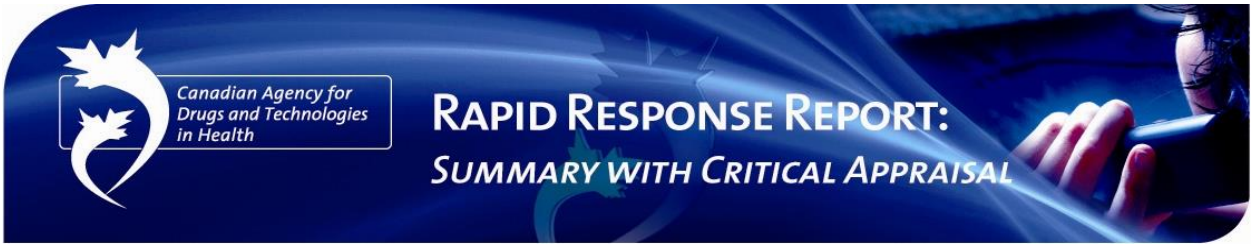


**TITLE: Fondaparinux versus Enoxaparin for Acute Coronary Syndrome: A Review of the Comparative Clinical Effectiveness and Cost-Effectiveness**

**DATE:** 3 September 2015

## CONTEXT AND POLICY ISSUES

Acute coronary syndromes (ACS) encompass a range of conditions from unstable angina to ST-segment-elevation myocardial infarction (STEMI) that arise from thrombus formation on an atheromatous plaque. ACS is among the most common presentation in emergency departments in North America[1] and effective initial treatment is important to reduce morbidity and mortality. The recommended initial therapeutic regimen for patients with ACS includes antithrombotic therapy, in which antiplatelet and anticoagulant treatment are combined, to prevent excessive coronary thrombosis, ischemic complications and further coronary events.[2] Although antithrombotic therapy is only one part of the treatment pathway, it represents a large fraction of the total costs associated with treatment of ACS.[3]

When prescribing anticoagulants, a balance must be struck between ischemic benefit and the increased risk of bleeding. Historically, unfractionated heparin was the most commonly used parenteral anticoagulant. However, unfractionated heparin has a variable dose response and narrow therapeutic window that requires close monitoring, and is associated with a greater risk for adverse events (e.g., higher risk of heparin-induced thrombocytopenia and osteoporosis) compared with other agents. Advances have led to the development of effective systemic anticoagulants that do not require frequent monitoring or dose adjustment, such as low molecular weight heparins including enoxaparin.[4] Low molecular weight heparins require less frequent dosing, do not need monitoring and have an improved safety profile compared with unfractionated heparin.[4] Following the success of enoxaparin in the past decade, other new antithrombotic agents have been introduced, including fondaparinux. Fondaparinux is a first-in-class factor Xa inhibitor. This synthetic, sulfated pentasaccharide selectively binds to anti-thrombin to indirectly inhibit factor Xa.[5]

Fondaparinux may offer both advantages and disadvantages when compared to older anticoagulants, such as enoxaparin. It is therefore important, in clinical practice, to assess the risk-benefit profile when determining which anticoagulant agent should be prescribed to patients. This should include considerations on both the clinical and economic evidence. The purpose of this review is therefore to compare the available evidence on fondaparinux to enoxaparin on patient with ACS in terms of their clinical effectiveness, safety and cost-effectiveness.

## RESEARCH QUESTIONS

1. What is the comparative clinical effectiveness of fondaparinux versus enoxaparin as first line anti-coagulation treatment agents for acute coronary syndromes?

2. What is the cost-effectiveness of fondaparinux versus enoxaparin as first line anti-coagulation treatment agents for acute coronary syndromes?

## KEY FINDINGS

Current evidence suggests that the clinical effectiveness of fondaparinux is similar to enoxaparin in terms of reducing the risk of ischemic events in patients with acute coronary syndrome. Randomized controlled trials have found that fondaparinux may have a better safety profile given lower incidences of major bleeding, although this has not been confirmed in subsequent observational studies. So far, no economic evaluations have been undertaken under a Canadian perspective. Despite this, economic evaluations in different settings have suggested that the main drivers likely to impact the cost-effectiveness of fondaparinux include the effect size of bleeding and the overall costs of the antithrombotic regimen.

## METHODS

### Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. The search was limited to English language documents published between January 1, 2005 and August 5, 2015.

### Selection Criteria and Methods

One reviewer screened the literature search results to identify relevant publications, including: health technology assessments (HTAs), systematic reviews (SRs) and meta-analyses (MA); randomized controlled trials (RCTs); non-randomized studies; and economic evaluations. The initial screen was based on title and abstract, and was followed by a full-text screen. Studies selected for inclusion were based on the criteria presented in Table 1. If a study generated multiple publications, reports were included if different outcomes were being presented.

| Table 1: Selection Criteria | |
|---|---|
| **Population** | Adult patients with acute coronary syndromes (e.g., ST segment elevation myocardial infarction [STEMI], non-ST segment elevation myocardial infarction [NSTEMI], unstable angina), in any setting |
| **Intervention** | Fondaparinux, as first line anti-coagulation treatment |
| **Comparator** | Enoxaparin |
| **Outcomes** | Clinical effectiveness (e.g., clinical benefit or harm, patient safety)<br>Cost effectiveness |
| **Study Designs** | Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, nonrandomized studies, economic evaluations |

**Exclusion Criteria**

Articles were excluded if there were a duplicate report of the same study; if they were already included in a selected SR or HTA; if they were published prior to 2005; or if they did not meet the specified inclusion criteria.

**Critical Appraisal of Individual Studies**

SRs were appraised using the AMSTAR (A Measurement Tool to Assess Systematic Reviews) checklist.[6] Items considered in the AMSTAR checklist include: a priori design of the review; duplicate independent reviewers; a priori defined eligibility criteria; comprehensive search of information sources; transparent reporting of study selection; clear presentation of study characteristics; assessment of studies' quality; scientifically-sound interpretation of the results; appropriate methods to combine data from studies; assessment of publication bias; and reporting of funding sources.[6]

Randomized trials were appraised using the Downs and Black checklist.[7] Concepts evaluated within this 27-item checklist included: reporting, external validity, internal validity (separated into bias and confounding) and power.[7] Observational studies were evaluated using the KCE checklist.[8] Potential sources of bias that were evaluated include selection, detection and attrition bias. In addition, questions concerning the identification of potential confounders and how they were taken into account were addressed.

Cost-effectiveness studies were appraised using the Drummond Checklist.[9] Items evaluated include: study design, data collection, and analysis and interpretation of results (such as: pre-defined research question; transparent reporting of data sources (e.g. effectiveness, health valuation; resource consumption; costs); relevant and clear description of comparators; application of discounting).[9]

In conducting the critical appraisal, an overall numeric score was not calculated for each study. Instead, the selected instrument was used to identify the strengths and limitations that were subsequently reviewed narratively for the studies that met our inclusion criteria.

## SUMMARY OF EVIDENCE

### Quantity of Research Available

A total of 130 citations were identified from the literature search. Following screening of titles and abstracts, 25 potentially relevant reports were selected for full-text review. No relevant reports were retrieved from grey literature sources. In total, 13 publications were found to meet the inclusion criteria and were included in this report. Of the studies included, two were SRs,[10,11] five were RCTs,[12-16] three were observational studies,[17-19] and three were economic analyses.[20-22] Amongst the five published RCTs, four were subgroup or re-analysis of the Fifth Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS-5) trial.[13-16] Appendix 1 presents the PRISMA flowchart[23] detailing the study selection. Articles of potential interest are noted in Appendix 2.

### Summary of Study Characteristics

A summary of the study characteristics are provided in Appendix 3.

<u>Comparative clinical effectiveness and safety of fondaparinux versus enoxaparin for acute coronary syndrome</u>

Nine studies addressed the clinical effectiveness and safety of fondaparinux compared to enoxaparin. Of these, one was a SR,[11] five were RCTs[12-16] that represented two unique trials, and three were prospective cohort studies.[17-19]

*Country of Origin*

The SR was conducted by a group of authors from Argentina and the United Kingdom.[11]

In terms of the two unique RCTs, OASIS-5 was a multinational, double-blinded, double-dummy trial that recruited from 576 trial sites within 41 countries[13-16] while Shah et al.[12] conducted a single-site, open-label trial in India.

Of the three observational studies, one was based on a perioperative database of all patients undergoing cardiac surgery in a single site in Sweden.[18] The remaining two studies were based on multi-site registries from France in which one was a two year registry within the Franche-Comté region capturing all patients admitted for ACS[16] while the other was a one-year nationwide registry of patients with acute myocardial infarction in 213 centers (representing 76% of active centers in France).[17]

*Patient Population*

The Cochrane SR was interested in identifying RCTs that have compared factor Xa inhibitors to unfractionated heparin or low molecular weight heparin in adult patients (≥18 years) with ACS (including unstable angina, STEMI and NSTEMI). The literature search encompassed the inception of the databases to December 2008.[11] Databases searched included The Cochrane Library, PubMed, EMBASE and LILACS. Four unique trials were identified in which two were specifically relevant to this review's research question by comparing fondaparinux to enoxaparin. Among these studies, one of the studies was the OASIS-5 trial.[5]

Several subgroup analyses were performed from the OASIS-5 trial,[5] in which four separate publications were identified in this review.[13-16] OASIS-5 randomized 20,078 patients with unstable angina or NSTEMI to either fondaparinux 2.5 mg once daily or to enoxaparin 1 mg/kg twice daily for a mean treatment duration of six days and subsequently followed patients for a maximum of 180 days. The mean age in both treatment groups was 66.6 years and both groups had predominantly more males (fondaparinux vs. enoxaparin: 62% vs. 61.4%). Individuals were excluded from the OASIS-5 trial if they had experienced a recent hemorrhagic stroke, had a serum creatinine of ≥ 265 umol/L, had other indications for anticoagulation, or had contraindications to low molecular weight heparin.[5]

Shah et al.'s[12] RCT recruited newly diagnosed patients with ACS from a single-center emergency setting. Their study similarly had more males (fondaparinux vs. enoxaparin: 74.4% vs. 77.7%) with the majority of patients' ages distributed between 48 to 57 years old. People were excluded from the study if they were receiving ongoing treatment for heparin or other anticoagulants, were experiencing STEMI, had a pacemaker, had a recent history of infection, had a history of gastrointestinal bleed or active peptic ulcer disease, or had major liver or kidney disease, although the diagnostic criteria for major kidney or liver disease was not defined.[12]

The three nonrandomized study designs employed a consecutive sampling strategy to include all patients who met their inclusion criteria and were admitted during a specific time period. Similar to the RCT, there were more males in the studies with a mean age ranging from 65 to 76.[17-19]

*Interventions and Comparators*

The majority of studies were parallel, two-arm trials in which fondaparinux was administered 2.5mg daily while enoxaparin was administered 1 mg/kg twice daily. The exception to this is the RCT by Shah et al. in which fondaparinux was reportedly administered 2.5 mg/kg once daily although this may be a topographic error.[12] One of the cohort studies was a three arm trial that also included an unfractionated heparin group although this arm is largely not discussed in this report as it is not a comparison that we are interested in.[19]

*Outcomes*

All studies reported on efficacy/effectiveness and safety. Efficacy/effectiveness outcomes tended to relate to incidence of death, myocardial infarction, refractory ischemia although this also included hematological parameters[18] and switches in anticoagulation therapy[19] in studies with a non-randomized trial design. Safety outcomes of interest were primarily focused on hematological adverse events.

