therapy in the Prevention of DVT in Randomised Controlled Studies[1]

	Control Group*			Antiplatelet Group			
Type of Patient	**No. of Trials**	Patients (N)	DVT (%)	Patients	**DVT (%)**	RR	**95% CI**
Orthopedic Traumatic	10	444	186 (42%)	454	163 (36%)	0.86	0.735 to 1.0%
Orthopedic Elective	13	436	232 (53%)	427	160 (37%)	0.70	0.61% to 0.82%
High Risk Medical	8	266	61 (23%)	261	39 (15%)	0.65	0.45% to 0.94%

*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).

Diagnosed by surveillance with objective methods (fibrinogen uptake in general surgery and phlebography in orthopaedic surgery)

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

Effect of Antiplatelet Therapy in the Prevention of PE in Randomised Controlled Studies[1]

	Control Group			Antiplatelet Group			
Type of Patient	**No. of Trials**	Patients (N)	DVT (%)	Patients	**DVT (%)**	RR	**95% CI**
Orthopedic Traumatic	11	494	34 (6.9%)	504	14 (2.8%)	0..40	0.22% to 0.71%
Orthopedic Elective	16	537	29 (5.4%)	529	14 (2.6%)	0.49	0.26% to 0.92%
High Risk Medical	9	280	8 (2.9%)	275	3 (1.1%)	0.38	0.10% to 1.42%

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

Antiplatelet Therapy in the Prevention of DVT in Randomised Controlled Studies[1]

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DVT diagnosed by surveillance with objective methods: Fibrinogen uptake in general surgery and phlebography in orthopaedic surgery

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

Antiplatelet Therapy in the Prevention of PE in Randomised Controlled Studies[1]

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

THR Prophylaxis Recommendations
General Considerations: GEC

- **Cochrane database review[1] and a separate meta-analysis[2] report GEC is effective in reducing DVT in hospitalized patients**
- **Limited robust studies specific to GEC in orthopedic surgery patients[3,4]**
- **Based on limited RCT and the availability of other more effective methods of prophylaxis, GEC stockings on their own are not recommended**

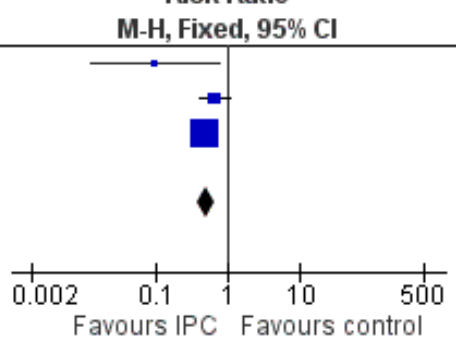
1. Amaragiri SV, et al. Cochrane Database Syst Rev. 2000; CD001484.
2. Wells PS, et al. Arch Intern Med. 1994; 154:67-72.
3. Ishak MA, et al. Br J Surg. 1981; 68:429-32.
4. Barnes RW, et al. Clin Orthop Relat Res. 1978; 61-7.

Effect of IPC in the Prevention of DVT in Randomised Controlled Studies in Hip Replacement

Study or Subgroup	IPC Events	IPC Total	Control (no prophylaxis) Events	Control (no prophylaxis) Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Hartman, elective & fract	1	53	10	52	9.2%	0.10 [0.01, 0.74]	1982
Gallus, elective	15	43	25	47	21.8%	0.66 [0.40, 1.07]	1983
Hull, elective	36	152	77	158	69.0%	0.49 [0.35, 0.67]	1990
Total (95% CI)		**248**		**257**	**100.0%**	**0.49 [0.37, 0.64]**	
Total events	52		112				

Heterogeneity: $Chi^2 = 3.84$, $df = 2$ ($P = 0.15$); $I^2 = 48\%$

Test for overall effect: $Z = 5.21$ ($P < 0.00001$)



DVT diagnosed by surveillance with phlebography or duplex ultrasound[1] in randomised controlled studies of patients having hip replacement[2-4]

1. Fisher CG, et al. J Orthop Trauma. 1995; 9:1-7.
2. Gallus A, et al. Br J Surg. 1983; 70:17-9.
3. Hull RD, et al. JAMA. 1990; 263:2313-7.
4. Hartman JT, et al. J Bone Joint Surg Am. 1982; 64:1059-62.

THR Prophylaxis Recommendations
General Considerations: IPC

- **IPC is effective in THR patients[1-3]**
  - DVT is reduced from 43.6% in the control groups to 21% in the compression groups (RR 0.48; 95% CI 0.36 to 0.64)
- **Modern technologies have made IPC devices light-weight, silent, more portable and more effective in preventing stasis by sensing venous volume**
  - Compression periods more readily follows venous refilling
  - Sleeve designs and materials have been used to improve patient compliance[4]
- **Recent study of 392 evaluable THR patients with IPC compared to LMWH found a similar rate of DVT (3%)[5]**

1. Gallus A, et al. Br J Surg. 1983; 70:17-9.
2. Hull RD, et al. JAMA. 1990; 263:2313-7.
3. Hartman JT, et al. J Bone Joint Surg Am. 1982; 64:1059-62.
4. Kakkos SK, et al. J Vasc Surg. 2001; 34:915-22.
5. Colwell CW, Jr., et al. J Bone Joint Surg Am. 2010; 92:527-35.

THR Prophylaxis Recommendations
General Considerations: Combined Modalities

- **3 RCT compared combined modalities with LMWH**
  - Study 1: Combination of LMWH plus IPC was more effective than LMWH plus GEC stockings (DVT incidence 0% versus 28%) in 131 THR or TKR patients[1]
  - Study 2: Combination of LMWH plus IPC was more effective than LMWH (DVT incidence 6.6% versus 19.5%) in 277 patients[2]
  - Study 3: Combination of LMWH plus IPC was more effective than LMWH (DVT incidence 0.4% versus 1.7%) in 1803 patients having various orthopedic operations. In the subgroup of 306 THR patients, The DVT incidence was 0% in the combined modalities group and 5.2% in the LMWH group ($P < 0.001$)[3]
- **A RCT in 121 evaluable THR or TKR patients compared IPC plus aspirin 100 mg daily to LMWH**
  - Incidence of postoperative venographic DVT was 6.6% in the IPC group and 28.3% in the LMWH group (RR 0.23; 95% CI 0.08 to 0.65).[173]

1. Silbersack Y, et al. J Bone Joint Surg Br. 2004; 86:809-12.
2. Edwards JZ, et al. J Arthroplasty. 2008; 23:1122-7.
3. Eisele R, et al. J Bone Joint Surg Am. 2007; 89:1050-6.
4. Gelfer Y, et al. J Arthroplasty. 2006; 21:206-14.

Prophylaxis Using Combination of Foot Impulse Technology (FIT) with Graduated Elastic Compression (GEC) on Proximal DVT (Orthopedic Patients)

		Control			Foot Impulse Technology (plus Additional Method of Prophylaxis)		
Author	**Diagnostic Method**	**Prophylaxis Method**	**N**	**Proximal DVT**	**Prophylaxis Method**	**N**	**Proximal DVT**
Hip Surgery							
Bradley et al, 1993[1]	VG	GEC	44	11 (25%)	FIT+GEC	30	2 (6.7%)
Fordyce et al1992[2]	VG	GEC	40	13 (32%)	FIT+GEC	39	2 (5%)
Santori et al, 1994[3]	US	LDUH	65	13 (20%)	FIT+GEC	67	2 (3.0%)
Warwick et al,1998[4]	VG	LMWH+GEC	138	27 (17.4%)	FIT+GEC	136	12 (9%)
Pitto et al, 2004[5]	US	LMWH	100	2+4 *(6%)	FIT+GEC	100	0+3 *(3%)
Knee Surgery							
Blanchard et al,1999[6]	VG	LMWH	60	2 (3.3%)	FIT only	48	4 (8.3%)
Wilson et al, 1992[7]	VG	Nil	32	6 (19%)	FIT only	28	0 (0.0%)
Westrich et al, 1996[8]	VG	Aspirin	83	49 (59%)	FIT+Aspirin	81	22 (27%)
Warwick et al, 2002[9]	VG	LMWH	99	57 (58%)	FIT	98	48 (54%)
Hip Fracture							
Stranks et al, 1992[10]	US	GEC	39	9 (32%)	FIT+GEC	41	0 (0.0%)

