VTE primary prevention, including hospitalised medical and orthopaedic surgical patients

Serena Granziera; Alexander T. Cohen
1Department of Medicine (DIMED), University of Padova, Padova, Italy; 2Department of Haematological Medicine, Guys and St Thomas’ NHS Foundation Trust, King’s College London, London, UK

Summary
Primary prevention is the key to managing a significant proportion of the burden of venous thromboembolism (VTE), defined as deep venous thrombosis (DVT) or pulmonary embolism (PE). This is because VTE may lead to sudden death or are often misdiagnosed and therefore treatment is not feasible. Primary prevention usually commences in hospital as VTE following hospitalisation adds to the significant disease burden worldwide. Numerous medical, surgical and other risk factors have been recognised and studied as indications for prophylaxis. The risk of VTE continues following admission to hospital with a medical or surgical condition, usually long after discharge and therefore prolonged primary prophylaxis is often recommended. Clinical and observational studies in surgical patients show this risk extends for months and perhaps more than one year, for medical patients the risk extends for at least several weeks. Specific groups of patients at higher risk of developing VTE primary prevention, either pharmaceutical or mechanical, is recommended. The aim of this review is to describe the population at risk, the main related risk factors and the approach to thromboprophylaxis in different populations.

Keywords
Venous thrombosis, prophylaxis, clinical studies, clinical trials, heparins/LMWH, oral anticoagulants

Introduction
Venous thromboembolism (VTE), defined as deep venous thrombosis (DVT) or pulmonary embolism (PE), following hospitalisation adds to the significant disease burden worldwide. The risk of venous thrombosis continues following admission to hospital with a medical or surgical condition, usually long after discharge (1, 2). Clinical and observational studies in surgical patients show this risk extends for months and perhaps more than one year, for medical patients the risk extends for at least several weeks. Specific groups of patients at higher risk of developing VTE have been identified, and, often, primary prevention, either pharmaceutical or mechanical, is recommended. The aim of this chapter is to describe the population at risk, the main related risk factors (Tables 1–3) and the approach to thromboprophylaxis in different populations.

Medical
General medicine
Hospitalised
Definition and risk
Hospitalised medical patients face a significant risk of VTE, with an eightfold increased risk according to American College of Chest Physicians (ACCP) (Table 1) (3). As many as 10–20% of hospitalised medical patients can be expected to develop clinical or asymptomatic VTE secondary to hospitalisation (4). Autopsy data suggest VTE contributes to around 10% of deaths among hospitalised medical patients (5–7). Acute congestive heart failure (NYHA class III or IV) and acute respiratory disease (respiratory failure or an exacerbation of chronic obstructive pulmonary disease, COPD) are well recognised as risk factors for VTE (8, 9). Medical conditions associated with an inflammatory response (acute infectious disease, rheumatologic disorders, and inflammatory bowel disease) have shown a clear association with VTE risk (10–12). Arterial thrombotic diseases, such as acute myocardial infarction (MI) or ischaemic stroke, are associated with a pro-thrombotic state and therefore to convey a risk of VTE.
The main pathophysiologic role among hospitalised medical patients is probably played by the alterations in circulating mediators of coagulation. Increasing amounts of data support the key role of inflammatory markers and tissue factor in activation of the coagulation cascade.

Extensive reviews have described the numerous known VTE risk factors in hospitalised patients (11, 13). The key risk factors for VTE are summarised in Table 1 (13). While a number of quantitative risk assessment models have been developed, none have gained widespread acceptance (14–16). Indeed, validation studies have generally failed to replicate the accuracy of such models to accurately stratify risk of VTE (17). The latest ACCP guidelines adopted the Padua Prediction Score (14). While no score has any clear advantage, the key feature of all is that risk increases rapidly with summation of even a few risk factors. The Padua Prediction Score, however, recognises many patients as at risk where the benefit of therapy has not been tested and may not perform as well as other scores (18).

Current treatment
The choice of VTE prophylaxis is fairly limited and therefore demanding. A longstanding cornerstone of thromboprophylaxis is the use of unfractionated heparin (UFH), and more recently low-molecular-weight heparin (LMWH), or fondaparinux (1, 19, 20). Mechanical prophylaxis has not generally been tested in medical patients except in those with ischaemic stroke where the results have been negative (21). Graduated compression stockings (GCS) or intermittent pneumatic compression (IPC) are used, particularly when bleeding risk prevents use of anticoagulants. The use of antiplatelet agents such as aspirin is not recommended for VTE prophylaxis as there is no evidence of their efficacy and they increase the risk of bleeding.

