

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

Medical Patients

Chapter 9

The Risk of VTE in Medical Patients

- **Autopsy studies show that only 25% of patients dying from PE in general hospitals have had recent surgery, while the rest were immobilized patients with medical illnesses¹**
- **Overall mortality in medical patients admitted to general hospitals is about 10%, and about 1 in 10 hospital deaths is due to PE^{1,2}**
- **Fatal PE is the leading cause of sudden death in hospitalized medical patients**
- **A population based case-cohort study estimated that in the absence of appropriate VTE prophylaxis, 1 of 20 hospitalized medical patients may suffer a fatal PE³**

1. Sandler DA, Martin JF. J R Soc Med 1989; 82(4):203-5.
2. Lindblad B, et al. BMJ 1991; 302(6778):709-11.
3. Heit JA, et al. Arch Intern Med 2000; 160(6):809-15.

Risk of VTE in Medical Patients

- **Acute medical conditions such as stroke, CHF, respiratory disease, or MI are associated with a high risk of VTE^{1,2}**

Risk Factors for VTE in Medical Patients¹⁻⁶

- **Reduced mobility**
- **Cancer with or without chemotherapy**
- **Prior VTE**
- **Advancing age**
- **Obesity**
- **Inherited or acquired coagulation disorders**
- **Infection**
- **Erythropoiesis-stimulating agents or blood transfusion within 90 days of hospitalization⁷**

1. Monreal M, et al. *Thromb Haemost* 1996; 75(2):251-3.
2. Levine MN, et al. *N Engl J Med* 1988; 318(7):404-7.
3. Goldhaber SZ, Tapson VF. *Am J Cardiol* 2004; 93(2):259-62.
4. Goodnough LT, et al. *Cancer* 1984; 54(7):1264-8.
5. Spyropoulos AC. *Chest* 2005; 128(2):958-69.
6. Zakai NA, et al. *J Thromb Haemost* 2004; 2(12):2156-61.
7. Rogers MA, et al. *Circulation* 2012; 125(17):2092-9.

Consequences of PE

- **At 4 years following acute PE, fewer than 50% of patients who initially survive will remain free of:¹**
 - ▶ MI
 - ▶ Stroke
 - ▶ Peripheral arterial disease
 - ▶ Recurrent VTE
 - ▶ Cancer
 - ▶ Chronic Thromboembolic Pulmonary Hypertension

VTE Represents a Pan-Vascular Syndrome

- **VTE is part of a pan-vascular syndrome that includes CAD, PAD, and cerebrovascular disease**
- **VTE and atherothrombosis share a common pathophysiology that includes inflammation, hypercoagulability, and endothelial injury^{1,2}**
 - ▶ Cigarette smoking, hypertension, diabetes, and obesity, which are often modifiable risk factors overlap with risk factors for atherosclerosis³
 - ▶ The Atherosclerosis Risk In Communities Study demonstrated that C-reactive protein levels (a marker of inflammation) > 90th percentile was associated with a marked increase in VTE⁴

1. Piazza G, Goldhaber SZ. Circulation 2010; 121(19):2146-50.

2. Prandoni P, et al. N Engl J Med 2003; 348(15):1435-41.

3. Goldhaber SZ. J Am Coll Cardiol 2010; 56(1):1-7.

4. Folsom AR, et al. Thromb Haemost 2009; 102(4):615-9.

Incidence of DVT * Without Prophylaxis

Stroke Patients

| Study | Patients (n) | DVT Incidence | 95% CI |
|---|-----------------|------------------|------------------|
| Czechanowski & Heinrich 1981 ¹ | 41 | 23 | |
| Dahan et al, 1986 ² | 27 | 3 | |
| Elias et al, 1990 ³ | 15 | 12 | |
| McCarthy et al, 1977 ⁴ | 16 | 12 | |
| McCarthy & Turner 1986 ⁵ | 161 | 117 | |
| Prins et al, 1989 ⁶ | 30 | 15 | |
| Sandset et al, 1990 ⁷ | 50 | 17 | |
| Turpie et al, 1987 ⁸ | 25 | 7 | |
| Warlow et al, 1972 ⁹ | 30 | 18 | |
| Total | 395 | 224 (56%) | 51% - 61% |

