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

VTE Diagnosis and Anticoagulant Treatment

Chapter 14

Diagnosis of DVT

- **Currently, duplex scanning is the initial diagnostic investigation of choice[1-4]**
  - Combines venous compression with blood flow detection
  - Sensitivity and specificity are >98% for DVT above the knee and >95% for DVT in the calf[5-10]

1. Zierler BK. Circulation 2004; 109:I9-14.
2. Kearon C, et al. Ann Intern Med 1998; 128:663-77.
3. Cogo A, et al. BMJ 1998; 316:17-20.
4. Birdwell BG, et al. Ann Intern Med 1998; 128:1-7.
5. Robertson PL, et al. Med J Aust 1995; 163:515-8.
6. Robertson PL, et al. Clin Radiol 1994; 49:382-90.
7. Rose SC, et al. Radiology 1990; 175:639-44.
8. Rosier H, et al. J Radiol 1992; 73:579-84.
9. Savy-Stortz C, et al. Presse Med 1995; 24:341-4.
10. Simons GR, et al. Am J Med 1995; 99:43-7.

Clinical Scoring Systems for Diagnosis of DVT

- **Several clinical scoring systems are available**
  - Wells[1-3]
  - Khan[4]
  - Constans[5]
  - Büller[6]
- **The Wells scoring system is widely used**
  - Classifies patients into probabilities of DVT being present
  - Low = 5%, Moderate = 17%, High = 53%

1. Wells PS, et al. Lancet 1997; 350:1795-8.
2. Wells PS, et al. Thromb Haemost 1999; 81:493-7.
3. Wells PS, et al. JAMA 2006; 295:199-207.
4. Kahn SR, et al. Thromb Haemost 1999; 81:353-7.
5. Constans J, et al. Am J Med 2003; 115:436-40.
6. Buller HR, et al. Ann Intern Med 2009; 150:229-35.

D-dimer ELISA Assay for Diagnosis of DVT

- **D-dimer ELISA assay is considered a 'rule-out' testing procedure for suspected DVT or PE[1]**
  - D-dimer assay lacks specificity because it is often elevated in the presence of many disorders other than DVT
  - Presence of a normal D-dimer test in patients with a low Wells pretest probability can rule out DVT[2,3]
- **Generally considered safe not to treat patients with pharmacologic therapy in the presence of a low Wells score and a normal D-dimer test[4-7]**

1. Wells PS, et al. N Engl J Med 2003; 349:1227-35.
2. Wells PS, et al. Lancet 1997; 350:1795-8.
3. Wells PS, et al. Thromb Haemost 1999; 81:493-7.
4. Cogo A, et al. BMJ 1998; 316:17-20.
5. Johnson SA, et al. JAMA 2010; 303:438-45.
6. Sevestre MA, et al. Thromb Haemost 2009; 102:166-72.
7. Stevens SM, et al. Ann Intern Med 2004; 140:985-91.

Diagnosis of PE

- **Chest multidetector-row (spiral) CT scan for diagnosis of PE is the gold standard[1]**
  - Traditional lung scanning is a second option reserved for patients where the use of contrast agent may be hazardous
- **Wells Scoring System uses a weighted point-score from history and physical examination**
  - May assist in categorizing clinical likelihood of presence of PE
  - Low probability= 1.3%, Moderate probability= 16.2%, High probability = 37.5%[2]
- **Other scoring systems are available[3,4]**
  - Simplified Wells system and Geneva score system

1. Schoepf UJ, et al. Circulation 2004; 110:3276-80.
2. Wells PS, et al. Ann Intern Med 2001; 135:98-107
3. Gibson NS, et al. Thromb Haemost 2008; 99:229-34.
4. Klok FA, et al. Arch Intern Med 2008; 168:2131-6..

Diagnosis of PE

- **Avoidance of unnecessary spiral CT scan protects from exposure to ionizing radiation[1,2]**
  - In young non-pregnant women with suspected PE and normal chest x-ray, nuclear perfusion lung scan may be preferred to CT lung scan in order to reduce lifetime radiation exposure
  - In women with suspected or confirmed pregnancy, the mother may likewise prefer nuclear perfusion lung scanning as an alternative to CT lung scanning to reduce fetal radiation exposure.
- **Nuclear ventilation lung scanning is not recommended in pregnancy[3]**

1. Rathbun SW, et al. Ann Intern Med 2000; 132:227-32.
2. O'Neill J, et al. Br J Radiol 2005; 78:46-50.
3. Stein PD, Matta F. Curr Probl Cardiol 2010; 35:314-76 .

