col for preclinical testing in humans has been proposed (Linder 2000), which might serve as a first step in this direction.

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Low-molecular-weight heparin as prophylaxis against thromboembolism after total hip replacement—The never-ending story?

Sir—We would like to add some information to the ongoing debate on thromboembolism in your Journal and, in particular, comment on the recent correspondence from Björn M Persson (Acta Orthop Scand 2000; 71: 215–216), whose fundamental question is whether the benefit of prophylaxis with low-molecular-weight heparin (LMWH) offsets the asserted increased risk of impaired primary wound healing and prosthetic fixation.

We should begin by answering Persson's first question: whether LMWH is worth its price in view of its higher monetary cost than that of warfarin or unfractionated heparin when, according to the meta-analysis by Murray et al. (1996) and Freedman et al. (2000), it has no advantage concerning mortality. The true cost of a management strategy can be assessed only by means of a complete health-economic analysis taking account total costs of care and not just drug costs. It has been convincingly shown that in-hospital prophylaxis with LMWH is cheaper than unfractionated heparin and warfarin (Anderson et al. 1993, Drummond et al. 1994, O'Brien et al. 1994, Menzin et al. 1995, Bergqvist et al. 1996a, Hull et al. 1997). Most of these health-economic evaluations use venographic data from clinical trials to estimate the risk of deep venous thrombosis (DVT) and pulmonary embolism (PE) using comparative prophylactic management strategies. This may be criticized, as the proportion of subclinical DVT that develops into symptomatic DVT or PE is not known. A retrospective study, however, has compared the cost savings of LMWH and warfarin, and shown that the savings are due to a reduced rate of DVT and PE, less bleeding, and lower laboratory and monitoring costs with LMWH (Saunders and Grant 1998). The cost-effectiveness of prolonged prophylaxis as compared to in-hospital prophylaxis has also been shown (Detournay et al. 1998, Bergqvist and Jönsson 1999), and a recent study showed LMWH to maintain a cost-effective advantage over warfarin

for post-discharge prophylaxis of 19–31 days (Friedman and Dunsworth 2000).

Since there is no advantage in mortality for LMWH over warfarin or UFH on the basis of the meta-analysis by Murray, we feel that the results of the analysis should not be taken at face value. We have commented previously about drawing conclusions from this meta-analysis in a letter to this Journal (Dahl et al. Acta Orthop Scand 1999, 70: 403–406). In their meta-analysis, Murray et al are not comparing like with like, as they themselves point out; they take no account of the different trial designs and methodology that were used in the studies. Pooling the results from several, sometimes small, trials with various types of comparisons in order to detect a reduction in mortality, and then drawing conclusions regarding PE from a meta-analysis of these studies is obviously open to error. A recent mortality study (Hunter et al. 2000) has shown a significantly lower 30-day mortality rate in patients who received in-hospital prophylaxis with low-molecular-weight heparin dalteparin than in those who received unfractionated heparin. Furthermore, in the clinical trials included in the meta-analysis, any DVTs detected were actively treated. Therefore, a difference in mortality between the LMWH groups and the comparator arm would be difficult to detect. However, in clinical studies comparing LMWH directly with warfarin or low-dose unfractionated heparin, LMWH has proved more effective (Eriksson et al. 1991, Hull et al. 1993, 2000, Francis et al. 1997).

In a subgroup analysis, the Pulmonary Embolism Prevention (PEP) trial showed a reduction of about one-third in the risk of in-hospital DVT and PE in patients given a 35-day treatment with aspirin (PEP Trial Collaborative Group 2000). This is lower than the 71% relative risk reduction in in-hospital DVT seen with LMWH in clinical trials (Clagett et al. 1995). While the PEP trial investigators comment that the risk of bleeding with aspirin is lower than with LMWH or UFH, they used different criteria to define bleeding so this conclusion is questionable in the absence of a direct comparison of all the subjects. In addition, the validity of the PEP trial results has recently been widely questioned and criticized concerning protocol handling and data collection, and presentation and interpretation of the data (Cohen and Quinlan 2000).

Persson also questions the validity of the conclusions drawn from clinical trials of prolonged thromboprophylaxis in which LMWH has been shown to reduce significantly the risk of venographically-diagnosed DVT. The studies in question consistently show at least a 50% reduction in risk of DVT with prolonged, out-of-hospital, LMWH thromboprophylaxis versus in-hospital prophylaxis (Bergqvist et al. 1996b, Planes et al. 1996, Dahl et al 1997, Lassen et al. 1998, Hull et al. 2000). The recently published study of prolonged prophylaxis with ardeparin after total hip or knee replacement (Heit et al. 2000) merits comment. Surprisingly, the study combined the hip and knee arthroplasty populations (about 60% of study patients were knee and 40% were hip arthroplasty patients) and used symptomatic DVT as an endpoint, rather than objective radiologically verified DVT. (Should we now perform in-hospital trials with clinical DVT as an endpoint? We would expect the incidence of posttraumatic DVT in such studies to be similar to that seen in postdischarge studies: 1–3%, with an associated mortality rate of around 1%). In knee arthroplasty patients, as in hip arthroplasty patients, the need for—and optimal duration of—out-of-hospital prophylaxis is uncertain, but current evidence suggests that it is different for the two populations (White et al. 1998, Dahl et al. 2000).