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

1. Czechanowski B, Heinrich F. Dtsch Med Wochenschr 1981; 106(39):1254-60.
2. Dahan R, et al. Haemostasis 1986; 16(2):159-64.
3. Elias A, et al. Rev Med Interne 1990; 11(1):95-8.
4. McCarthy ST, et al. Lancet 1977; 2(8042):800-1.
5. McCarthy ST, Turner J. Age Ageing 1986; 15(2):84-8.
6. Prins MH, et al. Haemostasis 1989; 19(5):245-50.
7. Sandset PM, et al. Semin Thromb Hemost 1990; 16 Suppl:25-33.
8. Turpie AG, et al. Lancet 1987; 1(8532):523-6.
9. Warlow C, et al. Lancet 1972; 1(7764):1305-6.

Incidence of DVT * Without Prophylaxis ICU Patients

| Study | Patients (n) | DVT Incidence | 95% CI |
|--|-----------------|------------------|------------------|
| Moser et al, 1981 ¹ (FUT) | 33 | 4 | |
| Cade, 1982 ² (FUT) | 60 | 17 | |
| Fraisse et al, 2000 ³ (Venography) | 85 | 24 | |
| Total | 178 | 45 (25%) | 19% - 32% |

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

1. Moser KM, et al. JAMA 1981; 246(13):1422-4.
2. Cade JF. Crit Care Med 1982; 10(7):448-50.
3. Fraisse F, et al. Am J Respir Crit Care Med 2000; 161(4 Pt 1):1109-14.

Incidence of DVT * Without Prophylaxis Myocardial Infarction Patients

| Study | Patients (n) | DVT Incidence | 95% CI |
|-------------------------------------|-----------------|------------------|------------------|
| Emerson & Marks, 1977 ¹ | 41 | 14 | |
| Handley, 1972 ² | 24 | 7 | |
| Nicolaides et al, 1971 ³ | 51 | 8 | |
| Warlow et al, 1973 ⁴ | 64 | 11 | |
| Total | 180 | 40 (22%) | 16% - 28% |

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

1. Emerson PA, Marks P. Br Med J 1977; 1(6052):18-20.
2. Handley AJ. Lancet 1972; 2(7778):623-4.
3. Nicolaides AN, et al. Br Med J 1971; 1(746):432-4.
4. Warlow C, et al. Lancet 1973; 2(7835):934-6.

Incidence of * Without Prophylaxis

General Medical Patients

| Study | Patients (n) | DVT Incidence | 95% CI |
|---|-----------------|------------------|------------------|
| Gallus et al, 1973 ²⁷ | 15 | 7 | |
| Belch et al, 1981 ²⁸ | 50 | 13 | |
| Prescott et al, 1981 ⁸⁷ | 45 | 4 | |
| Cade, 1982 ²⁹ | 67 | 7 | |
| Dahan et al, 1986 ³² | 131 | 12 | |
| Schonhofer & Kohler, 1998 ⁸⁸ | 196 | 21 | |
| Samama et al, 1999 ¹⁸ | 288 | 43 | |
| Oger et al, 2002 ⁸⁹ | 234 | 14 | |
| Total | 1026 | 121 (12%) | 10% - 14% |

