Diagnosis, treatment and management of venous thromboembolism: recent developments relevant to biomedical scientists

A. D. BLANN

Haemostasis, Thrombosis and Vascular Biology Unit, University Department of Medicine, City Hospital, Birmingham B18 7QH, UK

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ABSTRACT

Three documents from government-sponsored bodies have recently provided new guidance on the diagnosis, treatment and management of venous thromboembolism. The Report of the Independent Expert Working Group to the Chief Medical Officer makes recommendations on general administrative arrangements, and provides a strategy for thromboprophylaxis. Among the recommendations of Guideline 46 from the National Institute for Health and Clinical Excellence are that all patients about to undergo surgery should be assessed to identify their risk factors for developing veno-thromboembolic disease, and be offered graduated compression/anti-embolism stockings and/or pharmacoprophylaxis. The National Patient Safety Agency document focuses principally on the management of, and education in, the use of oral anticoagulants. The impact and implications of these three documents for haematology-based biomedical scientists, such as in leading a thrombosis team, directing clinical management, training of healthcare professions, and in patient education, will be discussed.

KEY WORDS: Heparin, low molecular weight. Pulmonary embolism. Thromboembolism. Venous thrombosis. Warfarin.

Introduction

The past 10 years have seen the growing realisation that venous thromboembolism (VTE), manifesting principally as deep vein thrombosis (DVT) and pulmonary embolism (PE), is not only a serious and life-threatening disease but is also amenable to relatively simple prophylaxis and treatment to minimise the risk of recurrence.[1,2] Risk factors for VTE include obesity, cancer, surgery (especially orthopaedic), pregnancy, the puerperium and synthetic hormone use, and inherited thrombophilias, and major treatments include both pharmacological (vitamin K antagonists [e.g., warfarin], unfractionated heparin, low molecular weight heparin [LMWH], fondaparinux and fibrinolysis) and non-pharmacological approaches (e.g., graduated elastic compression stockings [GECSs], intermittent pneumatic compression, inferior vena cava filters and surgical embolectomy).[3–6] Table 1 illustrates the effect of some of these treatments on the DVT rates following a high-risk procedure such as orthopaedic surgery.[7] Numerous guidelines are available from the UK Department of Health[6] and professional interest groups in the UK and USA[7–13] for both general and specific risk factors and situations.

The current interest in VTE can be traced to 2005, when the House of Commons Health Committee (HCHC) published its report on the prevention of VTE in hospitalised patients.[14] Responding to its recommendations, the Department of Health (via the Chief Medical Officer) appointed an independent expert working group and instructed the National Institute for Health and Clinical Excellence (NICE) to issue guidance. These documents have recently been published.[15,16] During the same time period, the National Patient Safety Agency (NPSA) also generated and published a set of guidelines that are summarised as actions that can make anticoagulation therapy safer.[17] The objective of this review is to comment on the implications of these publications for biomedical scientists.

Correspondence to: Dr. A. D. Blann
University Department of Medicine, City Hospital, Birmingham B18 7QH, UK.
Email: a.blann@bham.ac.uk

House of Commons Health Committee

The HCHC published its report on the prevention of VTE in hospitalised patients in February 2005.[14] Drawing on various sources, it found it "astonishing that there has been no development of national guidelines in England and Wales". Several conclusions and recommendations are relevant to biomedical scientists (e.g., that a thrombosis committee be established in each hospital, with a specialist thrombosis team), and suggests that these bodies should be modelled on existing blood transfusion teams and committees.

Thrombosis team

Historically, thrombosis teams have effectively been the group that managed the oral anticoagulant (warfarin) clinic, being probably led by a consultant haematologist with an interest in coagulation, alongside biomedical scientists directly involved in international normalised ratio (INR) generation and/or providing advice to patients and/or actual management of their INRs. Developing teams may have involved other healthcare professional such as clinical scientists, pharmacists and DVT nurses. A remit for a thrombosis team would be to assist in the implementation of the thrombosis committee's objectives (see below), promote

and provide advice and support to clinical teams on the appropriate thromboprophylaxis and risk assessment, actively promote the implementation of good thromboprophylaxis practice, and be a source of training for all hospital staff involved in dealing with patients at risk of VTE.

