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Venous thromboembolism

Management in general practice

The diagnosis, treatment and management of venous thromboembolism prophylaxis are increasingly becoming the responsibility of the general practitioner. Effective treatments exist, as do guidelines for management of hospitalised patients. However, very little research has been done into the implementation of management strategies in community based patients.

In 2008, an estimated 15 000–23 000 Australians experienced venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE).[1,2] Retrospective studies report mortality rates following VTE of 5–23%,[3] although in symptomatic patients with adequate anticoagulation, mortality is 1–2%.[4]

Venous thromboembolism also causes significant morbidity from complications including: recurrent thrombotic events, post-thrombotic syndrome (characterised by debilitating leg pain, painful swelling and fibrosis and, in severe cases, leg ulcers), and pulmonary hypertension. Post-thrombotic syndrome occurs in about one-third of DVT sufferers[5] and pulmonary hypertension in 4–5% of PE sufferers.[6]

General practitioners are at the frontline in the diagnosis and treatment of VTE. Hospitalisation for medical or surgical illness is a major risk factor for VTE,[7,8] however, the majority (74% of new VTE) occur after discharge.[7]

Hospital stays for surgical and medical patients are being shortened and prophylaxis duration recommendations are being extended.[9] This means, that in addition to VTE diagnosis and treatment, GPs are increasingly called upon to assess risk for VTE and implement and maintain prophylaxis according to current Australian and New Zealand guidelines.[10,11] Patient groups include at risk medical patients (eg. patients with chronic lung disease and cardiac failure) often managed through hospital in the home (HIH) and early discharge programs.[12]

Risk factors

Venous thromboembolism often results from a coincidence of several risk factors[13] (*Table 1*). Surgery has long been associated with VTE, but it is now evident that medical patients are also at risk, especially those with cancer, moderate to severe congestive heart failure (reported to increase risk by up to 40 fold depending on the degree of cardiac impairment), those with infectious diseases, and those with a history of VTE.[14]

Family history of VTE, especially unprovoked VTE, suggests underlying familial hypercoagulable state. Assessment for thrombophilia

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is recommended in newly diagnosed VTE patients under 60 years of age with no other identifiable precipitating risk factor. Conversely, despite a high media profile, air travel is rarely associated with VTE and is unlikely to be the sole risk factor in VTE sufferers.[15]

As most VTE is provoked by easily recognisable risk factors, effective prophylaxis offers the opportunity of major improvements in health care. Australian guidelines on VTE risk assessment and prophylaxis based on international recommendations suggest prophylaxis for hospitalised patients with an additional VTE risk factor.[11,13,16] With a shift from hospital based to community management, there may be a need to modify this approach. Guidelines should include advice on prophylaxis in nonhospitalised patients with significant VTE risk factors.

Prophylaxis in the general practice setting

Thromboprophylaxis can be achieved by physical or pharmacological means. The decision depends on patient risk factors, the availability of recommended medication and the clinical judgment of the treating doctor. The most effective anticoagulants (recommended for prophylaxis in highest risk patients) are the low molecular weight heparins (LMWH) and fondaparinux. The primary contraindication for pharmacological prophylaxis is a high risk of bleeding or a hypersensitivity to a specific anticoagulant that may result in an adverse reaction.

Mechanical prophylaxis, (ie. intermittent pneumatic compression [IPC] stockings or graduated compression stockings [GCS]) is recommended for patients with a higher than normal risk of bleeding or as an adjunct to more efficacious pharmacological prophylaxis.

It should be noted that aspirin, although more effective than placebo in preventing VTE in orthopaedic patients, is less effective than other thromboprophylactic agents and can cause bleeding.[17] *Table 2* summarises key recommendations for VTE prophylaxis.

