■ REVIEW ARTICLE

Orthopaedic thromboprophylaxis

LIMITATIONS OF CURRENT GUIDELINES

D. Warwick,
O. E. Dahl,
W. D. Fisher

*From the
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Thrombosis Forum*

Thromboprophylaxis remains a controversial subject. A vast amount of epidemiological and trial data about venous thromboembolism has been published over the past 40 years. These data have been distilled and synthesised into guidelines designed to help the practitioner translate this extensive research into 'evidence-based' advice.

Guidelines should, in theory, benefit patient care by ensuring that every patient routinely receives the best prophylaxis; without guidelines, it is argued, patients may fail to receive treatment or be exposed to protocols which are ineffective, dangerous or expensive.

Guidelines, however, have not been welcomed or applied universally. In the United States, orthopaedic surgeons have published their concerns about the thromboprophylaxis guidelines prepared by the American College of Chest Physicians. In Britain, controversy persists with many surgeons unconvinced of the risk/benefit, cost/benefit or practicality of thromboprophylaxis. The extended remit of the recent National Institute of Clinical Excellence thromboprophylaxis guidelines has been challenged.

The reasons for this disquiet are addressed in this paper and particular emphasis is placed on how clinically-acceptable guidelines could be developed and applied.

Existing guidelines in orthopaedics

There are several sets of guidelines available for the use of thromboprophylaxis in orthopaedic surgery. Some have been published in peer-reviewed journals such as the International Consensus Statement (ICS),¹ and those of the American College of Chest Physicians (ACCP)² and others by Government bodies such as the National Institute of Clinical Excellence (NICE),³ and the Scottish Intercollegiate Guidelines Network (SIGN).⁴ Guidelines should be based on established principles for scientific rigour.⁵⁻⁷

As new evidence emerges and as the consensus gradually evolves these guidelines should be updated. Existing guidelines can rapidly become obsolete, especially when advances such as effective extended duration prophylaxis in hip replacement or the arrival of new oral factor Xa and IIa inhibitors demand incorporation into the existing scheme.

Are guidelines followed?

Guidelines are not universally followed. The recent Parliamentary Select Enquiry in the United Kingdom⁸ revealed that routine thromboprophylaxis is rarely applied in an effective and consistent manner. A survey of

members of the British Orthopaedic Association showed widespread use of thromboprophylaxis but no apparent compliance with guidelines.⁹ Many readers will recognise from their own practice, from audit of their institution's practice or from discussions with colleagues, that guidelines are not routinely followed.

Why are guidelines not followed?

Lack of awareness. The surgeon or anaesthetist may be unaware of the guidelines and the evidence upon which they are based. The guidelines may have been published in a Journal which is not routinely read by the target audience. There may be no advocate in the institution to promote the application and funding of guidelines.

Personality. Some surgeons may feel that the use of guidelines would interfere with their perceived right to determine their own practice based upon their own personal experience and interpretation of the evidence. They may feel that each individual patient is so different that their personal practice cannot be constrained by a prescriptive guideline.

Constraints of scientific evidence. The recommendations from NICE,³ ACCP² and the ICS¹ rely upon a meticulous synthesis of the existing

■ D. Warwick, MD, FRCS (Orth),
Consultant Orthopaedic
Surgeon, Honorary Senior
Lecturer
University of Southampton,
Southampton University
Hospitals, Southampton, SO16
6UY, UK.

■ O. E. Dahl, MD, PhD, General
and Orthopaedic Surgeon,
Professor, Executive Director
Thrombosis Research Institute,
1 Manresa Road, Chelsea,
London, SW3 6LR, UK.

■ W. D. Fisher, MD, FRCS(Ed),
Orthopaedic Surgeon and
Assistant Professor
McGill University Health
Centre, 1650 Cedar Avenue,
Montréal, Quebec, HG3 1A4,
Canada.

