RISKS AND BENEFITS OF PROPHYLAXIS AGAINST VENOUS THROMBOEMBOLISM IN ORTHOPAEDIC SURGERY

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In the UK, the reports of the Thromboembolic Risk Factors (THRIFT) Consensus Group[1] and the Scottish Intercollegiate Guidelines Network Group (SIGN)[2] have recommended that pharmacological prophylactic regimens be used routinely after major orthopaedic procedures in the lower limb. In reaching these recommendations, attention was paid to estimates of the absolute risk of thromboembolic disease in these patients and to the evidence for the efficacy of the prophylactic regimes in reducing the relative risk of the outcomes on which the risk categories were based. The recommendations of the THRIFT report were based on a modified grading of risk[3] (Table I) determined by the rate of venographically measured, but rarely symptomatic, deep-vein thrombosis (DVT), and the incidence of fatal pulmonary embolism (PE). All patients suffering major trauma or undergoing surgery for fracture of the hip, total hip replacement (THR) or total knee replacement (TKR) were considered to be at high risk, justifying the use of specific prophylactic regimens in addition to general measures such as adequate hydration and early mobilisation.

The authors of the THRIFT report admitted that the use of pharmacological prophylaxis had been controversial. This debate has continued.[4-6] Although many more orthopaedic surgeons now use pharmacological prophylaxis than was the case a decade ago,[7,8] there are significant variations in practice. Prophylaxis is less commonly used after fracture of the hip, despite an apparent high absolute risk of both DVT and PE.[9,10] Many surgeons hold strong views that the recommendations are inappropriate because of anxiety about the incidence of the adverse effects of prophylaxis, particularly of wound complications,[8] unease with the accuracy and relevance of the level of thromboembolic events on which the recommendations are based, and by a growing awareness that the use of surrogate outcome measures, such as venographically-diagnosed DVT, may be misleading. Most published trials have been small, with power only to detect differences in radiological detection of DVT, but not of the number of clinically important events. Of 31 reports of trials[11-13] in elective orthopaedic surgery, comparing either low-dose heparin or antiplatelet agents with a placebo or with no prophylaxis, only seven were published in orthopaedic journals. These observations highlight the problems of the difficulty in diffusing medical information, and the importance of well-conducted meta-analyses.

If the guidelines are to be challenged it must be shown that the risk of thromboembolic events has fallen, or that critical reappraisal raises doubts about the balance of beneficial and adverse effects of prophylaxis on clinical events.

Surgical procedures, particularly on the lower limb, predispose to both venous thromboembolism and wound complications. Each operation carries its own absolute risk of these events (Table II). Each patient carries an intrinsic risk of developing DVT, and of experiencing complications such as a stroke, epistaxis, or gastrointestinal haemorrhage due to drug-induced hypocoagulability. Meta-analysis of data from trials of pharmacological agents has shown that the reduction in relative risk of developing radiological evidence of DVT, or of suffering a PE, is, however, relatively uniform across different surgical specialties, including orthopaedic surgery, and procedures. Thus, orthopaedic surgeons can draw on these overall data with some confidence in assessing the typical reduction in relative risk which pharmacological prophylaxis can offer. For an assessment of the reduction of absolute risk of thromboembolic events, and of the incidence of adverse effects, data from trials or audit of outcome of the relevant orthopaedic operations must be used. For high-risk procedures, benefit is likely to outweigh risk, but for those of low risk, risk may outweigh benefit.

An Editorial in this Journal in 1995[4] concluded that:

1. The rate of fatal PE after THR appeared to be 1 or 2 per 1000 operations, an order of magnitude lower than that generally accepted in previous reviews, and used to formulate guidelines for prophylaxis.

2. When assessing prophylaxis, the most important outcome measures were overall mortality and overall morbidity, including the incidence of a postphlebitic limb.

3. There was only weak evidence that prophylaxis was effective in preventing deaths after THR; too few data have been collected.