General VTE Treatment Considerations

- **Objectives of acute DVT treatment[1]**
  - Prevent death and disability from PE
  - Decrease risk of recurrent DVT
  - Avoid chronic pulmonary hypertension
  - Avoid peripheral venous disease
  - Avoid post-thrombotic syndrome
- **Note**
  - Asymptomatic below knee DVT can lead to subsequent development of the PTS [2,3] and that 18% of symptomatic calf DVT are associated with proximal extension or recurrence[4] indicating that below knee DVT merits treatment.

1. Buller HR , et al. Chest 2004; 126:401S-428S
2. Wille-Jorgensen P, et al. Thromb Haemost. 2005; 93:236-41.
3. Schindler OS, et al. J Orthop Surg (Hong Kong). 2005; 13:113-9.
4. Gillet JL, et al. J Vasc Surg. 2007; 46:513-9

General Considerations of Therapy
Anticoagulants

- **Initial parenteral heparin and subsequent long-term oral anticoagulation with VKA are both necessary[1,2]**
  - Initial therapy with VKA alone is associated with an unacceptable high rate of recurrent symptomatic VTE[1]
- **Multiple RCTs have resulted in LMWH replacing UFH in the initial treatment of choice for DVT[3-13]**
- **LMWH is as effective and safe as intravenous UFH in patients with acute PE[14-16]**

1. Brandjes DP, et al. N Engl J Med 1992; 327:1485-9.
2. Buller HR, et al. Chest 2004; 126:401S-428S.
3. Albada J, et al. Circulation 1989; 80:935-40.
4. Bratt G, et al. Thromb Haemost 1990; 64:506-10.
5. Collabor Eur Multicentre Study. Thromb Haemost 1991; 65:251-6 .
6. Breddin HK, et al. N Engl J Med 2001; 344:626-31.
7. Hull RD, et al. N Engl J Med 1992; 326:975-82.
8. Prandoni P, et al. Lancet 1992; 339:441-5.
7. Lopaciuk S, et al. Thromb Haemost 1992; 68:14-8.
10. Simonneau G, et al. Arch Intern Med 1993; 153:1541-6.
11. Lindmarker P, et al. Thromb Haemost 1994; 72:186-90.
12. Monreal M, et al. Thromb Haemost 1994; 71:7-11.
13. Alhenc-Gelas M, et al. Thromb Haemost 1994; 71:698-702.
14. Simonneau G, et al. N Engl J Med 1997; 337:663-9.
15. Findik S, et al. Respiration 2002; 69:440-4.
16. The Columbus Investigators. N Engl J Med 1997; 337:657-62.

General Therapy Considerations
Low-Molecular-Weight Heparins

- **Consistent dose-response with predictable bioavailability[1-5]**
  - LMWH does not require routine hematologic monitoring except platelet count
  - May be administered once daily
- **LMWH is the preferred treatment for patients with uncomplicated DVT as outpatients[6-15]**
- **Should be administered at least 5 days and discontinued when the INR is stable and therapeutic (2.0 to 3.0)[16,17]**

1. Breddin HK, et al. N Engl J Med 2001; 344:626-31.
2. Charbonnier BA, et al. Thromb Haemost 1998; 79:897-901.
3. Merli G, et al. Ann Intern Med 2001; 134:191-202.
4. Couturaud F, et al. Thromb Haemost 2001; 86:980-4.
5. Harenberg J, et al. Haematologica 2003; 88:1157-62.
6. Buller HR, et al. Chest 2004; 126:401S-428S.
7. Koopman MM, et al. N Engl J Med 1996; 334:682-7.
8. Levine M, et al. N Engl J Med 1996; 334:677-81.
9. Lapidus L, et al. Pathophysiol Haemost Thromb 2002; 32:59-66.
10. Rodger MA, et al. Thromb Res 2003; 112:13-8.
11. Segal JB, et al. Am J Med 2003; 115:298-308.
12. Spyropoulos AC, et al. Chest 2002; 122:108-14.
13. Boccalon H, et al. Arch Intern Med 2000; 160:1769-73.
14. Dunn AS, et al. Am J Med 2001; 110:458-62.
15. Schwarz T, et al. Br Med J 2001; 322:1212-3.
16. Gallus A, et al. Lancet 1986; 2:1293-6.
17. Hull RD, et al. N Engl J Med 1990; 322:1260-4.

