HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

11 June 2008

ARIXTRA 2.5 mg/0.5 ml, solution for injection in pre-filled syringe
Pack of 10 (CIP: 563 619-7)

Applicant: GlaxoSmithKline

Fondaparinux Sodium
ATC code : B01AX05

List I

Date of first Marketing Authorisation (MA): 21 March 2002

(Centralised European Registration Procedure)

Variation to the MA and extension of indication: 29 August 2007

Reason for request: **inclusion on the list of medicines approved for use by hospitals and various public services** in the extension of indication:
"Treatment of unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI) in patients for whom urgent (< 120 min) invasive management (percutaneous coronary intervention: PCI) is not indicated (see sections 4.4 and 5.1 of the SPC)".

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Fondaparinux Sodium[1]

1.2. Indications

"- Prevention of venous thromboembolic events in patients undergoing major orthopaedic surgery of the lower limbs such as hip fracture, major knee surgery or hip replacement surgery".
- "Prevention of venous thromboembolic events in patients undergoing abdominal surgery who are judged to be at high risk of thromboembolic complications, such as patients undergoing abdominal cancer surgery (see section 5.1)".
- "Prevention of venous thromboembolic events (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 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 unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI) in patients for whom urgent (< 120 min) invasive management (Percutaneous Coronary Intervention: PCI) is not indicated*: *(cf. Warnings/Precautions for use and Pharmacodynamics)*".

1.3. Dosage in the treatment of unstable angina/non-ST segment elevation myocardial infarction (UA/NSTEMI): solution for injection containing 2.5 mg/0.5 ml.

The recommended dosage of fondaparinux is 2.5 mg once daily administered by deep subcutaneous injection. Treatment should be initiated as soon as possible once diagnosis is established and should continue for up to a maximum of 8 days or until hospital discharge if that occurs earlier.

Patients managed by Percutaneous Coronary Intervention (PCI, or angioplasty),
In accordance with the SPC (Warnings/precautions for use of the SPC concerning the risk of guiding catheter thrombus):
- In STEMI patients undergoing primary PCI, the use of fondaparinux prior to and during PCI is not recommended. Similarly, in UA/NSTEMI patients with life-threatening conditions that require urgent revascularisation, the use of fondaparinux prior to and during PCI is not recommended. These are patients with refractory or recurrent angina associated with dynamic ST deviation, heart failure, major life-threatening arrhythmias or haemodynamic instability.
- In non-primary PCI (UA/NSTEMI and STEMI patients): the use of fondaparinux as the sole anticoagulant during PCI is not recommended.

1 At the 2.5 mg dose, fondaparinux does not affect routine coagulation tests such as activated partial thromboplastin time (aPTT), activated clotting time (ACT) or prothrombin time (PT)/International Normalised Ratio (INR) tests in plasma, or bleeding time or fibrinolytic activity. Fondaparinux does not cross-react with sera from patients with heparin-induced thrombocytopoenia.

Unfractionated heparin (UFH) should be administered during the PCI as per local clinical practice, taking into account the patient's potential risk of bleeding, including the time since the last dose of fondaparinux.
There are limited data on the use of UFH during non-primary PCI in patients treated with fondaparinux.
- In those patients who underwent non-primary PCI 6-24 hours after the last injection of fondaparinux, the median dose of UFH was 8,000 IU and the incidence of major bleeding was 2% (2/98).
- In those patients who underwent PCI < 6 hours after the last dose of fondaparinux, the median dose of UFH was 5,000 IU and the incidence of major bleeding was 4.1% (2/49).

The timing of restarting subcutaneous fondaparinux after catheter removal should be based on clinical judgment. In the pivotal UA/NSTEMI clinical trial, treatment with fondaparinux was restarted no earlier than 2 hours after catheter removal.

Specific situations

Renal impairment: Fondaparinux is mainly eliminated by the kidney.
Fondaparinux should not be used in patients with creatinine clearance <20 ml/min.
No dosage reduction is required for patients with creatinine clearance> 20 ml/min when the product is administered for the treatment of acute coronary syndrome. Patients whose creatinine clearance is < 50 ml/min have an increased risk of bleeding and should be treated with caution.

For the treatment of UA/NSTEMI and STEMI, there are limited clinical data available on the use of fondaparinux 2.5mg once daily in patients with creatinine clearance between 20 and 30 ml/min. Therefore the physician should determine if the benefit of treatment outweighs the risk.