<u>Comparative cost-effectiveness of fondaparinux versus enoxaparin for acute coronary syndrome</u>

Four studies were identified that addressed economic/cost issues pertaining to fondaparinux and enoxaparin in patients with ACS. Of these publications, one was a SR[10] whereas the remaining were economic evaluations: of which, one was a costing/budgetary impact analysis[22] and two were formal cost-effectiveness/cost-utility analyses.[20,21]

*Country of Origin*

The SR identified four full economic evaluations, published before 2010, that were relevant to our research question (i.e., fondaparinux versus enoxaparin in patients with ACS). The economic evaluations adopted a variety of health care payer perspectives including France, Spain, United States.[10]

Of the three additional economic analyses identified, one was a costing analysis from Switzerland.[22] The remaining two full economic evaluation adopted a Brazilian health care payer perspective[21] or a societal perspective from Thailand.[20]

*Patient Population*

Among the economic studies considered pertinent to this review from the previously conducted SR, all modelled a similar study population: non-ST elevation ACS with the patients' profile mirroring the OASIS-5 study.[10]

This is similar in the cost-effectiveness analyses[20,21] published that were separately identified in our review. Indeed, one publication noted that the patient population was identical to those recruited in the OASIS-5 trial.[21] The costing analysis was undertaken with patients admitted with the principal diagnosis of NSTEMI or unstable angina during a single calendar year at an academic hospital site.[22]

*Interventions and Comparators*

All studies identified in the SR modelled fondaparinux 2.5mg daily, to enoxaparin 1 mg/kg twice daily, although one further included other anticoagulant comparators such as unfractionated heparin and bivalirudin. In some cases, concomitant therapy with a glycoprotein (GP) IIb/IIIa inhibitor was modelled.

Similarly, individual economic evaluations only compared fondaparinux 2.5mg daily, to enoxaparin 1 mg/kg twice daily. The duration of treatment was an assumption that was specific to each model: one assumed patients would be treated for 3 days;[22] another assumed it would be six days;[20] while the last was variable (i.e., five days or 2.5 days if the patient was instead referred for coronary artery bypass graft or angioplasty).[21]

*Outcomes*

With the exception of the costing analysis in which the outcome was the cost difference between the treatment regimens,[22] the remaining economic evaluations reported the incremental cost-effectiveness ratio (ICER) to highlight the tradeoff between costs and clinical effect between interventions.[10,20,21] Change in clinical effect was either defined by quality-adjusted-life years (QALYs) or by clinical events such as the incidence of cardiovascular event or ischemic/hemorrhagic complications. Discounting was not performed in most of the identified studies given that the model's time horizon was less than a year. As Permsuwan et al.[20] selected a lifetime horizon, an annual discount factor of 3% was applied to both costs and outcomes.

## Summary of Critical Appraisal

A summary of the results of the critical appraisal are presented in Appendix 4.

Comparative clinical effectiveness and safety of fondaparinux versus enoxaparin for acute coronary syndrome

The SR by Brito et al. on factor Xa inhibitors for ACS was overall well conducted.[11] Adhering to the standards set for a Cochrane review, an *a priori* research question and protocol was previously published. Any changes to the review protocol were subsequently documented. Multiple databases were searched and the search was supplemented with hand searching. Study selection and extraction was conducted in duplicates and independently. A list of included studies was provided which summarized the key characteristics and main findings alongside the list of studies that were excluded during full-text screening. Employing the Cochrane Risk of Bias tool, Brito et al. noted that, amongst individual studies that have compared fondaparinux to enoxaparin, they were overall well conducted (i.e., low risk of bias). Publication bias was addressed by a funnel plot although this could be considered inappropriate given that fewer than ten articles were identified as part of this review.[11]

As noted above, the OASIS-5 trial identified in the Cochrane SR was considered a study with a low risk of bias. Beyond the critical appraisal by Brito et al,[11] two additional methodological concerns are noted here. Given that the study is a non-inferiority trial, intention-to-treat analysis would be considered a less conservative statistical approach. In addition, patient disposition was not reported and it is uncertain whether the numbers that have dropped-out were similar between groups. With respect to the post-hoc subgroup analyses of OASIS-5 that were identified as part of this review, these must be considered exploratory in nature. The analyses were not hypothesis-driven and no sample size calculation was performed to ensure that the comparisons were adequately powered to detect significant interaction effects. Furthermore, the analysis should be considered observational in nature as the comparisons were not randomized and indeed, in all four publications, the authors noted that the baseline characteristics differed between groups.

Shah et al[12] clearly described their patient population, the interventions and the outcomes of interest. Randomization appeared successful as the baseline characteristics between treatment groups are reported to be balanced. No dropouts occurred, removing the risk of attrition bias. Although the study was unblinded, given that the objective outcomes were evaluated (i.e., event incidence, hematological parameters), there is less concern that expectation bias was introduced. Even for more subjective measures, such as major and minor hemorrhage, a clear definition was provided. However, a sample size calculation was not conducted and it is uncertain whether the study was adequately powered. Furthermore, the study conducted multiple dependent comparisons without appropriate adjustment to prevent multiple comparison error. This may have inflated the type I error rate.

The observational studies were similar in design.[17-19] All clearly described the intervention and selected objective outcome measures that relied on administrative databases to verify the occurrence of an event. All studies reported adequate data management processes. One study further conducted checks to ensure coherence in the data and sampled a subset of medical records at each site to ensure data consistency.[19] Except in one study that did not report the rate of participation amongst the eligible study population,[17] the remaining two studies had nearly complete participation.[18,19] Issues of drop-outs were unlikely as data was collected from

several administrative databases and the outcomes were assessed over a short study duration (i.e., 30 days to a year). Indeed, the study with a one-year duration noted that follow-up exceeded 99%.[17] However, none of the studies provided a sample size calculation to ensure their study was adequately powered and often, the number of patients on fondaparinux was lower than enoxaparin, up to a fifth in one case.[17] Of greater concern though is the fact that, in all three cohort studies, baseline prognostic factors differed between treatment groups. Two studies identified from this review took an approach to account for these differences in their statistical analysis.[17,19] Nonetheless, differences in baseline prognostic factors highlights the potential for confounding given that there may be underlying patient population differences between groups which could have impacted the development of the outcome. In terms of patients who switched anticoagulant therapy, one study handled this by removing patients who received both treatment regiments over the course of the study.[18] Another conducted an analysis that compared initial and final anticoagulant therapy to address the potential for channeling bias.[19] This was important given than 12% of patients treated with enoxaparin switched to fondaparinux and treatment switchers may have been different from those who did not switch anticoagulant therapy. Lastly, some of the studies conducted multiple dependent comparisons without appropriate adjustment to prevent multiple comparison error.

Comparative cost-effectiveness of fondaparinux versus enoxaparin for acute coronary syndrome

The SR by Latour-Pérez et al. intended to identify full economic evaluations on anticoagulants for ACS.[10] Several reporting issues were noted that may have a questionable impact on the quality of their SR. No mention was made of whether the study was designed a priori and whether any changes were made during the conduct of the review. Methods on data extraction were missing, such as what data would be extracted and how many researchers were involved. Similarly, a list of excluded studies was not provided to help better understand what articles were deemed irrelevant. Otherwise, the strengths of this SR include: searching of multiple databases with hand-searching the bibliographies of relevant articles; study selection done independently in duplicate and transparent reporting of the studies considered relevant. The quality of most economic models was individually assessed by Latour-Pérez et al with the exception of one study whose format was a poster presentation. Amongst the remaining three trials that compared fondaparinux to enoxaparin, two of the studies had few methodological or reporting issues except in one case, there was a potential risk of commercial bias. The remaining study that compared fondaparinux to multiple anticoagulants therapies had several issues including: unclear study population, undated year of study costs, differences in clinical data (i.e., trials that were incorporated into the model had different inclusion criteria), and inappropriate measures for the outcomes (i.e., the quality of life for minor hemorrhage is equivalent to death).[10]

The two full economic evaluations that were identified additionally as part of this review were based on well-defined research questions and took good quality data that, when possible, were based on local sources.[20,21] The model's perspective and time horizon were stated. However, some methodological issues emerged specific to the conduct of sensitivity analysis that applied to either one or both studies. Neither model addressed structural uncertainty to determine the robustness of their model to the numerous assumptions that were made. In fact, some of the assumptions were questionable as one model selected a life-time study horizon but assumed patients treatment would only be in the first year.[20] Furthermore, the parameter distributions evaluated in probabilistic sensitivity analysis was not provided making it difficult to assess whether the uncertainty evaluated was adequate. In fact, one study selectively reported the

cost-effectiveness acceptability curve starting from $50,000/QALY onwards without justification.[20] As both models reflect the setting of a developing country, their generalizability to Canada is questionable.

The costing analysis by Kossovsky et al.[22] was overall well-conducted. The authors took the total inpatient costs of a group of inpatients from a single site to generate a regression that would be able to estimate the mean inpatient cost for ACS, with or without complications, adjusted by a person's age and sex. They then analyzed several scenarios, generalizing to the Swiss population, to determine a plausible range of potential cost savings by switching from enoxaparin to fondaparinux. However, the utility of this costing analysis may be limited to Switzerland. Firstly, the costing structure and healthcare delivery may be unique to a country. Secondly, an individual list of resources consumed was not provided which, if provided, could have helped evaluate the degree to which jurisdictions are similar in their approach to disease management and would have allowed re-calculation of costs by applying Canadian prices. The time horizon for this model was further limited as it was only interested in the inpatient period and treatment impact beyond the inpatient period was not captured.

**Summary of Findings**

Main study findings and author conclusions are provided in Appendix 5.