1. Bradley JG, et al. J Arthroplasty. 1993; 8:57-61.
2. Fordyce MJ, et al. J Bone Joint Surg Br. 1992; 74:45-9.
3. Santori FS, et al. J Bone Joint Surg Br. 1994; 76:579-83.
4. Warwick D, et al. J Bone Joint Surg Am. 1998; 80:1158-66.
5. Pitto RP, et al. J Bone Joint Surg Br. 2004; 86:639-42.
6. Blanchard J, et l. J Bone Joint Surg Br. 1999; 81:654-9.
7. Wilson NV, et al. J Bone Joint Surg Br. 1992; 74:50-2.
8. Westrich GH, et al. J Bone Joint Surg Am. 1996; 78:826-34.
9. Warwick D, et al. J Bone Joint Surg Br. 2002; 84:344-50.
10. Stranks GJ, et al. J Bone Joint Surg Br. 1992; 74:775-8.

THR Prophylaxis Recommendations
General Considerations: FIT

- **FIT combined with GEC is effective in reducing the incidence of proximal DVT in THR and TKR patients**
  - Less bleeding and swelling
  - Direct comparisons with chemical prophylaxis are sparse
  - Probable superiority to LDUH[1] and equivalence with LMWH for THR[2,3] but not for TKR[4]
- **IPC and FIT offer an alternative for patients with contraindications to chemical prophylaxis**

1. Santori FS, et al. J Bone Joint Surg Br. 1994; 76:579-83.
2. Pitto RP, et al. J Bone Joint Surg Br. 2004; 86:639-42.
3. Warwick D. J Bone Joint Surg Am. 1998; 80:141-2.
4. Blanchard J, et al. J Bone Joint Surg Br. 1999; 81:654-9.

THR Prophylaxis Recommendations
General Considerations: Rivaroxaban

- **Rivaroxaban is a new oral direct Xa inhibitor**
- **RECORD1 and RECORD2 compared rivaroxaban to enoxaparin in THR patients**
- **RECORD1: Both prophylaxis regimens given for 31-39 days[1]**
  - Superior efficacy with rivaroxaban was demonstrated, with an incidence of venographic VTE of 3.7% in the enoxaparin group and 1.1% in the rivaroxaban group ($P < 0.001$)
  - The incidence of major and non-major clinically relevant bleeding was 2.5% in the enoxaparin group and 3.2% in the rivaroxaban group (NS)
- **RECORD2 : Compared rivaroxaban administered for 35 days to short term enoxaparin (10-14 days) followed by placebo[2]**
  - Incidence of venographic VTE was 9.3% in the enoxaparin group and 2.0% in the rivaroxaban group ($P < 0.0001$)
  - Incidence of major and non-major clinically relevant bleeding was 2.8% in the enoxaparin group and 3.3% in the rivaroxaban group (NS)

1. Eriksson BI, et al. N Engl J Med. 2008; 358:2765-75.
2. Kakkar AK, et al. Lancet. 2008; 372:31-9.

THR Prophylaxis Recommendations
General Considerations: Apixaban

- **Apixaban is new oral direct Xa inhibitor**
- **Apixaban 2.5 mg orally twice daily was compared to enoxaparin 40 mg subcutaneously every 24 hours in a study of 5,407 THR patients[1]**
  - Apixaban therapy was initiated 12 to 24 hours after closure of the surgical wound; enoxaparin therapy was initiated 12 hours before surgery
  - Prophylaxis was continued for 35 days after surgery, followed by bilateral venographic studies
  - Incidence of the primary efficacy outcome (asymptomatic or symptomatic deep-vein thrombosis, nonfatal pulmonary embolism, or death from any cause during the treatment period) was 1.4% in the apixaban group and in 3.9% in the enoxaparin group (RR 0.36; 95% CI 0.22 to 0.54; $P < 0.001$) for both non-inferiority and superiority
  - Incidence of major and clinically relevant non-major bleeding was 4.8% with apixaban and 5.0% with enoxaparin($P > 0.05$)

1. Lassen MR, et al. N Engl J Med. 2010; 363:2487-98.

THR Prophylaxis Recommendations
General Considerations: Edoxaban

- **Edoxaban is a new oral direct FXa inhibitor that is 10,000-fold more selective for FXa than thrombin[1]**
- **STARS J-V trial (N=503), edoxaban (30 mg qd) resulted in significantly fewer VTEs than enoxaparin (2000 IU bid) (2.4% vs. 6.9%; *P*=0.0157 for superiority)[1]**
  - Difference in the incidence of major and clinically relevant non-major bleeding events between edoxaban (2.6%) and enoxaparin (3.7%) was not statistically significant (*P*=0.475)

1. Furugohri T, et al. J Thromb Haemost. 2008; 6:1542-9.

THR Prophylaxis Recommendations
General Considerations: Dabigatran

- **Dabigatran is a new oral direct inhibitor of thrombin**
- **2 RCT evaluated the efficacy and safety of dabigatran in patients having elective THR**
  - Study 1: RE-NOVATE[1]: 3 groups of patients received dabigatran 150 mg, dabigatran 220 mg or enoxaparin 40 mg for 25-35 days
  - Primary endpoint of total VTE and all-cause mortality occurred in 8.6%, 6.0% and 6.7% of the groups respectively ($P < 0.0001$ for non-inferiority of each group versus enoxaparin)
  - Study 2: RE-NOVATE II[2]: Dabigatran 220 mg was compared to 40 mg enoxaparin
  - Primary endpoint of total VTE and all-cause mortality occurred in 7.7% in the dabigatran and 8.8% in the enoxaparin group ($P < 0.0001$ for non-inferiority of dabigatran versus enoxaparin)
  - No significant difference in major bleeding between groups in either study

1. Eriksson BI, et al. Lancet. 2007; 370:949-56.
2. Eriksson BI, et al. Thromb Haemost. 2011; 105:721-9.

VTE Prophylaxis Recommendations
THR Orthopedic Surgery

- **Level of Evidence: High**
  - **LMWH initiated and dosed according to manufacturer's recommendations**
  - **Fondaparinux**
  - **Vitamin K antagonists (VKA)**
  - **Rivaroxaban**
  - **Apixaban**
  - **Dabigatran**

VTE Prophylaxis Recommendations
THR Orthopedic Surgery

- **IPC or FIT combined with GEC stockings are an alternative to LMWH if concerns regarding bleeding exist.**
  - Can be used as tolerated and then replaced with chemical prophylaxis as soon as safe and continued for the rest of the 5-week period of risk
  - Level of evidence: High
- **Desirudin is approved for short-term prophylaxis in patients with HIT**
  - Level of evidence: High

VTE Prophylaxis Recommendations
THR Orthopedic Surgery

- **LMWH combined with IPC is more effective than either modality alone and should be considered in all cases**
  - Level of evidence: High
- **Prophylaxis with LMWH should be initiated either before or after operation depending on the adopted regimen**
  - Level of evidence: High
- **Prophylaxis should be continued for 4-6 weeks with LMWH**
  - Level of evidence: High
- **Prophylaxis should be continued for 4-6 weeks with fondaparinux**
  - Level of evidence: Low

Total Knee Replacement (TKR) Surgery

The Risk of VTE
Orthopedic TKR Surgery

- **Data from THR should not be extrapolated to TKR**
- **Incidence of asymptomatic DVT detected by venography is higher in patients having TKR than THR**
- **Incidence of above knee DVT is lower than in patients having THR**

Frequency of All DVT in Total Knee Replacement Surgery in the Absence of Prophylaxis

Study	No. of Studies	Patients (n)	DVT Incidence	95% CI
Hull et al, 1979[1]		29	19	
Kim, 1990[2]		349244	80	
Leclerc et al, 1996[3]		3857	31	
Lynch et al, 1988[4]		2575	28	
Stringer et al, 1989[5]		55	31	
Stulberg et al, 1984[6]		49	41	
Wilson et al, 1992[7]		32	22	
Total	**7**	**541**	**252 (47%)**	**42% to 51%**

Diagnosed by surveillance with objective methods. Listed frequency is true for the total groups of patients. Presence of additional risk factors indicated in the text is likely to increase the risk of thromboembolism for individual patients.