Elderly patients: The elderly population is at increased risk of bleeding. As renal function is generally decreasing with age, elderly patients may show reduced elimination and increased plasma fondaparinux concentrations. Fondaparinux should be used with caution in these patients.

Patients with low body weight: Patients with a body weight < 50 kg are at increased risk of bleeding. Elimination of fondaparinux decreases with weight. Fondaparinux should be used with caution in these patients.

2. SIMILAR MEDICINAL PRODUCTS

2.1 ATC Classification (2007):

B	Blood and haematopoietic organs
B01A	Antithrombotics
B01AX	Other antithrombotic medicinal products
B01AX05	Fondaparinux

2.2 Medicines in the same therapeutic category

2.2.1 Comparator medicines

- Unfractionated heparins (UFN): CALCIPARIN and Heparin CHOAY.

  Indications (MA): treatment of unstable angina and non-Q-wave myocardial infarction, in the acute phase

  Dosage: This heparin must be administered subcutaneously.
  A direct intravenous bolus dose of 50 to 100 IU/kg of IV heparin may be administered at the same time as the first subcutaneous injection to reach effective blood heparin levels from the start of treatment.
  The initial dose is 500 IU/kg per 24 h subcutaneously in two (every 12 hours) or three (every 8 hours) divided doses per day, depending on the volume to be injected. The subcutaneous injection of more than 0.6 ml may reduce heparin resorption. The heparin dose will be then adjusted according to laboratory test results.

- Low molecular weight heparins (LMWH):
  - Dalteparin: FRAGMINE
  Indication (MA): Unstable angina and non-Q wave myocardial infarction in the acute phase, administered concurrently with aspirin (solution for injection containing 7500 IU anti-Factor Xa/0.75 ml and 10,000 IU anti-Factor Xa/1 ml)

  Dosage: Dalteparin sodium is administered in two subcutaneous injections per day (spaced 12 hours apart) of 120 IU anti-Xa/kg, with a maximum dose of 10,000 IU per injection, in combination with aspirin (recommended dosages: 75 to 325 mg orally, after a minimum loading dose of 160 mg). The recommended duration of treatment is approximately 6 days until clinical stabilisation.
  If thrombolytic treatment proves to be necessary, in the absence of clinical data on the co-administration of dalteparin and thrombolytics, it is recommended to stop dalteparin treatment and manage the patient in the usual way.

  - Enoxaparin: LOVENOX
  Indication (MA): treatment of unstable angina and non-Q-wave myocardial infarction in the acute phase, administered concurrently with aspirin (solution for injection containing 6000 IU anti-Factor Xa/0.6 ml, 8000 IU anti-Factor Xa/0.8 ml, 10,000 IU anti-Factor Xa/1 ml and 30,000 IU anti-Factor Xa/3 ml)
  (Treatment of ST segment elevation acute myocardial infarction in combination with a thrombolytic treatment in patients, whether or not they are eligible for secondary coronary angioplasty).

  Dosage: Enoxaparin is administered in two subcutaneous injections per day (spaced 12 hours apart) of 100 IU anti-Xa/kg each, in combination with aspirin (recommended dosages: 75 to 325 mg orally, after a minimum loading dose of 160 mg). The recommended duration of treatment is approximately 2-8 days until clinical stabilisation.

- Nadroparin: FRAXIPARIN

Indication (MA): Treatment of unstable angina and non-Q-wave myocardial infarction in the acute phase, administered concurrently with aspirin

Dosage: Nadroparin is administered in two subcutaneous injections per day (spaced 12 hours apart) of 86 IU anti-Xa/kg each, in combination with aspirin (recommended dosages: 75 to 325 mg orally, after a minimum loading dose of 160 mg).
The initial dose must be administered as an IV bolus and a SC injection of 86 IU anti-Xa/kg.
The recommended duration of treatment is approximately 6 days until clinical stabilisation with a dosage adjusted for body weight.

