Out of Hospital Antithrombotic Prophylaxis after Total Hip Replacement: Low-molecular-weight Heparin, Warfarin, Aspirin or Nothing?

A Cost-effectiveness Analysis

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Summary

Several studies have suggested that after hip replacement the risk of deep vein thrombosis and subsequent pulmonary embolism (PE) may persist for some weeks. Antithrombotic prophylaxis, however, is generally stopped at hospital discharge. Using a Markov-based decision analysis, we measured the clinical and economical consequences of extending prophylaxis after hospital discharge up to 4 weeks and 6 weeks, using either low-molecular-weight heparin (LMWH), warfarin, or aspirin. In the reference strategy, antithrombotic prophylaxis was stopped at hospital discharge. Outcome measures included the number of PE prevented, major haemorrhages induced, overall costs in Euro (EUR) and specific costs generated by each PE prevented for all strategies.

Extending prophylaxis up to 4 weeks after discharge was safe and cost saving for all prophylactic regimens, although LMWH was the most effective strategy. Our results were most sensitive to the rate of haemorrhages, the efficacy of treatment and its costs. Specifically, the number of PEs prevented exceeded that of haemorrhages induced if the efficacy of antithrombotic prophylaxis was ≥40% (assuming a low rate of haemorrhages of 0.1% per week), and ≥70% (assuming a high rate of haemorrhages of 0.25% per week). LMWH and warfarin remained cost saving unless their costs were more than doubled compared to that of baseline value. Although less effective than LMWH and warfarin, prophylaxis with aspirin was cost saving in all scenarios tested. Extending prophylaxis up to 6 weeks was also effective (the number of PEs prevented overwhelmed that of major haemorrhages induced), but only for the scenario of a low bleeding risk (0.1%/week). In this strategy, aspirin remained cost saving, while the costs for each PE prevented became high (EUR 10,000 to EUR 20,000) if the costs of LMWH and warfarin increased.

After hip replacement, extending antithrombotic prophylaxis up to 4 weeks after hospital discharge is effective and cost saving. Although LMWH is the most effective strategy, warfarin, and to a lesser extent aspirin may be alternate options if resources are a major concern.

Extending prophylaxis up to 6 weeks is more risky in patients at high bleeding risk, and generates additional costs.

Introduction

Strong clinical evidence supports the safety and effectiveness of perioperative prophylaxis against deep vein thrombosis (DVT) in the lower limbs for patients undergoing total hip replacement (1). Subcutaneous injections of unfractionated or low-molecular-weight heparin (LMWH) were proven effective in reducing this risk by about two-thirds (2-6). The duration of prophylaxis, however, remains uncertain. While prophylaxis is generally stopped at hospital discharge (7-10 days following surgery), the risk of DVT may persist for some weeks thereafter, as initially suggested in a large cohort of patients who underwent general surgery (7). By using systematic venography at the time of discharge from the hospital, DVTs were found in 15% to 25% of patients, half of them being proximal (8-11). Although most of these venous thrombi are asymptomatic, they are considered to be the source of most clinically important pulmonary emboli (1).

In a cost-effectiveness analysis, a six-week course of warfarin (INR 2.0-3.0) has been suggested to be a valuable option following total hip arthroplasty (12). Subsequently, LMWH extended beyond hospital discharge have been found in clinical trials to be effective in reducing the occurrence of DVT (5, 6, 13-15). Recently, it was shown that aspirin also reduced the risk of thromboembolism following hip fracture, although to a lesser degree than anticoagulation regimens. However, the question of whether and how long to extend prophylaxis into outpatient setting involves additional considerations. These include not just the effects seen in clinical trials but also the absolute risk of thromboembolism and of haemorrhages in a particular patient, and the costs of treatment. Therefore, we used decision analysis to assess the clinical benefits and the economic consequences of different management options for patients discharged from the hospital after hip replacement. Specifically, we measured the consequences of extending antithrombotic prophylaxis up to 4 weeks and 6 weeks, respectively, using either warfarin, LMWH or aspirin.

Methods

We used the D. Maker 7.1 (17) decision analysis program to create a model representing the different options available at hospital discharge for patients undergoing hip replacement and at risk of developing venous thromboembolism. Probabilities were derived from literature review. Sensitivity analyses were performed to test the stability of the results over a wide range of clinically relevant values.
Outcome Measures

For each strategy, the outcomes studied were the number of recurrent DVT and subsequent pulmonary embolism (PE), the number of major haemorrhages, the overall costs, and the marginal cost-effectiveness ratios in a hypothetical cohort of 10,000 patients followed over a 3-month period after hip replacement.