As expected, Heit et al. report that the rate of clinical DVT in their patients was around 2%, with or without prophylaxis. This finding may be due to an inadequately designed and performed study: a too low preestimated number of endpoints and premature termination of the study. In our view, the conclusion drawn by Heit et al. that asymptomatic DVT is clinically insignificant is not supported by our experience in clinical practice. Since symptomatic DVTs are treated, thereby reducing the risk of PE, it follows that nearly all fatal PEs after major surgery derive from untreated subclinical DVTs.

Some data show that reduction of venographic DVT results in a clinically significant reduction in clinical DVT. In an analysis of clinical trials of prolonged thromboprophylaxis, 1.7% of patients receiving prolonged thromboprophylaxis had objectively documented symptomatic venous throm-

boembolism compared to 3.4% of patients in the placebo groups, a reduction of 51% (p= 0.015) (Cohen and Khushal, in press). We would therefore argue that, in high-risk groups, prophylaxis should be considered for around one month.

However, the surveillance and documentation of the rate of fatal PE after hip replacement surgery are insufficient to indicate that PE is so infrequent as to be an insignificant risk. In the recently published Norwegian Arthroplasty Register, all patient categories had a higher mortality than the general population during at least the first 60 postoperative days (Lie et al. 2000). This occurred, although most of the patients had received some type of in-hospital thromboprophylaxis and those undergoing elective hip arthroplasty had been selected before surgery, so that any baseline medical diseases had been treated, thereby optimizing their health before surgery. Murray, in a recent coauthored article, has commented that the estimated rates of fatal PE after total hip replacement, based on his meta-analysis, are probably too low, having been 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' (Gillespie et al. 2000).

We do not know whether there is a rebound incidence of DVT after stopping prophylaxis 5 weeks after hip replacement. However, as previously referred to in a review article in this Journal (Dahl et al. 1998), studies have shown rebound activation of coagulation and an increase in clinical endpoints after cessation of anticoagulants. In hip surgery, we have indications of a second wave of activation of coagulation and formation of DVT when prophylaxis is stopped at discharge, about 1 week after surgery (Dahl et al. 1995, 1997). Taking into account available epidemiological data (Seagroatt et al. 1991, Warwick et al. 1995, Johnson et al. 1977, Lie et al. 2000), it is reasonable to assume that hypercoagulation-related vascular complications may occur for several weeks after hip replacement.

We now come to the core issue of a reported increase in loosening of prostheses and wound hematomas with heparin treatment of PE after total hip arthroplasty (Lawton and Morrey 1999). Wound secretion, bruising, hematoma and risk of infection, reoperation and revision surgery have to be taken seriously. However, no conclusions can presently be drawn regarding any potential role played by UFH, LMWH or cement loosening. The bleeding risk associated with treatment dosages is higher than that associated with prophylactic dosages of heparin (Lawton and Morrey 1999). Treatment dosages of UFH and LMWH also differ as regards to risk of bleeding complications, with a higher risk associated with UFH (Hull et al. 1992, Turkstra et al. 1997). However, further work is needed, first to define variables for monitoring these complications and hence to identify the risks for infection and the causes of prosthetic loosening.

Autopsy studies have shown that the majority of deaths after major orthopedic surgery may be attributed to hypercoagulation-related cardiovascular complications (NCEPOD; Campling et al. 1993,1994). Further, a recently abstracted autopsy-proven mortality study by Haas et al. (1999) showed that a significantly higher number of deaths was due to PE than have been claimed. This was most probably because the autopsy rate in this study was nearly 70%, which reduces the diagnostic failure of clinical death certificates.

It is our opinion that the ethical burden rests on our colleagues who neglect to protect their hip replacement patients from the risk of fatal PE. Evidence should guide our clinical decisions, not opinions and emotions.

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Sir—Despite the extensive replay above to my previous letter questioning the use of thromboprophylactic LMW-heparin for all total hip patients, I must repeat my question. There is still no reduction in mortality at 90 days. Although Dahl et al. refer to some still unpublished data, and question Murray's meta-analysis from England, some additional studies (Freedman et al. 2000) from Philadelphia, USA now support my opinion. They include 10,929 THA patients in 52 randomized studies with phlebography in all and 3-month follow-ups concerning complications and mortality. They report a 0.3% mortality rate at 90 days both with placebo and LMW-heparin and severe bleeding in 3% with and 0.3% without. So even if verified thrombosis was three times commoner without prophylaxis, the difference disappeared later. Dahl agrees there is an increased risk of rebound after cessation of treatment, which can occur even with prolonged treatment. We know that clinically detected thrombosis has a mean time of appearance around 30 days after surgery and it is misleading to compare the occurrence of thrombosis with phlebography on the last day of treatment in the group on prolonged treatment with another group on no treatment for 3 weeks. It would be more relevant to examine both groups 2 months after surgery to see whether the advantage of treatment remained.

So long as all studies (Salvati et al. 2000) show an equal mortality with or without prophylaxis using LMW-heparin, I cannot understand the last emotional sentence in Dahl's letter! Mortality after THA is 3 times commoner after causes other than thromboembolism and use of aspirin may have an evidence-based advantage, as suggested by a recent pulmonary embolism prevention study (Mahe et al. 2000). The increased risk of neurological damage from epidural catheters and simultaneous use of LMW-Heparin is a new cause of concern. In the present state of the art, I find no need to use thromboprophylactic treatment for all THA patients, but reserve it, and give prolonged treatment for selected cases with a history of thrombotic episodes in that patient or his family.

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