Given the efficacy of prophylaxis and clear guidelines at least for hospital patients, uptake of prophylaxis is still surprisingly poor. Hospital audits have found that only 59% (72% in Australia) of high risk surgical patients and 40–50% (42% in Australia) of eligible medical patients received VTE prophylaxis.[18,19] A United States study reported that although 62% of hospital patients were given prophylaxis, as few as 34% received guideline appropriate prophylaxis.[20]

Education programs, audits, hospital policy changes, and alert programs are currently being trialled and/or implemented in teaching hospitals across Australia. It is anticipated that if prophylaxis rates in hospitals are improved, a significant number of VTE cases within the community could be prevented. Importantly, in some cases VTE may actually originate before hospital admission, particularly in patients who are ill for some time before admission. One study of medical patients admitted to hospital found 5.5% had asymptomatic DVT on hospital admission; in patients over 80 years of age, the incidence was 17.8%.[21]

More research into optimal VTE prophylaxis in community based medical patients is warranted. However, evidence for prophylaxis in community based high risk patients following hospitalisation is already clear. Relative risk of symptomatic VTE following elective hip replacement is reduced by 64% with prophylaxis extended from 1 week to 1 month[22] and prolonging prophylaxis after hip fracture

Table 1. Risk factors associated with VTE[34]

General
• Older age
• Immobility, paresis
• Malignancy
• Obesity
• Previous VTE
• Family history of VTE
• Oral contraceptive pill, hormone replacement, tamoxifen
• Venous insufficiency/varicose veins
High risk clinical situations
• Surgery (especially hip and knee surgery or major surgery for malignancy)
• Pregnancy/puerperium
• Acute medical illness
• Congestive cardiac and respiratory failure
• Trauma
• Central venous catheter
Diseases associated with a prothrombotic state
• Myeloproliferative disorders
• Antiphospholipid syndrome
• Paroxysmal nocturnal haemoglobinuria
• Nephrotic syndrome
• Hyperviscosity syndrome
• Inflammatory bowel disease
Inherited thrombophilia
• Factor V Leiden mutation
• Antithrombin, protein C and protein S deficiency
• Prothrombin gene mutation (Factor II G20210A mutation)

reduced the incidence of VTE from 35.0 to 1.4%.[23] Prolonging prophylaxis for patients hospitalised with illnesses such as cancer, ischaemic stroke, heart failure, respiratory failure and infections from a mean of 10 days to a mean of 30 days, reduced VTE incidence by 44% (including a 73% reduction in symptomatic VTE).[9]

Implementation of a prolonged prophylaxis regimen in community based patients is limited by the fact that such a regimen will, in most cases, require regular injections. This is labour and resource intensive. However, oral medications are currently under development and prolonged prophylaxis may be more realistic in the future.

Treatment in the general practice setting

Diagnosis, particularly PE diagnosis, is difficult. In most cases GPs will refer patients to hospital initially to confirm the diagnosis and rule out significant complications. Once diagnosed, the aims of treatment are to relieve symptoms and minimise acute morbidity and mortality. General practitioners are increasingly involved in this initial management phase.

Adequate anticoagulation will prevent initial thrombus extension and embolisation (or re-embolisation), allow established thrombus to stabilise and absorb, and reduce the risk of post-thrombotic syndrome. Without adequate anticoagulation, 50% of patients will experience recurrent symptomatic VTE within 3 months.[24] Therapeutic anticoagulation reduces the incidence of recurrence to about 10% at 2 years.[25] However, even with adequate treatment, complete resolution of DVT is slow; in some studies, 50% of patients, particularly those with large DVT or malignancy, have an abnormal venous ultrasound 1 year after diagnosis and treatment.[26]

Table 2. Key indications, medications and duration of treatment recommended in community based patients with low bleeding risk[3,10,33–37]