Thrombosis committee

The Health Committee recommends that a thrombosis committee be formed, which should include representatives from all interested parties, including haematologists, surgeons, physicians, anaesthetists, obstetricians, nursing staff and pharmacists, that would ensure clinical governance and provide a local audit of thromboprophylactic procedures. A potential draft remit would be to promote best practice through local protocols based on national guidelines. In other words, to lead multiprofessional audit of the use of thromboprophylaxis within the trust, focus on specialties where risk is high, promote the education and training of all clinical and support staff, have the authority to modify existing VTE and risk-assessment protocols and to introduce appropriate changes in practice, consult with local patient representative groups, where appropriate, and contribute to clinical governance.

Although the report is a high-quality and well-referenced document, some would say, possibly quite rightly, that it falls short of offering firm practical advice. For example, it emphasises that patients from various clinical backgrounds may be at low-, medium- or high-risk of VTE,[18] and suggests risk factors, but fails to follow through by recommending firm treatment plans, although to some extent the NICE guidelines[16] (known to be in planning) address some points. The Chief Medical Officer subsequently commissioned an Independent Expert Working Group to provide an additional document.

Report of the Independent Expert Working Group

The Independent Expert Working Group published its report to the Chief Medical Officer on the prevention of VTE in hospitalised patients in March 2007.[14] The principal recommendation is a mandatory VTE risk assessment on every hospitalised patient on admission, as specified by the Health Committee Report. Other recommendations include calls for improved public and professional understanding of VTE, the establishment of VTE demonstration centres (i.e., centres of excellence), core standards to be set by the Department of Health, compliance with these standards, and evaluation of their impact on patients and the public of any future VTE strategy. The section on thromboprophylaxis strategy breaks down to four bullet points addressing medical patients, high-risk surgical/orthopaedic patients, intermediate-risk surgical patients, and low-risk surgical patients (Table 2).

Chapter 2 considers the epidemiology of VTE and further evaluation and improvement of healthcare. It provides some interesting data, such as that the total annual burden of VTE across the 25 member states of the European Union (population 454 million) is estimated to be 640,000 symptomatic DVTs and 383,000 PEs, that VTE-related deaths are estimated to be 480,000 annually, a figure that exceeds deaths due to acquired immune deficiency syndrome (AIDS), breast cancer, prostate cancer and road traffic accidents combined.[19] The last section of this chapter refers to the VERITY registry,[20] a UK prospective observation registry of (at the time of publication) 39,166 patients, making it the second most extensive VTE registry in the world.

Chapter 3 considers VTE in the wider context and briefly discusses immobility and travel-related VTE, inherited conditions predisposing to VTE, pregnancy and the puerperium, and oral contraception and VTE related to hormone treatment. Chapter 4 considers indicative resources and recommends the establishment of VTE demonstration centres with an expanded role addressing demonstration of best practice. The resources required for such a centre call for a VTE consultant lead and a VTE project manager at a combined cost of perhaps £240,000 over two years.

Finally, there is a mention of clinical negligence and litigation, with a veiled warning of potential consequences to those who may pay scant regard to these and other guidelines. The main chapters are supplemented by seven

Table 1. Rates of DVT following orthopaedic surgery and the effects of treatment.

	Elective hip replacement		Total knee replacement		Hip fracture	
	% DVT (95% CI)	%RRR	%DVT (95% CI)	%RRR	%DVT (95% CI)	%RRR
Untreated	54 (50–58)	–	64 (57–71)	–	48 (43-53)	–
GEC stockings	42 (38–48)	23	61 (52–69)	6	NA	NA
Aspirin	40 (38–45)	26	56 (51–61)	13	34 (27–42)	29
Vitamin K antagonists	22 (20–24)	59	47 (44–49)	27	24 (19–30)	48
Low-dose UFH	30 (27–33)	45	43 (37–50)	33	27 (16–40)	44
LMWH	16 (15–17)	70	31 (29–33)	52	27 (23–31)	44

From reference 7.

