Canadian Agency for Drugs and Technologies in Health

HTA

HEALTH TECHNOLOGY INQUIRY SERVICE (HTIS)

TITLE: Fondaparinux versus Enoxaparin for the Prevention of Venous Thromboembolism: A Comparative Clinical and Cost-Effectiveness Review

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CONTEXT AND POLICY ISSUES:

Venous thromboembolism (VTE) includes deep vein thrombosis (DVT) and pulmonary embolism (PE).[1] It is a relatively common complication associated with surgery, but can also occur in hospitalized patients not undergoing surgery and in the ambulatory population.[2] The risk of VTE is highest in patients with multiple risk factors (e.g. history of varicose veins, myocardial infarction, cancer, atrial fibrillation, ischemic stroke, or diabetes mellitus), as well as those undergoing orthopedic surgery (hip or knee arthroplasty or hip fracture surgery) and those with major trauma or spinal cord injury. In the absence of appropriate prophylaxis, the risk of DVT is about 10% to 20% in these patients, while the risk of fatal PE is about 0.2% to 5%.[2] Alternatives for prophylaxis of VTE include selective factor Xa inhibitors, low-molecular weight heparins, or vitamin K antagonists.[3]

Fondaparinux is a synthetic, specific inhibitor of factor Xa.[4] It potentiates the action of antithrombin III which selectively inhibits (neutralizes) factor Xa.[4] Neutralization of factor Xa interrupts the coagulation cascade and thus inhibits thrombin and clot formation.[4] In Canada, fondaparinux is marketed under the trade name Arixtra® and is indicated for the prevention of VTE post-surgery in patients undergoing orthopedic surgeries of the lower limbs such as hip fracture surgery, knee surgery, or hip replacement surgery.[4] Enoxaparin is a low molecular weight heparin with high affinity for binding to antithrombin III. It acts mainly by accelerating the rate of the neutralization of coagulation factors that are activated by antithrombin III (factors Xa and IIa).[5] Enoxaparin is marketed under the trade name Lovenox® in Canada and is approved for use in the prevention of DVT in orthopedic hip or knee surgery; high risk abdominal, gynecological, or urological surgeries; and colorectal surgery.[5] The approved dosing regimen for the prevention VTE with fondaparinux is 2.5mg once daily administered by subcutaneous injection starting six hours after surgery generally for about seven days.[4] The approved dosing regimen for enoxaparin for the prevention of VTE in hip or knee surgery is 30mg every 12 hours subcutaneously for seven to 14 days.[5]

Low molecular weight heparins are the most commonly used agents for prevention of VTE following orthopedic surgery.[6] Of the low molecular weight heparins, enoxaparin is the most thoroughly studied and the most frequently used.[6] Fondaparinux is also effective in preventing VTE in orthopedic surgery, but is more costly than enoxaparin.[6] Both the relative clinical effectiveness and cost-effectiveness are important to consider when selecting an agent for prevention of VTE. This report will review the evidence of clinical and cost-effectiveness of fondaparinux relative to enoxaparin, which could potentially help in decision-making at the level of the healthcare system.

RESEARCH QUESTIONS:

1. What is the comparative clinical effectiveness of fondaparinux versus enoxaparin for the prevention of venous thromboembolism?

2. What is the comparative cost-effectiveness of fondaparinux versus enoxaparin for the prevention of venous thromboembolism?

METHODS:

A limited literature search was conducted on key health technology assessment resources, including PubMed, The Cochrane Library (Issue 4, 2008), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international HTA agencies, and a focused Internet search. Results include articles published between 2003 and November 2008, and are limited to English language publications only. Filters were applied to limit the retrieval to systematic reviews, health technology assessments, meta-analyses, economic studies and randomized controlled trials.

From the literature search one health technology assessment, one meta-analysis, and 12 economic evaluations were identified. Given the large number of economic evaluations identified, only those published in 2005 or later or based on Canadian estimates are summarized below.