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

1. Gallus AS, et al. N Engl J Med 1973; 288(11):545-51.

2. Belch JJ, et al. Scott Med J 1981; 26(2):115-7.

3. Prescott SM, et al. Am Rev Respir Dis 1981; 123(1):32-6.

4. Cade JF. Crit Care Med 1982; 10(7):448-50.

5. Dahan R, et al. Haemostasis 1986; 16(2):159-64.

6. Schonhofer B, Kohler D. Respiration 1998; 65(3):173-7.

7. Samama MM, et al. N Engl J Med 1999; 341(11):793-800.

8. Oger E, et al. Thromb Haemost 2002; 88(4):592-7.

Incidence of DVT Without Prophylaxis

Geriatric Patients (>65 years)

| Study | Patients (n) | DVT Incidence | 95% CI |
|--------------------------------|--------------|---------------|-----------|
| Dahan et al, 1986 ¹ | 131 | 12 (9%) | 5% to 15% |

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

Underutilization of Prophylaxis Acutely Ill Medical Patients

- **Despite evidence on efficacy, DVT prophylaxis is underutilized in medical patients compared with surgical patients¹⁻⁵**
- **The ENDORSE study was a global cross-sectional study (68,183 patients, 358 hospitals, 32 countries, 6 continents)⁶**
 - ▶ Approximately half of the subjects were judged to be moderate to high risk of developing VTE
 - ▶ However, only 58% of surgical patients and 40% of medical patients at moderate to high risk received guideline-recommended VTE prophylaxis
 - ▶ US hospitals in the best performing quartile:⁷
 - had residency training programs (43% vs. 5%), a larger number of beds (277 vs. 140), and had adopted individualized hospital-wide VTE prophylaxis protocols (76% vs. 40%)

1. Goldhaber SZ, Turpie AG. *Circulation* 2005; 111(1):e1-3.
2. Goldhaber SZ, Tapson VF. *Am J Cardiol* 2004; 93(2):259-62.
3. Goldhaber SZ, et al. *Chest* 2000; 118(6):1680-4.
4. Eikelboom JW, et al. *Haematologica* 2004; 89(5):586-93.

5. Kucher N, et al. *N Engl J Med* 2005; 352(10):969-77.
6. Cohen AT, et al. *Lancet* 2008; 371(9610):387-94.
7. Anderson FA, et al. *Am J Med* 2010; 123(12):1099-1106

Duration of Thromboprophylaxis

- **Patients often receive less physical therapy after discharge, leading to a paradoxical worsening immobility and a presumed higher risk of VTE**
- **Decision to continue VTE prophylaxis after hospital discharge remains difficult**
- **In a review of 1897 VTE episodes occurring in the Worcester, MA healthcare system¹**
 - ▶ 74% of patients suffered DVT or PE in the outpatient setting, not during a hospitalization
 - ▶ 37% of patients with VTE had been hospitalized during the 3 months prior to developing acute VTE
 - ▶ Median length of hospitalization had been 4 days

Duration of Thromboprophylaxis

EXCLAIM Trial (38 days compared with 10 days followed by placebo)

- **The EXCLAIM trial studied extended duration VTE prophylaxis after hospital discharge in high risk medical patients (heart failure, respiratory insufficiency, infection, or reduced mobility)¹**
 - ▶ There was a reduction in symptomatic VTE among those patients receiving extended post-discharge prophylaxis (38 days) with enoxaparin 40 mg daily
 - ▶ At 38 days, VTE was reduced from 4.0% in the placebo group to 2.5% ($P = 0.0011$) in the enoxaparin group (RR 0.62; 95% CI 0.47 to 0.83)
 - ▶ Reduction in risk of VTE events persisted out to 90 days, 5.2% vs. 3.0% ($P = 0.0015$)
 - ▶ Major hemorrhage was more frequent in extended-duration enoxaparin treated patients (0.8% vs. 0.3%) (RR 2.68; 95% CI 1.25 to 5.75)