2.3 Medicines with a similar therapeutic aim

2.3.1 Platelet aggregation inhibitors, including aspirin (75 to 325 mg/day) and clopidogrel (PLAVIX) (75 mg/day):

PLAVIX

- Indication: prevention of atherothrombotic events in:
  - Patients suffering from myocardial infarction (starting between a few days and 35 days after), ischaemic stroke (starting between 7 days and 6 months after) or established peripheral arterial disease.
  - Patients with acute coronary syndrome: non-ST segment elevation acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction), including patients undergoing percutaneous coronary stent placement, in combination with acetylsalicylic acid (ASA).
  - ST segment elevation acute myocardial infarction, in combination with ASA in medically treated patients eligible for thrombolytic therapy.

2.3.2 Glycoprotein (GP) IIb/IIIa inhibitors

- Eptifibatide: INTEGRILIN

Indicated for use with acetylsalicylic acid and unfractionated heparin in the prevention of early myocardial infarction in unstable angina or non-Q-wave myocardial infarction patients for whom the last episode of chest pain occurred in the previous 24 hours and there are ECG changes and/or elevated cardiac enzyme levels. The patients most likely to benefit from treatment are those at high risk of developing myocardial infarction 3-4 days after the onset of acute angina symptoms, such as patients likely to undergo an early PCI (Percutaneous Coronary Intervention).

- Tirofiban: AGGRASTAT

Recommended indication for use in combination with aspirin and unfractionated heparin for the prevention of early myocardial infarction in unstable angina or non-Q-wave myocardial infarction patients whose last episode of chest pain occurred in the previous 12 hours and there are ECG changes and/or elevated cardiac enzymes. The patients most likely to benefit from treatment are those at high risk of developing myocardial infarction 3-4 days after the onset of acute angina symptoms, such as patients likely to undergo an early PTCA (Percutaneous Transluminal Coronary Angioplasty).

- Abciximab: REOPRO

Indication: ReoPro is indicated as an adjunct to heparin and aspirin for:
- Percutaneous Coronary Interventions:
- The prevention of ischaemic cardiac complications in patients undergoing a percutaneous coronary intervention (balloon angioplasty, atherectomy, and stenting).
- Unstable angina: short-term (one-month) reduction of the risk of myocardial infarction in unstable angina patients who do not respond to conventional medical treatment and who have been scheduled for a percutaneous coronary intervention.

3. ANALYSIS OF AVAILABLE DATA

Introduction

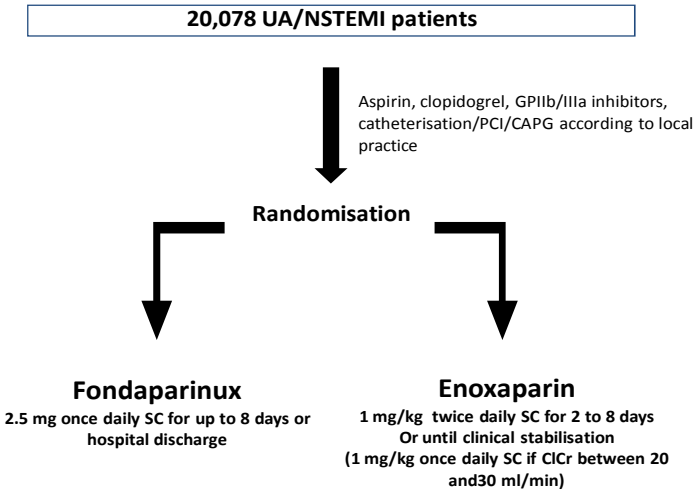
The MA granted to fondaparinux (ARIXTRA 2.5 mg) for the treatment of unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI) in patients for whom urgent (< 120 min) invasive management (percutaneous coronary intervention: PCI) is not indicated is based on the results of a single comparative clinical study ("OASIS-5").

3.1 Summary of the OASIS 5 study

Primary endpoint: to test the non-inferiority and superiority of fondaparinux (ARIXTRA 2.5 mg) versus enoxaparin (LOVENOX) at D9 in preventing death and ischaemic events in UA/NSTEMI patients according to the usual practices.

Design

OASIS-5 study design



The sample size calculation was based on a non-inferiority approach. The study had to be stopped after the occurrence of the first composite endpoint event in 1,414 patients. The estimated sample size of 16,000 patients for inclusion was based on a total incidence of primary endpoint events of 8%. However, the global incidence observed during an interim analysis (with blinded treatment groups) was 6.2%, which was lower than the estimate. An amendment to the protocol was made in order to:

- include a population with a higher risk of complications: patients aged under 60 years of age had to have ECG changes and biological markers compatible with myocardial ischaemia (amendment 2 of 6 January, 2004).
- increase the number of patients to 20,000.