Correspondence should be sent
to Mr D. Warwick; e-mail:
djwarwick@compuserve.com

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literature. Great weight is given to data from randomised controlled trials. These data are often derived from industry-sponsored antithrombotic drug development studies; surrogate endpoints such as venographically proven asymptomatic deep-vein thrombosis (DVT) are used which are not designed to solve clinical problems, but to demonstrate, statistically, the relative efficacy of a compound in a surgical patient model.¹⁰ Further, the data may be underpowered with respect to surgical-site bleeding. Clinical thrombotic events occurring during or shortly after surgery such as microembolism, fat embolism, myocardial infarction and stroke may gain little or no attention if the drug under investigation is administered after the event.

However, a randomised controlled trial has a number of limitations. Not infrequently, patients with other relevant medical conditions such as renal or cardiac disease, or patients at the extremes of age or weight are excluded. The conclusions of this study cannot, therefore, be applied to many groups of patients. Furthermore, the need for informed consent influences the random nature of patient selection to a certain extent. Thus, if evidence-based medicine was the only criterion for guidelines, the recommendations would be restricted to the same selected and well-defined patient group as the source trial.

A randomised study of thromboprophylaxis usually compares two drugs which are given at a certain dose, started at a set point and continued for a defined period. The outcome measure obtained, by venography or ultrasound for example, is observed at one moment in time and is thus a snapshot of a dynamic biological process. Many small and otherwise unimportant thrombi seen on venography will lyse over a period of days but will alter the true incidence of venous thrombi. The data derived from such a randomised clinical trial will show the outcome based upon this specific set of criteria.

The point at which prophylaxis is first administered may be critical for the outcome. A recent large population-based report has shown that the highest death rate is on the day of surgery and that most patients who die do so from a thrombotic event.¹¹ This is particularly seen in elderly patients who also have other medical problems. The trend for current industry studies to start all prophylaxis post-operatively may, therefore, be questioned. This has probably been driven by the move to same-day admission and the importance of the North American market. The United States healthcare system is extremely sensitive to any complication such as bleeding, which may prolong hospitalisation. A move towards a more individualised system of prophylaxis is a possible alternative approach. Elderly patients with a history of arterial and venous thrombosis or with a coagulopathy activated by trauma would probably benefit from pre-operative thromboprophylaxis, while a younger patient without a family history of thromboembolism and others with a history of inherent bleeding might benefit from post-operative thromboprophylaxis or even no anticoagulation at all.

Consequently, many randomised trials pose more questions than they answer.

There is also a discrepancy between statistical and clinical significance. A thromboprophylactic intervention may show, with great statistical significance, that the incidence of an outcome is reduced. Thus, a reduction in the incidence of asymptomatic DVT, from 16% to 9% for example, may be statistically significant but have no clinical significance.

Practicality. Guidelines can make clear recommendations that are easy to understand and which are logical and safe, regarding, for example, the administration of injections for an extended period of time, the use of a drug that requires monitoring, or the use of a mechanical device. However, pragmatic considerations may prevent translating this advice into practice. Who will give the drug, particularly after discharge?¹² A certain number of patients may manage to administer the drug themselves but some will be unable to do so, such as those with rheumatoid arthritis, Parkinson's disease or those who are frail. Who will apply and remove a foot compression device? After hip replacement, there would be a predictable risk of dislocation if the patient were to flex his leg in order to remove or apply the device. How will the patient be regularly monitored if a vitamin K antagonist is used?

Expense. All healthcare systems have financial constraints. Most new interventions have to be funded by the deletion of an existing intervention or a clear demonstration that a new intervention will save money. Since most studies are not based on clinical outcomes, this is overcome by modelling the clinical situation by extrapolating from surrogate outcome data. These studies nearly always show that the new regimen is superior to the old one. We have, therefore, to question the limitations of such modelling. Some costs are never properly assessed or are at least unknown. For example, in many systems the costs of an anticoagulant clinic are hidden within a salaried system. An analysis from Sweden showed that at least 50% of patients would have to inject themselves in order to justify the costs of a four-week extended low-molecular weight heparin regimen.¹³