General Considerations

Acutely Ill Medical Patients

- **All hospitalized medical patients should be assessed for risk of VTE and those at moderate or high risk should receive prophylaxis¹**
- **There are diverse approaches to improve clinical effectiveness of VTE prophylaxis among hospitalized patients²**
 - ▶ Computerized decision support with a single screen electronic alert (shown to reduce symptomatic VTE rate >40%)^{3,4}
 - ▶ Multi-screen alerts may be more effective than single screen alerts⁵
 - ▶ Electronic alert systems maintain their effectiveness over time⁶
 - ▶ Pharmacist-led multifaceted intervention management programs have shown to substantially reduce preventable VTE from 18.6 to 4.9 per 1000 patient discharges (95% CI 44 to 88%)⁷

1. Goldhaber SZ, Turpie AG. *Circulation* 2005; 111(1):e1-3.
2. Piazza G, Goldhaber SZ. *Am J Med* 2009; 122(3):230-2.
3. Piazza G, Goldhaber SZ. *Circulation* 2009; 120(12):1133-7.
4. Kucher N, et al. *N Engl J Med* 2005; 352(10):969-77.

5. Fiumara K, et al. *Thromb Haemost* 2010; 103(2):312-7.
6. Lecumberri R, et al. *Thromb Haemost* 2008; 100(4):699-704.
7. Mahan CE, et al. *Clin Appl Thromb Hemost* 2012; 18(1):45-58.

The IMPROVE Registry

Registry of 15,156 Hospitalized Medical Patients

- **VTE occurred in 184 patients**
- **45% of the 184 events occurred after discharge from hospital**
- **A risk assessment model for VTE was derived from this database using seven independent risk factors for VTE: ¹**
 - ▶ Previous VTE, known thrombophilia, cancer, age >60 years, lower limb paralysis, immobilization for at least one week and admission to ICU or CCU
 - ▶ This model has predicted patients with a very high risk of VTE and was validated in the MAGELLAN Study

IMPROVE Risk Model

Risk Score in Medical Patients*

| Score | Patients % (n) | 3-Month Expected VTE Risk (%) | Observed VTE Rate % (no. VTE events) | Observed PE Rate % (no. of PEs) |
|-------|-------------------|-------------------------------------|--|---------------------------------------|
| 0 | 27 (4029) | 0.4 | 0.4 (14) | 0.3 (11) |
| 1 | 42 (6350) | 0.6 | 0.6 (33) | 0.3 (19) |
| 2 | 16 (2420) | 1.0 | 1.5 (31) | 0.6 (13) |
| 3 | 9 (1335) | 1.7 | 1.6 (18) | 0.8 (9) |
| 4 | 5 (729) | 2.9 | 4.8 (30) | 2.8 (17) |
| 5-10 | 2 (262) | 7.2 | 8.1 (17) | 3.8 (7) |

* Patients with a score of ≥ 4 have a symptomatic VTE event rate of 5.7%

Padua Prediction Score

High Risk of VTE: ≥ 4

| Baseline Features | Score |
|--|-------|
| Active cancer ^a | 3 |
| Previous VTE (with the exclusion of superficial vein thrombosis) | 3 |
| Reduced mobility ^b | 3 |
| Already known thrombophilic condition ^c | 3 |
| Recent (≤ 1 month) trauma and/or surgery | 2 |
| elderly age (≥ 70 years) | 1 |
| Heart and/or respiratory failure | 1 |
| Acute myocardial infarction or ischemic stroke | 1 |
| Acute infection and/or rheumatologic disorder | 1 |
| Obesity (BMI ≥ 30) | 1 |
| Ongoing hormonal treatment | 1 |

^a Patients with local or distant metastases and/or in whom chemotherapy or radiotherapy had been performed in the previous six months

^b Bedrest with bathroom privileges (either due to patients limitations or on physicians order) for at least three days

^c Carriage of defects of antithrombin, protein C or S, factor V Leiden, G20210A prothrombin mutation, antiphospholipid syndrome