Discussion of the choice of non-inferiority margin

The non-inferiority margin was established at 1.185 on the basis of the results of a meta-analysis (Eikelboom, 2000) that showed that the risk of death or MI was halved with heparins (UFH/LMWH) **compared with a placebo** (or no treatment) in patients treated with aspirin

(odds ratio: 0.53; 95% CI: 0.38-0.73). Inversely, the increase in risk when there was no treatment compared with the use of the UFH/LMWH corresponding to an OR of 1.89 (95% CI: **1.37**-2.63) and a non-inferiority margin of 1.185 (1.37/2) was therefore chosen.

The application of this non-inferiority margin derived from the "death/MI" composite endpoint to the "death/MI/RI" composite endpoint was based on the results of the FRISC I study (FRagmin during Instability in Coronary Artery Disease [FRISC] study group, 1996) included in the meta analysis. In this study, the impact of the active treatment compared with the placebo was similar on the "death/MI" endpoint (Relative Risk [RR]: 0.37; 95% CI: 0.20-0.68) and on the death/MI/revascularisation endpoint for refractory/recurrent ischaemia" (RR: 0.38; 95% CI: 0.22–0.66).

Inclusion criteria:
- Patients hospitalised with symptoms suggesting unstable angina (UA) or ST segment depression who can be included and randomised within 24 hours
- Patients with at least two of the following three criteria:
    a. Age > 60
    b. Troponin T or I or CPK-MB above the upper limit of normal for the centre
    c. ECG changes compatible with myocardial ischaemia, i.e., ST segment depression of at least 1 mm in two contiguous leads or T-wave inversion of more than 3 mm or dynamic ST segment changes or transient ST segment elevation.

Exclusion criteria: severe renal failure in particular.

Treatments evaluated:
- fondaparinux: 2.5 mg SC once daily for 8 days or until hospital discharge
- enoxaparin: 1 mg/kg SC twice daily for 8 days or until hospital discharge

In the case of renal insufficiency and for a creatinine clearance of 20 to 30 ml/min, the enoxaparin dosage had to be reduced to 1 SC injection/day or every other day. The fondaparinux dosage remained unchanged.

Other treatments:
- All patients had to receive aspirin.
- Patients were managed according to the usual practices for the centres.
In particular, patients could undergo PTCA after starting the study treatment for one of the following reasons:
1) usual practice at the centre
2) necessary because of patient's clinical condition
3) refractory ischaemia.

- Treatments received in the event of an invasive strategy:
In the event of angioplasty during the treatment period:
- the patients were to be pre-treated with aspirin and clopidogrel for at least six hours before the procedure
- the patients were to receive double-blind, double-placebo:
    -> either an IV bolus of fondaparinux 2.5 mg **or 5 mg** for patients in the fondaparinux group, depending on when the angioplasty was performed,
    -> or an UFH for patients in the enoxaparin group, with a dosage based on the time of the last SC injection of the study drug and the possible use of a GP IIb/IIIa inhibitor:

Treatment procedures in the case of angioplasty (PCI) in OASIS-5

Fondaparinux 2.5 mg	Enoxaparin
Time between last SC injection of study treatment and PCI	
PCI less than 6 hours after the injection[1]	**PCI less than 6 hours after the injection**
- No IV injection if GP IIb/IIIa inhibitor	- No IV injection if GP IIb/IIIa inhibitor
- fondaparinux 2.5 mg IV if no GP IIb/IIIa inhibitor	- fondaparinux placebo if no GP IIb/IIIa inhibitor
PCI between 6 and 12 hours after the injection	**ICP between 6 and 12 hours after the injection**
- fondaparinux 2.5 mg IV + UFH placebo if GP IIb/IIIa inhibitor	- UFH 65 U/kg IV + fondaparinux placebo if GP IIb/IIIa inhibitor
- fondaparinux 5.0 mg IV + UFH placebo if no GP IIb/IIIa inhibitor	- UFH 100 U/kg IV + fondaparinux placebo if no GP IIb/IIIa inhibitor

[1]*If the last dose of study treatment had comprised a single injection (i.e., an injection of enoxaparin placebo), patients should have received an IV injection of fondaparinux 2.5 mg if a GP IIb/IIIa inhibitor was used and 5.0 mg if a GP IIb/IIIa inhibiter was not used.*

Continuation of study treatment after angioplasty was then left up to the investigator's discretion.