4. Mechanical methods were unlikely to cause complications, and were effective in decreasing thromboembolism after THR.

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Table I. Incidence (%) of venous thromboembolism. Risk categories used in the THRIFT report[1]

	Risk		
Event	Low	Moderate	High
Any radiologically diagnosed DVT	Less than 10	10 to 40	40 to 80
Any radiologically diagnosed proximal DVT	Less than 1	1 to 10	10 to 30
Fatal PE	0.0 to 0.1	0.1 to 1.0	1 to 10

Table II. DVT and PE after orthopaedic procedures on the lower limbs as estimates of percentage absolute risk without prophylaxis (95% confidence interval). Estimates over 2% are rounded

Procedure	Any DVT (radiology)	Proximal DVT (radiology)	Clinical DVT	Non-fatal PE	Fatal PE
THR[6,37]	32 (23 to 42)	16 (10 to 25)	1.9 (1.1 to 2.8)	1.2 (0.6 to 2.2)	0.3 (0.1 to 0.8)
TKR[38,39]	66 (58 to 76)	16 (10 to 24)	9 (7 to 11)	1.9 (1.2 to 3.0)	0.4 (0.1 to 1.1)
Hip fracture[10,24,40]	46 (36 to 57)	19 (14 to 26)	7 (4 to 11)	8 (4 to 13)	4 (2 to 7)

5. Unless subsequent trials, which would have to be very large, were to confirm the superiority of pharmacological over mechanical methods, the guideline recommendations for pharmacological prophylaxis were not justified.

6. For patients with intrinsic risk factors undergoing THR, however, the addition of pharmacological to mechanical methods may be appropriate.

How do these opinions stand now?

The risk of DVT. Ascertainment is difficult in thromboembolic disease. The most reliable data have been gathered from randomised controlled trials in which routine imaging of the veins of the lower limb has been carried out in small and sometimes selected groups of patients, usually over a period of a few days at one to two weeks after surgery. Strictly speaking, these are point prevalence data which underestimate the true incidence, since they fail to take account of thrombi which have resolved before imaging, or those which will form later. Although most DVTs appear to develop soon after injury or surgery, studies using serial venography have clearly shown that thrombi may form over a number of weeks.[13,14] Half of all diagnosed clinical thromboembolic events may occur after discharge from hospital.[15,16]

After THR or TKR, screening by bilateral ascending venography identifies radiological DVT at any level in the lower limb in 30% to 60% of patients, and DVT in the proximal segment in 10% to 20% (Table II). These levels are in the high-risk range in the THRIFT criteria. Radiological detection of DVT, however, is an intermediate outcome. We do not know how many individuals who have demonstrable DVT on imaging develop a clinical event resulting in death or morbidity. Although a prerequisite for such a happening, radiological evidence of DVT does not predict it.

Surveillance. At present, there is no case for routine screening with haemostatic tests, either preoperatively to assess risk, or postoperatively, to identify DVT.[17] Clinical monitoring of patients is unlikely to detect non-occlusive thrombi in the lower limbs, and probably in major hip or knee surgery, a proportion of occlusive thrombi. Routine serial monitoring of all asymptomatic patients using venography is not a feasible option, although routine plethysmography has been advocated,[18] as has, more recently, simplified compression ultrasound on two occasions a week apart.[19] We recommend, however, that further research precedes the general introduction of any programme of non-invasive monitoring over and above careful clinical surveillance. Ultrasound is unreliable as a screening tool in asymptomatic patients who have undergone joint replacement in the lower limb.[20-22] Pooling of the published trials of ultrasound up to 1997 gives a sensitivity for DVT of the proximal segment of 0.68 (95% CI 0.52 to 0.80) and specificity of 0.97 (95% CI 0.95 to 0.99). Strain-gauge plethysmography has a pooled sensitivity of 0.41 (95% CI 0.32 to 0.51) and a specificity of 9.83 (95% CI 0.68 to 0.92). Thus, a positive result on ultrasound 'rules in' a proximal DVT with confidence, but a negative result unfortunately does not rule it out. Although more convenient, and likely to be less expensive than ultrasound, strain-gauge plethysmography is less accurate, and the argument for its routine postoperative use is weak.

The risk of PE. Data on the incidence of PE have been derived from the control arms of randomised trials, from local and regional registers and audit projects, and from case series from individual units. The reference standard for the diagnosis of fatal PE is autopsy and for in-vivo PE is pulmonary angiography. Since autopsy rates are low and pulmonary angiography is rarely used, estimates of the incidence of PE are probably low. The rate of fatal PE must be less than the overall mortality. The data presented by Murray et al[5] suggested that the rate of fatal PE after THR in the last decade may have been as low as 1 to 2 cases per 1000. These figures, however, are prone to ascertainment bias, since they are drawn from a wide variety of studies of varying quality in which a uniform standard of reporting of death rates, and of cause of death, cannot be assumed. Other estimates from contemporary practice are somewhat higher.[6] It seems likely that the overall death rate after THR or TKR

Table III. Reduction of absolute risk of PE and proximal DVT, and estimate of additional wound complications per pulmonary embolism averted*