Review of Evidence

Acutely Ill Medical Patients

- **3 RCT's in the 1970's & 1980's demonstrated that LDUH was effective in preventing asymptomatic DVT when compared with no prophylaxis¹⁻³**
 - ▶ DVT ↓ from 21% to 5.5% (RR 0.25; 95% CI 0.14 to 0.47)
 - ▶ Significant differences in mortality using LDUH were not shown^{4,5}
- **2 RCT's demonstrated that LMWH was effective in preventing asymptomatic DVT when compared with no prophylaxis^{6,7}**
 - ▶ DVT ↓ from 13% to 4.7% (RR 0.36; 95% CI 0.22 to 0.59)

1. Gallus AS, et al. N Engl J Med 1973; 288(11):545-51.
2. Belch JJ, et al. Scott Med J 1981; 26(2):115-7.
3. Cade JF. Crit Care Med 1982; 10(7):448-50.
4. Halkin H, et al. Ann Intern Med 1982; 96(5):561-5.
5. Gardlund B. Lancet 1996; 347(9012):1357-61.
6. Samama MM, et al. N Engl J Med 1999; 341(11):793-800.
7. Dahan R, et al. Haemostasis 1986; 16(2):159-64.

Review of Evidence

Acutely Ill Medical Patients

- **An international RCT of VTE assessed the efficacy and safety of LMWH (dalteparin) for 14 days vs. placebo in acutely ill medical patients (n = 3706)¹**
 - ▶ By day 21, the incidence of VTE was reduced from 4.96% in the placebo group to 2.77% in the LMWH group (RR 0.55; 95% CI 0.38 to 0.80)
- **4 RCT's from 1996-2003 compared one daily dose of LMWH to LDUH (12- or 8- hourly)²⁻⁵**
 - ▶ No study showed any advantage for LMWH for asymptomatic DVT
 - ▶ A small advantage was apparent when the results were combined (4.24% vs. 5.77%) (RR 0.73; 95% CI 0.56 to 0.97)

1. Leizorovicz A, et al. Circulation 2004; 110(7):874-9
2. Lechler E, et al. Haemostasis 1996; 26 Suppl 2:49-56.
3. Bergmann JF, Neuhart E. Thromb Haemost 1996; 76(4):529-34.
4. Harenberg J, et al. Haemostasis 1996; 26(3):127-39.
5. Kleber FX, et al. Am Heart J 2003; 145(4):614-21..

Review of Evidence

Acutely Ill Medical Patients

- **Meta-analysis of 7 trials compared a prophylactic heparin treatment with a control (15,095 patients)¹**
 - ▶ Demonstrated a significant decrease in DVT and PE with risk reductions of 56% and 58%, respectively
 - ▶ No significant difference in the incidence of major bleeding or death
- **In the same publication, 9 trials compared LMWH to LDUH**
 - ▶ No significant difference regarding DVT, PE, or mortality
 - ▶ 52% lower incidence of major hemorrhage using LMWH (P = 0.049)

Review of Evidence

Acutely III Medical Patients

- **LIFENOX was a large (8,307 patients) multi-centre study that compared enoxaparin plus GEC with placebo plus GEC¹**
 - ▶ Enoxaparin plus GEC did not reduce the mortality rate or improve survival
 - ▶ Rate of death from any cause at day 30 was 4.9% in the enoxaparin plus GEC group and 4.8% in the placebo plus GEC group (RR 1.0; 95% CI 0.8 to 1.2)
 - ▶ Rate of major bleeding was 0.4% in the enoxaparin group and 0.3% in the control group (RR 1.4; 95% CI 0.7 to 3.1)

