Fondaparinux is licensed for the treatment of unstable angina (UA) or non-ST segment elevation myocardial infarction (NSTEMI) in patients for whom urgent (<120 mins) invasive management (percutaneous coronary intervention, PCI) is not indicated. For these indications, the recommended dose of fondaparinux is 2.5mg once daily, administered by subcutaneous injection. Treatment should be initiated as soon as possible following diagnosis and continued for up to a maximum of 8 days or until hospital discharge, whichever occurs earlier. This review covers the use of fondaparinux for acute coronary syndromes, specifically, the management of patients presenting with acute chest pain as unstable angina or NSTEMI.

Fondaparinux is not recommended as an option for use in the treatment of unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI) in patients for whom urgent (<120 minutes) invasive management (PCI) is indicated.

The Fifth Organisation to Assess Strategies in Acute Ischaemic Syndromes (OASIS-5) trial evaluated the efficacy and safety of fondaparinux and enoxaparin in high-risk patients with unstable angina or myocardial infarction without ST-segment elevation. The primary efficacy outcome of death, myocardial infarction or refractory ischaemia at 9 days occurred in 579 patients (5.8%) receiving fondaparinux, vs. 573 patients in the enoxaparin group (5.7%) (HR 1.01, 95% confidence interval 0.90 to 1.13, p = 0.007 for non-inferiority), confirming non-inferiority as the upper confidence limit is below the pre-specified boundary of 1.185. The primary safety objective was to determine whether fondaparinux was superior to enoxaparin in preventing major bleeding and was assessed by events by day 9, and was reported to have occurred in 217 patients (2.2%) in the fondaparinux group, compared to 412 patients (4.1%) in the enoxaparin group (HR 0.52, 0.44 to 0.61; p<0.001 for superiority).

In a separate subgroup analysis of OASIS-5 for patients who underwent PCI, death, MI or stroke had occurred in 197 patients (6.3%) on fondaparinux, compared to 190 patients (6.2%) in the enoxaparin group at day 9 (HR 1.03, 0.84 to 1.25; p=0.79). However, major bleeding by day 9 was statistically significantly reduced with fondaparinux compared with enoxaparin (73 patients (2.4%) vs. 155 patients (5.1%) respectively, HR 0.46, 0.35 to 0.61; p<0.00001).

Whilst the European Society of Cardiology (ESC) recommend the use of fondaparinux based on its efficacy and more favourable safety profile, the American College of Cardiology (ACC) in association with the American Heart Association (AHA) does not differentiate between the use of fondaparinux and enoxaparin or unfractionated heparin (UFH).

The Scottish Medicines Consortium (SMC) has accepted fondaparinux (Arixtra®) for use within NHS Scotland for the treatment of unstable angina or non-ST-segment elevation myocardial infarction (UA/NSTEMI) in patients for whom urgent (<120 minutes) invasive management (PCI) is not indicated.

The mean duration of treatment in the OASIS-5 trial was 5.4 days for patients on fondaparinux, and 5.2 days for patients on enoxaparin. Considering these treatment durations, a course of enoxaparin for a patient weighing an average of 70kg would be approximately £50 (range from £30 to £80 for a 3 to 8 day course duration, dose is weight-based) whilst a course of fondaparinux would be approximately £33 (range from £20 to £53 for a 3 to 8 day course duration, dose is 2.5mg regardless of body-weight).
Key unresolved issues

IMPORTANCE OF MAINTENANCE WITH SAME ANTICOAGULANT?
In a comparison of enoxaparin vs. UFH for patients with high risk UA/STEMI during PCI, the Superior Yield of the New Strategy of Enoxaparin, Revascularisation and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial concluded that more bleeding was observed with enoxaparin; A post-hoc analysis from SYNERGY suggested that some of the excess bleeding seen with enoxaparin could be explained by crossover to UFH at the time of PCI. The ACC guidelines therefore state that although this remains to be validated prospectively, it would appear reasonable to avoid excessive anticoagulation by avoiding the crossover of anticoagulants i.e. maintain consistent anticoagulant therapy from the pre-PCI phase throughout the procedure itself.

TREATMENT OF PATIENTS WITH IMPAIRED RENAL FUNCTION
Some may argue that use of fondaparinux offers an advantage in that no dosage adjustments are required in patients with renal impairment (compared to dose adjustments required for enoxaparin patients in whom the dose was reduced if the creatinine clearance was <30mL/min). However, it appears that patients with renal impairment (with a serum creatinine less than 265 micromol/L) were excluded from OASIS-5, and in practice, renal function is not a determinant for the initial dosing of anticoagulant in the acute setting. The SPC for fondaparinux states that it is contra-indicated in patients with a renal function <20mL/min.