Comparative clinical effectiveness and safety of fondaparinux versus enoxaparin for acute coronary syndrome

The Cochrane SR by Brito et al.[11] identified two trials that had compared fondaparinux to enoxaparin in patients with ACS. Meta-analytic results suggest that fondaparinux had a statistically significantly reduced risk of all-cause mortality at 30 days (relative risk [RR], 0.85; 95% confidence interval [CI]: 0.73 to 0.98) and bleeding outcomes at 30 days (major bleeding [defined as clinically overt bleeding that is either fatal, symptomatic intracranial, retroperitoneal, intraocular, a decrease in hemoglobin >3.0 g/dL or requiring transfusion of ≥2 U of red blood cells]: RR, 0.63; 95% CI: 0.55 to 0.73; minor bleeding [defined as any bleeding other than major bleeding except bleeding on venipuncture area]: RR, 0.34; 95% CI: 0.28 to 0.43). All-cause mortality at 90 to 180 days was not statistically different between treatment groups. Similarly, cardiovascular event rates were similar between treatment groups at 30 days and between 90 to 180 days. Subgroup analysis of ACS patients undergoing percutaneous coronary intervention (PCI), based on data from a single trial, found that the risk of major bleeding (RR, 0.47; 95% CI: 0.35 to 0.61) and minor bleeding (RR, 0.36; 95% CI: 0.26 to 0.50) at 9 days were statistically lower in people who received fondaparinux. Although the risk of catheter thrombosis was statistically higher (RR, 3.59; 95% CI: 1.64 to 7.84) in patients receiving fondaparinux than those receiving enoxaparin, this could be largely prevented by using a small dose of unfractionated heparin.[24]

The single-site, open-label RCT by Shah et al.[12] further supported that fondaparinux had a better safety profile amongst newly diagnosed ACS patients with unstable angina or NSTEMI as rates of hemorrhaging on enoxaparin at day 30 was 11.1% whereas no incidence of hemorrhaging was observed in patients receiving fondaparinux. Although the authors noted that fondaparinux had fewer recurrent angina or myocardial infarction events, the difference was not statistically significant (incidence: [Day 9] 6.6% vs. 4.4%; [Day 30] 4.4% vs. 3.3%; enoxaparin vs. fondaparinux). No differences were observed between treatment groups in the laboratory parameters (e.g., platelet counts, clotting time and bleeding time) ($P > 0.05$).

The Cochrane SR pooled data from two trials, one of which was the main analysis of the OASIS-5 trial. As identified in this review, subgroup analyses and analyses restricted to subsets of patient with certain characteristics from this trial have been published separately elsewhere. Findings of interest are highlighted below. Amongst patients undergoing PCI, no treatment group and catheterization access site interaction emerged for hemorrhagic outcomes and for ischemic events up to 180 days.[13] For instance, major bleeding was more frequently encountered when the femoral approach was used although reduction in major bleeding was observed to be in a similar range when patients were treated either by enoxaparin or by fondaparinux.[13] No significant interaction was noted between treatment groups and to concomitant medication usage (i.e., GP IIb/IIIa inhibitors or thienopyridines)[14] or to Global Registry of Acute Coronary Events (GRACE) risk scores.[15] At any risk strata, as assessed by the GRACE score, the balance between antithrombotic efficacy and bleeding risk was more favorable for fondaparinux than enoxaparin. Although the prevention of death, myocardial infarction and refractory ischemia was lower in the fondaparinux than the enoxaparin group, this difference was only statistically significantly different for the outcome of death at 30 days in the low and intermediate risk subgroups, however, fondaparinux was consistently associated with statistically significant lower rates of major bleeding across all risk groups.[15]

The primary OASIS-5 trial found that fondaparinux reduced fatal bleeding, non-fatal major bleeding and minor bleeding as well as the need for blood transfusion over the entire study period (up to 180 days) compared to enoxaparin. It was found that the vast majority of excess deaths in patients treated with enoxaparin occurred in patients who experienced bleeding. Major bleeding was associated with an increased risk of death or non-fatal adverse events, irrespective of treatment group (i.e., more than 90% of the 64 additional deaths observed in patients treated with enoxaparin compared with patients treated with fondaparinux occurred in those who experienced a bleeding event during the first 9 days).[16] This independent relation between bleeding and adverse outcome, and the greater bleeding events observed in patients treated with enoxaparin compared to fondaparinux is consistent with the conclusion that the benefits of fondaparinux in preventing non-fatal ischemic events and death are mediated by the reduction in bleeding events.[16]

Two of the included non-randomized trials lend support that no differences exist between fondaparinux and enoxaparin with respect to mortality at 30 days.[18,19] One study noted no difference in overall one-year mortality rates when using Cox multivariate analysis although an interaction was noted with concomitant use of unfractionated heparin. Multivariate adjusted analysis found that the one-year mortality was statistically significantly higher for fondaparinux monotherapy than enoxaparin monotherapy (hazard ratio [HR] 3.31; 95% CI: 1.84 to 5.97); whereas, the one-year mortality was lower in patients receiving fondaparinux and unfractionated heparin than in patients receiving enoxaparin monotherapy (HR, 0.28; 95% CI: 0.07 to 1.19).[17] With respect to the outcome of bleeding, the observational studies of patients from France and Sweden have found no difference relating to bleeding[17-19] or to specific hematological parameters (e.g., transfusion needs, frequency of transfusion of blood products) between enoxaparin and fondaparinux.[18] In addition, a greater risk of bleeding was noted in patients who had discontinued fondaparinux less than 36 hours prior to surgery as compared to patients who had discontinued more than 36 hours before surgery (729±309 mL vs. 547±290 mL, $P$ = 0.039).[18] The effect of time from discontinuation of enoxaparin to surgery was not explored.[18]

Comparative cost-effectiveness of fondaparinux versus enoxaparin for acute coronary syndrome

The SR on economic studies identified four model-based economic evaluations with a European or United States perspective. Amongst these studies, three compared only fondaparinux to enoxaparin and its ICER estimate came to one of two potential conclusions: in two models, fondaparinux was dominant (i.e., less costly but more effective) while another found that the ICER associated with fondaparinux was €2758/QALY. In terms of sensitivity analysis, this varied across a spectrum as one study performed none while another looked at both probabilistic and structural uncertainty. One study compared more than two anticoagulants (i.e., bivalirudin monotherapy, unfractionated heparin + GP IIb/IIIa inhibitor, enoxaparin + GP IIb/IIIa inhibitor, fondaparinux + GP IIb/IIIa inhibitor). Bivalirudin monotherapy dominated the enoxaparin and unfractionated heparin strategies and could be considered cost-effective compared to fondaparinux-based therapy.

Consistent findings in terms of fondaparinux being the dominant strategy have been noted in the two full economic analyses that were identified as part of this review – both of which adopted a developing country perspective (i.e., Brazil[21] and Thailand[20]). Although probabilistic sensitivity analysis in both models suggested minimal impact from parameter uncertainty (i.e., model findings remained in a situation of dominance),[20,21] one-way sensitivity analysis reported in one model found that it was most sensitive to the parameter of the cost of revascularization with major bleeding.[20]

The costing analysis by Kossovsky et al[22] similarly estimated that the use of fondaparinux would lead to significant cost savings in the Swiss health care system. Based on a group of patients admitted over the course of a year with a principal diagnosis of NSTEMI or unstable angina, a regression was derived to estimate the hospital costs according to the presence or absence of hemorrhagic complications. By assuming a reduction in the incidence of hemorrhagic complications similar to what was observed in the OASIS-5 trial (i.e., reduction of 46.3% for major bleeding episodes and 65.6% for minor bleeding episodes relative to enoxaparin), fondaparinux was found to generate cost savings ranging between 854,000 to 3,400,000 Swiss francs.[22]

**Limitations**

The clinical evidence is based on a handful of well-conducted RCTs that were described in a SR or identified separately in this review. Amongst the three trials, the largest was the OASIS-5 trial which involved 576 centers in 41 countries and was likely generalizable to a Canadian setting. The eligibility criteria required patients to meet at least two of three criteria: an age of at least 60 years, an elevated level of troponin or creatinine kinase MB isoenzyme or electrocardiographic changes indicative of ischemia. Exclusion criteria were limited to patients with contraindications to low-molecular weight heparin, recent hemorrhagic stroke or serum creatinine level of at least 265 umol/L. Although this review presented the findings of multiple subgroup analyses published from the OASIS-5 data, caution is needed in interpreting these findings as these analyses are inherently observational in nature and cannot be considered a randomized comparison. Indeed, the authors noted that the baseline characteristics of patients between treatment groups were different, which could have impacted the results of the comparisons between fondaparinux and enoxaparin.

Several cohort 'registry-based' studies have been subsequently published and included in this review. Given that fewer restrictions were imposed on the inclusion/exclusion criteria, these studies benefit from being more pragmatic as they evaluated the real-world effectiveness of antithrombotic therapies in a more representative population. Some differences observed between the patient populations in the observational study compared to the RCT included the fact that more males and patients presenting fewer comorbidities were found in the registries. However, a key methodological limitation is that these observational studies have inherent differences between treatment groups. Despite acknowledging prognostic imbalance, few studies attempted to adjust or account for these differences. As such, it is impossible to negate the potential impact of confounders on the findings of the observational studies and this may explain why the findings on bleeding outcomes are contradictory between the RCT and the observational studies.

Existing economic models have suggested that fondaparinux is the dominant or the most likely cost-effective strategy in patients with non-ST elevation ACS when compared to enoxaparin. However, all existing models discussed in this review have been based on the OASIS-5 trial data and, in terms of sensitivity analyses, the degree to which these have been conducted vary considerably across studies. Transferability may be a question, especially in the case of the costing analysis by Kossovsky et al.[22] The cost-effectiveness of fondaparinux will vary depending on local costs structures and treatment pathways.

Choosing the optimal antithrombotic regimen is a complex task as there may not be a single anticoagulant that 'fits all' and the risk-benefit profile of each therapy must be assessed for each individual scenario (e.g., patient with or without persistent ST elevation, managed conservatively or invasively, with or without concomitant therapy). There is less evidence comparing these two anticoagulants in patients with STEMI. Only one observational study was identified that included patients with STEMI although analysis was combined with patients with NSTEMI.[19] No economic literature was found to address the cost-effectiveness of fondaparinux in patients with STEMI.

## CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

This review addressed the comparative clinical, safety and cost-effectiveness of two specific anticoagulants, fondaparinux and enoxaparin, in patients with ACS. From the literature search, two SRs, five RCTs, three observational studies and three economic analyses were identified.