DVT: deep vein thrombosis, CI: confidence interval, UFH: unfractionated heparin,

LMWH: low molecular weight heparin, RRR: relative risk reduction.

NA: not available (insufficient powered data), GEC: graduated elastic compression.

Data are the rate of DVT, with lower rates due to the use of various therapies.

annexes on existing VTE guidelines and concludes with summary tables and an algorithm for the risk assessment of medical patients.[21]

National Institute for Health and Clinical Excellence: Guideline 46

The NICE Guideline 46 opens with the following statement: "This guidance represents the view of the Institute, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical guidance. The guidance does not, however, override the individual responsibility of healthcare professionals to take decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer".

The introduction provides a list of those surgical procedures where the scope of the NICE guideline is defined, although it points out that there may be other surgical procedures requiring an in-patient stay, and that healthcare professionals should exercise their clinical guidance when making decisions on the appropriateness of VTE prophylaxis. Following a section on patient-centred care, there are 10 key priorities for implementation (Table 3).

Section 1 on 'guidance' has points on assessment of risk factors (which consists of an extended list of patient-related risk factors for VTE [Table 4]), and the recommendation that healthcare professionals should offer advice on aspects such as immobility and travel and the use of combined oral contraceptive directly to patients, as well as providing verbal and written information on signs and symptoms of DVT and PE, the correct use of prophylaxis at home, and the implications of not using the prophylaxis correctly, as part of their discharge plan. The 25-point risk factor list is certainly more extensive than other guidelines (Table 4).

Section 1.2 refers to methods for reducing the risk of VTE in all surgical specialties (i.e., graduated compression/anti-embolism stockings, LMWH, fondaparinux, intermittent pneumatic compression or foot impulse devices, and vena caval filters). Subsections refer to regional anaesthesia, and that healthcare professions are required to advise and train patients in prophylaxis. Section 1.3 refers more specifically to reducing the risk of VTE by type of surgery (e.g., elective orthopaedic or vascular surgery). A common theme in several of these specialties is the combined provision of mechanical prophylaxis, LMWH and fondaparinux. There are caveats about the presence of additional risk factors, as indicated in Table 4. Notably, the use of LMWH or fondaparinux is recommended for four weeks after elective orthopaedic and hip fracture surgery. There are no recommendations about duration of anticoagulation for the other specialties. Subsequent sections deal with what the guideline covers, what it does not cover, implementation and recommendations for research.

Once more, the document fails to establish exactly who should implement its 10 key priorities. As such, the default position is generally assumed to be the consultant medical/surgical practitioner responsible for the patient. A guideline on thromboprophylaxis in medical patients is in development for publication in 2008. The Institute of Biomedical Science is a stakeholder.

Table 2. Thromboprophylaxis strategy.
The Independent Expert Working Group.

Medical patients
All patients should, as part of a mandatory risk assessment, be considered for thrombophylaxis. In particular, those patients likely to be in hospital longer than four days and with reduced mobility, with either severe heart failure, respiratory failure (due to exacerbation of chronic lung disease or pneumonia), acute infection, inflammatory illness or cancer (with additional risk factors for VTE) should be considered for the following regime: • Heparins (both unfractionated and LMWH) – LMWHs are the preferred prophylactic method • Aspirin is not recommended for thrombophylaxis in medical patients • Mechanical methods of prophylaxis have not to date been appropriately evaluated in acutely ill medical patients, and thus are not recommended at present.
High-risk surgical/orthopaedic patients
All patients should be managed according to the available evidence. Publication of the NICE clinical guideline on the prevention of VTE in patients undergoing orthopaedic surgery and other high-risk procedures is imminent.
Intermediate-risk surgical patients
These patients, or those with concomitant medical conditions, should, as part of mandatory risk assessment, be considered for the following thrombophylaxis measures: • GECSs combined with heparins (both unfractionated and LMWH) • Aspirin is not recommended for thrombophylaxis in intermediate-risk surgical patients.
Low-risk surgical patients
These patients do not require specific prophylaxis other than early mobilisation on account of the duration or nature of the surgical procedure, unless other factors are present that increase overall risk and thus place them in intermediate- or high-risk categories. Aspirin is not recommended for thrombophylaxis in low-risk surgical patients.