1. Hull R, et al. Thromb Res. 1979; 16:37-45.
2. Kim YH. J Bone Joint Surg Br. 1990; 72:779-83.
3. Leclerc JR, et al. Ann Intern Med. 1996; 124:619-26.
4. Lynch AF, et al. J Bone Joint Surg Am. 1988; 70:11-4.
5. Stringer MD, et al. J Bone Joint Surg Br. 1989; 71:492-7.
6. Stulberg BN, et al. J Bone Joint Surg Am. 1984; 66:194-201.
7. Wilson NV, et al. J Bone Joint Surg Br. 1992; 74:50-2.

TKR Prophylaxis Recommendations
General Considerations: IPC, FIT

- **IPC is effective in patients having TKR (RR 0.27; 95% CI 0.14 to 0.49)**
  - A small study demonstrated that IPC reduced the incidence of asymptomatic DVT from 65% to 6%[1]
  - Subsequent research found IPC to be more effective than aspirin[2]
  - IPC was found to be less effective than VKA for preventing venographically detected DVT (32% vs 19%)[3]
- **FIT has been shown effective[69, 130] but inferior to LMWH[4,5]**
- **Recent study (N=136 THR or TKR patients) of a mobile IPC device compared to LMWH, reported a DVT incidence of 6.6% in the IPC group and 28.3% in the LMWH group[6]**
  - Proximal DVT incidence was 1.6% with IPC and 10% with LMWH

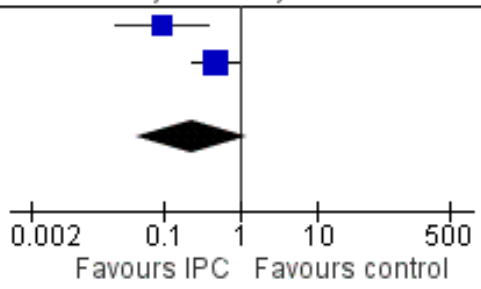
1. Hull R, et al. Thromb Res. 1979; 16:37-45.
2. Haas SB, et al. J Bone Joint Surg Am. 1990; 72:27-31.
3. Kaempffe FA, et al. Clin Orthop Relat Res. 1991; 89-97.
4. Blanchard J, et al. J Bone Joint Surg Br. 1999; 81:654-9.
5. Warwick D, et al. J Bone Joint Surg Br. 2002; 84:344-50.
6. Gelfer Y, et al. J Arthroplasty. 2006; 21:206-14.

Effect of IPC in the Prevention of DVT in Randomised Controlled Studies in Knee Replacement

Study or Subgroup	IPC Events	IPC Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Hull	2	32	19	29	43.7%	0.10 [0.02, 0.37]	1979
Haas (aspirin in control)	8	36	17	36	56.3%	0.47 [0.23, 0.95]	1990
Total (95% CI)		**68**		**65**	**100.0%**	**0.23 [0.05, 1.21]**	
Total events	10		36				

Heterogeneity: Tau² = 1.13; Chi² = 4.66, df = 1 (P = 0.03); I² = 79%

Test for overall effect: Z = 1.73 (P = 0.08)



DVT diagnosed by surveillance with phlebography or duplex ultrasound[1] in randomised controlled studies of patients having knee replacement[2,3]

1. Fisher CG, et al. J Orthop Trauma. 1995; 9:1-7.
2. Hull R, et al. Thromb Res. 1979; 16:37-45.
3. Haas SB, et al J Bone Joint Surg Am. 1990; 72:27-31.

TKR Prophylaxis Recommendations
General Considerations: LMWH

- **LMWH is more effective than placebo**
- **Venographically detected DVT was decreased from 65% in the placebo group to 19% in the LMWH group (RR 0.30; 95% CI 0.16 to 0.58)[1]**
- **Subsequent studies demonstrated that LMWH was more effective than LDUH (RR 0.75; 95% CI 0.58 to 0.92) and warfarin (RR 0.68; 95% CI 0.62 to 0.76)[2,3]**

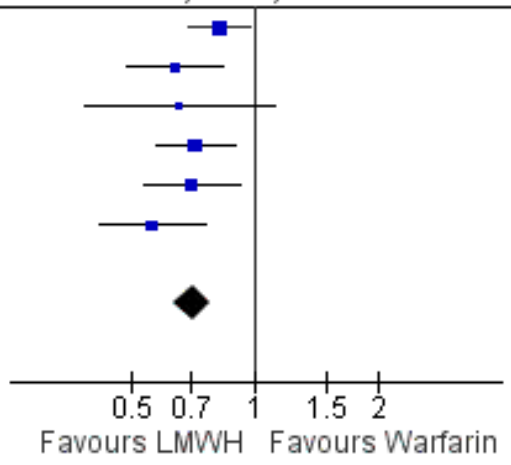
1. Leclerc JR, Geerts WH, et al. Thromb Haemost. 1992; 67:417-23.
2. Fauno P, et al. J Bone Joint Surg Am. 1994; 76:1814-8.
3. Colwell CW, Jr., et al. Clin Orthop Relat Res. 1995; 19-27.

Effect of Warfarin versus LMWH in the Prevention of DVT in Randomised Controlled Studies in Knee Replacement

	LMWH		Warfarin			Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year	M-H, Fixed, 95% CI
Hull	116	258	152	277	28.0%	0.82 [0.69, 0.97]	1993	
RDHAG	78	299	60	147	15.3%	0.64 [0.49, 0.84]	1994	
Hamulyak	16	65	23	61	4.5%	0.65 [0.38, 1.11]	1995	
Leclerc	76	206	109	211	20.5%	0.71 [0.57, 0.89]	1996	
Heit	62	231	85	222	16.5%	0.70 [0.53, 0.92]	1997	
Fitzgerald	44	173	80	176	15.1%	0.56 [0.41, 0.76]	2001	
Total (95% CI)		**1232**		**1094**	**100.0%**	**0.70 [0.63, 0.78]**		
Total events	392		509					

Heterogeneity: Chi² = 5.79, df = 5 (P = 0.33); I² = 14%

Test for overall effect: Z = 6.70 (P < 0.00001)



DVT diagnosed by surveillance with phlebography in randomised controlled studies of patients having knee replacement[1-6]

1. Hull R, et al. N Engl J Med. 1993; 329:1370-6.
2. Leclerc JR, et al.. Ann Intern Med. 1996; 124:619-26.
3. RD Heparin Arthroplasty Group. J Bone Joint Surg Am. 1994; 76:1174-85.
4. Hamulyak K, et al. Thromb Haemost. 1995; 74:1428-31.
5. Heit JA, et al. Thromb Haemost. 1997; 77:32-8.
6. Fitzgerald RH, Jr., et al. J Bone Joint Surg Am. 2001; 83-A:900-6.