Even if we accept that there is fairly good evidence that extended-duration chemical prophylaxis is likely to be cost-effective,¹⁴⁻¹⁶ many healthcare systems are unable to transfer any potential saving from reducing an undesired outcome (e.g. thromboembolism) into the expense required to give prophylaxis against that outcome. In some healthcare systems, such as the NHS with its recently-imposed tariff, the cost of an intervention such as hip replacement attracts a fixed re-imbursement. The superimposition of an additional cost for thromboprophylaxis may not lead to an automatic increase in that re-imbursement. An institution may, therefore, have to judge whether an effective thromboprophylaxis protocol, recommended by guidelines, would adversely affect its profitability and competitiveness. Patients themselves may not wish to underwrite the extra cost of thromboprophylaxis particularly since the

existence of a guideline would imply that the prophylaxis is an integral part of that surgery.

The cost-effectiveness of producing the guidelines may also be questioned. It is a very expensive process to review the literature systematically, develop a consensus and then publish recommendations. What is the cost-effectiveness of the guideline process, especially if there are other current guidelines themselves produced from the same evidence base but interpreted and produced by a different body of experts?

Introduction process. Many hospitals have a clear process by which a new intervention is introduced. For example, an individual physician or department will accumulate the evidence for that intervention and then present it to colleagues. If they agree that the intervention is beneficial, the evidence is presented to the hospital formulary committee. The committee judges the strength of evidence, the resources required and the problems of successful implementation. That same committee is likely to be overwhelmed with many competing applications for the same resource and has to balance the weight of that guideline with the weight of the other interventions that have to be covered by a limited budget. In many hospitals, the recommendations of this committee would then need to be ratified by the finance department, again with the possible rejection on financial grounds.

Established protocols. Many hospitals already have a thromboprophylaxis protocol which is applied routinely. Some hospitals have a routine in which mechanical devices are applied immediately after surgery and continue until the patient is fully mobile. The operative theatre staff, ward staff and patient are all involved in this process. Other hospitals have an established protocol using heparin derivatives or vitamin K antagonists which are given before or after surgery and monitored according to the routine that fits the logistics of their care plans. This routine measurement may continue in the community after discharge. When an institution has a well-established protocol, which itself may have incurred considerable effort and expense to introduce and maintain, it is questionable whether there is the motivation to change it in favour of an alternative.

Perception bias. The claim by haematologists, which has existed for the past 30 to 40 years, that major joint surgery poses a high-risk of fatal pulmonary embolism, is not believed by today's surgeons. The current overall death rate after hip replacement is less than 1%, of which fatal pulmonary embolism accounts for approximately 40%; the majority of patients die from thrombotic vascular events.^{11,17,18} Furthermore, a seemingly natural decline in the incidence of clinical DVT and pulmonary embolism has been observed which is difficult to attribute to the use of prophylaxis alone.^{11,19}

Surgeons rarely see venous thromboembolism. The rate of symptomatic DVT after hip replacement was between 3% and 4% 13 years ago²⁰ and has become even rarer in some regions.¹⁹ A hip surgeon performing 100 procedures per

year may expect to see two or three cases during that time. As many, if not most, occur after discharge from hospital, the individual surgeon may gain a falsely low perception of the rate of DVT in his or her practice unless he or she routinely reviews the patients and is informed of all the complications. It may be because the surgeon assumes these events are so rare that he may not seek to diagnose them, even if there are symptoms to support their diagnosis.

Conflicting evidence. Many surgeons, particularly those who are reluctant to use chemical thromboprophylaxis, may be influenced by evidence which has not been subjected to robust analysis. The SIGN guidelines from Scotland⁴ for example, recommend aspirin without any rational explanation, whereas other guidelines (ACCP, ICS)^{1,2} specifically advise against it. The prevention of pulmonary embolism study²¹ controversially concluded that aspirin should be used for a wide range of surgical conditions even though the data within that study showed that aspirin made no difference in the 4000 hip and knee arthroplasty patients for whom this intervention was examined in a randomised manner. A so-called 'opportunistic meta-analysis'²² showed an equivalent and very low death rate across a number of prophylactic interventions. However, this analysis was derived from a large number of heterogeneous randomised studies in which the patients who had died may have been excluded from the study as they had not been available for assessment of the outcome measure. In fact, death dominated by vascular fatalities is most likely on the day of surgery and the risk subsequently declines rapidly during the first month before it stabilises after approximately three months.^{11,19}

