Pharmacoeconomics of Thrombosis Management

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Venous thromboembolism (VTE) is the cause of significant morbidity and mortality and may lead to other complications, including recurrent VTE and long-term postthrombotic syndrome. Venous thromboembolism represents a huge health economic burden of nearly $500 million/year in the United States. Without adequate prophylaxis, patients undergoing major orthopedic surgery are at high risk of developing VTE. Prophylaxis with either unfractionated heparin or warfarin not only substantially reduces the risk of VTE after orthopedic surgery, but also is more cost-effective than no prophylaxis. Low-molecular-weight heparins (LMWHs) have been shown to be superior to unfractionated heparin or warfarin, and despite the fact that they are more expensive, they are cost-effective. Large-scale clinical trials have shown that fondaparinux further reduces the likelihood of VTE complications after major orthopedic surgery. A review of the pharmacoeconomic evaluations of fondaparinux leads to the conclusion that fondaparinux is a cost-effective alternative to LMWHs in VTE prophylaxis.

Key Words: venous thromboembolism, orthopedic surgery, thrombosis management, pharmacoeconomics, fondaparinux.

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The prevention and treatment of venous thrombosis can be accomplished with a variety of pharmacologic agents, including aspirin, warfarin, unfractionated heparin, low-molecular-weight heparin (LMWH), direct thrombin inhibitors, and fondaparinux. The decision to use one over the other is based on preference or purported differences in safety, efficacy, and cost.

Differences in safety and efficacy can best be determined by carefully controlled randomized trials. There is general agreement as to what constitutes a proper clinical trial for evaluating the safety and efficacy of antithrombotic agents. In fact, the American College of Chest Physicians sponsors a consensus conference of experts who periodically review all the published evidence regarding antithrombotic therapy and issue guidelines for its use in the prevention and treatment of thrombosis. These guidelines are published as a supplement to the journal *Chest*, with the most recent set being published in the January 2001 supplement.[1]

Differences in the cost of antithrombotic therapy have been assessed by a number of different pharmacoeconomic methods. Unfortunately, no clear consensus exists on what constitutes the best approach for assessing pharmacoeconomic differences, and no expert panel is evaluating all the published evidence from which guidelines can be derived. Nevertheless, it is incumbent on health care decision makers to examine the available pharmacoeconomic literature on the management of thrombosis and reach a reasonable conclusion about economically significant differences that may exist among alternative antithrombotic therapies.

The Disease Burden

Venous thromboembolism (VTE), which is a single disease entity that encompasses deep vein thrombosis (DVT) and pulmonary embolism, is an important cause of morbidity and mortality in patients undergoing major orthopedic surgery.[2–4]

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The immediate consequences of DVT can include pulmonary embolism and death. The long-term consequences include recurrent VTE and postthrombotic syndrome.

Without appropriate prophylaxis, the risk of VTE after major orthopedic surgery is approximately 50%. Most VTE events are asymptomatic. However, before the introduction of anticoagulant prophylaxis, 20–30% of asymptomatic DVTs extended into the popliteal vein, which resulted in a 40–50% risk of clinically detectable pulmonary embolism.[3] Several studies reported that the frequency of postthrombotic syndrome ranged from 35–69% within 3 years and 49–100% within 5–10 years of initial diagnosis of DVT.[4]

Postoperative prophylaxis with an anticoagulant has substantially reduced the VTE morbidity and mortality associated with major orthopedic procedures. According to one group of authors, after an episode of DVT, the cumulative rate of recurrent DVT ranged from 17% at 2 years to 30% at 8 years and the development of postthrombotic syndrome ranged from 25–30% during an 8-year follow-up period.[5–7]

Table 1. Rates of Venous Thromboembolism According to Prophylaxis in Patients Undergoing Major Orthopedic Surgery from Four Phase III Clinical Trials

Surgery	Enoxaparin	Fondaparinux
Hip replacement[25]	66/797 (8.3)	48/787 (6.1)
Hip replacement[26]	85/919 (9.2)	37/908 (4.1)
Knee replacement[27]	101/363 (27.8)	45/361 (12.5)
Hip fracture[28]	119/624 (19.1)	52/626 (8.3)

Data are no. of patients with venous thromboembolism/no. undergoing surgery (%).