TKR Prophylaxis Recommendations
General Considerations: Fondaparinux

- **Fondaparinux (2.5 mg once daily starting 6 h after surgery) was more effective than enoxaparin (30mg BID starting 12-24 h after surgery)[1]**
  - VTE (defined as venographically detected DVT, symptomatic DVT or symptomatic PE) was reduced from 27.8% in the enoxaparin group to 12.5% in the fondaparinux group (RR 0.45; 95% CI 0.32 to 0.62).
  - Major bleeding was more common with fondaparinux (2.1% vs 0.2 % p = 0.006)
  - Increased rate of bleeding with fondaparinux was driven by a minority of patients given fondaparinux within 6 h of surgery
- **Efficacy of fondaparinux confirmed in meta-analysis[2]**

1. Bauer KA, et al. N Engl J Med. 2001; 345:1305-10.
2. Turpie AG, et al. Arch Intern Med. 2002; 162:1833-40

TKR Prophylaxis Recommendations
General Considerations: Rivaroxaban

- **Two studies (RECORD3 and RECORD4) have compared rivaroxaban with enoxaparin in TKR patients**
- **RECORD3 study[1]: Both prophylactic regimens given for 10-14 days**
  - Primary endpoint of total VTE was 18.9 % enoxaparin and 9.6% for rivaroxaban,($P < 0.001$). Incidence of venographic DVT was 2.6% in the enoxaparin group and 1.0% in the rivaroxaban group (absolute risk reduction, 1.6%; 95% CI, 0.4 to 2.8; $P < 0.01$ for non-inferiority)
  - No significant difference in the incidence of major and non-major clinically relevant bleeding in the two groups
- **RECORD4 study[2] compared the efficacy and safety of rivaroxaban with the commonly used North American regimen of enoxaparin 30 mg twice daily until day 11 to 15**
  - Incidence of venographic VTE, PE or death reduced from 10.1% with enoxaparin to 6.9% with rivaroxaban (RR 0.69; 95% CI 0.51 to 0.92)
  - No significant difference in the incidence of major and non-major clinically relevant bleeding in the two groups

1. Lassen MR, et al. N Engl J Med. 2008; 358:2776-86.
2. Turpie AG, et al. Lancet. 2009; 373:1673-80.

TKR Prophylaxis Recommendations
General Considerations: Apixaban

- **2 RCT compared apixaban with enoxaparin**
- **Study 1: Overall rate of primary events was higher with apixaban (9.0%) than enoxaparin (8.8%) and did not meet the non-inferiority criteria[1]**
- **Study 2: Demonstrated superiority against enoxaparin 40 mg once daily[2]**
  - Primary efficacy outcome 15% with apixaban and 24% with enoxaparin (RR 0.62; 95% CI 0.51 to 0.74, P < 0.0001)
  - Nosignificant difference in bleeding between the two groups

1. Lassen MR, et al. N Engl J Med. 2009; 361:594-604.
2. Lassen MR, et al. Lancet. 2010; 375:807-15.

TKR Prophylaxis Recommendations
General Considerations: Dabigatran

- **2 RCT evaluated dabigatran in TKR patients**
- **Study 1: RE-MODEL[1]: Compared dabigatran 150 mg, dabigatran 220 mg and enoxaparin 40 mg for 6-10 days**
  - The primary endpoint of total VTE and all-cause mortality occurred in 40.5%, 36.4% and 37.7% of the groups respectively (P = 0.0003 and 0.017 for non-inferiority of each group versus enoxaparin)
- **Study 2: RE-MOBILIZE[2]: Compared dabigatran 150 mg, dabigatran 220 and enoxaparin 30 mg twice daily administered for 12-15 days**
  - Primary endpoint of total VTE and all-cause mortality occurred in 33.7%, 31.1% and 25.3% of the three groups respectively
  - Dabigatran 220 and 110 mg showed inferior efficacy to enoxaparin (P=.02 and P < .001 respectively)
  - No significant difference was observed in mortality rates
- **No difference in major bleeding events between the various groups in either study**

1. Eriksson BI, et al. J Thromb Haemost. 2007; 5:2178-85.
2. Ginsberg JS, et al. J Arthroplasty. 2009; 24:1-9.

TKR Prophylaxis Recommendations
General Considerations: Combined Modalities

- **3 RCT compared combined modalities with LMWH**
  - Study 1: Combination of LMWH plus IPC was more effective than LMWH plus GEC stockings (DVT incidence 0% versus 28%) in 131 THR or TKR patients[1]
  - Study 2: Combination of LMWH plus IPC was more effective than LMWH (DVT incidence 6.6% versus 19.5%) in 277 patients[2]
  - Study 3: Combination of LMWH plus IPC was more effective than LMWH (DVT incidence 0.4% versus 1.7%) in 1803 patients having various orthopedic operations. In the subgroup of 133 TKR patients, The DVT incidence was 3.8% in the combined modalities group and 7.4% in the LMWH group ($P < 0.038$)[3]

1. Silbersack Y, et al. J Bone Joint Surg Br. 2004; 86:809-12.
2. Edwards JZ, et al. J Arthroplasty. 2008; 23:1122-7.
3. Eisele R, et al. J Bone Joint Surg Am. 2007; 89:1050-6.

TKR Prophylaxis Recommendations
General Considerations: Duration of Prophylaxis

- **Extending prophylaxis in TKR patients with LMWH to 30-42 days post-discharge on symptomatic DVT in patients is less (OR 0.74; 95% CI 0.26 to 2.15; p> 0.05) than observed in THR patients (OR 0.33; 95% CI 0.19 to 0.56; p< 0.05)[1]**

1. Eikelboom JW, et al. Lancet. 2001; 358:9-15.

VTE Prophylaxis Recommendations
TKR Orthopedic Surgery

- **Level of Evidence: High**
  - LMWH initiated and dosed according to the manufacturer's recommendations
  - Warfarin (although less effective)
  - Rivaroxaban
  - Apixaban
  - Dabigatran
  - Fondaparinux

VTE Prophylaxis Recommendations
TKR Orthopedic Surgery

- **IPC is an alternative option**
  - Level of evidence: Moderate due to small study size
- **LMWH combined with IPC is more effective than LMWH prophylactic modality used alone and should be considered in all cases**
  - Level of evidence: High

Hip Fracture Surgery

The Risk of VTE
Orthopedic TKR Surgery

- **Hip fracture surgery patients have the highest rates of DVT (46-60%)[1-3] and fatal PE (2.5-7.5%)[3-5]**
- **VTE risk period persists for 2-3 months after hip fracture surgery in spite of common short-term prophylaxis[6,7]**
- **Three month risk of overall death is 13%[8]**
- **Majority of death due to vascular events despite short-term prophylaxis[9,10]**

1. Powers PJ, et al. Arch Intern Med. 1989; 149:771-4.
2. Snook GA, et al. Clin Orthop Relat Res. 1981; 21-4.
3. Agnelli G, et al. Thromb Haemost. 1992; 67:203-8.
4. Haake DA, et al. Clin Orthop Relat Res. 1989; 212-31.
5. Todd CJ, et al. BMJ. 1995; 311:1025.
6. Dahl OE, et al. Acta Orthop Scand. 2000; 71:47-50.
7. Dahl OE, et al. Acta Orthop Scand. 2003; 74:299-304.
8. Barrett JA, et al. Osteoporos Int. 2003; 14:889-94.
9. Lie SA, et al. Acta Orthop Scand. 2000; 71:19-27.
10. Lie SA, et al. Acta Orthop Scand. 2002; 73:392-9.

Frequency of All DVT in Hip Fracture Surgery in the Absence of Prophylaxis

Study	No. of Studies	Patients (n)	DVT Incidence	95% CI
Ahlberg et al, 1968[1]		45	16	
Checketts & Bradley, 1974[2]		26	13	
Darke, 1972[3]		66	11	
Galasko et al, 1976[4]		50	23	
Gallus et al, 1973[5]		23	11	
Kakkar et al, 1972[6]		50	20	
Lahnborg, 1980[7]		69	28	
Montrey et al, 1985[8]		81	22	
Morris & Mitchell, 1976[9]		74	50	
Morris & Mitchell, 1977[10]		76	49	
Myhre & Holen, 1969[11]		55	22	
Powers et al, 1989[12]		63	29	
Rogers et al, 1978[13]		37	19	
Svend-Hansen et al, 1981[14]		65	28	
Xabregas et al, 1978[15]		25	12	
Total	**15**	**805**	**353 (44%)**	**40% to 47%**

Diagnosed by surveillance with objective methods. Listed frequency is true for the total groups of patients. Presence of additional risk factors indicated in the text is likely to increase the risk of thromboembolism for individual patients.