Fear of bleeding. Any evidence from a study that showed potentially increased bleeding could be used by a cynical surgeon to justify a more conservative approach towards the relative risks and benefits of thromboprophylaxis. Surgeons are naturally concerned about post-operative bleeding. If a patient has unexpected bruising around the wound or haemorrhages, it is tempting for the surgeon to attribute this to the addition of chemical thromboprophylaxis even if the available evidence suggests that in fact, this method confers no additional risk of bleeding. There is little point in replacing one complication (peripheral thrombosis) with another (bleeding). The evidence that careful prophylaxis administered at an appropriate time after surgery causes surgical bleeding is sparse. There is no good evidence that bleeding after arthroplasty surgery compromises the outcome either in the short- or long-term. However, many studies do not clearly define bleeding, or use phrases such as 'minor wound bleeding' or 'bleeding index' which acknowledge there was bleeding but which cannot be meaningfully analysed.

A further factor has been the increased awareness of the risk of potentially serious epidural haematoma from anti-coagulant with neurocentral anaesthetic techniques. Although this is rare if guidelines are followed, there is a tendency for clinicians to restrict the use of effective anti-

coagulation in these situations. The introduction of alternative peripheral anaesthetic techniques will hopefully make this concern superfluous.

Nevertheless, a surgeon may reasonably consider bleeding to be a failure of their own surgical technique and an act of commission, whereas peripheral thrombosis might be regarded as a natural complication so failure to give thromboprophylaxis is not necessarily regarded as an act of omission. The simple line, hidden within the ACCP guidelines² that “we place a relatively low value on the prevention of venous thrombosis and a relatively high value on minimising bleeding complications” encapsulates this need for clinical balance.

What would the ideal guideline contain?

The model guideline should be designed around the following principles:

For those with a demonstrable risk of thrombosis, thromboprophylaxis should be started with an effective dose as close to the thrombogenic insult as possible, without introducing an equal or greater risk of complication, and continued until the risk of thrombosis has decreased to a clinically negligible rate, with due consideration to cost and practicality. Surgeons should also consider their threshold of comfort between thrombosis and bleeding based on their patient's individual risk factors when deciding when to begin treatment, i.e. before or after the operation. Individual patients may have their own risk factors for thrombosis and bleeding as well as a limited duration of risk for each. Ideally, therefore, the initiation and duration of prophylaxis should be tailored. The ideal chemical agent should be both injectable and oral, reversible, have a wide therapeutic and safety margin, and be predictable in nearly all patients without interaction including, for instance, the elderly and those with renal or liver impairment and be monitored with simple coagulation tests in critically-ill patients. The ideal mechanical method should be comfortable, quiet and cost-effective. The guideline should not constrain the surgeon or anaesthetist into a practice which is not available, practical, affordable or deliverable. All methods should have an acceptable compliance when handled by the patients themselves (such as self-administered drugs and mechanical devices).

Mortality data indicate that elective major joint surgery poses a generally low-to-modest risk to patients. It is the individual patient's other risk factors which dictate the level of risk. Several epidemiological studies have shown that the surgery on bones induces systemic activation of coagulation.²³ Post-mortem and cohort studies have shown that

most patients die from vascular events caused by thrombin-driven processes such as fat embolism, myocardial infarction, stroke and venous thromboembolism, therefore prophylaxis should ideally cover all thrombin-generated events.¹⁰ This is something which chemicals can do but mechanical methods cannot. Two further principles follow from this. First, prophylaxis protocols should be based on evidence of risk reduction for all arterial and venous symptomatic and fatal events rather than venous events alone. Secondly, pre-operative administration of chemical methods, whilst carrying a greater bleeding risk, would more logically cover the entire spectrum of arterial and venous events which are induced by thrombin generation during surgery and which are reflected in the early mortality of, in particular, elderly and unwell patients.^{11,19,24}