General Therapy Considerations
Fondaparinux

- **Fondaparinux is as effective as IV UFH for initial treatment of DVT and PE[1,2]**
  - May be administered once daily
  - Heparin-induced thrombocytopenia is very rare

1. Buller HR, et al. Ann Intern Med 2004; 140:867-73.
2. Buller HR, et al. N Engl J Med 2003; 349:1695-702.

General Therapy Considerations
Vitamin K Antagonists

- **Vitamin K antagonists (VKA) are effective for the treatment of VTE[1-3]**
  - Dosage should be adjusted to maintain the INR between 2.0 to 3.0 (target INR 2.5)
  - INR >4.0 is associated with an increased frequency of hemorrhagic complications
- **VKA may be started on the first day of UFH or LMWH therapy**
  - Exceptions include patients requiring thrombolysis, surgery, or co-morbidities that predispose to major bleeding[4-6]

1. Hylek EM, Singer DE. Ann Intern Med 1994; 120:897-902.
2. Hull R, et al. N Engl J Med 1982; 307:1676-81.
3. Koo S, et al. Arch Intern Med 2004; 164:1557-60.
4. Gallus A, et al. Lancet 1986; 2:1293-6.
5. Hull RD, et al. N Engl J Med 1990; 322:1260-4.
6. Leroyer C, et al. Haemostasis 1998; 28:70-7.

Major Bleeding Rates of VKA
According to INR Intensity

Trial	INR Range	Event Rate Per 100 Person-Years
Kearon et al, 1999[1]	2.0 – 3.0	3.8
Schulman et al, 1997[2]	2.0 – 2.85	2.4
Kearon et al, 2003[3]	2.0 – 3.0	0.9
Kearon et al, 2003[3]	1.5 – 1.9	1.1

1. Kearon C, et al. N Engl J Med 1999; 340:901-7.
2. Schulman S, et al. N Engl J Med 1997; 336:393-8.
3. Kearon C, et al. N Engl J Med 2003; 349:631-9.

General Considerations
Duration of Anticoagulation Therapy

- **The proper duration of anticoagulant treatment is a balance between preventing VTE recurrence and safety**
  - Estimated 5-year cumulative risk of recurrent VTE after stopping anticoagulation[1]
    - 3% if proximal DVT is provoked by surgery
    - 15% if provoked by a non-surgical reversible risk factor
    - 30% if unprovoked
  - Case-fatality rate of major bleeding complications is consistently around 11% while recurrent VTE decreases from 11 to 3.6% following anticoagulant treatment of 3-6 months %[2]
- **No validated tool to stratify the risk of major bleeding during extended anticoagulant therapy in VTE patients**

1. Kearon C, et al. Chest 2012; 141:e419S-94S.
2. Carrier M, et al. Ann Intern Med 2010; 152:578-89.

General Considerations
Compression Therapy & PTS

- **Effective compression will reduce edema and minimize the damage to the microcirculation[1,2]**
- **Four RCT involving 745 patients have demonstrated that in patients with proximal DVT elastic compression for 2 years will reduce the incidence of PTS from 39% to 19% (RR 0.49; 95% CI 0.38 to 0.62)[3,4]**
- **Appears that treatment with LMWH combined with early ambulation and elastic compression will further prevent the PTS[5,6]**

1. Pierson S, et al. JAMA 1983; 249:242-3.
2. Musani MH, et al. Am J Med 2010; 123:735-40.
3. Prandoni P, et al. Ann Intern Med 2004; 141:249-56.
4. Brandjes DP, et al. Lancet 1997; 349:759-62.
5. Ginsberg JS, et al. Arch Intern Med 2001; 161:2105-9.
6. Aschwanden M, et al. J Vasc Surg 2008; 47:1015-21.
7. Partsch H, et al. J Vasc Surg 2000; 32:861-9.
8. Partsch H, et al. Int Angiol 2004; 23:206-12.