Existing RCTs have reported that hemorrhagic outcomes at 30 days (i.e., both major and minor bleeding) are significantly lower in patients receiving fondaparinux than patients receiving enoxaparin. In particular, the OASIS-5 trial suggested that this may be independent of patients undergoing PCI, their baseline GRACE risk score or concomitant antiplatelet usage. Despite differences in hemorrhagic outcomes, one study noted no differences between treatment groups in terms of platelet counts, clotting time and bleeding time over the course of the study duration (i.e., up to 30 days). Meta-analytic results suggest that all-cause mortality at 30 days is statistically significantly lowered in fondaparinux and further analysis from the OASIS-5 study suggests that this is mediated by its reduction in bleeding. However, treatment-group differences in mortality could not be confirmed in a recently-conducted RCT (although this study was likely unpowered for this outcome) or in any of the observational studies (although the potential presence of confounders cannot be discounted).

It is difficult to answer with certainty which treatment modality would be most cost-effective given that no studies have been conducted under a Canadian perspective. Differences exist between countries in their healthcare delivery/management and their costing structure. However, given that consistent findings emerged from the economic models despite heterogeneous settings and perspectives, certain generalizations can be made. One of the main cost-effectiveness drivers identified was the effect size for bleeding events: larger differences in hemorrhagic outcomes between fondaparinux and enoxaparin is likely to lead to a more favorable economic profile given the cost-avoidance for treating such complications and the better quality of life outcomes. Another key driver is the costs of antithrombotic regimen. By intuition, if the cost of a complete drug regimen is less when using fondaparinux than enoxaparin, the cost-effectiveness of a fondaparinux strategy will appear more favorable.

In conclusion, current evidence suggests that the clinical effectiveness of fondaparinux is similar to enoxaparin in terms of reducing the risk of ischemic events in patients with ACS. RCTs have found that fondaparinux may have a better safety profile given lower incidences of major bleeding, although this has not been confirmed in subsequent observational studies. So far, no economic evaluations have been undertaken under a Canadian perspective. Despite this, economic evaluations in different settings have suggested that the main drivers likely to impact the cost-effectiveness of fondaparinux include the effect size of bleeding and the overall costs of the antithrombotic regimen.

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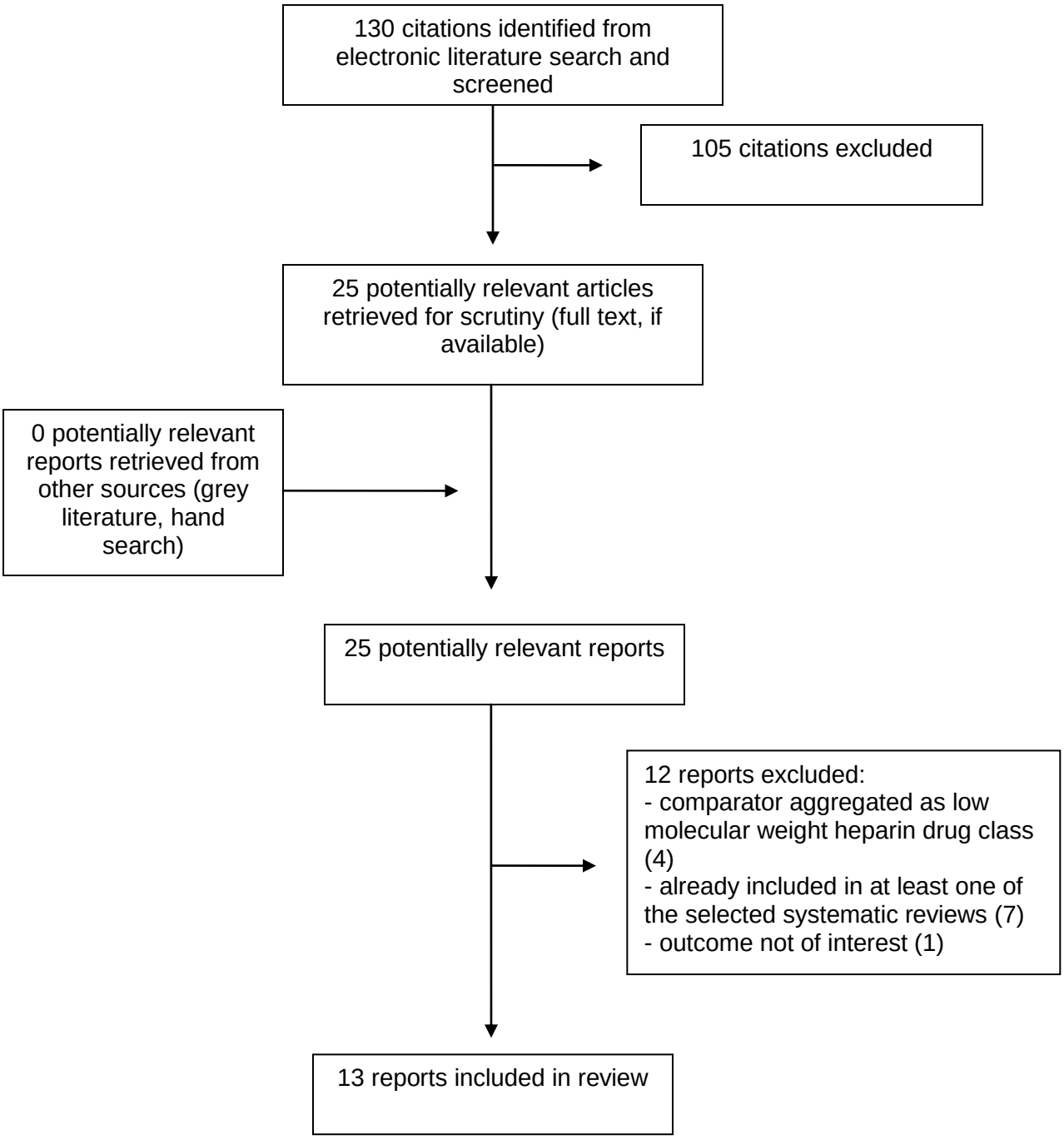
**APPENDIX 1: Selection of Included Studies**



## APPENDIX 2: Articles of Potential Interest

*Comparator: Aggregated Enoxaparin with other Low Molecular Weight Heparins*

Kadakia MB, Desai NR, Alexander KP, Chen AY, Foody JM, Cannon CP, et al. Use of anticoagulant agents and risk of bleeding among patients admitted with myocardial infarction: a report from the NCDR ACTION Registry--GWTG (National Cardiovascular Data Registry Acute Coronary Treatment and Intervention Outcomes Network Registry--Get With the Guidelines). JACC Cardiovasc Interv. 2010 Nov;3(11):1166-77.

Mehta SR, Boden WE, Eikelboom JW, Flather M, Steg PG, Avezum A, et al. Antithrombotic therapy with fondaparinux in relation to interventional management strategy in patients with ST- and non-ST-segment elevation acute coronary syndromes: an individual patient-level combined analysis of the Fifth and Sixth Organization to Assess Strategies in Ischemic Syndromes (OASIS 5 and 6) randomized trials. Circulation. 2008 Nov 11;118(20):2038-46.

Navarese EP, Andreotti F, Kolodziejczak M, Schulze V, Wolff G, Dias S, et al. Comparative efficacy and safety of anticoagulant strategies for acute coronary syndromes. Comprehensive network meta-analysis of 42 randomised trials involving 117,353 patients. Thromb Haemost. 2015 Jul 16;114(4). [Epub ahead of print]

Szummer K, Oldgren J, Lindhagen L, Carrero JJ, Evans M, Spaak J, et al. Association between the use of fondaparinux vs low-molecular-weight heparin and clinical outcomes in patients with non-ST-segment elevation myocardial infarction. JAMA. 2015 Feb 17;313(7):707-16.

*Outcome Not of Interest*

Anderson JA, Hirsh J, Yusuf S, Johnston M, Afzal R, Mehta SR, et al. Comparison of the anticoagulant intensities of fondaparinux and enoxaparin in the Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS)-5 trial. J Thromb Haemost. 2010 Feb;8(2):243-9.

## APPENDIX 3: Characteristics of Included Publications

| First Author/ Trial name, Publication Year, Country | Study design, Length of Follow-up | Patients Characteristics, Sample Size (n) | Intervention | Comparator(s) | Outcomes |
|---|---|---|---|---|---|
| **Systematic Reviews: Clinical Studies** | | | | | |
| Brito, 2011,[11] Argentina and the United Kingdom | Cochrane SR/MA of RCTs on the treatment comparing factor Xa inhibitors to UFH or LMWH during course of ACS<br><br>Included literature up to December 2008. No language restriction applied. | Four unique trials, 27,976 patients. Two studies compared fondaparinux to enoxaparin (n=21216).<br><br>Sample size ranged from 333 to 20078; age ranged from 48 to 68 years; 80% males; co-morbidities present (diabetes, arterial hypertension, heart failure, history of previous coronary events) | Fondaparinux | Enoxaparin, UFH | ○Mortality<br>○AMI or re-infarction<br>○Major and minor hemorrhagic event |
| **Systematic Reviews: Economic Studies** | | | | | |
| Latour-Pérez, 2012,[10] Spain | SR of economic evaluation based on RCTs of anticoagulants in patients with ACS.<br><br>Included literature up to May 2010. Uncertain on language restriction. | 22 economic evaluations. Four studies compared fondaparinux to enoxaparin. | Fondaparinux | Enoxaparin, bivalirudin | ○Incremental cost effectiveness ratio |

| First Author/ Trial name, Publication Year, Country | Study design, Length of Follow-up | Patients Characteristics, Sample Size (n) | Intervention | Comparator(s) | Outcomes |
|---|---|---|---|---|---|
| **Randomized Controlled Trials** | | | | | |
| OASIS 5,[5,13-16] Multi-national | Multi-center, double-blinded, double-dummy RCT<br><br>Length of follow-up: max 180 days | Fondaparinux (n=10,057), 62.0% male, mean age: 66.6<br><br>Enoxaparin (n=10,021), 61.4% male, mean age: 66.6<br><br>Inclusion criteria: Patients with unstable angina or NSTEMI | Fondaparinux, 2.5 mg QD for a mean of six days | Enoxaparin, 1 mg/kg BID for a mean of six days | ○ Mortality<br>○ MI<br>○ Refractory ischemia<br>○ Stroke<br>○ Major haemorrhagic event |
| Shah, 2014,[12] India | Single-center, open-label RCT<br><br>Length of follow-up: 30 days | Fondaparinux (n=90), 74.4% male, age distribution provided (mainly 48 to 57 years)<br><br>Enoxaparin (n=90), 77.7% male, age distribution provided (mainly 48 to 57 years)<br><br>Inclusion criteria: Newly diagnosed ACS patients reporting to medical emergency with unstable angina or NSTEMI | Fondaparinux, 2.5 mg/kg* QD [unknown duration of drug administration]<br><br>*Note that dosing may be a topographic error | Enoxaparin, 1 mg/kg BID [unknown duration of drug administration] | ○ Recovery<br>○ Recurrence of MI or angina<br>○ Major and minor haemorrhagic event |

