In recent months we have received a number of unsolicited contributions concerning this subject. The publication of the conclusions of a symposium in the February 2000 issue of the American volume of the *Journal of Bone and Joint Surgery*¹ together with the appearance of the results of the PEP trial in the *Lancet*² suggested that a selection of these papers might be grouped together and the subject discussed in an Editorial.

1. *J Bone Joint Surg [Am]* 2000;82-A:252-70.

2. The Pulmonary Embolism Prevention (PEP) Trial Collaborative Group. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: pulmonary embolism prevention (PEP) trial. *Lancet* 2000;355:1295-1302.

WHITHER THROMBOPROPHYLAXIS AFTER TOTAL HIP REPLACEMENT?

D. P. Thomas

The unwillingness of many orthopaedic surgeons to use prophylactic anticoagulant drugs in patients undergoing total hip replacement (THR) remains something of a mystery to non-surgeons. The reasons for this are probably complex, and undoubtedly vary from surgeon to surgeon, but it is clear that one important aspect is disagreement about the extent to which postoperative thromboembolism poses a significant hazard. The published assessments of risk of death from pulmonary embolism (PE) vary by at least an order of magnitude (below 0.1% to 1.0% or more), with some of the earlier literature quoting a rate of fatality after THR much higher than is experienced today.¹⁻³

Opinions range from those who hold that it is close to malpractice not to use some form of prophylaxis, which has been demonstrated in good clinical trials to be effective, to those who maintain that there is no convincing evidence of the need for prophylaxis with anticoagulant drugs.⁴ Both these viewpoints seem extreme and, although no final answers are yet available, there is clearly a need for a reasonable compromise which will appeal to most clinicians. Two crucial issues need to be addressed. Is there still a small, but appreciable, morbidity and mortality from

venous thromboembolism after THR? If there is, what is the best form of prophylaxis? The two methods currently favoured are anticoagulant drugs and mechanical methods to reduce stasis. Both of these raise further questions. If anticoagulants are used do the complications outweigh the benefits? If mechanical methods are employed, how good is the evidence that this non-pharmacological approach is effective?

Retrospective studies have claimed that the incidence of PE is now much lower than is stated in the older literature because of modern surgical techniques, better anaesthesia and earlier mobilisation of patients.⁵ Such arguments are plausible, and probably true to some extent, but do they warrant the claim that the risk is now so low that routine prophylaxis is unnecessary? It is suggested that using demonstrable deep-vein thrombosis (DVT) as an endpoint in clinical trials tends to exaggerate the risk of clinically significant thromboembolism. Clearly, radiologically demonstrated DVT does not equate to subsequent clinically significant PE. Nevertheless, the presence of overt thrombosis, however demonstrated, must be considered to be a manifestation of a thrombotic state, which has the potential to cause serious illness. The fact that many postoperative DVTs undergo spontaneous thrombolysis,⁶ and small emboli are tolerated by the pulmonary circulation with minimal symptoms,⁷ are indeed important safety factors, but should they be relied upon? Patients undergoing THR may not have the profound hypercoagulability often associated with malignant disease, but inevitably there is considerable tissue damage, and these patients are usually

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0301-620X/00/49973 \$2.00

J Bone Joint Surg [Br] 2000;82-B:469-72.

elderly. Such patients have always been considered to be at high risk of postoperative DVT and PE, and consequently are candidates for effective prophylaxis. The counter argument that there is little evidence that, after THR, patients come to significant harm from postoperative DVT, and that most patients survive thromboembolism, hardly seems a cogent case against efforts to minimise morbidity, if not mortality. In the Oxford Record Linkage study of 11 607 THRs, there were 93 deaths within 90 days of operation and 208 emergency readmissions within 28 days of discharge. While not all of these deaths were due to PE, most were ascribed to cardiovascular events, and thromboembolic disease was the commonest reason for emergency readmission.⁸

It is interesting to compare the results reported from three recent large retrospective studies, one British (Bristol) and two American (Boston and Los Angeles). In the Bristol series, a group of 12 teams at one centre reported their results for 1162 consecutive THRs carried out in 1990 and 1991, in which chemical thromboprophylaxis was not routinely used.² The death rate from PE was 0.34%, the total thromboembolic morbidity was 3.4%, and the 90-day all-cause mortality was 1.3%. The authors concluded that this considerable total early morbidity would justify prophylaxis, if this did not produce an alternative morbidity. The report from the Massachusetts General Hospital was of a series of 2736 patients operated on by one surgeon over almost three decades.⁹ In this study, in contrast to the Bristol experience, prophylaxis with warfarin was used in virtually all patients. The postoperative mortality rate at 90 days was 0.3%, and no patient died as the direct result of a known PE. Over a period of 27 years, two patients died from bleeding while receiving warfarin therapy. No deaths related to venous thromboembolic disease or its prophylaxis or treatment occurred after 1982 (1458 operations). Similarly, in the Los Angeles study, in which warfarin had also been used routinely since 1970, there was only one death from PE in over 4000 operations.^{10,11} These reports are all retrospective studies and, of course, not directly comparable. Nevertheless, it seems unlikely to be coincidental that the routine use of chemical thromboprophylaxis in Boston and Los Angeles is apparently associated with a lower mortality from PE.⁹⁻¹¹ An important point emerging from the Los Angeles study was that prophylaxis with warfarin was given for a mean of 15 days. Even so, twice as many pulmonary emboli were diagnosed after discharge than before.¹⁰ This clearly suggests that the risk of thromboembolism extends well beyond the immediate post-operative period.