Frequency of All DVT in Hip Fracture Surgery in the Absence of Prophylaxis

1. Ahlberg A, et al. Acta Chir Scand Suppl. 1968; 387:83-5.
2. Checketts RG, et al. Injury. 1974; 6:42-4.
3. Darke SG. et al. J Bone Joint Surg Br. 1972; 54:615-20.
4. Galasko CS, et al. Acta Orthop Scand. 1976; 47:276-82.
5. Gallus AS, et al. N Engl J Med. 1973; 288:545-51.
6. Kakkar VV, et al. Lancet. 1972; 2:101-6.
7. Lahnborg G. Acta Chir Scand. 1980; 146:319-22.
8. Montrey JS, et al. J Trauma. 1985; 25:534-7.
9. Morris GK, et al. Lancet. 1976; 2:869-72.
10. Morris GK, et al. Br Med J. 1977; 1:535-7.
11. Myhre HO, et al. Nord Med. 1969; 82:1534-8.
12. Powers PJ, et al. Arch Intern Med. 1989; 149:771-4.
13. Rogers PH, et al. J Bone Joint Surg Am. 1978; 60:758-62.
14. Svend-Hansen H, et al. Acta Orthop Scand. 1981; 52:77-80.
15. Xabregas A, et al. Med J Aust. 1978; 1:620-2.

Hip Fracture Surgery Prophylaxis Recommendations
General Considerations

- **Prophylaxis should start as soon as possible because the risks of DVT and PE including fatal PE are high**
- **Prophylaxis should be approached similar to elective hip surgery**

Hip Fracture Surgery Prophylaxis Recommendations
General Considerations

- **Delayed hospitalization or surgery with hip fractures is associated with high DVT incidence prior to surgery[1-4]**
  - Pre-operative DVT as shown by venography is up to 62% for all DVT and 14% for proximal DVT when the delay is 48 h or more[4]
- **Strongly recommended prophylaxis is commenced as close to the fracture as possible**
- **Prophylaxis should be restarted once post-operative haemostasis has been achieved**
- **None of the new oral anticoagulants have been tested in the hip fracture population**

1. Roberts TS, et al. Clin Orthop Relat Res. 1990; 198-203.
2. Girasole GJ, et al. Orthop Rev. 1994; 23:411-6.
3. Hefley FG, Jr., et al. J Bone Joint Surg Am. 1996; 78:581-3.
4. Zahn HR, et al. Injury. 1999; 30:605-7.

Hip Fracture Surgery Prophylaxis Recommendations
General Considerations: IPC, FIT with GEC

- **Reduction in asymptomatic DVT has been demonstrated by IPC (RR 0.2; 95% CI 0.07 to 0.55)[1] and FIT in combination with GEC (RR 0.32; 95% CI 0.32 to 0.67)[2]**
- **A recent study demonstrated a reduction in the combined endpoint of PE and proximal DVT from 12% in the group without prophylaxis to 4% in the IPC group[3]**
- **Additional studies are needed**

1. Hartman JT, et al. J Bone Joint Surg Am. 1982; 64:1059-62.
2. Stranks GJ, et al. J Bone Joint Surg Br. 1992; 74:775-8.
3. Fisher CG, Bet al. J Orthop Trauma. 1995; 9:1-7.

Hip Fracture Surgery Prophylaxis Recommendations
General Considerations: Antiplatelet Agents

- **Meta-analysis of antiplatelet therapy in traumatic orthopedic surgery is only slightly effective for protection against DVT (RR 0.86; 95% CI 0.73 to 1)[1]**
- **Observed reduction in the risk of PE is substantial (RR 0.4; 95% CI 0.22 to 0.71)**

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

Hip Fracture Surgery Prophylaxis Recommendations
General Considerations: Antiplatelet Agents

- **Aspirin (160 mg daily for 35 days) was studied in a RCT of hip fracture patients (N=13,356) and elective hip or knee arthroplasty (N=4,088 patients)[1]**
  - Study failed to detect any difference between the placebo and aspirin groups in the primary endpoint of total mortality
  - Subgroup analysis of hip fracture patients demonstrated aspirin reduced the incidence of symptomatic DVT by 29% (95% CI 3% to 48%; p=0.03) and PE by 43% (95% CI 18% to 60%; p=0.002)
  - PE or DVT was confirmed in 105 (1.6%) of 6,679 patients assigned aspirin compared with 165 (2.5%) of 6,677 patients assigned placebo, an absolute reduction of 9 per 1000 and relative risk reduction of 36% (95% CI 19% to 50%; p=0.0003)
  - Transfusion requirements and bleeding offset the reduction in VTE
- **Aspirin alone is not recommended for routine thrombophylaxis**

1. Pulmonary Embolism Prevention (PEP) trial. Lancet. 2000; 355:1295-302.

Hip Fracture Surgery Prophylaxis Recommendations
General Considerations: LDUH

- **LDUH has been demonstrated effective in reducing asymptomatic DVT in several older investigations (RR 0.51; 95% CI 0.42 to 0.62)** [1]
- **Significant reduction in total PE was not demonstrated**[1]
  - However, there was a significant reduction in fatal PE

1. Collins R, et al. N Engl J Med. 1988; 318:1162-73.

Hip Fracture Surgery Prophylaxis Recommendations
General Considerations: LMWH

- **LMWH has been compared against placebo,[1,2] LDUH,[3] danaparoid,[4] high dose (40mg enoxaparin) LMWH[5] and fondaparinux[6]**
- **LMWH has been found to be equally effective as LDUH without increase in hemorrhagic complications[7]**

1. Kalodiki EP, et al. Int Angiol. 1996; 15:162-8.
2. Lausen I, et al. Eur J Surg. 1998; 164:657-63.
3. Monreal M, et al. J Trauma. 1989; 29:873-5.
4. TIFDED Study Group. Haemostasis. 1999; 29:310-7.
5. Barsotti J, et al. J Orthop Trauma. 1990; 4:371-5.
6. Eriksson BI, et al. N Engl J Med. 2001; 345:1298-304.
7. Handoll HH, et al. Cochrane Database Syst Rev. 2002; CD000305.

Hip Fracture Surgery Prophylaxis Recommendations
General Considerations: VKA

- **Three RCT have demonstrated VKA are effective in preventing asymptomatic DVT with a 61% RR reduction for DVT and 66% for proximal DVT, compared with no prophylaxis[1-3]**
- **Hemorrhagic complications reported varied from 0% to 47% without any increased bleeding in the most recent trial[3]**

1. Powers PJ, et al. Arch Intern Med. 1989; 149:771-4.
2. Borgstroem S, et al. Acta Chir Scand. 1965; 129:500-8.
3. Hamilton HW, et al. J Bone Joint Surg Br. 1970; 52:268-89

Hip Fracture Surgery Prophylaxis Recommendations
General Considerations: Fondaparinux

- **Fondaparinux given for 11 days was more effective when compared with LMWH in reducing VTE from 19.1 % to 8.3% (RR 0.46; 95% CI 0.32 to 0.59) and proximal DVT from 4.3% to 0.9% (RR 0.22; 95% CI 0.09 to 0.53)[1]**
  - No difference in major bleeding but minor bleeding increased (2.1 % with enoxaparin to 4.1 % with fondaparinux group; p = 0.02)
- **Extending fondaparinux for an additional 3 weeks following initial 7 days of therapy reported venographic DVT in 1.4% of the extended fondaparinux group versus 35% with placebo (RR 0.04; 95% CI 0.01 to 0.13)[2]**
  - Symptomatic VTE was 0.3% with fondaparinux and 2.7% with placebo (RR 0.11; 95% CI 0.01 to 0.88)
  - No difference in hemorrhagic complications

1. Eriksson BI, et al. N Engl J Med. 2001; 345:1298-304.
2. Eriksson BI, et al. Arch Intern Med. 2003; 163:1337-42.

VTE Prophylaxis Recommendations
Hip Fracture Orthopedic Surgery

- **Level of Evidence: High**
  - LMWH initiated and dosed according to the manufacturer's recommendations
  - Adjusted dose VKA (INR range 2-3)
  - LDUH