| First Author/ Trial name, Publication Year, Country | Study design, Length of Follow-up | Patients Characteristics, Sample Size (n) | Intervention | Comparator(s) | Outcomes |
|---|---|---|---|---|---|
| **Non-randomized study designs** | | | | | |
| Puymirat, 2015,[17] France | Multi-center cohort [76% active centers]<br><br>Time of outcome assessment: one year | Fondaparinux (n=240), 72% male, mean age: 66.5<br><br>Enoxaparin (n=1027), 71% male, mean age: 67.0<br><br>Inclusion criteria: All patients admitted to intensive care units with NSTEMI | Fondaparinux, dosage unclear | Enoxaparin, dosage unclear | ○ In-hospital complications (MI, stroke, thrombosis, major and minor haemorrhagic event)<br>○ Use of different antiplatelet<br>○ Mortality |
| Landenhed, 2010,[18] Sweden | Single-center cohort<br><br>Time of outcome assessment: 21 weeks | Fondaparinux (n=67), 88.1% male, mean age: 67.1<br><br>Enoxaparin (n=80), 80% male, mean age: 65.9<br><br>Inclusion criteria: All patients admitted for CABG | Fondaparinux, 2.5 mg QD for a mean of 10.4 days | Enoxaparin, 1 mg/kg BID for a mean of 13.3 days | ○ Hematological parameters (e.g., coagulation status, postoperative bleeding)<br>○ Post-operative outcomes |
| Schiele, 2010,[19] France | Multi-center cohort [all cardiology centers in region of Franche-Comté]<br><br>Time of outcome assessment: 30 days | Fondaparinux (n=426), 66% male, mean age: 66<br><br>Enoxaparin (n=1694), 71% male, mean age: 65 | Fondaparinux, 2.5 mg QD, for two days to entire length of hospitalization | Enoxaparin, 1 mg/kg BID, for two days to entire length of hospitalization<br><br>UFH, initial bolus of 60 IU/kg; | ○ Use of different anticoagulants<br>○ Switch in anticoagulant use<br>○ Mortality |

| First Author/ Trial name, Publication Year, Country | Study design, Length of Follow-up | Patients Characteristics, Sample Size (n) | Intervention | Comparator(s) | Outcomes |
|---|---|---|---|---|---|
| | | UFH (n=754), 57% male, mean age: 76<br><br>Inclusion criteria: All patients admitted for ACS | | infusion of 12 to15 IU/kg/h; titrate to target aPTT of 50 to 75 seconds, for two days to entire length of hospitalization | ○ Major hemorrhagic event |
| **Economic Evaluations** | | | | | |
| Permsuwan, 2015,[20] Thailand | Type of analysis: Cost-utility analysis, 2 part decision tree and Markov model<br><br>Perspective: Thailand, societal<br><br>Duration: Lifetime | Identical to patients in OASIS-5 trial<br><br>Inclusion criteria: Patients with symptoms of ACS without ST elevation, aged ≥60 years | Fondaparinux, 2.5 mg QD for 6 days | Enoxaparin, 1 mg/kg BID for 6 days | ○ Incremental cost-effectiveness ratio<br><br>Structural assumptions: concomitant medication with UFH in patients undergoing PCI. Patient weight assumed 60 kg. Treatment effect would disappear by the first year. |
| Kossovsky, 2012,[22] Switzerland | Type of analysis: Costing analysis<br><br>Perspective: Switzerland<br><br>Duration: Hospital stay | Overall (n=281), 70.5% male, mean age: 68.1<br><br>Inclusion criteria: Patients admitted during a calendar year with principal | Fondaparinux, 2.5 mg QD for 3 days | Enoxaparin, 1 mg/kg BID for 3 days | ○ Costs |

| First Author/ Trial name, Publication Year, Country | Study design, Length of Follow-up | Patients Characteristics, Sample Size (n) | Intervention | Comparator(s) | Outcomes |
|---|---|---|---|---|---|
| | | diagnosis of NSTEMI or unstable angina | | | |
| Pepe, 2012,[21] Brazil | Type of analysis: Cost-effectiveness analysis, decision tree<br><br>Perspective: Brazil, direct health care payer<br><br>Duration: 180 days | Identical to patients in OASIS-5 trial<br><br>Inclusion criteria: Patients hospitalized with symptoms of ACS without ST elevation, aged ≥60 years | Fondaparinux, 2.5 mg QD, for five days following medical treatment or 2.5 days for those referred to CABG or angioplasty | Enoxaparin, 1 mg/kg BID, for five days following medical treatment or 2.5 days for those referred to CABG or angioplasty | ○ Incremental cost-effectiveness ratio<br><br>Structural assumptions: Patient could be submitted to either early invasive strategy or conservative strategy |

ACS = acute coronary syndrome; aPTT = activated partial thromboplastin time; BID = twice daily; CABG = coronary artery bypass grafting; LMWH = low molecular weight heparin; MA = meta-analysis; MI = myocardial infarction; NSTEMI = non-ST-segment MI; QD = once daily; RCT = randomized controlled trial; SR = systematic review; UFH = unfractionated heparin

## APPENDIX 4: Critical Appraisal of Included Publications

| First Author, Publication Year, Country | Strengths | Limitations |
|---|---|---|
| **Systematic Reviews: Clinical Studies** | | |
| Brito, 2011,[11] Argentina | A priori-designed SR with MAs. Changes between the protocol and the final review were transparently documented.<br><br>Clear description of literature search involving multiple databases and hand-searching.<br><br>Duplicate independent study selection and study extraction was performed.<br><br>Provides list of included & excluded studies alongside the baseline and key characteristics of the included studies.<br><br>Critical appraisal was conducted.<br><br>Addressed heterogeneity in the meta-analysis although this was based on a small number of studies. Applied random effects model unless there was no presence of statistical or clinical heterogeneity.<br><br>Conflict of interest/potential sources of funding were declared. | Despite the paucity of literature (n=4), a Funnel plot was performed to assess this type of bias. |
| **Systematic Reviews: Economic Studies** | | |
| Latour-Pérez, 2012,[10] Spain | Clear description of literature search with multiple database and hand-searching performed.<br><br>Duplicate independent study selection performed.<br><br>Provides list of included studies alongside a brief summary of these studies.<br><br>Conflict of interest/ potential sources of funding was declared. | Uncertain if the review was designed a priori as it is not registered. As such, it is not known if changes were done subsequently to the review starting.<br><br>Uncertain what data was planned to be extracted and how many individuals were involved in extracting the data.<br><br>Although quality of studies was assessed, the instrument (adapted by Evers et al) has not been validated.<br><br>List of excluded studies not provided. |

| First Author, Publication Year, Country | Strengths | Limitations |
|---|---|---|
| **RCTs** | | |
| OASIS 5,[5,13-16] Multi-national | **For the main trial:** | |
| | Clear description of characteristics of subjects, the interventions studied and standardization of outcome assessment.<br><br>Allocation concealed.<br><br>Randomization was conducted with baseline characteristics similar between treatment groups.<br><br>Study subjects, clinicians and outcome assessors were all blinded.<br><br>Study was registered. The pre-specified outcomes were completely reported.<br><br>Sample size calculated and achieved for the primary-event analysis. | Using intention-to-treat analysis for a non-inferiority trial is a less conservative approach. Sensitivity analysis of the findings, by a per-protocol analysis, was not described or presented.<br><br>The study did not report patient disposition (e.g., dropouts). Although intention-to-treat analysis was chosen to deal with drop-outs, it is uncertain whether rates were low and balanced between groups. |
| | **Specific to the numerous subgroup analyses:** | |
| | | Observational in nature as not based on randomized comparisons.<br><br>Baseline characteristics differed between treatment groups.<br><br>Uncertain if the study was adequately powered to detect interaction effects.<br><br>Analysis must be considered exploratory in nature as subgroups were not pre-specified. |
| Shah, 2014,[12] India | Clear description of characteristics of subjects, the interventions studied, and standardization of most of the outcome assessment.<br><br>Randomization was conducted. Appears adequate as baseline characteristics between groups are similar.<br><br>Uncertain the intended approach for the analysis set (i.e., intention to treat or per protocol) although no patients discontinued during the course of the study. | Study subjects and clinicians were not blinded (although this may not be a concern given the objective outcomes selected in this trial).<br><br>Uncertain whether allocation was concealed.<br><br>No sample size calculation was performed to ensure study was adequately powered.<br><br>Multiple dependent comparisons were conducted without taking into account adjustment for type I error inflation. |

| First Author, Publication Year, Country | Strengths | Limitations |
|---|---|---|
| **Non-randomized study designs** | | |
| Puymirat, 2015,[17] France | Clear description of interventions studied, and standardization of outcome.<br><br>Diagnosis and start of treatment likely occurred around the same time as inclusion criteria required patients to be admitted within 48 hours of symptom onset.<br><br>As this study is observational, clinicians selected the preferred treatment for their patients. Certain baseline characteristics differed between treatment groups although this difference was adjusted/accounted for in their analysis. | Uncertain the participation rate in this study from the overall population eligible. However, amongst those participating in the registry, follow-up was 99%.<br><br>Potential that residual confounding may have impacted study results given the observational nature of the study.<br><br>No sample size calculation performed to ensure study was adequately powered. Sample size in the fondaparinux arm nearly five folds smaller than enoxaparin. |
| Landenhed, 2010,[18] Sweden | Clear description of interventions studied, and standardization of outcome.<br><br>Complete participation rate as all patients meeting the inclusion criteria were recruited. It appears that all patients continued on follow-up. Measures to handle missing data were reported transparently.<br><br>Diagnosis and start of treatment likely occurred around the same time: inclusion criteria required patients to be admitted and treated within 48 hours of symptom onset. | This study is observational and many baseline characteristics differed between treatment groups (e.g., gender, hypercholesterolemia, previous myocardial infarction, previous angioplasty). High potential that confounders may have impacted study results.<br><br>No sample size calculation performed to ensure study was adequately powered. Sample size<br><br>No formal statistical tests conducted to adjust for differences in baseline characteristics.<br><br>Multiple dependent comparisons were conducted without taking into account adjustment for type I error inflation. |
| Schiele, 2010,[19] France | Given study was designed as registry-based, population eligible and that met the inclusion criteria were all included.<br><br>Clear description of interventions studied, and standardization of outcome. | Potential for residual confounding to impact on the study results given the observational nature of the study.<br><br>Sample size presented although no calculation was provided to justify rationale for the sample size stated. |