SUMMARY OF FINDINGS:

Health technology assessments

In 2004, SBU (a Swedish health technology assessment agency) conducted a health technology assessment of fondaparinux for the prevention of VTE following orthopedic surgery.[7] An English language summary of the report was available; however, the full version of the report was not available in English and as such, many details of the methodology of the review could not be determined.

Data from four randomized controlled trials (RCTs) were meta-analyzed. In the four trials fondaparinux was compared to enoxaparin administered for five to nine days in 7,000 patients who underwent hip replacement surgery, knee replacement surgery, or hip fracture surgery. The dosages of each medication were not included in the summary. They found that the prevalence of DVT was 6.8% in the fondaparinux group compared to 13.7% in the enoxaparin group. It was not stated if this difference was statistically significant; however, differences between groups in mortality and pulmonary embolism were described as nonsignificant. From this, it was concluded that fondaparinux lowered the risk of DVT relative to enoxaparin, but that patient benefit was uncertain. According the grading scheme that was used, this conclusion was

based upon Grade 1 Evidence (strong scientific evidence). Given that details of the included studies and methodology were not provided in the English language summary, it is not possible to comment on the generalizability of the conclusions or the limitations of the review. As well, no data on the relative efficacy of the two medications in different types of surgeries (e.g., hip replacement, major knee surgery, or hip fracture repair) were provided in the summary.

Systematic reviews and meta-analyses

Turpie *et al*. (2004)[8] pooled results from four multi-centre RCTs of fondaparinux compared to enoxaparin for prevention of VTE in major orthopedic surgery. The main objective of the analysis was to determine relevance of various efficacy end points established for thromboprophylaxis. Patients received either fondaparinux 2.5mg once daily or enoxaparin 30mg to 40mg every 12 to 24 hours for five to nine days. The patients included in the trials were 18 years of age or older who were scheduled to undergo hip replacement surgery, major elective knee surgery, or surgery to repair a fractured hip. The original primary efficacy end point of the original studies consisted of a composite of DVT detected by mandatory bilateral venography, documented symptomatic DVT, or PE up to day 11. As well, this meta-analysis included additional composite endpoints recommended by the European Committee for Proprietary Medicinal Products (CPMP) and the American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic Therapy. The CPMP composite endpoint consisted of proximal DVT, symptomatic proven PE, or death from any cause. The ACCP composite endpoint consisted of any proximal DVT, symptomatic proven DVT or PE, or fatal PE. A total of 7344 patients were included in the four trials, of which 5385 (73.3%) had data available for the present analyses.

A meta-analysis of the original primary efficacy endpoint found that fondaparinux showed superior efficacy over enoxaparin, with 6.8% of patients in the fondaparinux group and 13.7% of patients in the enoxaparin group having this outcome. This represented a common odds reduction of 55.2% (95% CI 45.8% to 63.1%) ($p < 0.001$) in favour of fondaparinux. For the ACCP composite endpoint, 1.7% of patients in the fondaparinux group and 3.3% of patients in the enoxaparin groups had this outcome. This represented a common odds reduction of 49.6% (95% CI 27.3% to 65.5%; $p < 0.001$) again in favour of fondaparinux. Using the CPMP composite endpoint, 2.1% of patients in the fondaparinux group and 3.9% of patients in the enoxaparin group had this outcome, representing a common odds reduction in favour of fondaparinux of 48.0% (95% CI, 27.3 to 63.2%; $p < 0.001$). When looking at each of the three surgeries separately, fondaparinux was superior to enoxaparin for all three composite endpoints in major knee and hip fracture surgery, but was not superior to enoxaparin for the ACCP and CPMP endpoints for elective hip replacement surgery. From this, the authors concluded that fondaparinux was more effective that enoxaparin in preventing VTE events in patients undergoing major orthopedic surgery, regardless of which endpoint was used in hip fracture and major knee surgery, but in hip replacement surgery it was only more effective using the original primary study endpoint. The medications were administered at the approved dosages in Canada, but as details of the original study populations were not provided it is difficult to comment on the generalizability of the results of the review. As well, patients in the included studies could not be treated with intermittent pneumatic compression, dextran, thrombolytic or anticoagulant agents, or aspirin or nonsteroidal anti-inflammatory drugs whenever possible, but could use graduated compression stockings and have physiotherapy. The degree to which practice in Canada coincides with these factors would impact the generalizability of results. In terms of limitations of this review, details of how the studies were identified, selected for inclusion, and how data were abstracted and handled were not described.