GENERALISABILITY OF BLEEDING RATES SEEN IN OASIS-5
There is some suggestion that bleeding rates with enoxaparin appear to be higher than those that would be expected in practice, and this may be as a result of a switch over from enoxaparin to heparin. However, according to a meta-analysis of 12 trials involving a total of 49,088 patients, use of enoxaparin amongst patients with NSTE ACS is associated with an overall incidence of 6.3% for major bleeding, compared to 5.4% for UFH (OR 1.13; 0.83 to 1.54, p=0.419). (Major bleeding rate reported in OASIS-5 was 4.1%)

Furthermore, a separate meta-analysis had shown that the incidence of death during the first 30 days is higher amongst those who develop major bleeding compared to those who do not (12.8% vs. 2.5%, p<0.0001). Additionally, the hazard ratio for death among those with major bleeding is significantly increased during the first 30 days (adjusted hazard ratio (HR)) 5.37, 95% CI 3.97 to 7.26, p < 0.0001, and therefore management strategies for NSTE ACS patients should consider the risks of bleeding.

MAINTENANCE OF BLINDING DURING OASIS-5
Although OASIS-5 investigators suggest that blinding was maintained at PCI, it is difficult to determine whether this was so as patients in the enoxaparin were required to receive UFH if their last dose of study drug was greater than 6 hours prior to procedure, whilst those on the fondaparinux were required to have a further dose of fondaparinux.

Background
Fondaparinux is a synthetic pentasaccharide and selective inhibitor of activated Factor X (Xa). The antithrombotic activity of fondaparinux is the result of antithrombin III (ATIII) mediated selective inhibition of Factor Xa. By binding selectively to ATIII, fondaparinux potentiates (by about 300 times) the innate neutralisation of Factor Xa by ATIII. Neutralisation of Factor Xa interrupts the blood coagulation cascade and inhibits both thrombin formation and thrombus development. Fondaparinux does not inactivate thrombin (activated Factor II) and has no effects on platelets.

Fondaparinux (Arixtra®) is licensed for the following indications (1):

- Prevention of Venous Thromboembolic Events (VTE) in patients undergoing major orthopaedic surgery of the lower limbs such as hip fracture, major knee surgery or hip replacement surgery.
- Prevention of VTE in patients undergoing abdominal surgery who are judged to be at high risk of thromboembolic complications, such as patients undergoing abdominal cancer surgery.
- Prevention of VTE in medical patients who are judged to be at high risk for VTE and who are immobilised due to acute illness such as cardiac insufficiency and/or acute respiratory disorders, and/or acute infectious or inflammatory disease.
- Treatment of unstable angina (UA) or non-ST segment elevation myocardial infarction (STEMI) in patients for whom urgent (< 120 mins) invasive management (PCI) is not indicated.
- Treatment of ST segment elevation myocardial infarction (STEMI) in patients who are managed with thrombolytics or who initially are to receive no other form of reperfusion therapy.
- Treatment of acute Deep Vein Thrombosis (DVT) and treatment of acute Pulmonary Embolism (PE), except in haemodynamically unstable patients or patients who require thrombolysis or pulmonary embolectomy.
This review covers the use of fondaparinux for acute coronary syndromes (ACS), specifically, the management of patients presenting with acute chest pain as unstable angina or NSTEMI. Acute coronary syndromes, defined as myocardial infarction with ST-segment elevation (STEMI), myocardial infarction without ST-segment elevation (NSTEMI), and unstable angina, share a common pathophysiology: atherosclerotic plaque rupture, erosion, or both with superimposed intracoronary thrombosis, known as atherothrombosis.

According to a meta-analysis published in the *European Heart Journal* which evaluated the efficacy and safety of enoxaparin compared to UFH in patients with ACS, use of enoxaparin amongst patients with NSTE ACS is associated with an incidence of 6.3% for major bleeding (see definition below), compared to 5.4% for UFH (OR 1.13; 0.83 to 1.54, p=0.419)(8). Researchers had sought to evaluate whether enoxaparin is favourable compared to UFH among patients with ACS when incorporating the safety and efficacy profiles.

The meta-analysis included data from 6 trials involving a total of 21,945 patients who had presented with NSTE ACS, and who had either received enoxaparin 1mg/kg twice daily, or UFH for a period of between 2 and 8 days. The composite endpoint of the analysis was net clinical events, defined as death, non-fatal MI, or non-fatal major bleeding by 30 days. Of the 6 trials that involved NSTE ACS patients, 5 trials had reported bleeding outcomes using the TIMI major bleeding criteria (defined as a decrease in haemoglobin of more than 5g/dL, or intracranial, or pericardial bleeding). One trial reported major bleeding defined as retroperitoneal haemorrhage, or bleeding at a specific site accompanied by a 3g/dL drop in haemoglobin or resulting in death or intracranial haemorrhage. The researchers had also reported that there was no difference in mortality between the two groups (3.0% for each, OR 0.99, 0.83 to 1.18; p=0.890). Furthermore, MI occurred statistically significantly less frequently in the enoxaparin group (8.0% vs. 9.1%, OR 0.87, 0.79 to 0.96, p=0.005), and the composite of death and non-fatal MI occurred in 10.0% of patients in the enoxaparin group compared to 11.0% of patients in the UFH group (OR 0.90, 0.81 to 0.996, p=0.043).

