

# REAL-WORLD REGISTRY STUDY CONFIRMS FONDAPARINUX OVER LOW-MOLECULAR-WEIGHT HEPARIN FOR NSTEMI

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## ABSTRACT

The pivotal Fifth Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS-5) trial demonstrated that fondaparinux was non-inferior to enoxaparin in reducing ischaemic outcomes in patients with a non-ST segment elevation myocardial infarction (NSTEMI). However, fondaparinux was associated with a lower number of patients experiencing major bleeding events. Based on these results suggesting a better benefit-to-risk ratio over enoxaparin, the European Society of Cardiology recommended fondaparinux as the first-line anticoagulation therapy in patients with an NSTEMI in 2007. A registry study conducted in Sweden provides real-life clinical data and confirms the clinical relevance of fondaparinux use over low-molecular-weight heparin in routine clinical care. This article aims to review the place of fondaparinux in acute coronary syndrome patients, and to provide an analysis of clinical trial data along with real-life data.

**Keywords:** Acute coronary syndrome (ACS), myocardial infarction (MI), fondaparinux, low-molecular-weight heparin (LMWH), registry data, NSTEMI: non-ST segment elevation myocardial infarction.

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## INTRODUCTION

Clinical research on antithrombotic therapy in acute coronary syndrome (ACS) is focussed on reducing ischaemic outcomes, ideally without compromising on safety and with special regard to bleeding events, which are associated with increased mortality rates.<sup>1</sup> Anticoagulants have demonstrated their efficacy in reducing the occurrence of major ischaemic events in ACS. This includes enoxaparin, a low-molecular-weight heparin (LMWH) which reduces the risk of death or myocardial infarction (MI) by 16% (odds ratio [OR]: 0.84, 95% confidence interval [CI]: 0.76-0.92) when compared with unfractionated heparin (UFH). Nevertheless, this benefit comes at the price of an increased risk of major bleeding (OR: 1.25, 95% CI: 1.04-1.50).<sup>2</sup>

Fondaparinux sodium (Arixtra®, Aspen Pharma) is a synthetic, selective anti-Xa anticoagulant that was

approved in Europe by the European Medicines Agency in 2007 for the treatment of unstable angina (UA) or non-ST segment elevation myocardial infarction (NSTEMI) in adults for whom urgent (<120 mins) invasive management (percutaneous coronary intervention [PCI]) is not indicated.<sup>3</sup> Fondaparinux is administered subcutaneously for a bioavailability of 100% and a half-maximal plasma level reached after 25 minutes; these pharmacokinetic properties allow for a once daily formulation without the need for laboratory monitoring.<sup>4</sup>

The pivotal Fifth Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS-5) trial demonstrated that fondaparinux was non-inferior to enoxaparin in reducing ischaemic outcomes in patients with an NSTEMI.<sup>5</sup> However, fondaparinux was associated with a significantly lower number of patients experiencing major bleeding events.

Based on these results suggesting a better benefit-to-risk ratio over enoxaparin, the European Society of Cardiology (ESC) recommended fondaparinux as the first-line anticoagulation therapy in patients with an NSTEMI in 2007.<sup>6</sup> This article aims to review the place of fondaparinux in ACS patients, and to provide an analysis of clinical trial data along with real-life data.

## THE NEED FOR REGISTRY DATA: LIMITATIONS OF RANDOMISED CONTROLLED TRIALS

The implementation of a clinical randomised controlled trial (RCT) is the best way to compare two treatment options because it eliminates the problem of confounding. However, the impact of RCTs today is often limited by selecting patients through the use of narrow inclusion criteria and multiple exclusion criteria. In addition, RCTs are conducted in selected expert centres with selected doctors, who are likely to monitor patients more closely due to the requirements of the study and the quality of care that is to be expected of a high-level care facility. These factors can have an impact on the clinical outcomes and the risk-benefit balance, which can be diverted from 'real-world' data that could be obtained in an unselected patient population.

In a recent study of MI survivors, the median age was 10 years older and the long-term risk was 2 to 3-times higher in real-world data from a national registry compared with results from recently performed RCTs. These results raise questions about the generalisability of the results from many RCTs. Our registries should therefore be used more often to evaluate new treatments and/or to confirm RCT results. The implementation of registry-based clinical RCTs is a new concept that may not only lower the costs of randomised studies but also increase the value of the results of such trials.