Review of Evidence

Acutely Ill Medical Patients

- **In a randomized double-blind trial involving acutely ill medical patients over the age of 60, fondaparinux was administered for 6 to 14 days¹**
 - ▶ The incidence of VTE (venographic asymptomatic DVT and symptomatic VTE) was reduced from 10.5% in the placebo group to 5.6% in the fondaparinux group (RR 0.50; 95% CI 0.28 to 0.91)
 - ▶ Symptomatic VTE occurred in five patients in the placebo group and none in the fondaparinux group (P = 0.029)
 - ▶ No PE in the fondaparinux group compared with 5 PE in the placebo group, all of which were fatal
 - ▶ Major bleeding occurred in one patient (0.2%) in each group
 - ▶ At the end of follow-up, 14 patients in the fondaparinux group (3.3%) and 25 in the placebo group (6.0%) had died (P = 0.073)

Review of Evidence

Acutely Ill Medical Patients

- **A meta-analysis of 9 RCT's compared the effect of pharmacological prophylaxis with no prophylaxis in hospitalized medical patients (n=19,958)¹**
 - ▶ Demonstrated a reduction in any PE from 0.49% to 0.20% (RR 0.43; 95% CI, 0.26 to 0.71)
 - ▶ Fatal PE was reduced from 0.41% to 0.15% (RR 0.38; 95% CI 0.21 to 0.69)
 - ▶ Non-significant reduction in symptomatic DVT (3 RCT) from 0.97% to 0.46% (RR 0.47; 95% CI, 0.22 to 1.00)
 - ▶ Non-significant increase in major bleeding from 0.45% to 0.59% (RR 1.32; CI, 0.73 to 2.37)
 - ▶ Pharmacological prophylaxis had no effect on all-cause mortality

Review of Evidence

Acutely Ill Medical Patients

- A systematic review of VTE prophylaxis in hospitalized medical patients and those with stroke (18 trials; 36,122 patients) investigated the effect of heparin prophylaxis (LDUH, LMWH, and fondaparinux)¹ on PE and total mortality
 - ▶ Heparin prophylaxis did not reduce total mortality
 - ▶ PE was reduced from 1.10% to 0.83% (RR 0.74; 95% CI 0.60 to 0.92)
 - ▶ In **medical patients** (10 trials; 20,717 patients), PE was reduced from 1.24% to 0.84% (RR 0.68; 95% CI 0.52 to 0.89), while major bleeding increased from 0.25% to 0.40% (RR 1.23; 95% CI 1.02 to 1.49)
 - ▶ In **patients with stroke** (5 trials; 14,862 patients), PE was reduced from 0.96% to 0.78% (RR 0.86; 95% CI 0.66 to 1.23), while major bleeding increased from 0.88% to 1.50% (RR 1.38; 95% CI 1.02 to 1.17 to 1.62)

Review of Evidence

Acute Ischemic Stroke

- **LDUH was effective in reducing asymptomatic DVT from 75% to 12.5% when compared with no prophylaxis in one study (RR 0.30; 95% CI 0.22 to 0.41)¹**
- **A low molecular weight heparinoid (danaparoid) was also effective (30.4% vs. 2.3%) (RR 0.14; 95% CI 0.03 to 0.64)²**
- **LMWH was effective in reducing asymptomatic DVT when compared with no prophylaxis in two small randomized studies but not in a third one³⁻⁵**

1. McCarthy ST, Turner J. Age Ageing 1986; 15(2):84-8.
2. Turpie AG, et al. Lancet 1987; 1(8532):523-6.
3. Elias A, et al. Rev Med Interne 1990; 11(1):95-8.
4. Prins MH, et al. Haemostasis 1989; 19(5):245-50.
5. Sandset PM, et al. Semin Thromb Hemost 1990; 16 Suppl:25-33.