An individual patient may fall into certain broad groups and the following categorisation may be considered:

1) Minimal risk of thrombosis as judged by the procedure, thrombosis risk assessment and cost-benefit considerations: no prophylaxis required. 2) Modest risk of thrombosis when the risk of bleeding outweighs the risk of thrombosis: mechanical methods without bleeding risk in the peri-operative phase to be replaced by chemical methods for the predicted duration of thrombosis risk once the bleeding risk has diminished. 3) High risk of thrombosis, which outweighs the risk of bleeding: start chemical and mechanical methods pre-operatively as close to surgery as possible to minimise the risk of intra- and peri-operative thrombin-driven and stasis-driven complications and continue mechanical methods until no longer suitable due to compliance and mobility. Continue chemical thromboprophylaxis, for the predicted duration of risk given that the drug does not introduce other side effects such as allergic reactions and liver toxicity.

How can the implementation of guidelines be improved?

Authoritative guidelines. The guidelines must be authoritative within each specialty so that the administering clinician can respect their authorship. The guidelines panel should be supported by statisticians and economists and its members should be industry-neutral.

Guidelines rather than protocols. The administering clinician should feel that their personal comfort with regard to side-effects can be accommodated within the guidelines. The guidelines should be flexible enough to accommodate the differing views of clinicians concerning side effects, for which the clinician may be held responsible, and the variability in patients' individual risk for thrombosis or bleeding. This variability can apply between hospitals, regions and countries dependent on the patient groups and populations they respectively handle.

Local co-ordinator. The application of guidelines in an institution requires the effort of many people. However, it may be that one individual in the department or in the hospital has a particular interest or drive to institute prophylaxis.

That individual may be crucial in determining whether the guidelines are acceptable and in introducing them despite the hurdles of resistance from colleagues, budget constraints, custom and practice, formulary committees and so on.

Opinion leaders. Clinicians are overwhelmed with changing information on all aspects of their practice. They rely on the opinion of their peers who have taken a special interest in, and are motivated to be up-to-date in their knowledge of, thromboprophylaxis. The acceptance, then dissemination, of new guidelines by opinion leaders in meetings, journals and case conferences can influence whether guidelines are acceptable. It is the responsibility of surgeons with an interest and the expertise in thrombohaemostatic literature to ensure the continuing exposure of his colleagues to these studies at both local and national meetings.

The drawback with the concept of opinion leaders is that the pharmaceutical companies or device manufacturers may promote their product through those opinion leaders with chairmanship of studies, advisory board work or sponsored lectures which may undermine their neutrality.

Clinical audit. Regular audit of compliance with guidelines and thrombo-embolic and bleeding complications may reinforce or detract from their use.

Accessible publications. Clinicians cannot synthesise all the information available in the literature. The well-researched guidelines like ICS¹ and ACCP² are published in journals which are unlikely to be read by most surgeons. The National Institute for Clinical Excellence have published their recent guidelines on their website.³ The editors of orthopaedic journals could perhaps publish a condensed version. Orthopaedic associations or NICE could disseminate a relevant abridged version by e-mail to all orthopaedic surgeons. Pocket guidelines can be made available and disseminated by interested groups.²⁵

Care plans. Formalised care plans would help the systematic application of guidelines as part of the routine, form-filling care of patients. Such care plans are routinely used for other aspects of safe routine practice such as pressure sore avoidance and prophylactic antibiotics.

Medicolegal pressure. Patients are becoming increasingly aware that many complications of treatment are preventable. Of all negligence claims against the NHS in the last ten years (approximately £68 000 000 paid or outstanding) 1.9% are related to thromboembolism.²⁶ The bodies covering negligence for both private and state health systems may consider that their exposure to claims could be reduced by expecting clinicians to follow peer-reviewed guidelines.

Cost-effectiveness. All healthcare systems have to judge the most appropriate and fruitful way of spending a limited healthcare budget. Effective prophylaxis may reduce costs if it can be shown that omitting prophylaxis would lead to thrombotic events which incur greater cost such as re-admission, radiology, treatment and monitoring. To this cost may be added the cost of successful litigation if the

claimant can show they have been harmed by a negligent omission of prophylaxis.