The Economic Burden

Despite the major reductions in VTE achieved with traditional anticoagulant prophylaxis, thromboembolic complications remain a costly complication of major orthopedic surgery. The economic burden of VTE approaches $500 million/year just based on Medicare figures.[8] This estimate does not reflect the additional cost of treating postthrombotic syndrome or the cost of treating anticoagulant-induced major bleeding episodes—costs that can be substantial. The estimate also does not include the indirect cost that the patient or employer must bear as a result of lost workdays. Moreover, in the Medicare patient, a VTE complication after major orthopedic surgery presents a significant economic loss to the hospital because the reimbursement for the diagnosis-related group often does not adequately cover the additional expense in treating postoperative complications.

Economic studies have shown that VTE prophylaxis with unfractionated heparin or warfarin after major orthopedic surgery not only reduces the rate of VTE morbidity and mortality, but also reduces the cost of health care.[9, 10] This is true because the additional resources that would be required in the diagnoses and treatment of VTE complications in patients who did not receive prophylaxis greatly exceed the cost of heparin or warfarin prophylaxis. Compared with the newer anticoagulants, heparin and warfarin are relatively inexpensive even when the cost of laboratory monitoring is included. The newer anticoagulants are, however, more clinically effective at preventing VTE events. But, are they cost-effective?

Before addressing this question, it might be instructive to determine beforehand the level of significance that must be reached before concluding that an intervention is cost-effective. This a priori level of significance is, of course, arbitrary, as in the case of assessing the statistical and clinical significance of differences in efficacy. The conventional level of statistical significance usually is set at 0.05. Judgments about clinically significant differences in outcomes depend to some extent on the severity of the outcome. For example, if the desired outcome is the patient's survival of a condition that is usually fatal, then any reduction in death attributed to the intervention would be considered clinically significant. Determining economic significance usually is based on either a cost-utility or cost-effectiveness measure. The vast majority of economic evaluations of VTE prophylaxis have employed a cost-effectiveness approach in which the outcome is expressed in terms of the cost/event averted or the incremental cost ratio. No one would dispute the fact that, if an intervention is found to be more effective and less expensive, then it is obviously cost-effective. If, on the other hand, an alternative intervention is more effective but also more expensive, then it would be helpful to determine if the additional benefit is worth the additional cost. An incremental cost analysis can be used for making such judgments. Some health economists reject the use of an incremental cost-effectiveness ratio, arguing that such ratios often imply a need for more resources, which raises such questions as, where would incremental resources come from, and what would have to be given up?[11]

Table 2. Expected Number of Symptomatic Venous Thromboembolic Events and Additional Cost of Care

	Expected No. of Events[a]			
Surgery	Enoxaparin	Fondaparinux	Difference	Additional Cost ($)[b]
Hip replacement	34	20	14	70,322
Knee replacement	7	3	4	9980
Hip fracture	12	8	4	54,264
Total				134,566

[a]Derived from the proportion of total events expected to be symptomatic if 2% of all patients receiving prophylaxis develop symptomatic venous thromboembolism.[21]
[b]Additional cost of care/event is $5023 for hip replacement, $2495 for knee replacement, and $13,566 for hip fracture.[23]

The Cost-Effectiveness of Newer Anticoagulants

Large-scale clinical trials have shown that newer anticoagulants, such as LMWH and fondaparinux, further reduce the likelihood of VTE complications associated with major orthopedic surgery.[12–14] As stated earlier, however, the newer agents are far more expensive than unfractionated heparin and warfarin, and this raises the question of whether the additional benefit is worth the additional cost.

This question has been addressed in a number of published economic studies comparing LMWH with either unfractionated heparin or warfarin.[15–19] In each of these studies, the LMWH was found to be cost-effective, despite the fact that its acquisition cost greatly exceeded that of heparin and warfarin. These economic studies for the most part used a decision analytic model in which symptomatic rates of VTE events are estimated from venographic rates observed in randomized controlled trials. The additional cost of diagnosing and treating the more frequent symptomatic VTE events the model predicts for patients receiving either heparin or warfarin more than offsets the difference in the acquisition cost of the LMWH.

Fewer studies have compared the cost-effectiveness of LMWH with that of fondaparinux. Preliminary data were presented at a scientific meeting, and, based on these data and the results of recently published randomized clinical trials and health care cost studies, one may speculate what shape economic studies are likely to take.