Review of Evidence
Long-term Low Intensity VKA Therapy

- **Low-dose warfarin (INR of 1.5 - 1.9) may be an option for extended periods of anticoagulation**
  - Low-dose warfarin vs. placebo in 508 patients for 6.5 months resulted 14 VTE recurrences with low intensity warfarin (n=255) versus 37 VTE recurrences in the placebo group (n=253) (RR 0.36; 95% CI 0.19 to 0.67; P = 0.001)[1]
- **Conventional anticoagulation versus low-dose warfarin (738 patients) with proximal DVT and PE[2]**
  - Incidence of VTE recurrence up to 4 years was increased from 2% with conventional intensity treatment to 4% with low intensity warfarin (RR 2.67; 95% CI 1.05 to 6.74)
  - Incidence of major hemorrhage was similar (2% in each group)
  - Risk of recurrent VTE increased with an INR < 2

1. Ridker PM, et al. N Engl J Med 2003; 348:1425-34
2. Kearon C, et al. N Engl J Med 2003; 349:631-9. .

Review of Evidence
Rivaroxaban

- **Oral direct inhibitor of factor Xa**
- **EINSTEIN DVT Study[1]**
  - Phase III non-inferiority study, in 3449 subjects with acute, symptomatic DVT
  - Subjects randomized to rivaroxaban or enoxaparin once daily followed by VKA for 3, 6, or 12 months
  - Recurrent VTE occurred in 2.1% in the rivaroxaban group and 3.0% in control group (RR 0.70; 95% CI 0.46 to 1.07; P< 0.0001 for non-inferiority and P = 0.076 for superiority of rivaroxaban)
  - Major bleeding or clinically relevant non-major bleeding occurred in 8.1% of patients in each group

1. Bauersachs R, et al. N Engl J Med 2010; 363:2499-510.

Review of Evidence
Rivaroxaban

- **EINSTEIN Extension Study[1]**
  - 1197 patients who had completed EINSTEIN DVT were randomized to continue with rivaroxaban or placebo for an additional 6-12 month period
  - VTE recurrence rate 1.3% with rivaroxaban versus 7.1% in the placebo group (RR 0.22; 95% CI 0.11 to 0.45; P < 0.001)
  - Non-fatal major bleeding rates were similar (P = 0.11)

1. Bauersachs R, et al. N Engl J Med 2010; 363:2499-510.

Review of Evidence
Rivaroxaban

- **EINSTEIN PE Study[1]**
  - 4,832 patients with symptomatic PE with or without DVT
  - Randomized to rivaroxaban (15 mg twice daily for 3 weeks, followed by 20 mg once daily) or standard therapy (enoxaparin followed by an adjusted-dose of VKA) for 3, 6, or 12 months
  - Rivaroxaban was non-inferior to standard therapy for symptomatic recurrent PE (RR 1.12; 95% CI 0.75 to 1.68; P=0.003 for non-inferiority
  - Major bleeding was 1.1% in the rivaroxaban group and 2.2% in the standard-therapy group (RR 0.49; 95% CI 0.31 to 0.79; P=0.003)

1. Buller HR, et al. N Engl J Med 2009; 366:1287-97.

Review of Evidence
Apixaban

- **Oral inhibitor of factor Xa**
- **Dose ranging study of 520 consecutive patients with symptomatic DVT against standard therapy (LMWH for a minimum of 5 days followed by VKA) for 3 months[1]**
  - Symptomatic recurrence of VTE and extension of thrombus reported 4.7% of patients in the apixaban groups versus 4.2% in the standard therapy group
  - Rate of major and clinically relevant non-major bleeding were similar: 7.3% in apixaban groups and 7.9% in the standard therapy group

1. Buller HR, et al. J Thromb Haemost 2008; 6:1313-8.

Review of Evidence
Dabigatran

- **Oral direct inhibitor of thrombin**
- **Phase III non-inferiority study[1]**
  - 2,539 patients with acute, symptomatic DVT initially treated with parenteral anticoagulation therapy for 8-11 days
  - Randomized to dabigatran or UFH or LMWH followed by VKA for 6 months
  - Recurrent VTE occurred in 2.4% in the dabigatran group versus 2.1% in the control group (RR 1.10; 95% CI 0.66 to 1.84; P< 0.001 for non-inferiority)
  - Major bleeding occurred in 1.6% of patients with dabigatran versus 1.9% in the standard therapy group (RR 0.83; 95% CI 0.46 to 1.49)
  - Adverse events leading to discontinuation of study drug occurred more in the dabigatran group (9.0%) than in the warfarin group (6.8%) (P = 0.05)