An analysis published in Circulation (9) explored the prognostic importance of major bleeding in patients presenting with acute coronary syndromes as presenting in the OASIS registry and the CURE randomised trial. The primary outcome of this analysis was death during the first 30 days of presentation with ACS; major bleeding was defined as bleeding that was significantly disabling, bleeding requiring at least 2 units of packed cells, or bleeding that was life-threatening. Life-threatening bleeding was defined as bleeding that was fatal, bleeding that was intracranial, bleeding that led to a reduction in the haemoglobin level of at least 5g/dL or led to substantial hypotension requiring the use of intravenous inotropes, bleeding that required surgical intervention, or bleeding that necessitated the transfusion of at least 4 units of blood. The analysis included data from 34,126 patients, of whom 783 (2.3%) developed major bleeding. According to the researchers, the incidence of death during the first 30 days was higher amongst those who developed major bleeding compared to those who did not (12.8% vs. 2.5%, p<0.0001). The hazard ratio for death among those with major bleeding was significantly increased during the first 30 days (adjusted hazard ratio (HR)) 5.37, 95% CI 3.97 to 7.26, p < 0.0001).

The authors therefore conclude that major bleeding in patients with ACS is associated with a 5-fold increase in the risk of death, and the implications of this in clinical practice should be borne in mind. Additionally, the authors conclude that strategies to minimise the risk of bleeding should be implemented, including avoiding excessive doses of anti-thrombotic therapies.

Because fondaparinux had previously been shown to be more effective than enoxaparin for the prevention of venous thrombosis in patients undergoing orthopaedic surgery, and was as effective as UFH or enoxaparin in patients with deep vein thrombosis or pulmonary embolism, the Fifth Organisation to Assess Strategies in Acute Ischaemic Syndromes (OASIS-5) was initiated to investigate the safety and efficacy of fondaparinux compared to enoxaparin for high-risk patients with unstable angina or myocardial infarction without ST-segment elevation.

**Existing guidelines for the management of unstable angina/N-STEMI**

The European Society of Cardiology (ESC), in their guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes state that acute treatment comprises four categories: anti-ischaemic agents, anticoagulants, anti-platelet agents and coronary revascularisation. The therapeutic approach is based on whether the patient is to be only medically treated (conservative management) or in addition, referred to angiography and revascularisation. Anticoagulants are administered to inhibit thrombin generation or activity, thus reducing further thrombus-related events, and are given in addition to anti-platelets as the combination is more effective than either treatment alone. However, there is an increased risk of bleeding, especially in elderly patients, patients with a history of bleeding, female patients, or those with renal impairment. Unfractionated heparins (UFH), low-molecular weight heparins (LMWH) and fondaparinux have been investigated for patients presenting with unstable angina or N-STEMI. The guidelines have provided the evidence base for the use of each of these.
The guidelines state that according to pooled analysis of 6 trials investigating short-term UFH vs. placebo or untreated controls, patients who received UFH showed a statistically significant reduction for death or MI of 33% (OR 0.67, 95% CI 0.45 to 0.99; p=0.045).

In a meta-analysis investigating LMWH (enoxaparin) compared to UFH, researchers showed no significant difference between the two drugs for death at 30 days (3.0% vs. 3.0%, OR 1.00, 95% CI 0.85 to 1.17, p not significant). However, a statistically significant combined endpoint of death or MI at 30 days was observed in favour of enoxaparin-treated patients (10.1% vs. 11.0%, OR 0.91, 95% CI 0.83 to 0.99).

Finally, with respect to fondaparinux, the guideline describes findings from the OASIS-5 study (as described in detail below), and states that if fondaparinux is chosen as anticoagulant therapy, it should be maintained for up to 5 days or until hospital discharge and cannot be used as sole anticoagulant during PCI procedures.

The guidelines make the following overall recommendation with respect to the use of anticoagulants:

- Anticoagulation is recommended for all patients in addition to anti-platelet therapy
- Anticoagulation should be selected according to the risk of both ischaemic and vascular events
- The choice of anticoagulant depends on the initial strategy, depending on whether the patient should undergo urgent invasive, early invasive or conservative management
- For an urgent invasive strategy, enoxaparin or bivalirudin should be started immediately.
- In the non-urgent situation where a decision between early invasive or conservative strategy is pending:
  ⇒ Fondaparinux is recommended on the basis of the most favourable efficacy/safety profile
  ⇒ Enoxaparin with a less favourable efficacy/safety profile than fondaparinux should be used only if the bleeding risk is low*
  ⇒ As the efficacy/safety profile of LMWHs other than enoxaparin, or UFH relative to fondaparinux is unknown, these anticoagulants cannot be recommended over fondaparinux
  ⇒ If patients are to undergo percutaneous coronary intervention (PCI), initial anticoagulation should be maintained, except if fondaparinux is used, where addition of UFH in a standard dose of 50-100IU/kg is required in addition to fondaparinux

*The guideline states that bleeding risk is increased with higher or excessive doses of antithrombotic agents, length of treatment, combinations of several antithrombotic drugs, switch between different anticoagulant drugs, as well as with older age, reduced renal function, low body weight, female gender baseline haemoglobin, invasive procedures, and a history of previous bleeding.