A valid cost-effectiveness study requires the accurate recording of relevant clinical events, both thrombotic, haemorrhagic and other adverse events. The cost of prophylaxis varies from region to region and from hospital to hospital. Mechanical methods are relatively expensive because of the capital cost of the compressor and the need to provide disposable stockings for each patient and to replace them when they fail. The NHS has recently introduced a 'tariff' for joint replacement. Insurance companies and managed care systems have set a re-imbursement for joint replacement. The addition of extra cost, such as extended duration chemical prophylaxis or in-hospital mechanical prophylaxis (both recommended by NICE), would have to be absorbed by the tariff. However, the present tariff may barely cover the cost of the procedure, and the addition of unfunded thromboprophylaxis would subtract from the profit that an institution needs to generate. Furthermore, there may be a dispute as to who is responsible for funding prophylaxis. Is it an intrinsic part of the joint replacement or does the responsibility fall to the primary care physician once the patient has left hospital? If effective thromboprophylaxis reduces re-admission and treatment costs, then why should the Orthopaedic department pay for that cost when the Haematology department benefits? If guidelines are to be accepted, their intrinsic cost must be properly integrated into the health system.

Education. Strategies to highlight the issues of thromboembolism to hospital medical staff, pharmacists, nurses, managers and patients would influence the application of guidelines.

Government pressure. In some countries, strong central government influence over health policy can be used to impose, or at least encourage, guidelines. In the United Kingdom, the Department of Health, concerned about the large number of deaths attributable to thromboembolism, commissioned an Independent Expert Working Party²⁶ following a Parliamentary Select Committee enquiry in 2005.⁸ The Government, having commissioned this work, will act to implement the recommendations. The United Kingdom Government's NICE clinical guidelines should be taken into account by the healthcare professionals when exercising their judgement. It may be that only with central pressure and support can guidelines be imposed which otherwise would falter because of very significant cost, variable awareness and controversial clinical acceptance.

Guidelines on antithrombotic drug development. Standardisation of antithrombotic drug development programs in humans is crucial to achieve conformity and to be able to determine the best form of treatment for a specific indication. The International Surgical Thrombosis Forum has established a program for surgical patients. This program has been exposed to the European Agency for the Evaluation of Medicinal Products which currently is revising its guidelines in this area. A compressed paper version

has been published in *International Angiology*.²⁷ The International Surgical Thrombosis Forum hope that this paper will provide the basis for further debate and research in this area.

Guidelines should be a useful tool to help clinicians provide universal thromboprophylaxis with due regard for efficacy, safety and cost. The guidelines should be based on a meticulous synthesis of the literature. They should be presented in a pragmatic way and should be respected by the administering clinician. Publication of guidelines is not enough. They need to be widely accepted, effectively introduced and financially-supported without commercial bias.

The following members of the International Surgical Thrombosis Forum have approved this manuscript: M. Snack-Rasmussen, Denmark; S. P. Frostick, United Kingdom; C. Colwell, United States; G. D. Paiment, United States; P. Wille-Jørgensen, Denmark; T. Wakefield, United States; F. Cushner, United States; S. Fujita, Japan; P. Mouret, Germany; E. Ramacciotti, United States; M. Gomes, United States; M. Marotti, Brazil; M. Ögren, Sweden; Y. Abe, Japan; R. Parakh, India; A. Sylvest, Denmark; C. Velpeau, France; S. L. Hamersley, United States; C. N. van Dijk, The Netherlands; J. I. Arcelus, Spain; M. Akagi, Japan; A. Planes, France; F. H. de A. Maffei, Brazil; G. H. Westrich, United States; A. Jawien, Poland; C.-J. Wang, Taiwan; C. Ryge, Denmark; J. Skinner, United Kingdom; J. P. Waddell, Canada; I. A. Greer, United Kingdom; R. M. Atkins, United Kingdom; M. H. Kurtoglu, Turkey; B. Jacobsen, South Africa.

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