Economic evaluations

In 2007, Lundkvist, *et al*.[9] estimated the costs and clinical effectiveness of extended prophylaxis (four weeks) of VTE events with fondaparinux relative to enoxaparin in hip fracture patients in Sweden. The dosing regimen of each drug was not described. A decision tree model was developed from the perspective of the health care payer for a hypothetical cohort of patients undergoing hip fracture surgery. The time horizon of the model was five years. Swedish unit costs associated with VTE-related care during acute and chronic phases of DVT, PE, major bleeding, death, and post-thrombotic syndrome were included in the model. Drug acquisition costs and the cost of administration by a nurse in 10% of patients were also included, but it was not clear if monitoring costs were captured as well. Costs were presented in 2005/2006 euros (€). Outcomes included the cost per VTE event avoided, death avoided, and cost per life year saved. The model assumed that hip fracture patients would have an average age of 76.6 years, hip fracture surgery patients are at risk of DVT and PE, and that either drug reduces the underlying risk. During the first 90 days, patients were assumed to be at risk of DVT and PE, and after that patients were assumed to be at risk of recurrent VTE events and post-thrombotic syndrome (PTS). Probability data used in the model came from one clinical trial that involved extended prophylaxis with fondaparinux, other clinical trials of fondaparinux, and other literature sources.

Based upon this model, fondaparinux and enoxaparin resulted in 10 and 38 VTE events per 1000 patients after 90 days, respectively. The cost of fondaparinux was €31 more per patient than enoxaparin after 90 days, but was €52 less than enoxaparin after five years. The incremental cost per VTE avoided with fondaparinux was €1,120 at 90 days. The cost per life year gained with fondaparinux was €360 after 90 days and the cost per death avoided was €2797. At five years, fondaparinux dominated enoxaparin in terms of cost per VTE avoided, death avoided, and life year gained. The authors concluded that fondaparinux was cost saving and more effective than enoxaparin when administered for extended prophylaxis. Limitations to this study include lack of information on the dosing regimens and the inclusion of only direct costs, which was, however, consistent with the study's perspective. In terms of generalizability, it is not clear if the clinical and cost inputs into the model would be generalizable to the Canadian healthcare system.

In 2006, Sullivan *et al*.[10] conducted a cost-effectiveness analysis of fondaparinux 2.5mg once daily compared with enoxaparin 30mg twice daily (both administered for seven days) for prophylaxis of VTE in patients undergoing hip fracture surgery. A decision analytic model was used to simulate patient outcomes and costs over various time points up to five years after surgery for a hypothetical cohort of 1000 patients undergoing hip fracture surgery in the United States receiving either fondaparinux or enoxaparin. The perspective of the analysis was that of a US health-care payer. In the model it was assumed that patients would be hospitalized for seven days for hip fracture surgery. Event rates of early thrombi, DVT and PE were taken from a number of previously published studies. Where data were not available from clinical studies of fondaparinux and enoxaparin in hip fracture patients, data were extrapolated from patients undergoing hip replacement surgery. Drug costs (acquisition, administration, and monitoring), costs associated with treating confirmed PE and DVT, major bleeding and PTS, and work-up costs for suspected but unconfirmed PE and DVT were included in the model. Resource use and costs were assessed in 2003 dollars and were derived from healthcare databases.