Concepts of the pathogenesis of venous thrombosis which have developed in recent years emphasise the role of hypercoagulability induced by surgical operations, leading to the local generation of the enzyme thrombin and subsequent thrombosis in areas of venous stasis.¹²⁻¹⁴ This sequence of events is most easily prevented by using drugs which either impair the formation of thrombin, such as

heparin and warfarin, or which directly inhibit it, such as hirudin. Some orthopaedic surgeons have accepted this approach. Others rely on mechanical methods of prophylaxis, such as compression stockings and/or intermittent inflatable boots. These passive measures have no obvious adverse consequences, unlike effective anticoagulation, but relying solely on such means implies rejection of the now extensive evidence for the efficacy of heparin, and its modern variant low-molecular-weight heparin (LMWH), in the prevention of postoperative DVT, with minimal risk of haemorrhage.¹⁵⁻¹⁷ Other chemical approaches to the prevention of postoperative DVT have included the use of dextran, warfarin and aspirin. None has been shown to be as effective as heparin. In a meta-analysis of 56 trials of methods designed to prevent venous thromboembolism after THR, all treatments studied reduced the risk of DVT, with the exception of aspirin. Only LMWH and stockings reduced the risk of PE; LMWH was the more effective, although at a small risk of clinically important bleeding.¹⁸

Why is there antipathy by some surgeons towards chemical prophylaxis? Perhaps the nature of the treatment plays a role, since a surgeon using prophylaxis is never aware of his successes in preventing emboli, but is painfully reminded of haemorrhagic complications. If the patient bleeds the surgeon feels responsible, but he gets no particular credit for the thromboemboli which he has prevented. There are other less obvious aspects relating to prophylactic anticoagulant therapy. Death from a massive PE in the unprotected patient has something of the aura of an 'Act of God', and therefore nobody can be blamed. It is seen as a most unfortunate occurrence, but such things can happen after major operations. An understandable fear of haemorrhage should not blind surgeons to the real dangers of thromboembolism, and current knowledge of the pathogenesis of venous thromboembolism should lead us to regard death from postoperative PE as essentially preventable. Surgeons want to give their individual patient the best possible treatment. This may involve accepting the concept of net gain in which several patients may be saved by a particular treatment at the cost of an occasional adverse reaction. An obvious example of this is the immunisation of children against infectious diseases, in which benefit to the many is sometimes overshadowed by widespread adverse publicity generated by side-effects suffered by the unfortunate few. Again, one comes up against the problem of not knowing about the lives saved by prophylaxis, while at the same time being forcefully reminded of the occasional complication. Adopting an epidemiological approach, looking at populations instead of individuals, does not come easily to many doctors. It is in the nature of prophylaxis that large numbers must be treated to benefit the few who would otherwise suffer from disease, be it poliomyelitis, measles or postoperative thromboembolism.

There is now a wealth of evidence that both standard heparin and LMWH have the ability to reduce markedly the prevalence of venous thromboemboli after THR.^{15,17,19,20}

The problem with using death as an endpoint for an operation with low mortality is that extremely large trials are needed to demonstrate that the overall mortality is reduced. Such trials have not been carried out. To argue from this that there is no good evidence that chemical prophylaxis is needed seems not only nihilistic, but also ignores much supporting evidence.⁴ Prospective studies have shown, consistently, that PE in unprotected patients after major operations represents an important cause of postoperative morbidity and mortality.^{19,21} Perhaps the crucial question is whether surgeons are prepared to accept a small risk of haemorrhage to avoid most thromboembolic complications of THR. Although a recent survey found that over 80% of British orthopaedic surgeons used anticoagulants, usually LMWH, other evidence suggests that almost 50% of them have stopped using such prophylaxis because of the incidence of haemorrhage.²² How realistic is this fear? Numerous recent studies have shown that the risk of significant haemorrhage is around 1%,²³ and when balanced against the risk of morbidity from thromboembolism, about 3%;² this seems a reasonable trade-off. While no effective chemical therapy is without some adverse reactions, neither is major surgery.