Review of Evidence

Acute Ischemic Stroke

- **A systematic review of 10 LMWH trials demonstrated that low dosage (< 100 IU/kg) did not reduce the incidence of DVT compared with the placebo groups¹**
- **However, higher doses reduced the incidence of:**
 - ▶ Symptomatic DVT from 5.5% to 2.7% (RR 0.51, 95% CI 0.35 to 0.75)
 - ▶ Symptomatic PE from 1.9% to 0.6% (RR 0.34, 95% CI 0.16 to 0.72)
 - ▶ Increased major intracranial hemorrhage from 1.1% to 2.6% (RR 1.33, 95% 1.13 to 1.55)

Review of Evidence

Acute Ischemic Stroke

- **Two trials have compared danaparoid and one LMWH (enoxaparin) with LDUH¹⁻³**
- **Meta-analysis calculated a reduction of asymptomatic DVT from 22% in the LDUH groups to 13% in the danaparoid or enoxaparin groups (RR 0.59; 95% CI 0.43 to 0.82)⁴**

1. Dumas R, et al. Age Ageing 1994; 23(6):512-6.
2. Turpie AG, et al. Ann Intern Med 1992; 117(5):353-7.
3. Hillbom M, et al. Acta Neurol Scand 2002; 106(2):84-92.
4. Counsell C, Sandercock P. Stroke 2002; 33(7):1925-6.

Review of Evidence

Acute Ischemic Stroke

- In the PREVAIL trial, 1762 patients with acute ischemic stroke, unable to walk unassisted were randomized within 48 h of symptoms to receive either enoxaparin 40 mg daily or LDUH 5000 U 12 hourly for 10 days¹
- Enoxaparin reduced the risk of VTE by 43% compared with UFH (10% vs. 18%) (RR 0.57; 95% CI 0.44 to 0.76)
- The occurrence of any bleeding was similar, 8% in each group (P = 0.83)
- The composite of symptomatic intracranial and major extracranial hemorrhage was 1%, similar between groups

Review of Evidence

Acute Ischemic Stroke

- **CLOTS Trial 1 investigated the effect of GEC on the incidence of DVT in immobile medical patients with stroke¹**
 - ▶ 2518 immobile patients were admitted to the trial within 1 week of acute stroke and were randomized to routine care plus thigh-length GCS (n=1256) or to routine care without GCS (n=1262)
 - ▶ The incidence of symptomatic or asymptomatic DVT on ultrasound was 10.0% in the GCS group and 10.5% in the group without stockings (RR 1.03; 95% CI 0.81 to 1.29)
 - ▶ Skin breaks, ulcers, blisters, and skin necrosis were significantly more common in patients allocated to GCS (16% vs. 5%) (RR 4.05, 95% CI 2.35-6.97)

Review of Evidence

Acute Ischemic Stroke

- **CLOTS Trial 2 also investigated the effect of GEC on the incidence of DVT in immobile medical patients with stroke¹**
 - ▶ 1552 patients were randomized to thigh-length stockings and 1562 patients to below-knee stockings while in the hospital
 - ▶ Incidence of symptomatic or asymptomatic DVT on ultrasound was 6.3% in the thigh length group and 8.8% in the knee length stockings (RR 0.71; 95% CI 0.55 to 0.91)
 - ▶ Skin breaks occurred in 61 patients who received thigh-length stockings (3.9%) and 45 (2.9%) who received below-knee stockings

Review of Evidence

Acute Hemorrhagic Stroke

- **In patients with acute hemorrhagic stroke, the efficacy of LDUH or LMWH in the prevention of VTE has not been studied in RCTs**
- **A RCT of 133 patients with documented intracerebral hemorrhage compared GEC alone to GEC combined with IPC¹**
 - ▶ The incidence of ultrasound detected asymptomatic DVT on day 10 was reduced from 15.9% in the GEC group to 4.7% in the GEC combined with IPC group (RR 0.29; 95% CI 0.08 to 1.00)