In one economic evaluation,[20] two cost-effectiveness analyses were conducted by using a cohort simulation model. Probabilities of VTE events were derived from objective outcomes obtained from a worldwide fondaparinux clinical trial program involving more than 7000 patients; these data were supplemented with estimates from the published literature. Using these data, the authors calculated outcome probabilities for a hypothetical cohort of United States patients receiving either fondaparinux or enoxaparin. Cost data were extracted from United States health care databases. Cost-effectiveness ratios were computed to assess the incremental cost/symptomatic VTE event averted during hospitalization and at 30 and 90 days and 5 years after discharge. For all time periods, the model predicted cost savings if fondaparinux was used instead of enoxaparin.

Table 3. Summary of Bleeding Parameters Across Four Major Clinical Trials[25–28]

Complication	Enoxaparin	Fondaparinux
Bleeding in critical organ	1	0
Bleed leading to repeat surgery	8	11
No. of transfusions	1889	1925

Another study suggested fondaparinux was more cost-effective than enoxaparin 40 mg once/day but less cost-effective than enoxaparin 30 mg twice/day.[21] One of the limitations in this study was the failure to account for cost savings associated with averting asymptomatic DVT, which may contribute to recurrent thrombotic disease or postthrombotic syndrome.[22]

In a recently published retrospective assessment of the cost of VTE in hospitalized patients undergoing major orthopedic surgery, cost data were obtained from 220 geographically diverse hospitals between January 1998 and June 1999.[23] The study measured the use of intensive care services, length of hospital stay, and estimated costs of inpatient care derived by applying hospital-specific cost:charge ratios. The additional cost of care for treating DVT averaged $5023 in total hip replacement, $2495 in total knee replacement, and $13,566 in hip fracture repair.

In a study of 1984 consecutive patients who underwent hip or knee arthroplasty, the rate of symptomatic VTE during enoxaparin prophylaxis was 2%.[24] The venographic rates of VTE observed in four large phase III clinical trials comparing enoxaparin with fondaparinux are presented in Table 1.[25–28] If one assumes a 2% rate of symptomatic VTE in patients receiving enoxaparin prophylaxis across all surgical groups, and if one assumes that most of these arise from underlying venographic-positive conditions, then the proportions of total VTE that are expected to be symptomatic are 7% for patients undergoing knee replacement, 23% for hip replacement, and 10% for hip fracture surgery. By using these estimated symptomatic rates and the cost of care from the previously mentioned study,[23] the additional cost incurred by the less-effective prophylactic regimen can be calculated. As shown in Table 2, the estimated additional cost of care in patients receiving enoxaparin exceeds $109,000. This does not, however, include the cost of prophylaxis or the cost of treating bleeding complications. The average wholesale acquisition cost of fondaparinux is approximately $6 more than the cost of enoxaparin given twice/day and $15 more than enoxaparin given once/day. A summary of bleeding parameters in all four phase III clinical trials of fondaparinux versus enoxaparin is shown in Table 3. As indicated, there were 9 clinically relevant bleeding events in the enoxaparin group and 11 in the fondaparinux group. Also, patients receiving fondaparinux required 36 more transfusions than patients who received enoxaparin. If the additional costs associated with fondaparinux do not exceed $135,000, then fondaparinux prophylaxis clearly would be more cost-effective than enoxaparin. If, however, the converse is true, an incremental cost analysis could be done to assess whether the additional benefit that derives from fondaparinux prophylaxis is worth the additional cost.

Most pharmacoeconomic evaluations of VTE prophylaxis in patients undergoing major orthopedic surgery have been based on short-term clinical end points. These studies have failed to take into account VTE events that occur long term, as well as the occurrence of post-thrombotic syndrome, a condition that adds considerably to the economic burden of VTE. Recommendations for conducting pharmacoeconomic analyses that include both immediate and long-term phases of VTE can be found in a recently published review.[29]

Conclusion

Anticoagulant prophylaxis has been shown to reduce significantly the rate of thromboembolic complications after major orthopedic surgery. Adjusted-dose heparin, LMWH, or warfarin is extremely cost-effective compared with no prophylaxis. Even though fondaparinux is more expensive than the traditional agents, its potential to further reduce the frequency of postoperative VTE makes it a cost-effective alternative.

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