With respect to the epidemiology of NSTE ACS, the European Society of Cardiology guidelines state that the annual incidence of hospital admission for the condition is in the range of 3 per 1,000 inhabitants, although there are no clear estimates for Europe as a whole because of the absence of a common centre for centralised health statistics.

The Scottish Medicines Consortium (SMC) has accepted fondaparinux (Arixtra®) for use within NHS Scotland for the treatment of unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI) in patients for whom urgent (<120 minutes) invasive management (PCI) is not indicated.

The American College of Cardiology (ACC) in association with the American Heart Association (AHA) have produced guidelines on the management of patients with unstable angina and non-ST-elevation myocardial infarction which state that anticoagulation with unfractionated heparin, low molecular weight heparins, fondaparinux or bivalirudin (for those that are due for invasive strategy) should be considered during initial management of these patients in order to modify the acute coronary syndrome disease process. Although the guideline does not endorse one anticoagulant over another, it suggests that each institution agree on an approved anticoagulant approach most consistent with local practice and preference. However, a LMWH or fondaparinux are preferable.

For patients undergoing PCI, the ACC/AHA guidelines state that patients receiving fondaparinux should receive additional UFH at a dose of 50 to 60 IU/kg as an intravenous bolus. For those patients who receive enoxaparin instead, and who are to undergo PCI, if the last dose of enoxaparin before PCI is more than 8 hours, patients should receive an additional dose of 0.3mg/kg subcutaneously.
Additionally, the following recommendations have been made with respect to anticoagulant therapies:

- For patients in whom a conservative strategy is selected, regimens using either enoxaparin or UFH or fondaparinux have established efficacy.
- In patients in whom a conservative strategy is selected and who have an increased risk of bleeding, fondaparinux is preferable.
- For patients in whom an initial conservative strategy is selected, enoxaparin or fondaparinux is preferable to UFH as anticoagulant therapy, unless coronary artery bypass grafting (CABG) is planned within 24 hours.

Finally, the All Wales Medicines Strategy Group (AWMSG) has issued the following advice on the use of fondaparinux:

- Fondaparinux is recommended as an option for use in the treatment of unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI) in patients for whom urgent (<120 minutes) invasive management (PCI) is not indicated.

**Dosing information**

1. Treatment of unstable angina/non-ST segment elevation myocardial infarction (UA/NSTEMI)

The recommended dose of fondaparinux is 2.5mg once daily, administered by subcutaneous injection. Treatment should be initiated as soon as possible following diagnosis and continued for up to a maximum of 8 days or until hospital discharge, whichever occurs earlier.

If a patient is to undergo percutaneous coronary intervention (PCI), unfractionated heparin (UFH) as per local practice should be administered during PCI, taking into account the patient's potential risk of bleeding, including the time since the last dose of fondaparinux. The timing of restarting subcutaneous fondaparinux after sheath removal should be based on clinical judgment.

Whilst no dosage reduction is necessary for patients with a creatinine clearance of >20mL/min, it is contra-indicated in patients with a creatinine clearance <20mL/min.

**Clinical evidence**

Non-ST elevation myocardial infarction and unstable angina

The Fifth Organisation to Assess Strategies in Acute Ischaemic Syndromes (OASIS-5) trial evaluated the efficacy and safety of fondaparinux and enoxaparin in high-risk patients with unstable angina or myocardial infarction without ST-segment elevation. The double-blind, double-dummy trial involved 20,078 patients from 576 centres who were randomised to either fondaparinux 2.5mg once daily receive either fondaparinux 2.5mg once daily to receive either fondaparinux 2.5mg once daily with placebo enoxaparin subcutaneously twice daily (n=10,057), or, enoxaparin 1mg/kg twice daily with placebo fondaparinux subcutaneously once daily (n=10,021). Patients were randomly assigned to a study group within 24 hours of the onset of symptoms of ACS and were eligible for inclusion if they fulfilled two of the following three criteria:

- If patients were at least 60 years of age
- Patients had an elevated troponin level or an elevated creatine kinase MB isoenzyme, or
- Electrocardiographic changes indicative of ischaemia.

Patients were excluded from the study if they had had a recent haemorrhagic stroke, or a serum creatinine concentration greater than 265micromol/L. In patients whose creatinine clearance was below 30mL/minute, the enoxaparin dosage was reduced to 1mg/kg once daily.

The primary efficacy outcome was to demonstrate non-inferiority of fondaparinux compared to enoxaparin at day 9, as measured by the incidence of death, myocardial infarction, or refractory ischaemia. The primary safety objective was to determine whether fondaparinux was superior to enoxaparin in preventing major bleeding and was assessed by events by day 9. Patients were followed up for a minimum of 90 days, and a maximum of 180 days.