Based upon this model fondaparinux was estimated to prevent 24 and 30 more instances of VTE per 1000 patients than enoxaparin, at one and three months, respectively and to prevent

7.9 more deaths from PE at three months. This would result in a cost-savings per patient of US$103 per patient at discharge, US$290 at one month, US$361 at three months, and US$466 after five years. Results were robust in sensitivity analyses that varied input parameters and assumptions of the model. The authors concluded that fondaparinux improved outcomes and was cost-saving relative to enoxaparin in preventing VTE in patients undergoing hip fracture surgery. One limitation of this study was that the efficacy of fondaparinux relative to enoxaparin was derived from a single study in which the dose of enoxaparin was 40 mg once daily. In Canada, the approved dosing regimen for this indication is 30mg every 12 hours. A further limitation of this study was that it only included direct costs, given the perspective of the analysis. In terms of generalizability, the clinical and cost inputs for the model could be different in the Canadian health care system.

In 2005, Bjorvatn *et al*.[11] conducted a cost-effectiveness analysis of fondaparinux 2.5mg once daily compared with enoxaparin 40mg once daily (both administered for seven days) for prophylaxis of VTE in patients undergoing orthopedic surgery (total knee replacement, total hip replacement, or hip fracture surgery) in Norway. A deterministic decision tree model was used, with model inputs from phase III clinical trials and country specific cost data from 55,000 patients who underwent surgery from 1999 to 2001. Wholesale drug costs and costs associated with treatment of DVT, PE, suspected DVT or PE, PTS, and treatment of bleeding associated with prophylaxis were included in the model. The risk of DVT, PE, and bleeding complications were estimated from clinical trials and cohort studies in total hip replacement, hip fracture, and total knee replacement. Economic consequences were extrapolated beyond the duration of the clinical trials to five years. The perspective of the analysis was that of a health authority. In the model it was assumed that patients with confirmed DVT would receive treatment but would remain at risk of PTS or recurrence of DVT. As well, it was assumed that patients with undetected DVT would remain at risk for long-term complications and PE. It was assumed that the bleeding associated with prophylaxis would only occur while patients were hospitalized and that episodes of VTE would extend the period of hospitalization. Outcomes were estimated for a hypothetical cohort of 10,000 patients. Costs were presented in 2003 Norwegian kroners (NOK) ($1US = 7.08 NOK).

Based upon the model, it was estimated that fondaparinux would prevent an additional 124, 87, 132, and 113 episodes of DVT and 53, 51, 84, and 67 PE events than enoxaparin in total knee replacement, total hip replacement, hip fracture surgery, and the three surgeries combined, respectively, in 10,000 patients at 90 days. In hip fracture, the cost of fondaparinux was less than that of enoxaparin by day 90 and less than the cost of enoxaparin in the remaining surgeries by the five-year follow-up. The incremental cost per DVT avoided with fondaparinux over enoxaparin was NOK36,375 at discharge; however, by 90 days fondaparinux produced a cost-saving of NOK6212 and NOK9762 per DVT and PE avoided, respectively in the three surgeries combined. In the individual surgeries, the incremental cost per DVT and PE-event avoided ranged from being cost-savings to costing an additional NOK31,176. The cost per death avoided with fondaparinux ranged from being cost-saving in hip fracture surgery to costing an additional NOK198,750 in total hip replacement. In the sensitivity analysis, the results were robust to changes in the main model parameters. The authors concluded that fondaparinux was more effective than enoxaparin in preventing VTE events and was cost-saving over time. They further concluded that the largest cost-savings were observed for hip fracture surgery. One limitation of this study was that it only included direct costs, given the perspective of the analysis. In terms of generalizability, the clinical and cost inputs for the model could be different in the Canadian health care system.