Novel oral anticoagulants (NOACS)
Two phase III clinical trials evaluated the efficacy and safety of the NOACs for VTE prophylaxis in acutely ill medical patients. The ADOPT trial, comparing an extended course of apixaban to a standard course of enoxaparin, reported a non-significant decrease in VTE related mortality but a significant increase in major bleeding risk (relative risk [RR] 2.6) (22). The MAGELLAN trial evaluated an extended course of rivaroxaban against a standard course of enoxaparin. It revealed rivaroxaban was non-inferior at day 10 and superior at days 30–35 with regards to VTE prevention; however, clinically relevant bleeding rates were increased in the rivaroxaban arm with a RR of 2.3 and 3.0 at day 10 and days 30–35, respectively (23). Therefore new studies are required before clinical use of any of these newer agents among medical patients for either short-term or extended prophylaxis (24).

Conclusion
VTE prophylaxis can at least halve the risk of VTE in medical patients (25, 26). While increasing adoption of VTE prevention strategies appears to have caused a decline in VTE incidence over time, this has disproportionally benefited surgical rather than medical patients. The period 1966–2000 saw a 71% reduction in autopsy-detected fatal PE rates among surgical patients, while among medical patients this decline was only 18% (27, 28). In conclusion, VTE thromboprophylaxis for medical hospitalised patients should be implemented widely.

Outpatients
Following hospital discharge, patients remain at risk for VTE for up to three months, with the peak incidence occurring within the first four weeks (1). Extended duration thromboprophylaxis regimens have successfully reduced the incidence of VTE in post-operative patients (29); however, acute medically ill patients have not been shown to obtain a favourable benefit-to-risk ratio from longer periods of prophylaxis with LMWH or NOACs (30, 31). Medical patients after hospitalisation may be at higher risk of developing VTE, particularly now that many are discharged earlier for recovery in the community setting, or when other risk factors are still present (e.g. reduced mobility).

New studies
There are two on-going studies in this field. The APEX and MARINER studies (32, 33). The aim of the APEX study is to determine whether extended administration of oral betrixaban (35–42 days) is superior to a standard short course of prophylaxis with subcutaneous enoxaparin (10 ± 4 days followed by placebo) in patients with known risk factors for post-discharge VTE. The MARINER study examines post discharge medical patients who are randomised to rivaroxaban or placebo. Both studies allow dose adjustment (33).

Bleeding risk

Patient related
The primary adverse effect of anticoagulation is the increased risk of major bleeding. The risk of bleeding is the most common

Table 1: VTE risk factors in medical patients.

<table>
<thead>
<tr>
<th>Acute illness</th>
<th>Clinical factors</th>
<th>Genetic factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute MI</td>
<td>Age &gt;60</td>
<td>Antithrombin deficiency</td>
</tr>
<tr>
<td>Acute heart failure –</td>
<td>History of VTE</td>
<td>Protein C deficiency</td>
</tr>
<tr>
<td>NYHA class III or IV</td>
<td></td>
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<tr>
<td>Acute infectious disease</td>
<td>History of malignancy</td>
<td>Protein S deficiency</td>
</tr>
<tr>
<td>Acute respiratory disease</td>
<td>Known thrombophilia</td>
<td>Hyperhomocysteinaemia</td>
</tr>
<tr>
<td>Acute rheumatic disease</td>
<td>Extreme limitation in</td>
<td>Raised prothrombin</td>
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<td></td>
<td>mobility</td>
<td>levels</td>
</tr>
<tr>
<td>Autoimmune diseases</td>
<td>Oestrogen therapy or</td>
<td>Factor V Leiden</td>
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<td></td>
<td>pregnancy</td>
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<tr>
<td>Ischaemic stroke</td>
<td>Obesity</td>
<td>Raised factor VIII levels</td>
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<td></td>
<td>Varicose veins</td>
<td>Hyperfibrinogenenaemia</td>
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contraindication to pharmacological thromboprophylaxis (Table 4). Although pharmacologic prophylaxis is associated with a small risk of major bleeding (<1%) in most patients, there are some patients for whom anticoagulant prophylaxis is inappropriate (25). An analysis of the IMPROVE registry resulted in a bleeding risk score. Use of LMWH was associated with a nonsignificant increase in major bleeding rates, adding an absolute 0.5% risk of bleeding compared with no anticoagulant therapy (34). The aim of the bleeding risk score is to identify patients at admission at risk of bleeding and to guide the choice of the most appropriate mode of VTE prophylaxis (mechanical or pharmacologic). The bleeding risk score has yet to be validated in subsequent cohorts (3).