## AVAILABLE CLINICAL DATA FOR FONDAPARINUX VERSUS LMWH IN NSTEMI

### OASIS-5 Study

OASIS-5 was a randomised, double-blind, parallel-group trial that aimed to compare fondaparinux (2.5 mg per day for up to 8 days) with enoxaparin (1 mg/kg twice daily [once daily in those with renal dysfunction] for up to 8 days) in patients

with NSTEMI (n=20,078).<sup>5</sup> The primary endpoint was occurrence of death, MI, or refractory ischaemia at Day 9. Fondaparinux was demonstrated as non-inferior to enoxaparin in reducing ischaemic outcomes. However, fondaparinux had a lower risk of in-hospital and post-hospitalisation bleeding events, including major bleeding (180 days of follow-up: 4.3% versus 5.8%; hazard ratio [HR]: 0.72, 95% CI: 0.64-0.82; p<0.001), which in turn was associated with short and long-term reductions in mortality.

In addition, fondaparinux was demonstrated to be slightly safer with respect to the occurrence of stroke compared with enoxaparin (180 days of follow-up: 1.3% versus 1.7%; HR: 0.78, 95% CI: 0.62-0.99; p=0.04). In a *post hoc* analysis of the trial results, patients with moderately reduced renal function, despite being exposed to a higher risk of bleeding,<sup>7</sup> were associated with a higher reduction in bleeding events in the fondaparinux group compared with the LMWH treatment group.<sup>8</sup> Patients undergoing PCI over the course of a hospitalisation generated similar results to those from the general OASIS-5 cohort, despite a higher risk of thrombus formation on the angioplasty device in the fondaparinux group.<sup>9</sup> Administration of UFH during PCI successfully prevented almost all cases of catheter thrombosis without leading to increased bleeding risk.<sup>9</sup>

### Data from SWEDEHEART

While the well-designed OASIS-5 study demonstrated the favourable efficacy and safety profiles for fondaparinux, new clinical data and real-world data describing daily clinical practice are still relevant and help refine ACS management. In a study published in February 2015, routine clinical practice results from the robust, large, and independent Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) registry database confirmed the OASIS-5 findings.<sup>10</sup>

SWEDEHEART is a national Swedish registry launched in 2009 after the merger of several coronary artery disease (CAD) registries initiated in previous decades, thus containing data from the beginning of the 1990s. This registry aims to support the improvement of care and evidence-based development of therapy for CAD.

This registry encompasses all consecutive patients hospitalised for ACS or undergoing coronary

angiography/angioplasty or heart surgery for any indication in one of the 72 Swedish hospitals that provide care for acute cardiac diseases. As it has become an integrated part of patient care in these facilities, about 80,000 new cases are entered into the registry every year, including 20,000 with acute MI, 10,000 with UA, 25,000 with other causes for their symptoms, 40,000 undergoing coronary angiography/angioplasty, and 7,000 undergoing heart surgery.<sup>11</sup>

This online case report database is shared among all hospitals and comprises 106 variables, including patient demographics, admission logistics, risk factors, past medical history, medical treatment before admission, electrocardiographic changes, biochemical markers, other clinical features and investigations, medical treatment in hospital, interventions, hospital outcome, discharge diagnoses, and discharge-medications. The database also includes additional variables such as whether the patient is younger than 75 years and hospitalised for acute MI, undergoing coronary angiography/angioplasty, or operated for cardiac or thoracic aortic disease.

## OBJECTIVES

The SWEDEHEART registry study was a prospective cohort study that aimed to assess the rate of ischaemic and bleeding events among a wide range of non-selected, non-trial patients with NSTEMI who were treated with either fondaparinux or LMWH.<sup>10</sup> This study also aimed to assess the association between the two anticoagulants and outcome, both in patients with reduced renal function and in patients undergoing PCI.

## METHODS AND PATIENTS

All patients aged 18 years or older who had NSTEMI that had been registered for the first time (n=40,616; median age: 73 years; 37.2% female) and who were treated at one of the 72 Swedish hospitals providing acute cardiac care with either fondaparinux or LMWH between 1<sup>st</sup> September 2006 and 30<sup>th</sup> June 2010 were included in the study. The outcomes were severe in-hospital bleeding events and death, and 30 and 180-day major bleeding, death, stroke, and recurrent MI.