The Decision Model

We compared four management options. Under the first strategy, antithrombotic prophylaxis was stopped at hospital discharge. Under the second strategy, prophylactic oral anticoagulation with warfarin (targeted INR 2.0-3.0) was administered to all patients up to 4 weeks after hospital discharge. In the third and fourth strategies, once-daily subcutaneous LMWH and aspirin (160 mg) were administered during the same time period, respectively. The specific doses used for the particular LMWH evaluated are summarized in Table 1.

All strategies lead to a common subtree representing the risks of developing thromboembolic and/or haemorrhagic complications. These clinical events may recur over time, therefore, we used a Markov model (18). In a Markov model, patients in a hypothetical cohort are exposed to the same set of chance events repetitively over time, and time is modelled as a series of cycles. In our model, each cycle represented one week. During each weekly cycle, recurrent chance events (recurrent DVT, PE, major haemorrhage) may lead to a transition to a different state of health. The process of moving from one state of health to another depends on the probability of those events, derived from the literature. The simulation ultimately calculated the number of patients having suffered those events. If antithrombotic prophylaxis is stopped at hospital discharge, patients with undiagnosed DVT (proximal or distal) incur the risk of developing recurrent DVT, which may lead to symptomatic PE. These patients are then treated appropriately with oral anticoagulants. If prophylaxis is prolonged up to 4 or 6 weeks after discharge, those with undiagnosed DVT (proximal or distal) incur the risk of recurrent DVT and subsequent PE diminished by the efficacy of prophylactic therapy. In these strategies, however, all patients, including those without DVT at discharge, incur the risks of major haemorrhages during 4 or 6 weeks, depending on the initial strategy.

In formulating our model, we made a number of simplifying assumptions:

1. All patients received perioperative antithrombotic prophylaxis during 7 to 10 days.
2. Based on pooled data suggesting that the majority of DVT in patients discharged from hospital after hip replacement are clinically silent (1), we assumed that all DVT present at discharge are asymptomatic.
3. We assumed that all DVTs were present at discharge from hospital which may slightly underestimate the effects of oral anticoagulant therapy.
4. The risk of developing recurrent thrombosis in patients with DVT at discharge was based on a weekly-dependent exponential declining slope (see next section). In this model, the risk of subsequent PE (with or without symptoms) was considered to be constant once recurrent DVT has occurred.
5. The risk of developing recurrent DVT in untreated patients with distal DVT was half that of proximal DVT, derived from published data on the outcome of patients with distal DVT (19).

Table 1: Specific doses of LMWH used in the studies evaluating the efficacy of prophylactic LMWH against out-of-hospital DVT after elective arthroplasty

<table>
<thead>
<tr>
<th>Studies</th>
<th>Type of LMWH</th>
<th>Daily doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planes et al.⁵</td>
<td>Enoxaparin</td>
<td>4,000 IU</td>
</tr>
<tr>
<td>Bergqvist et al.⁶</td>
<td>Enoxaparin</td>
<td>4,000 IU</td>
</tr>
<tr>
<td>Lassen et al.¹⁹</td>
<td>Dalteparin</td>
<td>5,000 IU</td>
</tr>
<tr>
<td>Dahl et al.¹⁴</td>
<td>Dalteparin</td>
<td>5,000 IU</td>
</tr>
<tr>
<td>Hull et al.¹⁵</td>
<td>Dalteparin</td>
<td>5,000 IU*</td>
</tr>
</tbody>
</table>

* The initial dose was 2,500 IU, then the daily dose was 5,000 IU

Summary of the Data Employed

Table 2 lists the baseline values for each variable used in the model and gives the ranges of estimates derived from the literature (MEDLINE search 1966-2000) and tested in the sensitivity analyses. The following paragraphs give details and justifications for the data used.

Incidence of DVT at discharge. After hip replacement, the incidence of DVT detected by routine venography done at the time of hospital discharge ranges from 15% to 25% (1, 8-11).

Location of DVT at discharge. Results of routine venography suggest that about one half of all cases of DVT are found in the distal veins, the remaining being proxima (20-23).

Risk of recurrent proximal DVT. Among patients with proximal DVT treated inadequately, more than 20% of those who had recurrent DVT did so within the first week, while another 10% did so within the second week and the third week. Only 5% of patients had recurrent events between the fourth week and the end of the 3-month period (24). At the end of the third month, the weekly risk of DVT is 0.9% (95% CI, 0.6% to 1.2%) (25-28). Based on these data, an exponential regression model of the weekly-dependent declining rate of recurrent DVT in untreated patients with proximal DVT has been calculated (29). The declining exponential regression model is: [Exp(-0.29 x Week-0.98), R² = 0.94].

Pulmonary embolism. Pulmonary embolism has been reported in 20% to 50% of patients with proximal DVT, depending on the accuracy of the diagnostic method(s) and the presence or absence of symptoms (30). For our analysis, we used the more conservative figure of 20% (30), likely to represent symptomatic event, but also tested more extreme scenarios (10%).