1. Schulman S, et al. N Engl J Med 2009; 361:2342-52.

Review of Evidence
Dabigatran

- **RE-SONATE Study**
  - 1,343 patients that completed anticoagulation therapy (6-18 months) for VTE
  - Randomized to continue dabigatran or placebo for a further 6 month period[1]
  - Recurrence rate of VTE was 0.4% in the dabigatran group and 5.6% in the placebo group (RR 0.08; 95% CI 0.02 to 0.25; P < 0.001)
  - Non-fatal major bleeding was similar in both groups (P = 0.996)

1. Schulman S, et al. ISTH. Kyoto, 2011.

Review of Evidence
Dabigatran

- **RE-MEDY Study[1]**
  - 2,856 patients who had completed anticoagulation (3-12 months) for VTE
  - Randomized to dabigatran or conventional warfarin for up to 36 months
  - VTE recurrence rate was 1.8% in the dabigatran group versus 1.3% in the warfarin group (RR 1.44; 95% CI 0.78 to 2.64; P < 0.027 for non inferiority)
  - Rate of major bleeding was 0.9 % with dabigatran versus 1.8% with warfarin (HR 0.52; 95% CI 0.27 70 1.02; P = 0.058)
  - More reports of acute coronary syndrome were observed with dabigatran than warfarin (0.9% vs. 0.2%; P= 0.02)

1. Schulman S, et al. ISTH. Kyoto, 2011.

Review of Evidence
Aspirin

- **RCT of aspirin (100 mg daily for 2 years) versus placebo for the prevention of recurrent VTE[1]**
  - 402 patients who completed 6-18 months standard therapy for initial VTE
  - Incidence of recurrent VTE was 6.6% in the aspirin group versus 11.2% in the placebo group (RR 0.58; 95% CI 0.36 to 0.93)
  - No differences in major bleeding observed
  - Investigators concluded that extended treatment with aspirin may be an appropriate choice in patients at high risk of bleeding with VKA

1. Becattini C, et al. N Engl J Med 2012; 366:1959-67.

Review of Evidence
Long Term Treatment with LMWH

- **5 studies (1,818 patients) compared LMWH to VKA therapy for 3-6 months for VTE recurrence[1-5]**
  - Incidence of recurrent VTE was 4.0% with LMWH versus 6.2% with VKA (RR 0.68; 95% CI 0.45 to 1.022)
- **4 studies (1,201 patients) compared LMWH to VKA in cancer patients for 3-12 months for VTE recurrence[6-9]**
  - Incidence of recurrent VTE reported as 7.5% with LMWH versus 16.1% with VKA (RR 0.46; 95% CI 0.33 to 0.65)
- **Major bleeding in these studies was 3.2% with LMWH and 3.9% with VKA (RR 0.83; 95% CI 0.56 to 1.22)[10]**

1. Hull RD, et al. Am J Med 2007; 120:72-82.
2. Hull RD, et al. Am J Med 2009; 122:762-769 e3.
3. Lopez-Beret P, et al. J Vasc Surg 2001; 33:77-90.
4. Romera A, et al. Eur J Vasc Endovasc Surg 2009; 37:349-56.
5. Lopaciuk S, et al. Thromb Haemost 1999; 81:26-31.
6. Lee AY, et al. N Engl J Med 2003; 349:146-53.
7. Hull RD, et al. Am J Med 2006; 119:1062-72.
8. Deitcher SR, et al. Clin Appl Thromb Hemost 2006; 12:389-96.
9. Meyer G, et al. Arch Intern Med 2002; 162:1729-35.
10. Kearon C, et al. Chest 2012; 141:e419S-94S.

Review of Evidence
Long Term Treatment with LMWH

- **Initial LMWH for 5 days followed by VKA prevents thrombus extension and embolization but does not directly lyse the thrombus**
- **Long term treatment with LMWH demonstrated better recanalization versus standard therapy[1-6]**
  - Meta-analysis (5 studies) reported total recanalization favored long-term LMWH (RR 0.66; 95% CI 0.57 to 0.77; P < 0.0001)[7]
  - Large multicentre study of 480 patients demonstrated a reduction in PTS (RR 0.77; P=0.001)[8]
  - Pooled analysis of 2 studies yielded an 87% risk reduction with LMWH in incidence of venous ulcers (P = 0.019)[7-9]

1. Lopez-Beret P, et al. J Vasc Surg 2001; 33:77-90.
2. Romera A, et al. Eur J Vasc Endovasc Surg 2009; 37:349-56.
3. Das SK, et al. World J Surg 1996; 20:521-6; discussion 526-7.
4. Daskalopoulos ME, et al. Eur J Vasc Endovasc Surg 2007; 34:353-4.
5. Gonzalez-Fajardo JA, et al. J Vasc Surg 1999; 30:283-92.
6. Kakkar VV, et al. Thromb Haemost 2003; 89:674-80
7. Hull RD, et al. Am J Med 2011; 124:756-65.
8. Hull RD, et al. Am J Med 2009; 122:762-769 e3.
9. Daskalopoulos ME, et al. Eur J Vasc Endovasc Surg 2005; 29:638-50.