| First Author, Publication Year, Country | Strengths | Limitations |
|---|---|---|
| | As this study is observational, clinicians selected the preferred treatment for their patients. Certain baseline characteristics differed between treatment groups although this difference was adjusted/accounted for in their analysis.<br><br>Uncertain if data were missing from the database although computerized checks were performed to ensure coherence of the data.<br><br>During the one-month longitudinal follow-up, patients were permitted to switch anticoagulant and analysis compared initial anticoagulant and final anticoagulant therapy to assess channeling bias. | |
| **Economic Evaluation** | | |
| Permsuwan, 2015,[20] Thailand | Study based on well-defined question, description of competing treatments and clinical effectiveness of the therapies.<br><br>Perspective, time horizon, study design and discounting were stated.<br><br>When and if possible, data incorporated into model came from Thai sources.<br><br>Parameter uncertainty addressed through the conduct of sensitivity analyses. The range in which the parameters varied was provided in the one-way sensitivity analysis. | Quantities for resource utilization are not presented separately.<br><br>Assumptions to model are clearly reported although some may be unrealistic. For instance, model assumes patients with recurrent ACS would not receive any further treatment.<br><br>Never addressed model robustness to structural uncertainty.<br><br>Not only are the parameter distributions not detailed in the probabilistic analysis, the authors selectively reported the axis of their cost-effectiveness acceptability curve.<br><br>Generalizability of model from Thailand to Canada remains uncertain. |
| Kossovsky, 2012,[22] Switzerland | Study based on well-defined question, description of the competing treatments and effectiveness of the therapies.<br><br>Perspective of costing analysis was defined.<br><br>Statistical analysis chosen was able to factor the highly skewed nature of costs data. | Itemization of individual resource utilization not presented.<br><br>Time horizon was defined narrowly as the duration of inpatient hospital stay. This would not be able to capture long-term treatment impact. |

| First Author, Publication Year, Country | Strengths | Limitations |
|---|---|---|
| | Scenario analysis conducted to assess the potential cost savings under different situations. | Generalizability of findings from Switzerland to Canada remains uncertain given differences in cost structure between countries. |
| Pepe, 2012,[21] Brazil | Study based on well-defined question, description of competing treatments and clinical effectiveness of the therapies.<br><br>Perspective, time horizon, study design and discounting were stated.<br><br>Costing data came from sources from Brazil. Quantities for resource utilization are presented separately.<br><br>Assumptions to model are clearly reported. | Never addressed model robustness to structural uncertainty.<br><br>Parameter uncertainty addressed through the conduct of sensitivity analyses. The range in which the parameters varied was however is unclear.<br><br>Generalizability of model from Thailand to Canada remains uncertain. |

MA = meta-analysis; RCT = randomized controlled trial; SR = systematic review

## APPENDIX 5: Summary of Main Study Findings and Author's Conclusions

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Study Findings (statistical significance bolded)</th><th>Authors' Conclusions</th></tr>
<tr><td colspan="3">Systematic Reviews: Clinical Studies</td></tr>
<tr><td>Brito, 2011,[11] Argentina</td><td>
<ul>
<li>4 RCTs involving 27,976 patients (range: 333 to 20078/trial). 2 trials compared FD to EX.
<ul>
<li>Primary findings, RR:</li>
</ul>
</li>
</ul>
<table>
<tr><th>Outcome</th><th># studies</th><th># of patients</th><th>Statistical method</th><th>Effect size for FD (95% CI)</th></tr>
<tr><td>All-cause mortality, 30 days</td><td>2</td><td>21216</td><td>Fixed</td><td>0.85 (0.73 to 0.98)</td></tr>
<tr><td>All-cause mortality, 90 to 180 days</td><td>1</td><td>20078</td><td>Fixed</td><td>0.90 (0.80 to 1.00)</td></tr>
<tr><td>Non-fatal AMI or re-infarction, 30 days</td><td>2</td><td>21216</td><td>Random</td><td>1.00 (0.84 to 1.18)</td></tr>
<tr><td>Non-fatal AMI or re-infarction, 90 to 180 days</td><td>1</td><td>20078</td><td>Fixed</td><td>0.94 (0.82 to 1.07)</td></tr>
<tr><td>Major bleeding, 9 days</td><td>2</td><td>21216</td><td>Random</td><td>0.92 (0.15 to 5.66)</td></tr>
<tr><td>Major bleeding, 30 days</td><td>1</td><td>20078</td><td>Random</td><td>0.63 (0.55 to 0.73)</td></tr>
<tr><td>Minor bleeding, 30 days</td><td>1</td><td>20078</td><td>Random</td><td>0.34 (0.28 to 0.43)</td></tr>
</table>
<ul>
<li>Subgroup: Patients undergoing PCI (from one study)</li>
</ul>
<table>
<tr><th>Outcome</th><th># of patients</th><th>Statistical method</th><th>Effect size (95% CI)</th></tr>
<tr><td>All-cause mortality, 30 days</td><td>6177</td><td>Fixed</td><td>0.94 (0.67 to 1.33)</td></tr>
<tr><td>Non-fatal AMI or re-infarction, 30 days</td><td>6177</td><td>Fixed</td><td>1.05 (0.86 to 1.29)</td></tr>
<tr><td>Major bleeding, 9 days</td><td>6177</td><td>Random</td><td>0.47 (0.35 to 0.61)</td></tr>
<tr><td>Catheter thrombosis</td><td>6238</td><td>Random</td><td>3.59 (1.64 to 7.84)</td></tr>
</table>
</td><td>"The therapeutic efficacy of factor Xa inhibitors in ACS seemed to be related to a reduced risk in all-cause mortality at 90 to 180 days, with a better safety profile than enoxaparin in terms of reduce incidence of major and minor bleeding" (p. 2)</td></tr>
</table>

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Study Findings (statistical significance bolded)</th><th>Authors' Conclusions</th></tr>
<tr><td colspan="3">Systematic Reviews: Economic Studies</td></tr>
<tr><td>Latour-Pérez, 2012,[10] Spain</td><td>• 22 model-based economic evaluations in which efficacy outcomes were based on RCT. Four studies compared FD to EX.<br>• Economic SR:<br>○ Sculpher et al, 2007 (French health care system): ICER for FD €2758/QALY. No sensitivity analysis conducted.<br>○ Sculpher et al, 2009 (US health care system): FD dominant (0.04 QALYs, cost savings of $200). FD was dominant under most scenarios except when incorporating a covariate into the regression model, however, the covariate was not described.<br>○ Latour-Perez et al, 2009 (Spanish health care system): FD dominant (0.023 QALYs, cost savings of $55). Net health benefits increased directly with the risk of bleeding, bleeding severity score and inversely associated with age.<br>○ Maxwell et al, 2009 (US health care system): Bivalirudin dominant over UFH and EX. ICER for FD compared to bivalirudin: $2569/additional patient treated without complications). Probabilistic sensitivity analysis suggests high uncertainty in the model findings.</td><td>"Compared with enoxaparin, the use of fondaparinux in patients with NSTE-ACS managed with an early invasive strategy appears to be cost effective, even in patients with a low risk of bleeding." (p. 585)</td></tr>
<tr><td colspan="3">RCTs</td></tr>
<tr><td>Shah, 2014,[12] India</td><td>• 180 patients (EX: 90, FD: 90). Baseline characteristics appear balanced (EX: 84.4% were NSTEMI cases, 15.5% were unstable angina cases; FD: 93.3% were NSTEMI cases, 6.7% were unstable angina cases)<br>○ Primary findings:
<table>
<tr><th>Outcome</th><th>EX (n=90)</th><th>FD (n=90)</th></tr>
<tr><td colspan="3">On Day 9</td></tr>
<tr><td>Recurrent MI or angina</td><td>6.6%</td><td>4.4%</td></tr>
<tr><td>Hemorrhage</td><td>3.3%</td><td>1.1%</td></tr>
<tr><td>Mortality</td><td>0</td><td>0</td></tr>
<tr><td colspan="3">On Day 30</td></tr>
<tr><td>Recurrent MI or angina</td><td>4.4%</td><td>3.3%</td></tr>
<tr><td>Hemorrhage*</td><td>11.1%</td><td>0%</td></tr>
<tr><td>Mortality</td><td>0</td><td>0</td></tr>
</table>
* statistically significant difference between treatment groups<br>○ Mean bleeding time: no significant difference observed on day 0, 9 or 30 (ranged between 2.6 to 2.8 minutes)<br>○ Mean clotting time: no significant difference observed on day 0, 9 or 30 (ranged between 5.4 to 5.6 minutes)</td><td>"FD appeared to be better than EX in efficacy, as was indicated by a numerically more decrease in recurrence of angina or MI. FD regimen group also had better safety profile, as there was no incidence of haemorrhage at 30 days Therefore, we conclude that FD is an attractive option than EX in UCAD (unstable coronary artery disease) patients.." (p. 31)</td></tr>
</table>