VTE Prophylaxis Recommendations
Hip Fracture Orthopedic Surgery

- **IPC or FIT combined with GEC should be used when contraindications for pharmacological prophylaxis are present**
  - **Level of evidence: Low**
- **If surgery is likely to be delayed, prophylaxis should be initiated with LMWH or IPC or FIT plus GEC as close to the fracture as possible**
  - **Level of evidence: Low)**
- **Prophylaxis should be provided for 4-5 weeks after surgery**
  - **Level of evidence: High**

Knee Arthroscopy

The Risk of VTE
Knee Arthroscopy

- **Knee arthroscopy is a very common procedure**
  - Varies from a simple diagnostic technique to an extensive repair of injured soft tissues
- **Symptomatic VTE is very rare**
  - However, use of a tourniquet, manipulation of the leg and distension of the joint with fluid may all associate this procedure with a risk of VTE
- **Universal prophylaxis would be very expensive with uncertain cost benefit and risk benefit ratios**

The Risk of VTE
Knee Arthroscopy

- **The frequency of DVT in patients undergoing arthroscopic procedures in the absence of prophylaxis varies greatly between studies**
- **Symptomatic DVT occurs in ~0.6%[1]**
- **Meta-analysis of six studies[2-7] demonstrated asymptomatic DVT occurs in ~9.9%**
  - Very large range reported:
    - Ultrasound demonstrates rates from 6%[8] to 16%[6]
    - Venography from 3.1%[211] to 17.9%[2]

1. Dahl OE, et al. Acta Orthop Scand. 2000; 71:47-50.
2. Demers C, et al. Arch Intern Med. 1998; 158:47-50.
3. Williams JS, Jr., et al. Arthroscopy. 1995; 11:701-5.
4. Delis KT, et al. Thromb Haemost. 2001; 86:817-21.
5. Wirth T, et al. Arthroscopy. 2001; 17:393-9.
6. Michot M, et al. Arthroscopy. 2002; 18:257-63.
7. Durica S, et al. Thromb Haemost. 1997; 77(suppl):183.
8. Hoppener MR, et al. Acta Orthop. 2006; 77:767-71.

The Risk of VTE
Knee Arthroscopy

- **Clinical VTE and fatalities are rare but the large number of knee arthroplasty patients makes VTE complications potentially relatively frequent**
- **A clear correlation between age and degree of trauma with VTE exists[1]**
- **Prophylaxis in patients with additional risk factors or when extensive surgery beyond simple diagnostic procedures is justified**

1. Stringer MD, et al. J Bone Joint Surg Br. 1989; 71:492-7.

Frequency of All DVT in Knee Arthroscopy Surgery in the Absence of Prophylaxis

Study	No. of Studies	Patients (n)	DVT Incidence	95% CI
Stringer et al, 1989[1]		48	2	
Demers et al, 1998[2]		184	33	
Williams et al, 1995[3]		85	3	
Jaureguito et al, 1999[4]		239	5	
Delis et al, 2001[5]		102	8	
Wirth et al, 2001[6]		111	5	
Michot et al, 2002[7]		63	10	
Total	**7**	**832**	**66 (8%)**	**6% to 10%**

Diagnosed by surveillance with objective methods. Listed frequency is true for the total groups of patients. Presence of additional risk factors indicated in the text is likely to increase the risk of thromboembolism for individual patients.

1. Stringer MD, et al. J Bone Joint Surg Br. 1989; 71:492-7.
2. Demers C, et al. Arch Intern Med. 1998; 158:47-50.
3. Williams JS, Jr., et al. Arthroscopy. 1995; 11:701-5.
4. Jaureguito JW, et al. Am J Sports Med. 1999; 27:707-10.
5. Delis KT, et al. Thromb Haemost. 2001; 86:817-21.
6. Wirth T, et al. Arthroscopy. 2001; 17:393-9.
7. Michot M, et al. Arthroscopy. 2002; 18:257-63

Knee Arthroscopy Prophylaxis Recommendations
General Considerations: LMWH

- **Meta-analysis of 4 RCT with LMWH given for 5-7 days reported the risk reduction of thrombotic events was 0.16 (95% CI 0.05-0.52) compared with placebo (0.76% vs 8.2%)[1]**
  - All thrombotic events except 1 PE (LMWH group) were distal
  - Adverse effects were more frequent in the intervention group (RR 2.04; 95% CI 1.21 to 3.44) (9.5% vs 4.5%)
  - NNH was 20 for adverse effects

1. Ramos J, et al. Cochrane Database Syst Rev. 2008; CD005259.

Knee Arthroscopy Prophylaxis Recommendations
General Considerations: LMWH

- **Recent study involving 1,317 patients compared LMWH with GEC[1]**
  - 3 month cumulative incidence of asymptomatic proximal DVT, symptomatic VTE, and all-cause mortality was 3.2% (21 of 660 patients) in the GEC group and 0.9% (6 of 657 patients) in the LMWH group (RR 0.29; 95% CI 0.12 to 0.71)
  - Incidence of major or clinically relevant bleeding was 0.3% with GEC and 0.9% with LMWH (NS)

1. Camporese G, et al. Ann Intern Med. 2008; 149:73-82.

VTE Prophylaxis Recommendations
Knee Arthroplasty

- **Simple diagnostic arthroscopy:**
  - Careful risk assessment should be undertaken
  - Routine prophylaxis is not recommended unless other risk factors are present
    - Level of evidence: Low
- **Arthroscopic surgery (e.g. ligament reconstructions):**
  - LMWH starting before or after surgery
    - Level of evidence: Moderate
  - IPC in the presence of contraindications to LMWH until full ambulation
    - Level of evidence: Low

Isolated Below Knee Injuries and Plaster Casts

The Risk of VTE
Isolated Below Knee Injuries and Plaster Casts

- **Patients with below knee injuries and immobilization:**
  - DVT incidence in the range of 10-35% depending on the type and severity of injury[1-6]
  - Risk of clinical PE in the range of 0.4-2.1%[7]
- **RCT following Achilles tendon injury reported a 29% DVT prevalence and no PE in 49 patients treated surgically, but a 39% DVT prevalence and 3 PE in 46 treated non-operatively[8]**
- **Frequency of symptomatic events is unknown**

1. Hjelmstedt A, et al. Acta Chir Scand. 1968; 134:209-18.
2. Abelseth G, et al. J Orthop Trauma. 1996; 10:230-5.
3. Kujath P, et al. Haemostasis. 1993; 23 Suppl 1:20-6.
4. Kock HJ, et al. Lancet. 1995; 346:459-61.
5. Jorgensen PS, et al. Thromb Res. 2002; 105:477-80.
6. Lassen MR, et al. N Engl J Med. 2002; 347:726-30.
7. Barrett JA, et al. Osteoporos Int. 2003; 14:889-94.
8. Nilsson-Helander K, et al. Am J Sports Med. 2007; 35:421-6.

Frequency of All DVT in Patients with Isolated Lower Limb Injuries in the Absence of Prophylaxis

Study	No. of Studies	Patients (n)	DVT Incidence	95% CI
Hjelmstedt & Bergwall, 1968[1]		76	34	
Abelseth et al, 1996[2]		82	18	
Kujath et al, 1993[3]		127	21	
Kock et al, 1995[4]		163	7	
Lassen et al, 2002[5]		159	29	
Jorgensen et al, 2002[6]		77	10	
Lapidus et al, 2007[7]		96	27	
Goel et al, 2009[8]		111	14	
Total	**8**	**891**	**160 (18%)**	**16% to 21%**

Diagnosed by surveillance with objective methods. Listed frequency is true for the total groups of patients. Presence of additional risk factors indicated in the text is likely to increase the risk of thromboembolism for individual patients.