Major bleeding was defined as clinically overt bleeding that was either fatal, or the patient experienced one of the following:

- Symptomatic intracranial haemorrhage
- Retroperitoneal haemorrhage
- Intraocular haemorrhage leading to significant vision loss

A decrease in haemoglobin of at least 3.0g/dL or bleeds requiring transfusion of two or more units of red blood cells or equivalent of whole blood

Minor bleeding was considered to be any other clinically significant bleeding not meeting the definition for major bleeding and leading to interruption of study drug for at least 24 hours, surgical intervention or transfusion of one unit of blood. The Thrombolysis in Myocardial Infarction (TIMI) criteria was also used to report rates of bleeding where, bleeding was considered to be severe if the patient had:

- Fatal haemorrhage
- Intracranial haemorrhage
- Cardiac tamponade
- A clinically significant haemorrhage with a decrease in haemoglobin of at least 5g/dL, with each blood transfusion unit counting for 1.0g/dL of haemoglobin.
- Bleeding is further classified as to whether it was CABG related i.e. if it occurred within 7 days of CABG surgery, or non-CABG related

Cardiac catheterisation was allowed at any time, and for these patients aspirin in combination with
Fondaparinux for the Treatment of Unstable Angina or NSTEMI

• The primary efficacy outcome of death, myocardial infarction or refractory ischaemia at 9 days occurred in 579 patients (5.8%) receiving fondaparinux, vs. 573 patients in the enoxaparin group (5.7%) (HR 1.01, 95% confidence interval 0.90 to 1.13, p = 0.007 for non-inferiority), confirming non-inferiority as the upper confidence limit is below the prespecified boundary of 1.185. The rates of the main secondary outcome (death or myocardial infarction) were similar at 4.1% for patients randomised to fondaparinux and 4.1% for patients randomised to enoxaparin (HR = 0.99, 0.86 to 1.13).
• At 30 days, there was a trend towards a lower rate of death, myocardial infarction, or refractory ischaemia with fondaparinux than with enoxaparin (8.0% vs. 8.6%; HR 0.93, 0.84 to 1.02) and of the composite of death or myocardial infarction (6.2% vs. 6.8%; HR 0.90, 0.81 to 1.01, p = 0.07 for superiority). The differences were due to a statistically significant reduction in mortality with fondaparinux (2.9% vs. 3.5% with enoxaparin; HR 0.83, 0.71 to 0.97; p=0.02 for superiority)
• For the safety assessment, by day 9, major bleeding occurred in 217 patients (2.2%) in the fondaparinux group, compared to 412 patients (4.1%) in the enoxaparin group (HR 0.52, 0.44 to 0.61; p<0.001 for superiority)
• Fondaparinux was also associated with a statistically significant reduction in the number of patients with fatal bleeding (7 vs. 22 in the enoxaparin group; p=0.005) and severe bleeding according to the Thrombolysis in Myocardial Infarction (TIMI) criteria (70 vs. 126 in the enoxaparin group, HR 0.55, 95% CI 0.41 to 0.74, p<0.001)
• The composite of death, MI, refractory ischaemia or major bleeding at 9 days occurred in 737 patients (7.3%) in the fondaparinux group, compared to 905 patients (9.0%) in the enoxaparin group (HR 0.81, 0.73 to 0.89, p<0.001 for superiority)
• At 180 days, death, myocardial infarction or refractory ischaemia occurred in 1222 patients (12.3%) receiving fondaparinux, vs. 1308 patients in the enoxaparin group (13.2%) (HR 0.93, 0.86 to 1.00, p = 0.06 for superiority)
• Additionally, at 180 days, major bleeding occurred in 417 patients (4.3%) in the fondaparinux group compared to 569 patients (5.8%) in the enoxaparin (HR 0.72, 0.64 to 0.82, p<0.001 for superiority)
• The composite of death, MI, refractory ischaemia or major bleeding at 180 days occurred in 1493 patients (15.0%) of patients in the fondaparinux group, compared to 1698 patients (17.1%) in the enoxaparin group (HR 0.86, 0.81 to 0.93, p<0.001 for superiority)
• Among patients undergoing PCI in hospital, the rates of the combination of death, myocardial infarction, and refractory ischaemia 9.3% in the fondaparinux group and 8.6% in the enoxaparin group by day 9, and at the end of study (12.9% in the fondaparinux group and 12.3% in the enoxaparin group)
• In a subgroup analysis, the rate of bleeding was consistently lower in the fondaparinux group, regardless of whether patients received unfractionated heparin at randomisation (2.0% in the fondaparinux group vs. 4.0% in the enoxaparin group among patients who did not receive unfractionated heparin (p<0.001), and 3.0% vs. 5.0% respectively amongst those who received unfractionated heparin (p<0.003))

The researchers concluded that this study showed that fondaparinux and enoxaparin have similar efficacy, and fondaparinux appears to reduce the incidence of major bleeding.

A sub-group analysis published in the Journal of the American College of Cardiology prospectively evaluated the safety and efficacy of fondaparinux compared with enoxaparin in patients enrolled in the OASIS-5 trial who underwent PCI during the study period (6). Please see above for details of the OASIS-5 trial.
According to the researchers, the administration of study drugs during PCI maintained the double-blind, double-dummy design, and the dose of the study drug administered at PCI was determined by the time that had elapsed since administration of the last subcutaneous injection of the study drug, and by the concurrent use of glycoprotein IIb/IIIa inhibitors.