Drug related
Different anticoagulants are associated with different bleeding complications and care should be taken when they are combined with drugs with antithrombotic properties such as antiplatelet agents (e.g. aspirin and clopidogrel) and non-steroidal anti-inflammatory drugs (35, 36).

Critically ill
Critically ill patients are at substantial risk for VTE. The PROTECT study found that once-daily dalteparin is as efficacious as twice-daily UFH in the prevention of DVT and is associated with a similar risk of major bleeding (37). The ACCP guidelines suggest the use of LMWH or UFH in critically ill patients. The use of intermittent pneumatic compression (IPC), but not GCS, was associated with a significantly lower VTE risk in a randomised trial (38). IPC should be considered in medical intensive care unit patients at increased risk of bleeding. However, a number of contraindications to mechanical thromboprophylaxis are recognised.

Cancer – medical oncology

Inpatients
VTE is the most common complication in patients with cancer, and the second most common cause of death in patients with aggressive cancer (39, 40). Many cancers, including tumours of the pancreas, prostate, lung, breast, stomach, and colon, have been associated with a prothrombotic state characterised by clotting factor abnormalities, endothelial dysfunction, and abnormal blood flow due to increased viscosity or stasis (41). Risk factors associated with malignancy are shown in Table 2. Rates up to 60% for VTE in cancer patients have been reported (42). The attributable risk (absolute risk percentage) that cancer contributes to VTE is 18.0% (95% confidence interval [CI] 13.4–22.6) (43). Hence, there is a strong case for the use of thromboprophylaxis in cancer patients with medical conditions, and studies such as the MEDENOX and the PREVENT have shown the potential benefits of LMWH and fondaparinux in cancer patients (1, 19, 20).

Indwelling catheters
The use of central venous catheters (CVCs) increases the risk of VTE in cancer patients. There is some evidence for the use of thromboprophylaxis in patients with CVCs (44), although data is not promising; routine thromboprophylaxis is not recommended (3).

Outpatient chemotherapy
Active cancer requiring therapy is also strongly associated with VTE; nevertheless, evidence on the benefit of thromboprophylaxis in this class of patients is unclear. The Khorana risk score, externally validated in other cohort studies (45), identifies patients at high risk. Although data are still limited, patients at high risk (Khorana score ≥3) should benefit from LMWH for a period of 12 weeks after initiation of a new systemic therapy regimen. Cancer patients at high risk of bleeding should receive mechanical prophylaxis.

Chronically immobilised
Chronically immobile bedridden patients are no more prone to clinically overt venous thromboembolic events than institutionalised mobile patients (46). Until further studies are performed concerning the impact of very prolonged immobilisation on the risk of VTE, there is no evidence to support primary prevention after the first three months of immobilisation and ACCP guidelines suggest against it (3).

Pregnancy
Acute VTE poses significant problems in pregnancy, a time when objective diagnosis and prompt treatment are essential. Events can occur at any stage in pregnancy, but the period of greatest risk is in the weeks after delivery. LMWH is the agent of choice for prevention of venous thromboembolism in pregnancy, and prevention should be provided for at least six weeks before and for at least six weeks after delivery in those at high risk, for example those with previous VTE and certain thrombophilias. NOACs are not recommended for use in pregnancy (47).
Travel

VTE is a risk in passengers on >4 hour trips by plane, train or car, particularly for those with pre-existing risk factors. However, the overall absolute risk of traveller's thrombosis is low with one event in 4,656 flights or 215 events per 1 million travellers (48). Preventive measures should be considered in accordance with an individual's VTE risk category. There is little evidence to support empirical preventive measures such as in-flight exercises and avoiding dehydration. However, they have a reasonable theoretical basis and are easily implemented, thereby supporting their use. There is weak evidence for the use of GCS and LMWH and they are recommended for trips of longer duration, in passengers at moderate or high risk of VTE (49). NOACs may make a better alternative to parenteral anticoagulants and are likely to be more efficacious than aspirin.