1. Hjelmstedt A, et al. Acta Chir Scand. 1968; 134:209-18.
2. Abelseth G, et al. J Orthop Trauma. 1996; 10:230-5.
3. Kujath P, et al. Haemostasis. 1993; 23 Suppl 1:20-6.
4. Kock HJ, et al Lancet. 1995; 346:459-61.
5. Lassen MR, et al. N Engl J Med. 2002; 347:726-30.
6. .Jorgensen PS, et al. Thromb Res. 2002; 105:477-80.
7. Lapidus LJ, et al. Acta Orthop. 2007; 78:528-35.
8. Goel DP, et al. J Bone Joint Surg Br. 2009; 91:388-94.

Isolated Below Knee/Plaster Casts Prophylaxis
General Considerations

- **Studies and recommendations are difficult to devise secondary to heterogeneity of patient population**
- **Clinical risk assessment is mandatory**
- **Risk of compartment syndrome, exacerbated by chemical thromboprophylaxis, must be considered in tibial fractures**

Isolated Below Knee/Plaster Casts Prophylaxis
General Considerations: LMWH

- Study of 253 patients with plaster casts of which the majority had soft tissue injuries, ultrasound incidence of DVT at cast removal was reduced from 17% in the control group to 5% in a **LMWH** group[1]
- Second study of 339 patients, DVT incidence was reduced from 4% in the control group to zero in the **LMWH** group[2]
- The risk reduction in both studies was 0.21 (95% CI 0.09 to 0.49)

1. Kujath P, et al. Haemostasis. 1993; 23 Suppl 1:20-6.
2. Kock HJ, et al. Lancet. 1995; 346:459-61.

Isolated Below Knee/Plaster Casts Prophylaxis
General Considerations: LMWH

- The 5 week incidence of venographic DVT in patient with lower leg fractures was reduced in each of three studies;
  - 18% in the control group to 10% in the LMWH group (n=293)[1]
  - 13% to 11% (n=150)[2]
  - 13% to 9% (n=238)[3]
- Difference in each study DVT was not significant ($p > 0.05$)
- Patients with Achilles tendon repair had notable reductions in DVT with LMWH; 21% to 6%[1] and 29% to 10%[2]
  - However, in a more recent study[4] (N=93) LMWH was ineffective (28% vs 21%)

1. Lassen MR, et al. N Engl J Med. 2002; 347:726-30.
2. Jorgensen PS, et al. Thromb Res. 2002; 105:477-80.
3. Goel DP, et al. J Bone Joint Surg Br. 2009; 91:388-94.
4. Lapidus LJ, et al. Acta Orthop. 2007; 78:528-35.

Isolated Below Knee/Plaster Casts Prophylaxis
General Considerations: LMWH

- Cochrane review of 1,490 randomised patients concluded an odds ratio of 0.49 for LMWH (95% CI= 0.34 to 0.72) which supports a significant risk reduction for patients immobilized in plaster[1]
  - Symptomatic VTE was significantly reduced (OR 0.16; 95% CI 0.05 to 0.56)
  - Complications were not increased in the LMWH group
- More effective methods are needed in well-defined groups of patients

1. Testroote M, et al. Cochrane Database Syst Rev. 2008; CD006681.

VTE Prophylaxis Recommendations
Isolated Below Knee/Plaster Casts

- **Currently available data based on a mixture of different types of injury suggest that routine LWMW prophylaxis should be considered for isolated limb trauma in the absence of contraindications**
  - Level of evidence: Moderate
- **Prophylaxis needs to be administered in the outpatient setting until the patient is weight bearing**

Multiple Trauma

The Risk of VTE
Multiple Trauma

- **Incidence of DVT in patients who have sustained major trauma is in excess of 50%[1-6]**
- **PE is the third leading cause of death in those who survive beyond the first day[1, 7-9]**
- **Risk is particularly high in patients with spinal cord injury, pelvic fracture and requiring surgery[1,2,10-12]**

1. Geerts WH, et al. N Engl J Med. 1994; 331:1601-6.
2. Kudsk KA, et al. Am J Surg. 1989; 158:515-9.
3. Geerts WH, et al. N Engl J Med. 1996; 335:701-7.
4. Meissner MH. Semin Vasc Surg. 1998; 11:274-82.
5. Rogers FB. Surgery. 2001; 130:1-12.
6. Rogers FB, et al. J Trauma. 2002; 53:142-64.
7. O'Malley KF, et al J Trauma. 1990; 30:748-50.
8. Rogers FB, et al. J Trauma. 1993; 35:637-41; discussion 41-2.
9. Acosta S, et al. Lakartidningen. 1998; 95:5762-3.
10. Meissner MH, et al. J Trauma. 2003; 54:224-31.
11. Velmahos GC, et al. J Trauma. 2000; 49:140-4.
12. Velmahos GC, et al. J Trauma. 2000; 49:132-8; discussion 9.

Frequency of All DVT in Multiple Trauma in the Absence of Prophylaxis

Study	No. of Studies	Patients (n)	DVT Incidence	95% CI
Freeark et al, 1967[1]		124	4	
Geerts et al, 1994[2]		349	201	
Kudsk et al, 1989[3]		38	24	
Shackford et al, 1990[4]		25	1	
Total	**4**	**536**	**270 (50%)**	**46% to 55%**

Diagnosed by surveillance with objective methods. Listed frequency is true for the total groups of patients. Presence of additional risk factors indicated in the text is likely to increase the risk of thromboembolism for individual patients.

1. Freeark RJ, et al. Arch Surg. 1967; 95:567-75.
2. Geerts WH, et al. N Engl J Med. 1994; 331:1601-6.
3. Kudsk KA, et al. Am J Surg. 1989; 158:515-9.
4. Shackford SR, et al. Am J Surg. 1990; 159:365-9.

Multiple Trauma Prophylaxis Recommendations
General Considerations

- **Patients with multiple injuries have a particularly high risk for VTE**
- **Tissue factor released by multiple injuries is potentiated by surgical intervention and the subsequent prolonged immobility[1] which produces marked venous stasis**
- **Routine venography has shown a DVT frequency of 58% in these patients[2]**
- **Well-designed studies in this area are few and thromboprophylaxis has to be assessed according to the risk for bleeding**

1. Meissner MH, et al. J Trauma. 2003; 54:224-31.
2. Geerts WH, et al. N Engl J Med. 1994; 331:1601-6.

Multiple Trauma Prophylaxis Recommendations
General Considerations: LMWH

- **In absence of intracranial bleeding and when bleeding is under control, LMWH (enoxaparin 30 mg BID) started within 36 hours of injury is more effective than LDUH (5 000 IU BID)[1]**
  - LMWH reduced the incidence of venographic DVT from 44% in the LDUH to 31% in the LMWH group (RR 0.70; 95% CI 0.51 to 0.97)
- **The superiority of LMWH to LDUH has been confirmed by a subsequent study and a meta-analysis[2,3]**
  - A RCT comparing nadroparin (fixed dose versus weight-adjusted dose) did not demonstrate any significant difference (0% vs 3%)[4]

1. Geerts WH, et al. N Engl J Med. 1996; 335:701-7.
2. Rogers FB. Surgery. 2001; 130:1-12.
3. Cohn S, et al. J Trauma. 1999; 47:1160-1.
4. Haentjens P. Injury. 1996; 27:385-90.

Multiple Trauma Prophylaxis Recommendations
General Considerations: IPC

- **5 RCT tested the efficacy of IPC in multiple trauma[1-5]**
  - Study 1: 304 patients with pelvic fractures were studied in a small and underpowered trial that the DVT reduction from 11% in the control group to 6% in the IPC group was not significant ($p > 0.05$)[1]
  - Study 2: 149 multiple trauma patients compared IPC to FIT with an incidence of DVT of 6% and 21% respectively ($p < 0.02$)[2]
  - Study 3: IPC or FIT were compared with enoxaparin 30 mg BID in 372 patients with an incidence of DVT of 0.8% in the enoxaparin group, 2.5% in the IPC group and 5.7% in the FIT[3]
  - Study 4: Compared LMWH with IPC in 442 trauma patients[4] and reported incidence of DVT was 0.5% with LMWH and 2.7% with IPC
  - Study 5: Compared LMWH with IPC in 120 trauma patients[5] and found the incidence of DVT was 6.6% with LMWH and 3.3% with IPC
- **Mechanical methods are attractive when chemical prophylaxis is contraindicated**

1. Fisher CG, et al. J Orthop Trauma. 1995; 9:1-7.
2. Elliott CG, et al. J Trauma. 1999; 47:25-32.
3. Knudson MM, et al. J Trauma. 1996; 41:446-59.
4. Ginzburg E, et al. Br J Surg. 2003; 90:1338-44.
5. Kurtoglu M, et al. World J Surg. 2004; 28:807-11.