Centres also had the option of continuing study drug after the revascularisation procedure. Table 1 below shows drug administration regimens during PCI.

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<th>Table 1: Drug administration regimens during PCI</th>
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<td><strong>Patients randomised to fondaparinux</strong></td>
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<td>Last fondaparinux dose &lt;6 hours</td>
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**GP IIb/IIIa inhibitor received**
- No additional study drug given (patients were considered fully anticoagulated on fondaparinux)
- IV fondaparinux 2.5mg was used for the procedure
- No additional study drug given (patients were considered fully anticoagulated on enoxaparin)
- Study UFH was used for the procedure. As a guideline to the investigator, the dose of UFH was 65 IU/kg

**GP IIb/IIIa inhibitor not received**
- IV fondaparinux 2.5 mg was used for the procedure
- IV fondaparinux 5mg was used for the procedure
- No additional study drug given (patients were considered fully anticoagulated on enoxaparin)
- Study UFH was used for the procedure. As a guideline to the investigator, the dose of UFH was 100 IU/kg

Safety was assessed by evaluating rates of major bleeding, and efficacy was evaluated using the composite of death, myocardial infarction, or stroke at days 9, 30, and 180. Major bleeding was defined as clinically overt bleeding that was either fatal, intracranial, retroperitoneal, intraocular, a decrease in haemoglobin of ≥3g/dL or requiring a red blood cell transfusion of > 2units. After isolated reports of catheter thrombosis in a small number of patients, the protocol was amended to include instructions for flushing the catheter after study drug administration, and centres were reminded that it was permissible to administer open label UFH before PCI in addition to the protocol-mandated study drug. Guiding catheter-related thrombus was reported as an adverse event in the first 4,480 PCIs performed, and was routinely collected in the final 1,758 patients undergoing PCI after implementation of the modification to the case report forms.

To assess the potential impact of additional UFH, the rates of catheter thrombus and major bleeding were examined separately using 2 approaches:

- In patients randomised to enoxaparin the use of protocol-mandated UFH during PCI was assessed according to whether the PCI was performed < 6 hours after the last dose of enoxaparin (where no UFH was given by protocol) or > 6 hours after the last enoxaparin dose (where UFH was recommended).

- The use of additional open-label UFH immediately before PCI was evaluated in both treatment groups.

Of the 20,078 patients enrolled in OASIS-5, 14,206 patients underwent heart catheterisation, of which 12,715 patients underwent the procedure during the study drug administration period. A total of 8,100 patients underwent revascularisation, of which 6,238 patients underwent PCIs and 1,862 patients underwent CABGs. Overall, 1,414 and 1,420 patients in the fondaparinux and enoxaparin respectively had early PCI within 24 hours of randomisation, 1,976 and 1,972 respectively had PCI within 48 hours, and 1,158 and 1,162 patients respectively had a PCI between 48 hours and 8 days.

The following overall results were presented for patients undergoing PCI:

- At day 9, death, MI or stroke had occurred in 197 patients (6.3%) on fondaparinux, compared to 190 patients (6.2%) in the enoxaparin group (HR 1.03, 0.84 to 1.25; p=0.79), and the trend was similar both at days 30 (HR 1.00, 0.83 to 1.20; p=0.99) and days 180 (HR 0.99, 0.85 to 1.16; p=0.95).

- Major bleeding at day 9 was significantly reduced with fondaparinux compared with enoxaparin (73 patients (2.4%) vs. 155 patients (5.1%) respectively, HR 0.46, 0.35 to 0.61; p<0.00001), and this trend was similar both at days 30 (2.9% vs. 5.4%, HR 0.52,
0.40 to 0.67; p<0.00001) and days 180 (3.4% vs. 6.3%, HR 0.53, 0.42 to 0.68; p<0.00001)
TIMI major bleeding occurred in 44 patients in the enoxaparin group (14.4%) and 19 patients (6.2%) in the fondaparinux group (HR 0.43, 0.25 to 0.73; p=0.0019) at day 9; the trend was similar in that fewer patients on fondaparinux compared to enoxaparin experienced TIMI major bleeding at days 30 (0.8% vs. 1.5%, HR 0.54, 0.33 to 0.87; p=0.012) and at day 180 (0.9% vs. 1.7%, HR 0.52, 0.33 to 0.82; p=0.0052)
The composite of death, MI, stroke or major bleeding at day 9 occurred in 255 patients (8.2%) in the fondaparinux group vs. 318 patients (10.4%) in the enoxaparin group (HR 0.78, 0.67 to 0.93; p=0.004), and this trend was similar both at days 30 (9.5% vs. 11.8%, HR 0.80, 0.69 to 0.93), and at days 180 (12.7% vs. 14.8%, HR 0.84, 0.74 to 0.96; p=0.013)

The following results were presented after protocol amendment following catheter thrombosis:

- When PCI was performed <6 hours after the last dose of enoxaparin the rates of abrupt closure did not differ between the enoxaparin and the fondaparinux groups (5.9% fondaparinux alone vs. 6.2% for enoxaparin alone, HR 0.96, 0.73 to 1.26; p=0.78)
- When PCI was performed after 6 hours from the last subcutaneous enoxaparin dose and UFH was added in the enoxaparin group (but not the fondaparinux group) abrupt/threatened abrupt closure was reduced (6.6% for fondaparinux alone vs. 4.3% for UFH added to enoxaparin; RR 1.40, p= 0.048)
- The addition of UFH to the enoxaparin group 6 hours after the last enoxaparin dose lowered the rate of abrupt/threatened abrupt closure compared with those undergoing PCI with enoxaparin alone (4.3% for UFH added to enoxaparin vs. 6.2% for enoxaparin alone, HR = 0.70; p=0.026

Table 2 below shows some PCI-related angiographic and clinical outcomes according to the use of open-label UFH given in the catheterisation laboratory before PCI following protocol amendment.

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<tr>
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<th>No UFH before PCI</th>
<th></th>
<th>UFH before PCI</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fondaparinux (%)</td>
<td>Enoxaparin</td>
<td>HR (95% CI)</td>
<td>Fondaparinux (%)</td>
</tr>
<tr>
<td>Number randomised</td>
<td>793</td>
<td>810</td>
<td>-</td>
<td>75</td>
</tr>
<tr>
<td>Death/MI/ stroke/ major bleed at day 30</td>
<td>80 (10.1)</td>
<td>90 (11.1)</td>
<td>0.90 (0.67-1.22)</td>
<td>4 (5.3)</td>
</tr>
<tr>
<td>Major bleed at day 30</td>
<td>26 (3.3)</td>
<td>35 (4.3)</td>
<td>0.75 (0.45-1.25)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Death/MI/ stroke/ major bleed at study end</td>
<td>101 (13.2)</td>
<td>109 (13.6)</td>
<td>0.94 (0.72-1.24)</td>
<td>5 (6.7)</td>
</tr>
<tr>
<td>Catheter thrombus</td>
<td>9 (1.1)</td>
<td>4 (0.5%)</td>
<td>2.30 (0.71-7.4)</td>
<td>1 (1.3)*</td>
</tr>
</tbody>
</table>

*This patient had received a suboptimal dose of UFH

The authors concluded that fondaparinux is superior to enoxaparin in preventing major bleeding while maintaining superior efficacy resulting in superior net clinical benefit for patients undergoing PCI for NSTE ACS.

In a separate analysis published in the European Heart Journal, researchers evaluated data from the OASIS-5 trial to examine the effect of fondaparinux compared to enoxaparin on different types of bleeding and the impact of bleeding on death and recurrent ischaemic events. The following results were reported at day 9, with respect to bleeding (table 3):
Of these, during follow-up to 180 days, 990 patients (4.9%) developed major (including fatal) bleeding and 423 patients (2.1%) developed minor bleeding. The following results were reported with respect to clinical outcomes:

- During the first 30 days, approximately 1 in 6 of all deaths occurred in patients who experienced any bleed (major or minor).
- More than 90% of the 64 excess deaths in patients treated with enoxaparin compared with fondaparinux occurred in patients who experienced bleeding during the first 9 days.
- During the 180 days of study follow-up, approximately 1 in 8 of all deaths occurred in patients who experienced bleeding during the first 9 days.
- The composite of outcome of death/MI/stroke and bleeding showed a similar pattern: During the first 30 days, approximately 1 in 7 of the composite outcome occurred in patients who experienced bleeding, and during 180 days of study follow-up approximately 1 in 9 of these events occurred in patients who experienced bleeding the first 9 days.
- In the overall patient population, major bleeding during the first 30 days was associated with about a 4-fold increase in death/MI/stroke or the individual components of this outcome (21.8% vs. 6.2%, HR 3.00; 95% CI 3.30–4.82), and a similar increase in each of the individual components of this composite outcome: death (8.4% vs. 2.7%, HR 3.46; 2.60–4.60), MI (8.3% vs. 3.4%, HR 4.39; 3.45–5.59), and stroke (3.0% vs. 0.7%, HR 4.66; 2.83–7.65), p<0.0001 for each analysis.

The researchers concluded that a quarter of those patients who developed major bleeding in OASIS-5 experienced death, MI or stroke during follow-up till 180 days. However they also highlight that this analysis has the following limitations:

- The study was not powered to determine the effect of fondaparinux compared with enoxaparin for uncommon but serious outcomes such as intracranial bleeding.
- The association between bleeding and outcomes in the OASIS-5 trial is subject to other confounding factors i.e. older and sicker patients are more likely to experience bleeding, and are also more likely to experience MI, stroke or death.
- Very few minor bleeds were reported after day 9, raising the possibility that minor bleeding after the period of study drug administration was under-reported.

### Cost
- Enoxaparin 1mg/kg bd for 2 to 8 days – Assuming an average weight of 70kg, the dose is 70mg bd – Approximately £10 per day
- Fondaparinux 2.5mg od for up to 8 days or until discharge - £6.66 per day.