Indication for therapy	Medication*	Therapy duration
Prevention of VTE		
• Orthopaedic surgery		
– elective total hip replacement	• LMWH/fondaparinux + GCS/IPC	• 35 days (not less than 10 days)
– elective total knee arthroplasty	• LMWH/fondaparinux + GCS/IPC	• 35 days (not less than 10 days)
– hip fracture surgery	• LMWH/fondaparinux + GCS/IPC	• 35 days (not less than 10 days)
• Major surgery (intra-abdominal or surgery lasting >45 minutes) and age >40 years	• LMWH/UFH/fondaparinux + GCS/IPC	• Until discharge or up to 28 days if high risk
• Medical Illness with additional risk factors†	• LMWH/UFH/fondaparinux	• To resolution of acute illness
• Pregnancy and postpartum + additional risk factors	• LMWH	• 4–6 weeks postpartum
• Travel >5000 km‡	• Adequate hydration, exercise, avoid alcohol, nonrestrictive clothing	• Duration of flight
Treatment of VTE**		
• First episode secondary to reversible risk factors	• LMWH/fondaparinux then OAC	• 3–6 months
• First episode idiopathic VTE	• LMWH/fondaparinux then OAC	• 6 months+
• First episode in patients with cancer	• LMWH (at least 3–6 months then OAC)	• Until cancer resolves
• First episode in patients with antiphospholipid antibody	• LMWH/fondaparinux then OAC	• 12 months†
• Recurrent VTE secondary to reversible risk factors	• LMWH/fondaparinux then OAC	• 6 months
• Recurrent idiopathic VTE	• LMWH/fondaparinux then OAC	• 12 months†
• Pregnancy	• LMWH	• Until at least 6 weeks postpartum and 6 months postdiagnosis
• First episode provoked distal DVT	• LMWH then OAC	• 6 weeks
• First episode unprovoked distal DVT	• LMWH then OAC	• 3 months

* Renal impairment, particularly in the elderly needs to be considered in dosing LMWH and antithrombotic drugs cleared by the kidneys but assuming normal creatinine clearance: for prophylaxis: UFH 5000 IU bd or tds; low molecular weight heparin (LMWH), eg. enoxaparin 40 mg, daltaparin 5000 IU; fondaparinux 2.5 mg. For treatment: LMWH, eg. 100 IU/kg daltaparin bd or 1 mg/kg/day enoxaparin bd; fondaparinux 7.5 mg; OAC, eg. warfarin adjusted to INR 2.5±0.5. If chemical prophylaxis is contraindicated, mechanical methods (eg. GCS or IPC) should be used

** GCS recommended in all cases for up to 2 years

† Ischaemic stroke, history of VTE, active cancer, decompensated cardiac failure, acute on chronic lung disease, acute on chronic inflammatory disease, age >60 years

‡ If traveller has very high risk of recurrent VTE, eg. cancer or history of VTE, GCS during flight or 1 dose of LMWH before departure may be considered

IPC = intermittent pneumatic compression stockings; UFH = unfractionated heparin; OAC = oral anticoagulant; GCS = graduated compression stockings

In most instances (*Table 2*), pharmacological treatment for VTE consists of:

- initiating immediate acting subcutaneous LMWH or unfractionated heparin (intravenous or subcutaneous) or fondaparinux (subcutaneous) with oral warfarin, and
- continuing the injected drug for at least 5 days and until international normalised ratio (INR) is therapeutic (2.5±0.5).

The therapeutic effectiveness and safety of warfarin relies on maintaining the INR in the therapeutic range.[27] Key recommendations on when to cease warfarin and how to proceed when INR goes above the therapeutic range are provided in *Table 3*. A high variability in dose response between patients and significant interactions with drugs and diet means that warfarin therapy is difficult and time consuming to manage.[27] Nonetheless, it remains the most effective and cost efficient drug currently available for the treatment of the majority of patients with VTE.[10,28]

Low molecular weight heparins may be preferred to warfarin in some patients, including cancer patients for whom treatment with warfarin is associated with an increased risk of bleeding and VTE recurrence; monotherapy with LMWH instead of warfarin can halve VTE recurrence in these patients.[29] Low molecular weight heparins are also recommended over warfarin for long term therapy in pregnant women (due to the teratogenic effects associated with warfarin), and as bridging therapy in patients scheduled to undergo surgery (due to LMWH's shorter half life therapeutic anticoagulation can continue closer to surgery time).