In 2004, Dranitsaris[12] conducted an economic evaluation of fondaparinux compared to enoxaparin (both administered for seven days) in patients undergoing orthopedic surgeries including total knee replacement, total hip replacement, or hip fracture surgery. The authors did not state what dosages of the two medications were used. A cohort deterministic computer model was used in the analysis to determine outcomes over the 90 day period following surgery. The perspective of the analysis was that of an institution or hospital formulary decision-maker. Drug costs (acquisition, dose preparation, and administration), diagnostic tests, physician visits, nursing time, management of adverse effects, and hospital length of stay were included in the model. These costs were obtained from a survey of four large Canadian hospitals and were presented in 2003 Canadian dollars. Clinical and safety data were obtained from a meta-analysis of RCTs and from individual trials where the drugs were compared. The estimates were generated for a hypothetical cohort of patients, with the proportion of patients undergoing each surgery type being based on the number of each procedure performed in Canada in 1999/2000. Other model assumptions were not stated but referenced to an earlier UK-based study.[13]

According to the model, fondaparinux would prevent an additional 16 VTE's per 1000 patients and produce a savings of $55 per patient relative to enoxaparin across the three surgeries. Given that 50,693 surgeries were performed in 1999/2000, it was estimated that an additional 538 DVT's and 276 PE's would be avoided in a year with fondaparinux over enoxaparin. In the individual surgeries, $40, $81, and $49 per patient would be saved with fondaparinux in total hip replacement, hip fracture surgery and total knee replacement, respectively. The authors concluded that there would be cost-savings with the use of fondaparinux relative to enoxaparin. One limitation of this study was that cost estimates were derived from a survey of only four institutions. This could impact the generalizability of the results to other Canadian institutions. Another limitation of this study was that the perspective was that of the hospital, but given Canada's universal health care system, a societal perspective would likely be more relevant.

Eight additional economic evaluations published between 2003 and 2004 compared fondaparinux to enoxaparin for the prevention of VTE in orthopedic surgeries including hip fracture surgery, elective hip replacement surgery, and major knee surgery.[13-20] These studies were based upon European and US cost data. In five of the studies, fondaparinux was cost-savings in the prevention of VTE events relative to enoxaparin.[13-15,18,19] Where fondaparinux was not found to be cost-saving, the cost per VTE avoided was US$573.20[20] in hip fracture surgery and €239[17] in total hip replacement. The remaining study found that fondaparinux was cost-saving relative to enoxaparin 40mg once daily in elective hip surgery, but cost an additional US $50,172 per VTE avoided compared to enoxaparin 30mg twice daily.[16]

Limitations

The evidence of the relative clinical efficacy of fondaparinux and enoxaparin comes from meta-analyses of RCTs,[7,8] which is generally regarded as higher quality evidence. However, little detail was provided about the quality of the included RCTs and methodologies of the reviews. Thus, it is not clear if the outcomes of the reviews could have been biased in some way. In terms of the economic evaluations, while a large number were identified and seemed to consistently favour fondaparinux over enoxaparin, only one Canadian economic evaluation was identified. Further, all economic evaluations were carried out from the perspective of a health care payer. However, given that Canada has a universal health care system, a societal perspective and the inclusion of indirect costs would likely be more relevant. Finally, all economic evaluations were based upon simulation models and hypothetical cohorts of patients,

rather than clinical studies where both the costs and consequences of prophylaxis were determined in the same group of patients.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

From two systematic reviews of RCTs that compared fondaparinux to enoxaparin,[7,8] fondaparinux appeared to be more effective that enoxaparin in preventing VTE events in patients undergoing major orthopedic surgeries, when all three surgery types were analyzed together (total hip replacement, hip fracture repair, and major knee surgery). As well, based on one systematic review, fondaparinux was more effective than enoxaparin in preventing VTE events in patients undergoing either hip fracture repair or major knee surgery.[8] At the same time, cost-effectiveness analyses comparing the two drugs in preventing VTE in major orthopedic surgeries appeared to favour fondaparinux over enoxaparin, particularly in hip fracture surgery. However, the generalizability of the majority of studies to the Canadian health care system is uncertain given that the costs and consequences of the two drugs were not based upon Canadian data. Thus, the relative cost-effectiveness of the two medications remains somewhat uncertain, particularly given that the one Canadian economic evaluation was not from a societal perspective. The limited Canadian cost-effectiveness information should perhaps be considered when deciding whether to use fondaparinux or enoxaparin for prevention of VTE.

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