National Patient Safety Agency

The NPSA document[17] differs radically from those already described, not merely because it refers predominantly to oral anticoagulation as is most frequently delivered by warfarin, although use of heparin is briefly addressed. In addition, its prescriptions are more demanding as action steps and are strongly emphasised. These are as follows:

- Ensure all staff caring for patients on anticoagulation therapy have the necessary work competences. Any gaps in competence must be addressed through training to ensure that all staff may undertake their duties safely.
- Review and, where necessary, update written procedures and clinical protocols for anticoagulant services to ensure they reflect safe practice, and that staff are trained in these procedures.
- Audit anticoagulant services using BSH (British Society for Haematology)/NPSA safety indicators as part of the annual medicines management audit programme. The

audit results should inform local actions to improve the safe use of anticoagulants, and should be communicated to clinical governance, and drugs and therapeutics committees (or equivalents). This information should be used by commissioners and external organisations as part of the commissioning and performance management process.

- Ensure that patients prescribed anticoagulants receive appropriate verbal and written information at the start of therapy, at hospital discharge, on the first anticoagulant clinic appointment, and when necessary throughout the course of their treatment. The BSH and the NPSA have updated the patient-held information (yellow) booklet.
- Promote safe practice with prescribers and pharmacists to check their patients' blood clotting (INR) is being monitored regularly and that the INR level is safe before issuing or dispensing repeat prescriptions for oral anticoagulants.
- Promote safe practice for prescribers co-prescribing one or more clinically significant interacting medicines for patients already on oral anticoagulants, to make arrangements for additional INR blood tests, and to inform the anticoagulant service that an interacting medicine has been prescribed. Ensure that those dispensing clinically significant interacting medicines for these patients check that these additional safety precautions have been taken.
- Ensure that dental practitioners manage patients on anticoagulants according to evidence-based therapeutic guidelines. In most cases, dental treatment should proceed as normal and oral anticoagulant treatment should not be stopped or the dosage decreased inappropriately.
- Amend local policies to standardise the range of anticoagulant products used, incorporating characteristics identified by patients as promoting safer use.
- Promote the use of written safe practice procedures for the administration of anticoagulants in social care settings. It is safe practice for all dose changes to be confirmed in writing by the prescriber. A risk assessment should be undertaken on the use of monitored dosing systems for anticoagulants for individual patients. The general use of monitored dosage systems for anticoagulants should be minimised as dosage changes using these systems are more difficult.

The 12 references are followed by an appendix on safety indicators for anticoagulant services.

The Alert is directed towards all NHS and independent organisations in England and Wales (therefore, notably, not Scotland or Northern Ireland, although the former has its own SIGN document[11]).

As regards action, unlike the report of the Independent Expert Working Group and the NICE report, the NPSA report does describe clear lines of responsibility. The document states that the chief pharmacist/pharmaceutical advisor should lead the response to this alert, supported by the chief executive, medical director, nursing director and clinical governance lead/risk manager. It is notable that haematologists are absent from this list. In addition, it gives a clear instruction that an action plan (is) to be agreed and actions started by 2 July 2007, and that all actions are to be completed by 31 March 2008. Other groups recommended to be informed are medical staff, nursing staff, pharmacy staff, general practitioners, community practitioners, dental surgeons, the patient advice and liaison service staff in England, community health councils in Wales, and medical laboratory scientists (sic). Thirteen bodies (e.g., the Healthcare Commission, NHS Direct) have been informed.

Table 3. NICE key priorities for implementation.