	Event	Absolute risk	Absolute risk reduction (ARR)	NNT to prevent one event (1/ARR)†	Additional significant bleeding complications per event prevented
THR	Any PE	0.015	0.0075	133	Less than 1
	Fatal PE	0.003	0.0015	666	3
	Proximal DVT	0.16	0.08	13	Less than 1
TKR	Any PE	0.020	0.01	100	Less than 1
	Fatal PE	0.001	0.0005	2000	10
	Proximal DVT	0.16	0.08	13	Less than 1
Hip fracture	Any PE	0.12	0.06	17	Less than 1
	Fatal PE	0.04	0.02	50	Less than 1
	Proximal DVT	0.19	0.095	11	Less than 1

* we have used the median estimates from Table II, and assumed the use of an agent which halves the relative risk of DVT (within the range reported for LMWH) and reduces clinical events proportionally. For the incidence of wound complications if LMWH were used, we extracted data on significant bleeding complications from trials in which patients undergoing total joint replacement have been randomised to LMWH or a placebo.[23,30] These trials rarely reported their criteria and the incidence of complications varied from none in either arm to 10% over both groups. There was an excess of five bleeding events per 1000 participants in the LMWH group
† NNT, number needed to treat; ARR, absolute risk reduction

is between 0.1% and 0.5%. Thus, these procedures carried out in individuals without high personal intrinsic risk have a moderate rather than a high risk of fatal PE. In elderly people undergoing surgery for fracture of the hip, the incidence of fatal PE is probably higher than in elective surgery, at around 4%.[10,23,24] This is within the high-risk category under the THRIFT classification. Data from the PEP study, produced after this review, suggest that even after fracture of the hip the incidence of fatal PE is much lower.

Information on the incidence of non-fatal PE is also approximate. The quoted rates have usually been based on clinical pulmonary events in which the likelihood of embolism has been considered moderate to high on the evidence of lung scans. As the length of stay in hospital falls, more episodes of PE will occur after discharge, most within three months of surgery. Without careful audit, or record linkage, these events may remain unknown to the surgical team. Systematic reviews of randomised trials and large audit programmes indicate that the incidence of non-fatal symptomatic PE in contemporary practice is between 1% and 2% (Table II). This morbidity cannot be neglected simply because precise information about incidence is difficult to obtain.

The incidence of postphlebitic limb and leg ulcers. Chronic venous disease in the lower limb is common in older people, and as a result the additional morbidity after surgery to the hip or knee is difficult to estimate accurately.[25] About 25% of patients with chronic leg ulcers have a definite history of DVT.[26] Over 60% of patients who had experienced a major proximal DVT after hip surgery have been reported to show evidence of markedly abnormal venous function on foot volumetry.[27] There is a possible association between asymptomatic DVT after THR or TKR and the later development of clinically significant chronic venous disease of the lower limb.[28]

Benefits and risks of pharmacological agents
Low-dose heparin and antiplatelet agents. There is strong overall evidence across all surgical trials for the effectiveness of low-dose heparin (LDH) and for antiplatelet agents in reducing the incidence of radiological DVT and PE, either class of agent effecting a typical reduction of 40% to 60% in the incidence of both DVT and PE.[11,12] Adverse effects have generally been poorly reported, but the absolute excess of episodes of bleeding for the use of either agent calculated in the meta-analyses appears to be about 2%, approximately the same as the incidence of any PE after joint replacement in the lower limb. Overall analyses indicate that prophylaxis with either heparins or antiplatelet agents may increase deaths due to causes other than fatal PE, but all-cause mortality is either reduced or unchanged.[11,12,24]

Low-molecular-weight heparin (LMWH). This is the current favourite pharmacological prophylaxis among orthopaedic surgeons in the UK.[7,8] Most randomised, controlled trials have been comparisons with LDH. Overall, these have shown LMWH to be more effective than LDH in reducing the incidence of PE and DVT. Some well-devised studies, however, have found LMWH to be only slightly superior to LDH in preventing radiological DVT, and have shown no significant difference between the two agents for PE.[23,24,29-31]

Reports of the incidence of bleeding complications after LMWH show marked differences between trials. Bias in ascertainment or reporting seems likely, as some trials reported no bleeding complications. Although many surgeons have the impression that bleeding is much more common when LMWH is administered,[8] pooling of the published data indicate that the excess of bleeding complications with LMWH is smaller than with LDH or antiplatelet agents, at round 0.5% (Table III).

Recently, more attention has been paid to thromboembolic events after discharge from hospital.[13,14] The incidence of radiological DVT is significantly reduced by continuing LMWH prophylaxis for a month but no useful data are available for PE.

Oral anticoagulants. Oral anticoagulants, although broadly as effective as heparins, carry the disadvantage of requiring regular laboratory control.[1] We do not consider them further in this review.