Review of Evidence
Idraparinux for DVT Treatment

- **Synthetic pentasaccharide inhibitor of factor Xa mediated through antithrombin**
- **RCT of 2,904 DVT patients compared idraparinux (2.5 mg once weekly) to standard therapy[1]**
  - DVT recurrence was 2.9% in the idraparinux group versus 3% in the standard therapy group demonstrating non-inferiority
  - Clinically relevant bleeding was 4.5% in the idraparinux group versus 7% in the standard therapy group (P = 0.004)
- **RCT of 1,215 patients that completed anticoagulant therapy compared idraparinux (2.5 mg once weekly) to placebo for 6 additional months[1]**
  - Recurrent VTE was 1% in the idraparinux group and 3.7% in the placebo group (P < 0.001)
  - Idraparinux had a higher incidence of major bleeding (3.1% vs 0.9%)

1. Buller HR, et al. N Engl J Med 2007; 357:1094-104.

Review of Evidence
Idraparinux for PE Treatment

- **Two studies investigated idraparinux for PE treatment**
  - First study (n=2,215 patients)[1]
    - Incidence of VTE recurrence with idraparinux (2.5 mg SQ weekly) at 3 months was 3.4% compared with 1.6% in the standard therapy group (OR 2.14; 95% CI 1.21 to 3.78)[1]
    - Failed to meet non-inferiority requirement
  - Second study (n=3,202 patients)[2]
    - Idrabiotaparinux has similar pharmacodynamic properties as idraparinux and the advantage of rapid neutralization by IV Avidin
    - Incidence of recurrent PE was 2% in the idrabiotaparinux group and 3% in the warfarin group (P for non-inferiority = 0.0001)
    - Clinically relevant bleeding occurred in 5% of patients in the idrabiotaparinux group and 7% in the warfarin group (OR 0.67; 95% CI 0.49 to 0.91) (P for superiority =0.0098)

1. Buller HR, et al. N Engl J Med 2007; 357:1094-104.
2. Buller HR, et al. Lancet 2012; 379:123-9.

Review of Evidence
Duration of Anticoagulation Therapy

- **Four studies involving 1736 patients with first unprovoked DVT or PE compared 3 months versus 6-12 months of anticoagulation with VKA[1-4]**
  - Incidence of VTE recurrence was 9.7% in the 3 month group and 9.6% in the 6-12 month group (RR 0.99; 95% CI 0.74 to 1.32)
  - Major hemorrhage increased from 0.93% in the 3 month group to 2.4% in the 6-12 month group (RR 2.5; 95% CI 1.16 to 5.83)

1. Pinede L, et al. Circulation 2001; 103:2453-60.
2. Agnelli G, et al. Ann Intern Med 2003; 139:19-25.
3. Agnelli G, et al. N Engl J Med 2001; 345:165-9.
4. Campbell IA, et al. Br Med J 2007; 334:674-80.

Review of Evidence
Duration of Anticoagulation Therapy

- **Four studies involving 676 patients, the majority with second unprovoked VTE compared 3-6 months of anticoagulation with VKA (INR 2-3) to an indefinite duration of anticoagulation[1-4]**
  - Follow-up was 1.4 to 4 years
  - Incidence of VTE recurrence was reduced from 18.8% in the 3-6 month group to 2.7% in the indefinite duration group (RR 0.18; 95% CI 0.09 to 10.36)
  - Major hemorrhage increased from 1.5% in the 3-6 month group to 4.6% in the indefinite duration group (RR 3.03; 95% CI 1.12 to 8.19)

1. Kearon C, et al. N Engl J Med 1999; 340:901-7.
2. Schulman S, et al. N Engl J Med 1997; 336:393-8.
3. Palareti G, et al. N Engl J Med 2006; 355:1780-9.
4. Farraj RS. Saudi Med J 2004; 25:848-51.