• Patients should be assessed to identify their risk factors for developing VTE
• Healthcare professionals should give patients verbal and written information, before surgery, about the risks of VTE and the effectiveness of prophylaxis
• In-patients having surgery should be offered thigh-length graduated compression/anti-embolism stockings (GC/AES) from the time of admission to hospital unless contraindicated (e.g., in patients with established peripheral arterial disease or diabetic neuropathy). If thigh-length stockings are inappropriate for a particular patient for reasons of compliance or fit, knee-length stockings may be used as a suitable alternative.
• The stocking compression profile should be equivalent to the Sigel profile, and approximately 18 mmHg at the ankle, 14 mmHg at mid-calf and 8 mmHg at the upper thigh
• Patients using GC/AES should be shown how to wear them correctly by healthcare professionals trained in the use of that product. Stocking use should be monitored and assistance provided if they are not being worn correctly
• Intermittent pneumatic compression or foot impulse devices may be used as alternatives or in addition to GC/AES while surgical patients are in hospital
• In addition to mechanical prophylaxis, patients at increased risk of VTE because they have individual risk factors and patients undergoing orthopaedic surgery should be offered low molecular weight heparin (LMWH). Fondaparinux, within its licensed indications, may be used as an alternative to LMWH
• LMWH or fondaparinux therapy should be continued for four weeks after hip fracture surgery
• Regional anaesthesia reduces the risk of VTE compared with general anaesthesia. Its suitability for an individual patient and procedure should be considered, along with the patient's preferences, in addition to any other planned method of thromboprophylaxis
• Healthcare professionals should encourage patients to be mobile as soon as possible after surgery.

Implications for biomedical scientists

The laboratory

The work of the vast majority of biomedical scientists in haematology will be unaltered by these initiatives. It could be argued that increased use of unfractionated heparin will lead to more requests for activated partial thromboplastin time, but in practice the use of this product is rapidly diminishing. It follows that the increased use of LMWH may lead to increased requests for estimation of anti-factor Xa activity. In many cases, however, the use of LMWH is in standard doses and is generally at a fixed dose, possibly adjusted for body weight, without the requirement for

monitoring. Increased requests for D-dimer estimations is a common theme and is an additional and considerable drain on budgets, and is alluded to briefly in the Health Committee report, although in future venography may reduce the use and/or requirement for a D-dimer test.[22] However, the emphasis on identifying risk factors (Table 4) may lead to more work for the laboratory in the detection of, and/or screening for, thrombophilia via high levels of coagulation factors (e.g., factor VIII), hyperhomocysteinaemia, low activated protein C resistance (e.g., as may be caused by factor V Leiden), protein C, S and antithrombin deficiency, and prothrombin 2021A gene mutation. This may have budgetary implications. A long-established UK guideline for thrombophilia exists.[23]

Table 4. Patient-related risk factors for VTE.

Active cancer or cancer treatment
Active heart or respiratory failure
Acute medical illness
Age over 60 years
Antiphospholipid syndrome
Behcet's disease
Central venous catheter *in situ*
Continuous travel of more than three hours approximately four weeks before or after surgery
Immobility (e.g., paralysis or limb in plaster)
Inflammatory bowel disease (e.g., Crohn's disease or ulcerative colitis)
Myeloproliferative diseases
Nephrotic syndrome
Obesity (body mass index > 30 kg/m^2)
Paraproteinaemia
Paroxysmal nocturnal haemoglobinuria
Personal or family history of VTE
Pregnancy or puerperium
Recent myocardial infarction or stroke
Severe infection
Use of oral contraceptives or hormone replacement therapy
Varicose veins with associated phlebitis
Inherited thrombophilias, for example: • high levels of coagulation factors (e.g., factor VIII) • hyperhomocysteinaemia • low activated protein C resistance (e.g., factor V Leiden) • protein C, S and antithrombin deficiency • prothrombin 2021A gene mutation

Management and practice of thromboprophylaxis

The major group of biomedical scientists likely to be influenced by these developments will be those involved in interacting directly with patients on oral anticoagulants (almost all being warfarin), as are described in the NPSA document,[17] and as such would already be part of a hospital thrombosis team. Many oral anticoagulant clinics are now led and managed almost entirely by biomedical scientists, often with support from nurses and pharmacists. Scientist managers not only offer advice on dosing to individual patients but also in many cases write and deliver advice notes to patients, so the NPSA alert will provide extra support for this role.