Surgical

Orthopaedic surgery

Total hip replacement (THR), total knee replacement (TKR) and hip fracture surgery (HFS)

Definition and risk

Patients undergoing major orthopaedic surgery (THR, TKR and HFS) are at high risk of developing post-operative VTE. With contemporary surgical techniques and current methods of prophylaxis, about 1–3% of patients develop a symptomatic DVT and 0.2–1.1% a PE within 35 days of surgery (36, 50, 51).

Current treatment

Thromboprophylaxis is strongly recommended in major orthopaedic surgery. The available prophylaxis options are LMWH, fondaparinux, UFH and VKAs for all three areas. Dabigatran, apixaban, and rivaroxaban are recommended after THR or TKR, and will be discussed later. Each agent is usually given for at least 10 days after knee arthroplasty, extending to 35 days after hip arthroplasty and HFS (52, 53).

The most recent ACCP guidelines recommend the use of aspirin for primary VTE prophylaxis in orthopaedic surgery patients (36). In our opinion, recommendations for aspirin are based on data from studies with methodological limitations: the Pulmonary Embolism Prevention (PEP) study compared aspirin with placebo irrespective of the concurrent use of anticoagulant prophylaxis (54). However, it had altered primary endpoint definitions, misrepresentation of bleeding event data, and the APT meta-analysis demonstrated a modest reduction in VTE in patients undergoing orthopaedic surgery (55). However, several limitations of this analysis have been identified, including the lack of homogeneity of the studies with respect to study design (e.g. emergency trauma patients were included in the overall elective orthopaedic population (56)), treatments and outcomes.

Current guidelines emphasize that clinicians need to weigh the efficacy of agents for VTE prophylaxis against the risk of bleeding complications for the patients. Bleeding at the operative wound site post-surgery is generally considered to be the most important adverse event associated with the use of anticoagulant drugs, occurring in about 1–2% of patients. In patients with very high risk of bleeding the guidelines recommend the use of mechanical prophylaxis only (36).

NOACS

In contrast to the recommendations for aspirin, there are robust, randomised clinical trial data to support the ACCP recommendations for the use of the direct oral anticoagulants (29, 57–64). These studies have demonstrated reductions in risk of VTE of up to 70% compared with standard of care, LMWH, without significant increases in the risk of major bleeding in THR and TKR.

Conclusion

VTE prophylaxis with anticoagulant drugs should always be recommended in patients undergoing major orthopaedic surgery, unless the risk of bleeding overrides the benefits.

Trauma without lower extremity fractures

Soft tissue injuries such as tears of the knee cartilages or the Achilles tendon are associated with VTE and although pharmacological thromboprophylaxis is not routinely recommended, we recommend it in high risk cases such as those with plaster cast immobilisation (65).
Venous Thromboembolism

Other fractures (excluding hip fractures)

Spinal, pelvic, acetabular and lower limb fractures, femoral, tibial and fibular have all been associated with VTE (66–68). The more proximal fractures seem to have higher risk of VTE. The prevention of VTE in these patients is controversial and practice varies from no therapy to routine thromboprophylaxis (69). Thromboprophylaxis in patients with lower-leg immobilisation results in a non-significant two-thirds reduction in VTE (ACCP) (70).

Knee arthroscopy

The risk of VTE following arthroscopy varies with the extent and type of the procedure (e.g. the length of procedure, the use of tourniquets, diagnostic versus more invasive therapeutic arthroscopies) and the patient risks (e.g. a history of prior VTE) (71, 72). Current guidelines do not recommend routine use of thromboprophylaxis (ACCP), but higher risk procedures and high risk patients should be offered thromboprophylaxis.

Other joint replacements and arthroscopies

Ankle, shoulder and elbow surgery are associated with a significant but lower risk of VTE. Inflammatory arthritis and associated medical conditions are risk factors in this setting. No recommendations can be made on current data; however, the use of anticoagulant thromboprophylaxis is suggested for those at high risk (73, 74).

General trauma

This may vary from major blunt trauma to the head, spinal cord, thorax and abdomen to more peripheral injuries to the limbs (covered in the orthopaedics section) (75). VTE is not uncommon but so is an associated increased bleeding risk. Guidelines recommend the use of anticoagulant thromboprophylaxis or mechanical thromboprophylaxis (ACCP) (36).