Major haemorrhage. The rate of major bleeding complications with chronic anticoagulants correlates with the intensity of anticoagulant therapy and with patients characteristics, including both co-morbid conditions and age (31). With oral anticoagulants, the incidence of major bleeding events ranges between 0.5% per week in low-risk settings (e.g., moderately intense INR, absence of comorbidities such as gastrointestinal bleeding, hypertension, cerebrovascular disease, liver or renal insufficiency, concomitant use of non-steroidal anti-inflammatory agents), to 0.25% per week in high-risk settings (e.g., INR above the upper limit of the therapeutic range, ≥1 of the above-mentioned risk factors for bleeding). The rate of major bleeding with prophylactic LMWH is low. After elective arthroplasty, major bleeding occurred in none among more than 800 patients undergoing out-of-hospital prophylaxis against DVT. Weekly major bleeding events occurred in less than 0.1% of patients with prophylactic low-dose aspirin (16).

Treatment efficacy. The efficacy of prophylaxis in preventing recurrent DVT ranges between 40% and 80%, depending on the anticoagulant regimen (1, 3-6, 13-16).
Cost Analysis

All costs were calculated from the perspective of the health care system and were expressed in Euro (EUR). Indirect costs, such as lost earnings due to poor health were not estimated. These costs are likely to be correlated with direct health care costs. Table 3 summarizes our hospital’s average variable costs for each of the outcome modeled. These costs are comparable with those of other institutions (33, 34). Variable costs assume that the institutional superstructure is already in place (e.g., laboratories or hospital beds). Data are from fiscal year 1999.

Incremental or marginal costs represent the additional costs of switching from one treatment strategy (e.g., no prophylaxis), to a new strategy (e.g., LMWH for 4 weeks), whereas the marginal cost-effectiveness analyses reveal the additional costs expended to gain additional benefits between the two different approaches. In the present analysis, we defined the marginal cost-effectiveness as the additional costs per additional PE prevented.

Sensitivity Analyses

Our model was most sensitive to the rate of bleeding, the duration of prophylaxis, its efficacy and its costs. Figure 1 balances the number of PEs prevented and that of major haemorrhages induced if antithrombotic prophylaxis is administered in a hypothetical cohort of 10,000 patients. Assuming that prophylaxis was extended up to 4 weeks after hospital discharge and that the rate of haemorrhages was low (0.1% per week), the number of haemorrhages induced was overwhelmed by that of PEs prevented only if the efficacy of prophylaxis was 40%. In patients with a higher risk of haemorrhages (0.25% per week), this threshold increased up to 70%. Assuming that prophylaxis was prolonged up to 6 weeks, these figures increased up to 50% and 80%, respectively.

As expected, increasing the costs of antithrombotic regimens increased the total costs of prolonged prophylaxis. Figure 2 represents the marginal cost-effectiveness ratio (expressed as the additional costs expended per each additional PE prevented) of prolonged antithrombotic prophylaxis as a function of its costs and its efficacy. Specifically, extending prophylaxis up to 4 weeks remained effective and less costly (i.e., cost saving) unless the antithrombotic regimen were moderately effective and expensive (Fig. 2A). Prolonging prophylaxis up to 6 weeks increased the additional costs for each PE prevented and remained cost saving provided the costs of prophylaxis were low. The costs for each PE prevented became high (EUR 10,000 to 20,000) if the costs of LMWH or warfarin were doubled. (Fig. 2B).

Results

Baseline Analysis

Over a 3-month period, our model predicted 1172 cases of recurrent DVTs and 234 symptomatic PEs among 10,000 patients if antithrombotic prophylaxis was stopped at hospital discharge. In comparison, prolonging prophylaxis up to 4 weeks after discharge reduced the number of recurrent DVTs and PEs and was less costly, despite the occurrence of bleeding complications. These figures are summarized in Table 4 for the different prophylactic regimens.
We performed additional sensitivity analyses on the risk of recurrent DVT, the location of DVT (proximal vs distal) and the risk of subsequent PE. Even when the rate of PE was as low as 10%, the ranking of the strategies remained unchanged and prophylaxis extended up to 4 weeks remained cost saving except in extreme scenarios.

**Discussion**

The present study shows that among patients with no particular risk factors for bleeding, extending prophylaxis up to 4 weeks after discharge is safe and effective. For all scenarios tested, including that of a low
Fig. 1 Number of pulmonary embolisms prevented and major hemorrhages induced over a 3-month period for a hypothetical cohort of 10,000 patients discharged from hospital after hip replacement and assuming that antithrombotic prophylaxis is prolonged up to 4 weeks. These figures are represented by different efficacy of prophylaxis.