Curiously, biomedical scientists are not mentioned in the Report of the Independent Expert Working Group in the list of possible members of a thrombosis committee, although (one presumes) this seems to be an innocent oversight.[15] In practice, this list may also include biomedical and clinical scientists, representatives from clinical governance boards, general practice and primary care trusts (PCTs).

Biomedical scientists are already likely to be promoting best practice through local protocols based on national guidelines (e.g., references 9 and 10, and their antecedents) but seem unlikely to lead multiprofessional audit of the use of thromboprophylaxis in their trusts.

The major recommendations of the Independent Expert Working Group[16] and NICE[17] are of the assessment of each patient's risk of VTE. Nursing and/or medically qualified staff seem best placed to perform this task, as they are likely to interact directly with the patient at an early stage of their thromboprophylaxis treatment plan. Indeed, virtually all of the NICE recommendations (Table 3) seem unlikely to be of direct interest to biomedical scientists, mainly as emphasis is on surgical in-patients and the use of LMWH and fondaparinux.

Professional training and education

Given the resource, biomedical scientists are likely to be able to directly promote the education and training of all clinical and support staff. Of the three documents, the NPSA Alert,[17] considering as it does oral anticoagulation with (mostly) warfarin, is most likely to directly influence biomedical scientists involved in this area. The first action point emphasises the need for competence via training. As specific healthcare professions are not named, there is no bar to cross-profession training.

Thus, an additional role that scientist managers will seek to formalise will be the training of their own scientist staff, and therefore they will be in a position to provide training (on probably exactly the same syllabus) to other healthcare professionals (e.g., nurses, pharmacists) working in this area. Thus, scientists are already likely to be implementing many of the Health Committee's recommendations, and these may indeed be factored in to job descriptions. If not, this issue should be addressed. However, training other hospital staff such as nurses and pharmacists would clearly need some organisation, consent and consensus.

Training and education modules are available on the internet,[17,18,24] although these may be directed towards medically qualified staff. These web modules include starting and maintaining patients on anticoagulants, prevention of hospital-acquired VTE,[17,24] managing anticoagulation in patients requiring dental surgery, dispensing oral anticoagulants, preparing and administering heparin therapy, and reviewing the safety and effectiveness of an anticoagulant service.[17] The NPSA packages refer to an appropriate knowledge and skills framework level. Similar issues in safety and training in the management of oral anticoagulation have also been published recently.[25]

Educating the public

Biomedical scientists in oral anticoagulant clinics are also in an excellent position to offer advice and guidance to patients

who start on this therapy, and to explain issues as outlined in the yellow book of patient records that carry serial INR data. In many cases, biomedical scientists may write particular advice documents under the direction of the head of service, who is likely to be at consultant level, although local lines of accountability are likely to be flexible. This is particularly applicable to out-reach clinics and services that are often run by biomedical scientists at sites (e.g., PCTs, GP surgeries) remote from the laboratory. This is strikingly similar to Annex 4 of the report of the Independent Expert Working Group,[15] which provides core elements of a VTE education strategy, although this focuses primarily on the public. This aspect of patient education could also extend to patients on the ward, and those likely to self-dose with LMWH, although it could be argued that nurses may be the more efficient conduit.

Conclusions

Perhaps the most far-reaching aspect of these documents is the suggestion by the Independent Expert Working Group[15] of the development of a VTE demonstration centre (i.e., a centre of expertise/excellence), headed by a dedicated VTE consultant lead and with a VTE project manager. There is no implication that such a lead should be medically qualified, and so, given the existing and developing skills of biomedical and clinical scientists, an adequately qualified member of either profession would be a strong candidate. Clearly, the same can be said of the project manager role.

To some extent, these three new documents provide an update on a previous guideline on oral anticoagulation (and aspirin) considered to be a gold standard, including recommendations on practice, management, training and audit.[26] The forward-thinking biomedical scientist is likely to view these three new documents as an opportunity to develop their skills, and that of the service, with more formal roles in training, writing, audit and patient education. As such, they will be at the forefront of practitioners continuing the move from traditional laboratory-only roles to take up responsibilities across their hospital trust, beyond the trust, and with other healthcare professions. □

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