The mean duration of treatment in the OASIS-5 trial was 5.4 days on fondaparinux, and 5.2 days for patients on enoxaparin. Considering these treatment durations, a course of enoxaparin for a patient weighing an average of 70kg would be approximately £50 (range from £30 to £80 for a 3 to 8 day course duration) whilst a course of fondaparinux would be approximately £33 (range from £20 to £53 for a 3 to 8 day course duration).
According to a Health Technology Assessment on the cost-effectiveness of alternative strategies for the initial medical management of non-ST-elevation acute coronary syndrome, NHS Hospital Episode Statistics suggest that the incidence of unstable angina is around 1000 cases per million total population per year or around 10 per acute hospital per week (7). Based on these estimates, this implies an annual incidence within the UK of around 59,756. This implies that if all these patients received fondaparinux instead of enoxaparin for a mean duration of 5 days, it would result in a saving of over £1 million per year.

### Points for consideration

In a comparison of enoxaparin vs. UFH for patients with high risk UA/STEMI during PCI, the Superior Yield of the New Strategy of Enoxaparin, Revascularisation and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial concluded that more bleeding was observed with enoxaparin; A post-hoc analysis from SYNERGY suggested that some of the excess bleeding seen with enoxaparin could be explained by crossover to UFH at the time of PCI. The ACC guidelines therefore state that although this remains to be validated prospectively, it would appear reasonable to avoid excessive anticoagulation by avoiding the crossover of anticoagulants i.e. maintain consistent anticoagulant therapy from the pre-PCI phase throughout the procedure itself. As seen in the sub-group analysis of patients undergoing PCI, use of UFH before PCI in the enoxaparin group resulted in an increase in the incidence of major bleeding. However, the meta-analysis evaluating the safety and efficacy of enoxaparin compared to UFH in patients with NSTE ACS had reported an overall major bleeding rate of 6.3% with enoxaparin, compared to 4.1% as reported in OASIS-5.

The ACC/AHA guidelines on the management of patients with NSTEMI/UA undergoing PCI state that for patients receiving enoxaparin, if the last dose is given greater than 8 hours prior to procedure, patients are required to receive additional 0.3 mg/kg IV bolus of enoxaparin. Furthermore, the ESC guidelines also state that no additional UFH is required if PCI is carried out within 6-8 hours of subcutaneous enoxaparin. In the OASIS-5 trial, patients received UFH if the last enoxaparin dose was given > 6 hours prior to procedure, and this may have led to an increased incidence of bleeding events.

Some may argue that use of fondaparinux offers an advantage in that no dosage adjustments are required in patients with renal impairment (compared to dose adjustments required for enoxaparin patients in whom the dose was reduced if the creatinine clearance was <30mL/min). However, it appears that patients with renal impairment were excluded from the trial, and in practice, renal function is not a determinant for the dosing of anticoagulant in the acute setting. The SPC for fondaparinux states that it is contra-indicated in patients with a renal function <20mL/min.

During the conduct of OASIS-5, catheter-associated thrombus was reported 3 times more frequently with the fondaparinux strategy in patients undergoing PCI (0.9% vs. 0.3%). Prescribers were therefore reminded of the need for adequate flushing of the line or permission for the use of open-label UFH in this group of patients. Additionally, there is some speculation that enoxaparin was possibly associated with a lower incidence of catheter-related thrombus because patients received additional UFH at PCI if the last dose of enoxaparin was greater than 6 hours prior to procedure (when PCI was performed <6 hours of the last enoxaparin dose, the rates of abrupt closure did not differ between the enoxaparin and the fondaparinux groups – 5.9% for fondaparinux vs. 6.2% for enoxaparin, HR 0.96, 0.73 to 1.26; p=0.78).

To date, the only anticoagulant that has been evaluated with fondaparinux during PCI is UFH, and based on limited experience, the OASIS-5 investigators recommend an UFH dose of 50 to 60 IU/kg IV when fondaparinux-treated patients are taken for PCI. However, this UFH recommendation is not fully evidence-based, given its inconsistent and uncontrolled use in OASIS-5. Therefore, additional clinical trial information is needed to establish more rigorously the safety of intravenous UFH at the time of PCI in patients receiving fondaparinux as initial medical treatment.

Although researchers in OASIS-5 suggest that blinding to treatment was maintained at PCI, it is difficult to determine how this was done as patients who had received enoxaparin > 6 hours prior to anticipated procedure were required to have additional UFH, whilst those in the fondaparinux arm were required to receive an additional dose of fondaparinux (please refer to dosing table 1).

Because the anticoagulant effect of UFH can be more readily reversed than that of fondaparinux, UFH is favoured over fondaparinux in patients likely to undergo CABG within 24 hours.

Fondaparinux is not recommended as an option for use in the treatment of unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI) in patients for whom urgent (< 120 minutes) invasive management (PCI) is indicated.
References:

1. Fondaparinux (Arixtra 2.5 mg/0.5 mL solution for injection, pre-filled syringe) Summary of Product Characteristics. Date of revision 19 March 2008
3. Scottish Medicines Consortium. Fondaparinux (Arixtra®) for unstable angina or non-ST-segment elevation myocardial infarction

The document reflects the views of LNDG and may not reflect those of the reviewers