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Study Findings (statistical significance bolded)</th><th>Authors' Conclusions</th></tr>
<tr><td>Hamon, 2011,[13] Multi-national<br><br>Trial name: OASIS 5</td><td>
<ul>
<li>OASIS-5: Analysis restricted to subset of patients who underwent an early invasive strategy (14,159 patients). Patients separated by the approach to access site (radial: 1398, femoral: 12761). Several differences observed between access-site groups in terms of baseline characteristics. Factorial analysis by access site and treatment group (uncertain sample size within each unit).
<ul>
<li>Major bleed:</li>
</ul>
</li>
</ul>
<table>
<tr><th rowspan="2">Access Site</th><th colspan="2">Treatment Group</th><th rowspan="2">HR (95% CI)</th><th rowspan="2">$P_{int}$*</th></tr>
<tr><th>EX</th><th>FD</th></tr>
<tr><td colspan="5">On Day 9</td></tr>
<tr><td>Femoral (n=7013)</td><td>4.8%</td><td>2.3%</td><td>0.48 (0.37 to 0.62)</td><td rowspan="2">0.65</td></tr>
<tr><td>Radial (n=872)</td><td>2.4%</td><td>0.9%</td><td>0.36 (0.11 to 1.16)</td></tr>
<tr><td colspan="5">On Day 30</td></tr>
<tr><td>Femoral (n=7013)</td><td>5.2%</td><td>3.0%</td><td>0.56 (0.44 to 0.72)</td><td rowspan="2">0.37</td></tr>
<tr><td>Radial (n=872)</td><td>3.1%</td><td>1.1%</td><td>0.35 (0.12 to 0.98)</td></tr>
<tr><td colspan="5">On Day 180</td></tr>
<tr><td>Femoral (n=7013)</td><td>6.1%</td><td>4.0%</td><td>0.64 (0.51 to 0.79)</td><td rowspan="2">0.31</td></tr>
<tr><td>Radial (n=872)</td><td>3.9%</td><td>1.5%</td><td>0.39 (0.16 to 0.96)</td></tr>
</table>
*$P_{int}$ = P for interaction; significance testing between method of access site and treatment group
</td><td>"In ACS patients undergoing an early invasive strategy, radial access is associated with similar rates of composite ischaemic outcome and is associated with a substantial decrease of major bleeding in comparison to conventional femoral access leading to a better clinical outcome. A fondaparinux based-strategy, which provides anti-ischaemic protection not inferior to enoxaparin, can be favourably associated with radial access to optimise patient outcome[…]" (p. 96)</td></tr>
<tr><td>Budaj, 2009,[16] Multi-national<br><br>Trial name: OASIS 5</td><td>
<ul>
<li>OASIS-5: Analysis restricted to subset of patients experiencing a bleeding outcome. 990 had major bleeding and 423 had minor bleeding. Several differences observed in baseline characteristics by occurrence of bleeding complications. Factorial analysis by bleeding event and treatment group (uncertain sample size within each unit).
<ul>
<li>Primary findings:
<ul>
<li>First 30 days: 1 in 6 deaths occurred in patients with bleeding complications in the first 9 days. More patients experienced bleeding in the first 9 days and death in FD than EX group (75 vs. 37).</li>
<li>180 days follow-up: 1 in 8 deaths occurred in patient with bleeding complications during the first 9 days. More patients experienced bleeding in the first 9 days and death in FD than EX group (141 vs. 76).</li>
<li>Similar association between treatment group and bleeding observed for the composite outcome (i.e., death, MI and stroke).</li>
<li>Vast majority of excess deaths in patients treated with EX occurred in patients who experienced bleeding.</li>
</ul>
</li>
</ul>
</li>
</ul>
</td><td>"[…] our analyses involving more than 20 000 patients in the OASIS-5 trial demonstrate that the routine use of fondaparinux in place of enoxaparin in patients with ACS will reduce the risk of bleeding by up to one-half and that prevention of bleeding translates into substantial reductions in both morbidity and mortality during 180 days of follow-up. Increasing recognition that bleeding is an independent determinant of outcome in patients with ACS should prompt efforts to</td></tr>
</table>

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Study Findings (statistical significance bolded)</th><th>Authors' Conclusions</th></tr>
<tr><td></td><td></td><td>reduce the risk of bleeding and thereby improve clinical outcomes by appropriate selection of antithrombotic therapies as well as judicious use of invasive revascularization procedures" (p. 660)</td></tr>
<tr><td>Jolly, 2009,[14] Multi-national<br><br>Trial name: OASIS 5</td><td>
<ul>
<li>OASIS-5: Analysis restricted to subset of patients treated with GP IIb/IIIa inhibitors or thienopyridines (20,078 patients, in which 3639 received GP IIb/IIIa and 13,531 received thienopyridines). Several differences observed in baseline characteristics between patients who received concomitant medication compared to those who have not. Factorial analysis by concomitant medication and treatment group.
<ul>
<li>Primary findings, at 30 days in those treated with GP IIb/IIIa Inhibitor, n(%):</li>
</ul>
</li>
</ul>
<table>
<tr><th>GP use</th><th colspan="2">Treatment Group</th><th>Adjusted HR for FD (95% CI)</th><th>$P_{int}$*</th></tr>
<tr><th></th><th>EX</th><th>FD</th><th></th><th></th></tr>
<tr><td colspan="5">Death, MI, refractory ischemia</td></tr>
<tr><td>Yes (n=3630)</td><td>232 (13.2)</td><td>220 (11.8)</td><td>0.87 (0.72 to 1.06)</td><td rowspan="2">0.63</td></tr>
<tr><td>No (n=16.448)</td><td>632 (7.7)</td><td>585 (7.1)</td><td>0.93 (0.82 to 1.04)</td></tr>
<tr><td colspan="5">Death</td></tr>
<tr><td>Yes (n=3630)</td><td>64 (3.6)</td><td>58 (3.1)</td><td>0.85 (0.59 to 1.23)</td><td rowspan="2">0.89</td></tr>
<tr><td>No (n=16.448)</td><td>288 (3.5)</td><td>237 (2.9)</td><td>0.79 (0.66 to 0.95)</td></tr>
<tr><td colspan="5">MI</td></tr>
<tr><td>Yes (n=3630)</td><td>129 (7.4)</td><td>118 (6.4)</td><td>0.83 (0.64 to 1.07)</td><td rowspan="2">0.46</td></tr>
<tr><td>No (n=16.448)</td><td>282 (3.5)</td><td>269 (3.3)</td><td>0.99 (0.83 to 1.17)</td></tr>
<tr><td colspan="5">Major bleeding</td></tr>
<tr><td>Yes (n=3630)</td><td>146 (8.3)</td><td>96 (5.2)</td><td>0.60 (0.46 to 0.78)</td><td rowspan="2">0.86</td></tr>
<tr><td>No (n=16.448)</td><td>349 (4.3)</td><td>218 (2.7)</td><td>0.62 (0.52 to 0.73)</td></tr>
</table>
*$P_{int}$ = P for interaction; significance testing between method of access site and treatment group
</td><td>"In patients receiving GP IIb/IIIa inhibitors or thienopyridines, fondaparinux reduces major bleeding and improves net clinical outcome compared with enoxaparin." (p. 468)</td></tr>
</table>

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Study Findings (statistical significance bolded)</th><th>Authors' Conclusions</th></tr>
<tr><td></td><td>
○ Primary findings, at 30 days in those treated with thienopyridines, n(%):
<table>
<tr><th>Thienopyridines use</th><th colspan="2">Treatment Group</th><th>HR (95% CI)</th><th>$P_{int}$*</th></tr>
<tr><th></th><th>EX</th><th>FD</th><th></th><th></th></tr>
<tr><td colspan="5">Death, MI, refractory ischemia</td></tr>
<tr><td>Yes (n=13,532)</td><td>616 (9.1)</td><td>586 (8.6)</td><td>0.94 (0.84 to 1.06)</td><td>0.61</td></tr>
<tr><td>No (n=6545)</td><td>248 (7.5)</td><td>219 (6.7)</td><td>0.87 (0.72 to 1.05)</td><td></td></tr>
<tr><td colspan="5">Death</td></tr>
<tr><td>Yes (n=13,532)</td><td>218 (3.2)</td><td>178 (2.6)</td><td>0.79 (0.64 to 0.96)</td><td>0.59</td></tr>
<tr><td>No (n=6545)</td><td>134 (4.1)</td><td>117 (3.6)</td><td>0.84 (0.65 to 1.10)</td><td></td></tr>
<tr><td colspan="5">MI</td></tr>
<tr><td>Yes (n=13,532)</td><td>305 (4.6)</td><td>291 (4.3)</td><td>0.95 (0.81 to 1.12)</td><td>0.85</td></tr>
<tr><td>No (n=6545)</td><td>106 (3.3)</td><td>96 (3.0)</td><td>0.92 (0.69 to 1.21)</td><td></td></tr>
<tr><td colspan="5">Major bleeding</td></tr>
<tr><td>Yes (n=13,532)</td><td>360 (5.4)</td><td>229 (3.4)</td><td>0.62 (0.52 to 0.73)</td><td>0.92</td></tr>
<tr><td>No (n=6545)</td><td>135 (4.2)</td><td>85 (2.6)</td><td>0.62 (0.47 to 0.83)</td><td></td></tr>
</table>
*$P_{int}$ = P for interaction; significance testing between method of access site and treatment group
</td><td></td></tr>
<tr><td>Joyner, 2009,[15] Multi-national<br><br>Trial name: OASIS 5</td><td>
• Subgroup analysis of OASIS-5, according to GRACE risk scores (20,078 patients) Factorial analysis by GRACE risk categorization and treatment group (uncertain sample size within each unit).
○ Primary findings:
<table>
<tr><th>GRACE Risk Group*</th><th colspan="2">Treatment Group</th><th>Adjusted HR for FD (95% CI)</th></tr>
<tr><th></th><th>EX</th><th>FD</th><th></th></tr>
<tr><td colspan="4">Death, MI, refractory ischemia (Day 9)</td></tr>
<tr><td>Low</td><td>3.5%</td><td>3.7%</td><td>1.06 (0.82 to 1.36)</td></tr>
<tr><td>Intermediate</td><td>5.2%</td><td>5.3%</td><td>1.01 (0.82 to 1.23)</td></tr>
<tr><td>High</td><td>8.5%</td><td>8.3%</td><td>0.98 (0.83 to 1.16)</td></tr>
<tr><td colspan="4">Death, MI, refractory ischemia (Day 180)</td></tr>
<tr><td>Low</td><td>7.7%</td><td>7.0%</td><td>0.90 (0.75 to 1.08)</td></tr>
<tr><td>Intermediate</td><td>11.3%</td><td>10.2%</td><td>0.89 (0.77 to 1.03)</td></tr>
<tr><td>High</td><td>21.1%</td><td>20.1%</td><td>0.95 (0.85 to 1.06)</td></tr>
<tr><td colspan="4">Death (Day 30)</td></tr>
<tr><td>Low</td><td>1.4%</td><td>0.9%</td><td>0.62 (0.39 to 0.98)</td></tr>
<tr><td>Intermediate</td><td>2.4%</td><td>1.7%</td><td>0.69 (0.49 to 0.96)</td></tr>
<tr><td>High</td><td>6.9%</td><td>6.4%</td><td>0.92 (0.76 to 1.12)</td></tr>
<tr><td colspan="4">Death, MI, stroke (Day 30)</td></tr>
<tr><td>Low</td><td>4.6%</td><td>4.0%</td><td>0.88 (0.70 to 1.11)</td></tr>
<tr><td>Intermediate</td><td>6.2%</td><td>5.0%</td><td>0.80 (0.66 to 0.98)</td></tr>
<tr><td>High</td><td>12.0%</td><td>11.1%</td><td>0.93 (0.80 to 1.07)</td></tr>
</table>
</td><td>"The GRACE score predicted both bleeding and mortality in patients with ACS. The efficacy and safety of fondaparinux were consistent in all risk groups supporting its use in a broad range of ACS patients." (p. 502)</td></tr>
</table>