Review of Evidence

Duration of Thromboprophylaxis

- **The MAGELLAN Trial¹ studied extended duration of prophylaxis with rivaroxaban for 35 days vs. enoxaparin for 10 days followed by placebo in acutely ill medical patients (N=8101)**
 - ▶ The incidence of asymptomatic proximal DVT detected by ultrasound, symptomatic DVT or PE and VTE related death at 10 days was 2.7% in both groups (RR 0.97; 95% CI 0.71 to 1.33) (P = 0.0025 for non-inferiority)
 - ▶ At 35 days, there was a reduction in in the primary efficacy outcome from 5.7% in the placebo group to 4.4% in the rivaroxaban group (RR 0.62; 95% CI 0.77 to 0.96) (P = 0.021 for superiority)

Review of Evidence

Duration of Thromboprophylaxis

- **The MAGELLAN Trial¹**

- **Safety:**

- ▶ At 10 days, clinically relevant bleeding was increased from 1.2% in the enoxaparin/placebo group to 2.8% in the rivaroxaban group (RR 2.21; 95% CI 1.58 to 3.08)
- ▶ Major hemorrhage was more frequent in rivaroxaban treated patients (0.6% vs. 0.3%) (RR 2.18; 95% CI 1.07 to 4.45)
- ▶ At 35 days, clinically relevant bleeding was increased from 1.7% in the placebo group to 4.1% in the extended prophylaxis group (RR 2.4; 95% CI 1.83 to 3.20)
- ▶ Major hemorrhage was more frequent in the extended-duration rivaroxaban treated patients (1.1% vs. 0.4%) (RR 2.87; 95% CI 1.60 to 5.16)

Review of Evidence

Duration of Thromboprophylaxis

- **The ADOPT Trial¹**

- ▶ 4495 evaluable acutely ill medical patients received either apixaban 2.5 mg twice daily for 30 days or enoxaparin 40 mg daily administered for 6 to 14 days
- ▶ The primary efficacy outcome (asymptomatic proximal DVT detected by ultrasound, symptomatic DVT or PE and VTE related death) at 30 days was 2.7% in the apixaban group and 3.1% in the enoxaparin group (RR 0.87; 95% CI 0.62 to 1.23) (P = 0.44)
- ▶ Major bleeding was more frequent in the apixaban group (0.47% vs 0.19%) (RR 2.58; 95% CI 1.02 to 7.24; P = 0.04)

VTE Prophylaxis Recommendations

Medical Patients

- **All acutely ill medical patients should be routinely assessed for risk of VTE and considered for thromboprophylaxis. In particular, patients over the age of 40 with acute medical illness and/or reduced mobility with one of the following morbidities:**
 - ▶ acute heart failure NYHA class III/IV
 - ▶ respiratory disease (respiratory failure with or without ventilation or exacerbation of respiratory disease)
 - ▶ active cancer requiring therapy
 - ▶ acute infective disease including severe infection and sepsis
 - ▶ thrombophilia
 - ▶ rheumatic disease
 - ▶ ischemic stroke or
 - ▶ acute myocardial infarction

VTE Prophylaxis Recommendations

Medical Patients

- ▶ **Patients with acute medical illness with lower limb paralysis or reduced mobility and one of the following risk factors should also be considered for prophylaxis:**
 - history of VTE
 - malignant disease or
 - age over 75

VTE Prophylaxis Recommendations

Medical Patients

- **For acutely ill medical patients, prophylaxis with LDUH (5000 IU bid or tid) or LMWH (enoxaparin 40 mg daily or dalteparin 5000 U daily) for 6-14 days are recommended**
 - ▶ Level of evidence: High
- **Single daily doses of 2.5 mg of fondaparinux is an alternative**
 - ▶ Level of evidence: High

VTE Prophylaxis Recommendations

Medical Patients

- **In patients with suspected or proven hemorrhagic stroke and in those with ischemic stroke in whom the risks of prophylactic anticoagulant therapy are perceived to outweigh the benefits, IPC combined with GEC is recommended**
 - ▶ Level of evidence: Moderate
 - ▶ This recommendation is based on extrapolation of data from trials in neurosurgical patients, surgical patients and one randomized controlled study in patients with ischemic hemorrhagic stroke.