Multiple Trauma Prophylaxis Recommendations
General Considerations: IVC Filters

- **RCT of the use of IVC filters to prevent PE in trauma patients in the absence of DVT have not been performed**
- **Systematic review of 7 observational studies suggested a potential reduction in PE but an associated 2% to 6% incidence of complications[1]**
  - IVC occlusion, filter migration and thrombosis at the insertion site

1. Rajasekhar A, et al. J Thromb Thrombolysis. 2011; 32:40-6.

VTE Prophylaxis Recommendations
Multiple Trauma

- **LMWH starting as soon as bleeding risk is acceptable**
  - Level of evidence: High
- **IPC in the presence of contraindications to LMWH**
  - Level of evidence: High
- **Continued until full ambulation**
- **Electrical stimulation of calf muscles may be considered in patients when pharmacological prophylaxis is contraindicated and IPC cannot be applied**
  - This is by extrapolation from studies in general surgery
  - Level of evidence: Low
- **The use of IVC filter for primary prevention of PE when LMWH or IPC are contraindicated is not recommended**
  - Level of evidence: Low

Elective Spine Surgery

The Risk of VTE
Elective Spine Surgery

- **Elective spine surgery consists of a mixture of types of surgical procedures ranging from simple laminectomy to complicated multilevel fusion**
  - Procedures performed with posterior, anterior or combined approach
- **Data are very limited for efficacy and safety for different prophylactic methods**
- **Incidence of DVT detected by routine venography in the absence of prophylaxis has been found to be 18%[1,2]**
- **Review of studies on complications in patients having spinal fusion reported a 3.7% incidence for symptomatic DVT and 2.2% for PE[3]**

1. Oda T, et al. Spine. 2000; 25:2962-7.
2. Tetzlaff J, et al. Reg Anesth Pain Med. 1994; 19(suppl):28.
3. Turner JA, et al. Spine. 1992; 17:1-8.

Frequency of All DVT in Elective Spine Surgery Patients in the Absence of Prophylaxis

Study	No. of Studies	Patients (n)	DVT Incidence	95% CI
West et al, 1992[1]		41	6	
Oda et al, 2000[2]		110	17	
Total	**2**	**151**	**23 (15%)**	**10% to 22%**

Diagnosed by surveillance with objective methods. Listed frequency is true for the total groups of patients. Presence of additional risk factors indicated in the text is likely to increase the risk of thromboembolism for individual patients.

1. West JL, et al. Spine. 1992; 17:S254-7.
2. Oda T, et al. Spine. 2000; 25:2962-7.

Elective Spine Surgery Prophylaxis
General Considerations: IVC Filters

- **2 small RCT, one comparing no prophylaxis with LDUH[1] and the other with enoxaparin[2] demonstrated that prophylaxis reduces the incidence of asymptomatic DVT from 20% and 10% respectively to 0%**

1. Gallus AS, et al. JAMA. 1976; 235:1980-2.
2. Macouillard G, et al. Thromb Haemost. 1993; 69:646.

VTE Prophylaxis Recommendations
Elective Spine Surgery

- **Mechanical methods with the use of IPC before operation**
  - Level of evidence: Low
- **LMWH initiated post-surgical**
  - Level of evidence: Low
- **Duration of prophylaxis: Hospitalization period**
  - Level of evidence: Low

Spinal Cord Injury

The Risk of VTE
Spinal Cord Injury

- **Incidence of silent DVT in the absence of prophylaxis is approximately 35%[1,2]**
- **In spinal cord injury patients, PE is the third leading cause of death[1,2]**
  - In a series of 1,649 patients undergoing rehabilitation, symptomatic DVT occurred in 10% and PE in 3%[3]

1. Waring WP, et al. Paraplegia. 1991; 29:8-16.
2. DeVivo MJ. Arch Phys Med Rehabil. 1999; 80:785-90.
3. Chen D, et al. Arch Phys Med Rehabil. 1999; 80:1397-401.

Frequency of All DVT in Spinal Cord Injury Patients in the Absence of Prophylaxis

Study	No. of Studies	Patients (n)	DVT Incidence	95% CI
Bors et al, 1954[1]		99	58	
Brach et al, 1977[2]		10	9	
Rossi et al, 1980[3]		18	13	
Silver, 1974[4]		32	8	
Watson, 1974[5]		234	42	
Frisbie & Sasahara, 1981[6]		17	1	
Merli et al, 1988[7]		17	8	
Myllynen et al, 1985[8]		9	9	
Yelnik et al, 1991[9]		22	12	
Total	**9**	**458**	**160 (35%)**	**31% to 39%**

Diagnosed by surveillance with objective methods. Listed frequency is true for the total groups of patients. Presence of additional risk factors indicated in the text is likely to increase the risk of thromboembolism for individual patients.

1. Bors E, et al. Surg Gynecol Obstet. 1954; 99:451-4.
2. Brach BB, et al. J Trauma. 1977; 17:289-92.
3. Rossi EC, et al. Br J Haematol. 1980; 45:143-51.
4. Silver JR. Paraplegia. 1974; 12:188-96.
5. Watson N. Paraplegia. 1974; 12:197-201.
6. Frisbie JH, et al. Paraplegia. 1981; 19:343-6.
7. Merli GJ, et al. Arch Phys Med Rehabil. 1988; 69:661-4.
8. Myllynen P, et al. J Trauma. 1985; 25:541-3.
9. Yelnik A, et al. Paraplegia. 1991; 29:253-60.

Spinal Cord Injury Prophylaxis Recommendations
General Considerations

- **3 studies have compared LDUH with placebo[1-3]**
  - LDUH was associated with a non-statistical reduction in the number of DVT (20.0% vs 29.4%; OR 0.55; 95% CI 0.11 to 2.64 P=0.46)[4]
- **5 studies have compared LDUH with LMWH[5-9]**
  - Meta-analysis reported that LMWH was associated with a non-statistically significant reduction in the rate of all VTE (24.4% vs 22.7%; OR 0.78; 95% CI 0.24 to 2.53; P=0.60) and a significant reduction total PE (3.1% vs 9.2%; OR 0.29; 95% CI 0.09 to 0.95; P=0.04)[4]
  - LMWH was associated with a nearly significant reduction in major bleeding compared to LDUH (2.4% vs 5.2%; OR 0.50; 95% CI 0.24 to 1.04 P=0.07)[4]

1. Frisbie JH, et al. Paraplegia. 1981; 19:343-6.
2. Merli GJ, et al. Arch Phys Med Rehabil. 1988; 69:661-4.
3. Merli GJ, et al. Paraplegia. 1992; 30:558-62.
4. Paciaroni M, et al. Thromb Haemost. 2008; 99:978-80.
5. Green D, et al. Ann Intern Med. 1990; 113:571-4.
6. Spivack SB, et al. J Spinal Cord Med. 1997; 20:402-5.
7. Thumbikat P, et al. Spinal Cord. 2002; 40:416-20.
8. Anon. J Trauma. 2003; 54:1116-24; discussion 25-6.
9. Anon. J Trauma. 2003; 54:1111-5.

VTE Prophylaxis Recommendations
Spinal Cord Injury

- **LMWH and/or LDUH**
  - Level of evidence: Moderate
- **LMWH plus IPC**
  - Level of evidence: Low
- **Initiation of prophylaxis:**
  - IPC and GEC on admission and LMWH when bleeding risk is acceptable
  - Level of evidence: Low
- **Duration of prophylaxis: LMWH and IPC for 3 months and continuation with GEC indefinitely**
  - Level of evidence: Low