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Study Findings (statistical significance bolded)</th><th>Authors' Conclusions</th></tr>
<tr><td></td><td>
<table>
<tr><td colspan="4">Death, MI, stroke (Day 180)</td></tr>
<tr><td>Low</td><td>7.1%</td><td>6.2%</td><td>0.87 (0.72 to 1.04)</td></tr>
<tr><td>Intermediate</td><td>10.2%</td><td>8.7%</td><td>0.85 (0.73 to 0.99)</td></tr>
<tr><td>High</td><td>20.7%</td><td>19.1%</td><td>0.92 (0.82 to 1.03)</td></tr>
<tr><td colspan="4">Major bleeding (Day 9)</td></tr>
<tr><td>Low</td><td>2.9%</td><td>1.6%</td><td>0.55 (0.39 to 0.77)</td></tr>
<tr><td>Intermediate</td><td>4.1%</td><td>2.2%</td><td>0.53 (0.40 to 0.70)</td></tr>
<tr><td>High</td><td>5.5%</td><td>2.8%</td><td>0.50 (0.38 to 0.64)</td></tr>
</table>
* GRACE risk score: low corresponds to a GRACE score < 118; intermediate corresponds to a GRACE score between 118 to 142; high corresponds to a GRACE score >142
</td><td></td></tr>
<tr><td colspan="3">Non-randomized study designs</td></tr>
<tr><td>Puymirat, 2015,[17] France</td><td>
<ul>
<li>4169 patients with acute MI in which 1734 had NSTEMI (EX: 1027, FD: 240). Differences between treatment group with respect to study site, dyslipidemia and previous CABG.</li>
<li>Perioperative:
<ul>
<li>Median time from symptom onset to first call: (not different) EX (108 minutes) vs. FD (97.5 minutes)</li>
<li>Use of antiplatelet drugs: Similar except GP IIB-IIIA inhibitors higher in patients treated with FD.</li>
<li>In-hospital mortality and in-hospital complications:</li>
</ul>
<table>
<tr><th rowspan="2">Outcome</th><th colspan="2">Treatment Group</th><th rowspan="2">Adjusted OR for FD (95% CI)</th></tr>
<tr><th>EX (n=1027)</th><th>FD (n=240)</th></tr>
<tr><td>Death</td><td>0.6%</td><td>2.1%</td><td>1.68 (0.12 to 23.4)</td></tr>
<tr><td>Recurrent MI</td><td>1.1%</td><td>1.7%</td><td>2.40 (0.54 to 10.67)</td></tr>
<tr><td>Stroke</td><td>0%</td><td>0%</td><td>-</td></tr>
<tr><td>Stent thrombosis</td><td>0.3%</td><td>0%</td><td>-</td></tr>
<tr><td>Transfusion</td><td>5%</td><td>2.1%</td><td>0.36 (0.13 to 1.03)</td></tr>
</table>
<ul>
<li>In patients receiving FD, major bleeding, recurrent MI and in-hospital death not significantly different in patients receiving additional UFH and in those who were not. It is uncertain what the patient indication was for those receiving concomitant UFH as clinical characteristics of patients treated with EX were similar with or without UFH, as was the case with FD.</li>
</ul>
</li>
<li>One year:
<ul>
<li>Death rates, adjusted: [Cox multivariate analysis] 1.35 (95% CI: 0.70 to 2.51).</li>
<li>Interaction between FD and UFH use for one year survival (HR 3.31, 95% CI: 1.84 to 5.97)</li>
<li>Survival rate:</li>
</ul>
<table>
<tr><td></td><td>EX</td><td>FD</td></tr>
<tr><td>Without UFH</td><td>95.1%;</td><td>88.0%</td></tr>
<tr><td>With UFH</td><td>93.1%</td><td>96.9%</td></tr>
</table>
</li>
</ul>
</td><td>"Our data show that in this real-world French cohort of NSTEMI patients, most of whom were managed invasively, there was no evidence that fondaparinux was superior to enoxaparin as regards early ischaemic or bleeding events or 1-year mortality. The combination of fondaparinux with UFH, however, was associated with lower 1-year mortality, when compared with fondaparinux used as the sole anticoagulant in this population[…]" (p 217-218)</td></tr>
</table>

| First Author, Publication Year, Country | Main Study Findings (statistical significance bolded) | Authors' Conclusions |
|---|---|---|
| Landenhed, 2010,[18] Sweden | • 147 patients (EX: 80; FD: 67). Outside of peripheral arterial disease being greater in EX group compared to FD group, all other demographic variables similar between groups.<br>• Hematological parameters, preoperative antiplatelet or anticoagulant therapy: no differences.<br>○ Time from last dose of anticoagulant to surgery (hrs): EX (22.6±8.7) vs. FD (41.4±16.8) (*P* = 0.0001)<br>○ Increased bleeding, 12 hours post-operative, in patients who discontinued FD less than 36 hours before surgery than those who discontinued more than 36 hours before surgery (729±309 mL vs. 547±290, *P* = 0.039)<br>• Postoperative outcomes similar between treatment groups | "*This study suggests that preoperative treatment with fondaparinux for NSTE-ACS is as safe as enoxaparin in terms of postoperative bleeding and transfusion needs. Findings support discontinuation of fondaparinux at 36 h prior to surgery*." (p. 100) |
| Schiele, 2010,[19] France | • 2874 patients (UFH: 754, EX: 1694, FD: 426). Significant differences in many baseline characteristics between treatment groups.<br>• At 1 month, no significant differences in outcomes between EX and FD. | "*Between 2006 and 2007, the use of fondaparinux in patients with acute coronary syndromes increased considerably, either because it was used instead of enoxaparin or because of a switch from UFH. Adjusted mortality in patients treated with fondaparinux was lower than with UFH and similar to enoxaparin*" (p. 190) |
| **Economic Evaluations** | | |
| Permsuwan, 2015,[20] Thailand | • FD was dominant under both a societal and healthcare payer perspective by costing 962 THB (29.2 USD) and 1286 (39 USD) less than EX respectively. Under both perspectives, it provides 0.04 additional QALYs in NSTE-ACS patients.<br>• Under both model perspectives:<br>○ One-way sensitivity analysis: model was most sensitive to the cost of revascularization with major bleeding. As the price decreased, FD provided less cost savings. However, in all cases, FD remained dominant.<br>○ Probabilistic sensitivity analysis: little uncertainty in the parameters varied (probability FD cost-effective compared to EX was >90% across all willingness to pay thresholds studied, e.g., 50,000 to 500,000 THB/QALY) | "*In summary, our cost-effectiveness results show that, compared with enoxaparin, fondaparinux is a cost-effective strategy for treating only patients with NSTE-ACS in Thailand from both provider and societal perspectives* […]" (p. 8) |

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Study Findings (statistical significance bolded)</th><th>Authors' Conclusions</th></tr>
<tr><td>Kossovsky, 2012,[22] Switzerland</td><td>
<ul>
<li>Over the course of one year, 281 patients identified with primary diagnosis of NSTEMI or unstable angina.</li>
<li>Mean hospital stay: 8 days (IQR: 5 to 13 days)</li>
<li>Haemorrhagic complications generated higher hospital costs, longer total hospital length of stay and longer stay in intensive care unit<br>Age- & sex-adjusted median hospital costs (by regression)
<table>
<tr><th>Independent variable</th><th>Median costs in Swiss Francs (95% CI)</th><th>P - value</th></tr>
<tr><td>Major haemorrhagic episodes</td><td>19,057 (3005 to 35,110)</td><td>0.02</td></tr>
<tr><td>Minor haemorrhagic episodes</td><td>16,890 (6763 to 27,019)</td><td>0.001</td></tr>
<tr><td>Age (per year)</td><td>19 (-188 to 226)</td><td>0.86</td></tr>
<tr><td>Sex (men vs. women)</td><td>-3,768 (-10,073 to 2538)</td><td>0.24</td></tr>
<tr><td>Constant</td><td>28,244 (8647 to 47,839)</td><td></td></tr>
</table>
</li>
<li>According to Geneva University Hospital, the costs of drugs and complications (i.e., major and minor hemorrhagic events) were higher in patients receiving EX than FD. Overall cost savings was estimated to be 330,000 Swiss Francs (95% CI: 124,000 to 536,000).</li>
<li>Similar findings of cost savings found across different scenarios.</li>
</ul>
</td><td>"In conclusion, the use of fondaparinux instead of enoxaparin in patients with NSTE-ACS and without an early invasive approach could yield substantial savings at the local as well as at the national level in Switzerland, mainly by reducing the incidence of costly haemorrhagic complications." (p. 5)</td></tr>
<tr><td>Pepe, 2012,[21] Brazil</td><td>
<ul>
<li>Cost analysis: On Day 9, FD generated less cost when compared to EX (cost savings of 85 USD). In general, 80% of total costs was associated with invasive treatments (e.g., PCI, CABG) while drug cost accounted ~10% of total costs. 77% of the cost difference related to the cost of treating bleeding complications, 16% related to drug costs alone while remaining 7% related to difference in total cost of treatment among comparators.</li>
<li>Economic analysis: FD dominant of EX as lower cost and greater benefit (defined as composite outcome of cardiovascular event and major bleeding).
<ul>
<li>One-way sensitivity analysis: no variables able to change the results obtained.</li>
<li>Probabilistic sensitivity analysis: Across all willingness-to-pay thresholds, FD would be the most cost-effective strategy 99.9% compared to EX.</li>
</ul>
</li>
</ul>
</td><td>"The use of fondaparinux for the treatment of patients with ACS-WSTE [without ST-segment elevation] is superior to that of enoxaparin in terms of prevention of further cardiovascular events at lower cost" (p. 613)</td></tr>
</table>

ACS = acute coronary syndrome; CABG = coronary artery bypass graft; CI = confidence interval; EX = enoxaparin; FD = fondaparinux; GP = glycoprotein; GRACE = Global Registry of Acute Coronary Events; HR = hazard ratio; ICER = Incremental cost-effectiveness ratio; IQR = interquartile range; MI = myocardial infarction; mo = month; NSTE = non-ST-elevation; *P* = probability value; PCI = percutaneous coronary interventions; QALY = quality-adjusted life year; RCT = randomized controlled trial; RR = risk ratio; SR = systematic review; THB = Thailand baht; UFH = unfractionated heparin; US = United States; USD = US dollars; vs = versus