Mechanical methods

Thromboembolism stockings. A meta-analysis[32] has provided strong evidence that overall, after trials in a number of surgical specialties involving abdominal surgery, the reduction in risk for radiological DVT from the use of thromboembolism stockings is large (pooled odds ratio 0.28, 95% CI 0.23 to 0.42). In surgery of the lower limb, the situation is less clear. The results of the trials are heterogeneous and no formal meta-analysis has been completed. The heterogeneity may point to variation in the stockings themselves and their mode of use.[33]

Calf and foot pumps. In surgery of the lower limb, the use of these devices appears to have a protective effect similar in size to pharmacological prophylaxis[24,34] without risk of excess haemorrhagic episodes. Mechanical methods carry a smaller risk of soft-tissue complications than heparins, but there are some problems with compliance.[34]

High-risk patients. Epidemiological studies[1] have indicated that the incidence of DVT increases with age. The main risk factors for clinically-significant DVT which should be sought in every patient undergoing major surgery of the lower limb and probably during significant prolonged immobilisation in plaster, are a history of previous DVT or PE, clinical evidence of venous insufficiency, marked obesity, pregnancy or the puerperium, high-dose oestrogens, malignancy, inflammatory bowel disease, paralysis of the lower limb and a range of less common diseases and abnormalities in coagulation, some of which are likely already to have presented with DVT or PE.

Making a choice for the individual patient. In Table III we have estimated the number of additional patients who would expect significant bleeding complications if a policy of using LMWH were adopted in place of no pharmacological prophylaxis. These recommendations are sensitive to the absolute risk of thromboembolic events in each patient group, the absolute risk of adverse effects of prophylaxis and the relative reduction of risk for thromboembolic events afforded by prophylactic agents.

If a policy were designed only to prevent fatal PE, then there would be a significant trade-off in bleeds per operation. If the policy were based on the risk of fatal or non-fatal PE, or of venographically diagnosed proximal venous thrombosis, then the balance, assuming that the published data are approximately correct, is, overall, in favour of administration of LMWH to patients undergoing THR or TKR. If LDH or antiplatelet agents were used, the latter would be cheaper than either heparin formulation.[35]

Information on the combination of the two classes of agent, which in practice occurs frequently in patients with chronic arthritis who continue to use non-steroidal anti inflammatory agents, is sparse both in respect of effectiveness and of side-effects.[12]

If the risk of adverse effects from bleeding has been underestimated, as many surgeons suspect, or if the risk of thromboembolic events were shown to be lower than the lower confidence intervals from recent data, the balance of risks and benefits would move against anticoagulation. It is important that more reliable data are obtained on the frequency and nature of adverse events after anticoagulation, as these are less secure than the data for clinical thromboembolic events. The development and testing of a clinical model of risk for individual patients may allow a more confident preoperative categorisation.

Implications for practice. Orthopaedic surgeons should use pharmacological prophylaxis for all high-risk patients in whom the potential benefits appear to outweigh the risks. The inclusion of mechanical prophylaxis should be considered. In patients without personal risk factors who are mobilised very soon after surgery, THR and TKR are moderate- rather than high-risk procedures. Personal risk factors add to the danger of surgery or immobilisation and patients with one or more should be considered at high risk. All patients undergoing operation for fracture of the hip are at high risk, as are those with major trauma.[36] For patients at moderate risk, the use of alternative mechanical methods, such as foot pumps, may be justified. The optimum duration of prophylaxis is not known, particularly after discharge from hospital. Current information is mostly based on programmes of administration for seven to ten days.

Implications for research. When assessing prophylaxis, the most important outcome measures should be the incidence of clinically relevant events, namely PE and a post-phlebitic limb. The overall mortality will always be greater than the incidence of fatal PE, and has the benefit of being easier to ascertain. The influence on PE and increased mortality from other causes, however, may be obscured if death is used as the main measure of outcome. To improve understanding of the benefits and risks of pharmacological prophylaxis, data should be sought not only on the incidence of fatal and non-fatal PE, but on fatal and non-fatal haemorrhage, including wound complications, epistaxis, haemorrhagic stroke and gastrointestinal bleeding. Information should be presented separately for patients with personal risk factors, and for those having different methods of prophylaxis.

Better data on the incidence of significant bleeding complications when different agents are used are particularly needed, as are details of death other than due to PE.

Given its low overall absolute risk after THR or TKR, a trial large enough to ascertain a difference between two methods of prophylaxis in the prevention of fatal PE would not be feasible to mount, requiring up to 100 000 participants.

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