**Table 1: Clinical outcomes according to treatment group.**

Outcome	Fondaparinux group (n=14,791), %	LMWH group (n=26,825), %	Odds ratio (95% confidence interval)*
<b>Bleeding</b>			
In-hospital	1.1	1.8	0.54 (0.42-0.70)
30 days	1.4	2.1	0.56 (0.44-0.70)
180 days	1.9	2.8	0.60 (0.50-0.74)
<b>Death</b>			
In-hospital	2.7	4.0	0.75 (0.63-0.89)
30 days	4.2	5.8	0.83 (0.72-0.96)
180 days	8.3	11.8	0.77 (0.69-0.86)
<b>MI</b>			
30 days	9.0	9.5	0.94 (0.84-1.06)
180 days	14.2	15.8	0.97 (1.89-1.06)
<b>Stroke</b>			
30 days	0.5	0.6	1.11 (0.74-1.65)
180 days	1.7	2.0	0.98 (0.79-1.22)
<b>Bleeding, death, MI, or stroke</b>			
30 days	14.0	16.85	0.83 (0.75-0.90)
180 days	22.7	27.5	0.81 (0.75-0.88)

\*Adjusted for admitting hospital, calendar time, and baseline characteristics.

LMWH: low-molecular-weight heparin; MI: myocardial infarction.

Logistic regression was used to determine the OR and CI for the occurrence of an event at each time point. Adjustments for year, admitting hospital, baseline characteristics, and in-hospital revascularisation were performed.

## RESULTS

### Patient Population

While the rates of prior bleeding events and haemorrhagic stroke were similar between both treatment groups, patients who received fondaparinux were younger (mean: 2 years younger) and fewer had prior MI (28.2% versus 32.2%), and fewer patients had been previously diagnosed with congestive heart failure (14.5% versus 18.7%) when compared with the LMWH group. Overall, 41.6% of patients underwent PCI during the initial hospital stay, with a difference between both treatment groups (fondaparinux: 46.4%; LMWH: 38.9%).

### Therapy Use

Overall, 36.4% of patients (n=14,791) received fondaparinux while hospitalised versus 63.6% of patients (n=25,825) who received LMWH (mainly enoxaparin). Fondaparinux use increased from 0.7% of patients during the first calendar year to 84.8% in the final calendar year of the study. This steep increase can be linked to the ESC and the Swedish National Board of Health and Welfare recommendations for fondaparinux as the first-choice therapy in NSTEMI in the early phase of the study.<sup>6</sup>

### Severe Bleeding Events and Death Rates

The odds of severe bleeding and death in routine clinical care were lower in the fondaparinux treatment group versus LMWH, either during the initial hospitalisation or at 30 or 180 days of follow-up (Table 1). However, the rates of MI and stroke were comparable between both treatment groups.

Overall, the real-life data from the SWEDEHEART study support the OASIS-5 study that was published in 2006, as the results match those obtained in the clinical trial setting.

### Patient Subpopulations

In patients with renal dysfunction, bleeding rates were lower in the fondaparinux group versus the LMWH group during hospitalisation and at 30 and 180 days follow-up, although the results

were not significant due to wide CIs in patients with severely impaired renal function. Similar results were observed among patients with impaired renal function for in-hospital and 30-day death events. As renal dysfunction was associated with a significant, 5-fold higher rate of severe bleeding, the prevention of such events might translate into fewer death events.

However, in patients with the lowest estimated glomerular filtration rate (eGFR; patients with  $eGFR \leq 15$  mL/min/1.73 m<sup>2</sup>), these results were not statistically significant, possibly due to a low number of patients and a wide CI. It is to be noted that severe renal dysfunction ( $eGFR < 20$  mL/min/1.73 m<sup>2</sup>) is a contraindication to fondaparinux and dose adjustment may be needed for LMWH. Patients who underwent PCI during the first hospitalisation generated comparable results to the general population. The OR suggested a benefit from fondaparinux over LMWH with regard to in-hospital bleeding events and mortality, although the results did not reach statistical significance (OR: 0.89, 95% CI: 0.57–1.38; and OR: 0.67, 95% CI: 0.33–1.05, respectively).

## DISCUSSION

This registry study conducted in Sweden provides real-life clinical data and confirms the clinical relevance of fondaparinux use over LMWH (the majority of which was enoxaparin) in routine clinical care. The authors acknowledge that the study was limited by its observational design that can generate residual confounding, and the possibility of bleeding being under-reported in registries. There was also a lack of information on the dose and duration of the therapies used, which could have provided more in-depth insights into the benefits of fondaparinux regimens over LMWH.

One of the strengths of this study was the population-based design, which provided a wide range of clinical settings and patients, and the availability of variables such as baseline kidney function and history of prior cardiac intervention. Another strength was the broad coverage of the SWEDEHEART registry in Sweden, as 86% of the total ACS patients were captured. The consistency between the clinical trial findings and the registry data obtained in a broader, heterogeneous population provides a robust platform of risk-benefit balance for fondaparinux to warrant the implementation of guideline recommendations in NSTEMI management.

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