Author's response to reviews

Title: Cost-effectiveness of fondaparinux versus enoxaparin in non-ST-elevation acute coronary syndrome in Canada (OASIS-5)

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Author's response to reviews: see over
Dear Timothy Shipley:

Executive Editor BioMed Central
BMC Cardiovascular Disorders

Please find below the responses to the questions generated by the reviewers of our study Cost-effectiveness of fondaparinux versus enoxaparin in non-ST-elevation acute coronary syndrome in Canada (OASIS-5)

Reviewer 1: Stjepan Juristic

This is an interesting manuscript involving the pressing topic of economic impact of new therapies. It considers both short and long term costs of the use of fondaparinux in patients with acute coronary syndromes. Considering the complex subject, mainly focused on economic features more than on medical ones, it is quite difficult to make a proper revision for a physician. The basis seem to be well posed, and the analysis is complete. The two limits I see are: - to use US patients derived from OASIS-5 trial, but to use a life-time model in a Canadian hospital setting for cost-effectiveness analysis, while these populations may not be comparable. - when considering bleedings, to assume that they are not affecting long-term prognosis, while a major bleeding may affect it.

Response:

Some of the reviewer’s concerns are acknowledged in the limitations section:

At baseline in OASIS-5, Canadian patients were generally similar to those in the overall trial with some clinical differences against the US population. Mainly, the US patients were less likely to have unstable angina (rather than MI), had undergone more revascularization procedures, were more likely to be diabetic, and were less likely to have ST-segment depression.

Differences in medical care between Canada and the United States have been reported in the contemporary management of patients with non–ST-elevation MI and UA. Several studies have reported findings in which angiography, angioplasty, and bypass surgery are more common in the United States than in Canada. The differences could be explained in the availability on-site facilities in different institutions across Canada which could lead to longer waiting times which could have an impact on long outcome of this population. This could be reflection of longer stay in ICU and general ward

Reviewer 2: Flavia Ballocca
This study refers to the OASIS-5 trail that had three conclusions: First that Fondaparinux has similar efficacy with Enoxaparin in short-term outcome. Secondly that Fondaparinux is reducing major bleeding compared to Enoxaparin and because of that thirdly the reduced bleeding with the usage of Fondaparinux results with a lower long-term mortality and morbidity. Taking advantage of the large OASIS-5 trial the authors assessed whether Fondaparinux is cost-effective versus Enoxaparin in NSTEMI ACS in Canada. However, there are different limitations like the modeling of cost-effectiveness in multinational trials as argued by the authors in the present paper. The main finding in the paper was that over an 180-day period fondaparinux was protective and cost-effective strategy compared to enoxaparin. Major Compulsory Revisions: There are several points that need clarification and/or further work;

1. The study use clinical effectiveness on a 2006 published key clinical-trial, the OASIS-5 trial. Despite the highly internal valid findings from this trial the authors should discuss in greater depth possible limitations of the present paper.

Response:
The current manuscript addresses the 2 most important limitations of the analysis:

From the perspective of modeling the cost-effectiveness of products studied in multinational trials because studies which are powered on overall event rates, not event rates in individual countries. To better inform payers in Canada, the model was based on Canadian resource use from the trial, while using whole trial event rates. Country resource use and cost data are required for decision making

Population based on a multinational trial that could impact the interpretation of the results: Population differences participating in the study in which, Canadian patients were generally similar to those in the overall trial with some differences with the US population which were less likely to have unstable angina (rather than MI), had undergone more revascularization procedures, were more likely to be diabetic, and were less likely to have ST-segment depression

2. Are patients with renal insufficiency excluded? This question is interesting regarding the limited evidence of fondaparinux in patients with renal insufficiency.

Response: patients with serum creatinine level of at least 3 mg per deciliter (265 μmol per liter) were excluded from OASIS 5 Trial.

The following paragraph in the background has been included in the manuscript providing more information regarding the population included in OASIS 5

The Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators (OASIS-5) trial randomized 20,078 patients with NSTE-ACS to fondaparinux or enoxaparin. Patients were randomly assigned to a study group within 24 hours after the onset of symptoms and were eligible if they met at least two of the three following criteria: an age of at least 60 years, an elevated level of troponin or creatine kinase MB isoenzyme, or electrocardiographic
changes indicative of ischemia. Patients with contraindications to low-molecular-weight heparin, recent hemorrhagic stroke, indications for anticoagulation other than an acute coronary syndrome, or a serum creatinine level of at least 3 mg per deciliter (265 μmol per liter) were excluded.¹⁵

The Trial showed similar rates of ischemic events at 9 days but, by 180 days, fondaparinux reduced major bleeding and improved mortality and morbidity.

3.- Are the Canadian patients from one hospital or from database of the Ontario Health Insurance Program? This should be made more clear to the reader.

Response:

The 1403 patients Canadian patients included in this analysis represent multiple hospitals across Canada. Approximately 47 centers across Canada.

The following information has been added to the methodology section:

Clinical events and resource use over a mean follow-up of 173 days (range, 90-180 days) where used from the OASIS-5 trial. This trial involved 20,078 patients with NSTE-ACS which were randomized to either fondaparinux (2.5 mg daily) or enoxaparin (1 mg per kg twice daily) for a mean of 5 days. This was a global study in which 41 countries participated including multiple hospitals across Canada.