Fig. 2 Additional costs in Euro (EUR) per additional pulmonary embolism prevented as a function of the weekly costs of antithrombotic prophylaxis (horizontal axis). These results are presented for different efficacy of prophylactic regimen. For combination of value falling below the “zero” line, prolonged antithrombotic prophylaxis is cost saving compared to stopping it. For combination of values falling above the “zero” line, extending prophylaxis generates additional costs for each PE prevented. Figure 2A represents the consequences of extending prophylaxis up to 4 weeks, while Figure 2B the consequences of extending prophylaxis up to 6 weeks.
efficacy regimen like aspirin, the number of PE prevented exceeded that of major haemorrhages induced. Even in the setting of a high risk of bleeding, prophylaxis using highly effective regimens (LMWH or oral anticoagulation) remained effective, while the risks of using lower efficacy regimen such as aspirin, although rarely associated with a high bleeding rate, exceeded its benefits. In terms of cost-effectiveness, extending prophylaxis up to 4 weeks, using LMWH or oral anticoagulation was cost saving, or generated low incremental cost-effectiveness ratios compared to other interventions, depending on the costs of prophylaxis which may vary between countries. Aspirin prophylaxis, however, remained cost saving over all plausible ranges of costs. Under the strict condition that the risk of bleeding be low, extending prophylaxis up to 6 weeks was also effective compared to withholding prophylaxis at discharge. Such a low bleeding risk, however, might not be achieved among the elderly, representing the majority of patients undergoing hip replacement. In addition, the marginal cost-effectiveness ratios generated by this strategy may be high, exceeding EUR 10,000 per each additional PE prevented.

Our results assume that one pulmonary embolism prevented equals one major bleeding episode induced, which is certainly not true, also perhaps from a medicolegal point of view. It is our impression, however, that the decision whether to give prophylaxis to a patient is mostly influenced by the frequency at which the two potentially fatal clinical events may occur. Ideally, we recognise that long-term morbidities from intracranial bleeding (for instance, hemiplegia), recurrent deep vein thrombosis (the post-thrombotic syndrome), and pulmonary embolism (pulmonary hypertension) should be stratified by degree of disability, with a utility (or value) specified for each category. The incidence of chronic disability after these events is uncertain, however, and has not been characterized well enough to make such adjustments reliable.

These conclusions may, however, be challenged on the basis of several limitations. First, while the data concerning the effects of LMWH were derived from studies that assessed specifically the use of these drugs in the setting of after-discharge thromboembolism, this was not the case for warfarin and aspirin. However, warfarin has been largely used for thromboprophylaxis, especially in the U.S., and we used quite robust efficacy and safety data. On the other hand, although the PEP trial (16) did not compare aspirin with placebo specifically after discharge from hospital, the antithrombotic effect observed in that study was particularly obvious after the first postoperative week. Moreover, the results of the PEP trial parallel the conclusions of the meta-analysis by the Antiplatelets Trialists’ Collaboration that showed a highly significant reduction in postoperative deep vein thrombosis and pulmonary embolism with aspirin (35). Second, most patients in the PEP trial had hip fracture and not elective total hip arthroplasty.

Nevertheless, a large subset of patients actually had hip replacement and the results did not appear to differ among the two groups of patients. Third, and more importantly, one might challenge our choice to focus on all embolic events rather than symptomatic complications only actually treated in clinical practice. Our choice is supported by the two following arguments: 1) symptomatic events are quite rare and the incidence rates subject to wide variations and a large uncertainty depending upon the index of clinical suspicion; 2) even asymptomatic DVTs are known to produce fatal PE and the best way to prevent the latter event is probably to avoid all (symptomatic and asymptomatic) postoperative DVTs. Furthermore, symptoms and clinical relevance may not overlap completely, thus, a painful calf DVT is certainly less dangerous than an asymptomatic iliac vein thrombosis. Lastly, the model predicted 11.7% DVT (both symptomatic and asymptomatic) and 2.3% symptomatic PE over a 3-month period following hip replacement. This figure is compatible with a recent meta-analysis comparing the effectiveness of extended out-of-hospital LMWH prophylaxis versus placebo after hip arthroplasty. In the placebo group (862 patients), the frequency of out-of-hospital proximal DVT (both symptomatic and asymptomatic) was 11.2%, and that of symptomatic thromboembolic events was 4.2% (32).

In another study that focused on symptomatic events, 2% of patients who had no prolonged prophylaxis experienced PE or died, of whom 0.8% had objectively confirmed PE (36).

In conclusion, extending antithrombotic prophylaxis into the outpatient setting raises important issues for the patient and the community. Our decision analysis handles part of this complexity and suggests that after hip replacement prolonging antithrombotic prophylaxis up to 4 weeks after hospital discharge using aspirin, LMWH or oral anticoagulation is safe and cost-effective. Choosing one of these options mainly depends upon which aspect is privileged: if efficacy is the first concern, then LMWH or oral anticoagulants should be used, if resources are a major concern, aspirin offers an attractive alternative.

References


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