A number of new compounds are currently undergoing evaluation in clinical trials. These agents promise weekly subcutaneous dosing (idraparinux) or are orally administered drugs requiring no dose monitoring (eg. rivaroxaban, apixaban, dabigatran). They can be given from the time of diagnosis and continued for 6–12 months or longer if indicated. The major drawback for all these compounds (as with LMWH and fondaparinux) is lack of an effective antidote.

Whatever the drug being prescribed, Australian guidelines recommend continuation of treatment for at least 3 months for provoked VTE and 6–12 months for unprovoked VTE.[10] In some cases, treatment may be continued indefinitely. Each patient's management needs to be customised. Treatment decisions depend on the patient's predisposition to VTE (provoked or unprovoked), the site and extent of thrombus, the presence or absence of symptomatic embolism, and bleeding risk.

Management in the general practice setting

Outpatient management of VTE is becoming increasingly feasible. Deep vein thrombosis patients can be safely managed as outpatients and new compounds may soon streamline treatment. However, it is time consuming with very little financial gain for GPs to manage patients on oral anticoagulants. Also, GPs may only manage a few such patients at any one time, making expertise difficult to build.

Australia may need to look at different models for the management of VTE patients in the community. Perhaps interested GPs could contribute as part of a shared care network. An alternative model is that of the Anticoagulation Clinic at St George Hospital in Sydney, New South Wales. The clinic manages the stabilisation phase of patients on warfarin therapy and any immediate complications or less than routine management decisions, while GPs maintain overall holistic care of the patient and their ongoing treatment. Research into the optimisation of GP management of VTE treatment is being undertaken,[30–32] and initiatives by the National Institute of Clinical Studies of the National Health and Medical Research Council have highlighted VTE prevention as an area for improvement.[33]

Table 3. Key recommendations on warfarin dosing and management[27]

Clinical situation	Recommendation
• Warfarin initiation dose	
– majority of patients	• 5–10 mg for 1 or 2 days with subsequent doses based on INR response
– elderly or bleeding risk patients	• ≤5 mg for 1 or 2 days with subsequent doses based on INR response
• Frequency of dose monitoring	
– initially	• 1 or 2 days after commencement of warfarin and until stable
– when dose is stable	• weekly then fortnightly and then no less than 4 weekly
• INR above therapeutic range	
– >3 and <5; no significant bleeding	• lower or omit dose, monitor more frequently and resume at lower dose when INR therapeutic
– ≥5 with or without bleeding	• cease warfarin and refer to haematologist to manage with vitamin K as appropriate
• Patient requires invasive procedure	• Consider referring to a haematologist or hospital in the home for management of bridging therapy, alternatively:
– low risk of VTE*	– stop warfarin 4–7 days pre-surgery
– intermediate risk of VTE	– stop warfarin 4–7 days pre-surgery, cover patient with low dose UFH or LMWH 2 days pre-surgery; commence LMWH and warfarin postoperatvely
– high risk of VTE	– stop warfarin 4–7 days pre-surgery, cover patient with full dose UFH or LMWH 2 days pre-surgery until 5 hours or 12–24 hours respectively pre-surgery; commence LMWH and warfarin postoperatively
– low risk of bleeding (eg. gynaecologic or orthopaedic surgery)	– continue warfarin at a lower dose (eg. INR 1.3–1.5) for 4–7 days pre-surgery; restart LMWH and warfarin postoperatively

* Low risk VTE includes no recent (>3 month) VTE

Conclusion

Venous thromboembolism is a community based illness associated with significant morbidity and mortality. Risk factors are well characterised. Nonetheless there is evidence that prophylaxis for high risk patients in hospitals is far from adequate. Effective treatment exists for VTE but

requires early detection and intervention. Due to a narrow therapeutic window and high variability between patients, conscientious monitoring, adjustment and individual patient customisation is required.

Research has looked at the management of VTE by specialists and anticoagulant clinics, but assessment of community management of VTE treatment is lacking. As more VTE patients are being managed by GPs in Australia, more research is needed to look at whether patients are being managed according to accepted guidelines and whether GPs are adequately supported to manage these patients.

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