VTE Prophylaxis Recommendations
Treatment of VTE - Methods

- **Initial treatment is with IV UFH, LMWH or fondaparinux for at least 5 days**
  - Level of evidence: High
- **LMWH is preferred in most patients. VKA therapy should be commenced on day 1 and continued according to the INR. Initial therapy with LMWH, IV UFH or Fondaparinux should be discontinued when the stable INR is in the therapeutic range (2.0-3.0)**
  - Level of evidence: High

VTE Prophylaxis Recommendations
Treatment of VTE - Methods

- **Rivaroxaban or dabigatran are an alternative therapy in countries where they have been approved. While the former can be used as a single therapy, the latter should be preceded by one week of parenteral anticoagulation with either LMWH or fondaparinux**
  - Level of evidence: High
- **In patients with a history of cancer, LMWH for 3-6 months is the initial treatment**
  - Level of evidence: High
- **During pregnancy, LMWH is the treatment of choice throughout pregnancy and for the first 6 weeks after delivery**
  - Level of evidence: Low

VTE Prophylaxis Recommendations
Treatment of VTE - Methods

- **LMWH for 3-6 months is an alternative to VKA therapy**
  - Level of evidence: High
- **Isolated calf DVT should be treated for 3 months**
  - Level of evidence: Moderate
- **Or isolated calf DVT should be followed by serial ultrasonography on two occasions if anticoagulation is contraindicated**
  - Level of evidence: Low

VTE Prophylaxis Recommendations
Treatment of VTE – Duration of Anticoagulation

- **All patients should receive long-term antithrombotic therapy for at least 3 months**
  - Level of evidence: High
- **In patients with a major provoking risk factor that has been removed 3 months is sufficient**
  - Level of evidence: High

VTE Prophylaxis Recommendations
Treatment of VTE – Duration of Anticoagulation

- **In patients with an unknown risk factor, the duration of anticoagulant therapy may be indefinite. The decision as to the length of therapy is based upon the balance of benefit and harm/bleeding and the patient's preference**
  - Level of evidence: High
- **Patients on continued therapy should undergo periodic reconsideration. The review process involves balance of benefit and harm**
  - Level of evidence: Low

VTE Prophylaxis Recommendations
Treatment of VTE – Duration of Anticoagulation

- **In patients with a minor provoking risk factor, the duration of anticoagulant therapy is uncertain and should be based once again upon the same principles**
  - Level of evidence: Low
- **In patients with more than one episode of VTE the duration of anticoagulant therapy is indefinite**
  - Level of evidence: High

VTE Prophylaxis Recommendations
Treatment of VTE – Duration of Anticoagulation

- **For the long-term prevention of recurrent VTE in patients requiring indefinite anticoagulation rivaroxaban or dabigatran (when approved) can be considered after completing 3-12 months of conventional anticoagulation**
  - Level of evidence: Moderate
- **Immediate mobilization with GEC stockings to be worn for at least 2 years at an ankle pressure of 30-40 mmHg (class II) leads to a more rapid reduction of pain and swelling and reduces the occurrence of PTS**
  - Level of evidence: High

LMWH and Renal Insufficiency
Prophylactic Doses

- **An increased risk of bleeding has not been reported in patients with renal insufficiency receiving prophylactic dosages of LMWH**
- **It is advised that for prophylaxis in patients with severe renal insufficiency, prophylactic doses of LMWH should be adjusted down according to creatinine clearance and manufacturer's instructions**

LMWH and Renal Insufficiency
Therapeutic Doses

- **Dalteparin and tinzaparin may have problems in severe renal failure because they are eliminated mainly through the kidneys**
- **In patients with renal insufficiency, LMWH in therapeutic doses poses a high risk of major bleeding due to its prolonged half-life**
- **The actual risk of major bleeding has not been assessed in prospective studies**

LMWH and Renal Insufficiency
Therapeutic Doses

- **Major bleeding in patients with a creatinine greater than 2 mg/dL and a similar number of patients receiving enoxaparin at equal or greater doses for the same indications has been assessed in 1 retrospective study[1]**
  - Major bleeding occurred in 1 (2%) of 50 patients with normal renal function and 16 (30%) of 53 patients with serum creatinine greater than 2 mg/dL ($P < 0.001$)
- **Although protamine sulphate is efficacious in stopping LMWH induced bleeding in some animal models, there are only limited data for humans**

1. Gerlach AT, et al. Pharmacotherapy 2000; 20:771-5.