What other approaches have been tried? Over the years, there have been many small studies using mechanical methods, such as foot pumps, which aim to prevent thromboembolism by reducing venous stasis. In a study comparing LMWH with the use of a foot pump,²⁴ it was concluded that the pump is a suitable alternative to LMWH for prophylaxis after THR. Proximal vein thrombosis was observed in 17 patients who used the foot pump, compared with 12 who received LMWH, but this difference was not statistically significant. Interestingly, there was also no difference in the requirements for transfusion or intraoperative blood loss between the two groups, although there were more soft-tissue problems in the patients who received enoxaparin. Of the 124 patients in the study, however, 39 reported discomfort, disturbance of sleep or had stopped using the pump. There are good experimental reasons for believing that reducing stasis is as effective as countering hypercoagulability in the prevention of DVT. It has been shown in extensive animal experiments that stasis alone or hypercoagulability alone does not produce venous thrombosis, but the simultaneous combination of the two does so, rapidly.^{12,13} If venous stasis can be prevented after operation the incidence of DVT may well be reduced. Whether the use of a foot pump for seven to ten days is as effective, efficient and comfortable for the patient as chemical prophylaxis has yet to be demonstrated. While avoiding stasis by mechanical means is a valid approach, more evidence from large clinical trials is needed before it can be generally accepted as matching the effectiveness of anticoagulants. A major difficulty with mechanical methods is the increasing evidence which shows that many thromboemboli develop after hospitalisation. Patients may benefit from prophylaxis for a month to six weeks after operation

and there are obvious practical difficulties in the longer-term use of mechanical methods.^{20,25-27} There are good theoretical grounds for believing that short-term neutralisation of the increased generation of thrombin associated with surgery is insufficient to prevent late thromboembolism.²⁷ There is, of course, no reason why both mechanical methods and chemical prophylaxis should not be used, especially in patients at very high risk of postoperative thromboembolism.

In animal models low concentrations of heparin have been shown to be highly effective in preventing stasis thrombosis.²⁸ This has now been amply confirmed by numerous clinical trials. The advent of LMWH, in terms of effectiveness, ease of use, and minimal risk, represents an important therapeutic advance in achieving effective prophylaxis throughout the period of maximum risk after major surgery. Warfarin, while undoubtedly effective in preventing thromboembolism after THR,⁹ requires careful laboratory control, unlike LMWH. The way forward in resolving this dilemma of whether or not to use chemical prophylaxis, would be to identify thrombophilic patients before operation. This would allow surgeons to be selective, and to concentrate prophylactic efforts on patients in whom the risk/benefit ratio is likely to be highly favourable. Unfortunately, preoperative haemostatic tests such as impaired fibrinolytic and coagulation activation markers, do not add significantly to the prediction of DVT from clinical variables such as age and obesity.²⁹ Our understanding of the genetic factors involved in venous thrombogenesis has increased dramatically in recent years, and the prospect is emerging that many thrombophilic patients may be recognised before operation. The finding of two prothrombotic mutations, with relatively high prevalence in white Europeans, has transformed our previous inability to identify such patients. The commonest mutation is in coagulation Factor V, in which arginine is replaced by glutamine at position 506 in the protein, so that Factor V is inactivated more slowly by the endogenous anticoagulant, activated protein C.³⁰ This defect, known as Factor V Leiden, is found in between 2% and 15% of the white population, and at least one in five of patients presenting with evidence of venous thromboembolism has the defect. Heterozygous carriers have a risk of DVT which is seven times higher than that in the general population, and for homozygous carriers the risk is 80 times as high. The other prothrombotic mutation involves a guanine-to-adenine transition at nucleotide 20210 of the gene encoding prothrombin, the inactive precursor of thrombin.³¹ In white patients, the reported prevalence of carrier states varies from 0.7% to 4% and such carriers have a risk of DVT some three to six times that in the general population. Because of the high prevalence of these mutations, many of the patients who are most at risk of developing DVT can now be identified. It is likely that more genetic defects will be discovered and, in future, prophylactic efforts could be concentrated on patients with a known defect in their endogenous anti-

coagulant or fibrinolytic mechanisms. The increased likelihood of excessive generation of thrombin in such patients is logically counteracted by anticoagulant drugs, as well as by measures to reduce stasis. Even now, any patient with a family history of venous thrombosis, or indeed previous thrombotic episodes of any kind, should be screened at least for Factor V Leiden before major surgery. In the relatively near future, it may therefore be possible to confine prophylaxis primarily to those patients identified to be most at risk by screening for thrombophilia.

Postoperative thromboembolism remains a significant cause of morbidity and probably mortality after unprotected THR. This unwelcome complication can be largely prevented by anticoagulants but, as with all effective drugs, there is a price to pay. The balance, in terms of preventing thromboembolism as weighed against haemorrhagic complications, favours using anticoagulant prophylaxis in patients undergoing THR. While mechanical methods of prophylaxis have also been shown to be effective, and undoubtedly have a role to play in patients unsuited for anticoagulants, confining their use to the immediate post-operative period does not prevent the development of late thromboemboli. In terms of efficacy and convenience, the evidence that modern anticoagulants prevent postoperative thromboembolism far exceeds that for other prophylactic regimens.

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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