Other surgery

Abdominal and pelvic surgery

A large body of evidence has demonstrated the risks of VTE and benefits of thromboprophylaxis in abdominal and pelvic surgery. Risk stratification in general, abdominal and pelvic surgery requires evaluation of both procedure and patient related risk factors. Open abdominal and pelvic procedures are associated with higher VTE risk compared with others including laparoscopic appendectomy and cholecystectomy (Table 3) (35). Patient related risk factors include many of the factors mentioned above for the medically ill patients, including age, cancer, infections and many others (35). Anticoagulant thromboprophylaxis, with UFH, LMWH, or fondaparinux, is recommended in these patients during inpatient stay and for up to 1–2 weeks in non-cancer patients. In very high risk patients such as those with thrombophilia, severe obesity or previous VTE, anticoagulants are also recommended along with mechanical methods. The usual consideration of mechanical methods in those with contraindications for anticoagulants also applies.

Cancer surgery

This subgroup of patients is at particularly high risk of thrombosis, due to the combination of two powerful risk factors for hypercoagulability: cancer and surgery (76). Risk factors associated with malignancy are shown in Table 2. Moreover, in the post-operative period cancer patients are often confined to bed, and may receive chemotherapy or radiotherapy. Extended duration (four weeks) thromboprophylaxis with LMWH is recommended after abdominal or pelvic surgery in patients with cancer (35).

Thoracic surgery

The risk of VTE in patients undergoing thoracic surgery is relatively high, with incidence rates between 7% among patients who did not receive prophylaxis and 1.2% among patients who received it (77, 78). Bleeding and thrombotic risk profile of patients undergoing thoracic surgery is similar to that of patients undergoing abdominal and pelvic surgery. Therefore, although more randomised clinical trials are needed, pharmacologic prophylaxis is recommended to all patients without high risk of bleeding.

Cardiac surgery

Consensus on thromboprophylaxis after open heart surgery is yet to be found, with the European Association for Cardio-thoracic Surgery (EACTS), advising that all patients who undergo cardiac surgery receive prophylactic anticoagulation from the first postoperative day (79). The ACCP guidelines suggest the use of mechan-
ical prophylaxis over pharmacologic prophylaxis (35). The frequent use of antiplatelet agents is likely to increase the risk of bleeding in this subgroup of patients (80). Data on thrombotic and bleeding risk are limited, and definitive conclusions cannot be taken.

Craniotomy

Patients undergoing craniotomy, especially in case of brain tumours, are at increased risk of developing VTE. Nevertheless, the post-operative risk of bleeding limits the use of thromboprophylaxis (LMWH and UFH) to patients with very high risk of venous thrombosis (81). Mechanical prophylaxis should be given to patients undergoing craniotomy (35).

Spinal surgery

Incidence rates of VTE in spinal surgery patients range between 0.5% and 2.5%, although the rate may increase to 15% if asymptomatic patients are included (82, 83). Bleeding complications of thromboprophylaxis may be magnified in the setting of spinal surgery, and therefore, questions remain as to whether its administration should be standardized (84). Guidelines suggest mechanical prophylaxis over LMWH and UFH in patients undergoing spinal surgery, with pharmacologic prophylaxis at later stages and only for patients at high risk of VTE (35).

Caesarean section

Caesarean section combines the thrombotic risk of pregnancy with the risk of surgery. The use of LMWH is recommended in patients with at least one major or two minor additional risk factors by ACCP and the Royal College of Obstetrics and Gynaecology (85, 86). Nevertheless, large randomised trials in women undergoing caesarean section are still missing.

Conflicts of interest

A. T. Cohen is a medical consultant, and has received consultancy and clinical trial funding from many pharmaceutical companies, incl. Bayer, Boehringer-Ingelheim, BMS, Daiichi, GSK, Johnson & Johnson, Mitsubishi Pharma, Pfizer, Portola, Sanofi-Aventis, Schering-Plough, and Takeda. He is an advisor to the UK Government Health Select Committee, the all-party working group on thrombosis, the Department of Health, and the NHS, on the prevention of VTE. He is also and Advisor to Lifeblood: the thrombosis charity and is the founder of the European educational charity the Coalition to Prevent Venous Thromboembolism. S. Granziera reports no conflicts of interest.

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