- In the case of a coronary artery bypass graft (CABG), the study treatment had to be stopped if possible 24 hours before the procedure and resumed 48 hours afterwards.

Primary endpoint: the first occurrence of one of the composite endpoint events (death/MI/refractory ischemia [RI]) up to and including D9.

Secondary endpoints, including:
- efficacy endpoints up to and including D14, D30, D90, D180:
  . the first occurrence of one of the death/MI/RI composite endpoint events;
  . the first occurrence of one of the death/MI composite endpoint events;
  . the occurrence of a death, MI, or RI (considered separately).
- Tolerance endpoints:
  - incidence of major bleeding events[2] up to and including D9
  - the following events were also recorded in patients who underwent PCI:
    . complications at the vascular access site (e.g., pseudo-aneurysm requiring a surgical intervention, haematoma, or arteriovenous fistula).
    . acute occlusion of the coronary artery, onset of an angiographic thrombus, "no-reflow" phenomenon, dissection, or perforation.

Results of the OASIS-5 study

The patients were followed for 90 to 180 days.

Populations evaluated:
- 20,078 patients were randomised: 10,057 in the fondaparinux group and 10,021 in the enoxaparin group.
- The average age of the patients was 67 with approximately 60% ≥ 65.
- Nearly 40% of the patients had mild renal insufficiency (creatinine clearance of 50 to 80 ml/min) and 17% had moderate renal insufficiency (creatinine clearance of 30 to 50 ml/min).

2 A bleeding event was defined as major when it was overt bleeding and: fatal, symptomatically intracranial or retroperitoneal or intraocular requiring surgery or associated with associated with a significant loss of vision, a drop in blood haemoglobin levels of more than 3 g/dl or a transfusion of more than two units.

Treatment procedures:

- *Overall*, 70% of the patients were included in a centre with a cardiac catheterisation laboratory.
- All patients received the standard medical treatment for UA/NSTEMI and 63% underwent coronary angiography, 34% underwent angioplasty and 9% underwent aortocoronary bypass surgery.

The interventions performed during the hospital stay were similar for the two treatment groups:

Interventions performed during hospitalisation in OASIS-5 (randomised patient population)

	Fondaparinux (n=10,057)	**Enoxaparin (n=10,021)**
Interventions, n (%)		
Coronary angiography	6390 (63.5)	6325 (63.1)
PCI	3454 (34.3)	3435 (34.3)
CABG	965 (9.6)	897 (9.0)
Thrombolysis	28 (0.3)	25 (0.2)
Aortic counterpulsation	154 (1.5)	141 (1.4)

Medications received during hospitalisation, in particular:

- Most of the patients (97.5%) were treated with aspirin; more than 70% received a thienopyridine (clopidogrel in 63% of cases or ticlopidine), and less than 20% received a GP IIb/IIIa inhibitor.
- nearly 20% received a LMWH.

The two groups were similar with respect to the use of these medicinal products during hospitalisation.

NB: The treatments prescribed on discharge from hospital were similar for the two groups (in particular coronary interventions). Thienopyridines were prescribed in nearly 40% of patients at D180.

Clinical characteristics (seriousness) of OASIS-5 patients

Seventy-six percent (76.0%) of the patients were at least 60 years of age; 80.4% had dynamic ST segment or T wave changes; 70.6% had elevated cardiac enzymes (troponin T or I or CPK-MB), over 80% of the patients (16,241/19,993) had at least two of the three eligibility criteria.

This population was at moderate to high risk of ischaemic complications and had the characteristics of a population eligible for early invasive management (< 72 hours).

Remarks

The management of patients with non-ST depression acute coronary syndrome (Non-ST ACS) depends on clinical urgency: patients in a life-threatening situation require emergency (within 120 minutes) coronary reperfusion (angioplasty or aortocoronary bypass surgery). Those with a stable clinical condition but a high risk of death or ischaemic complications also require invasive management, but within 24 to 72 hours (depending on clinical recommendations). The other patients are treated by medication alone.

Most of the patients who were managed invasively in the OASIS 5 study were treated early, i.e., within 72 hours (70.1% [8,919/12,715] of patients underwent coronary angiography and 61.8% [4,254/6,889] of patients underwent PCI).

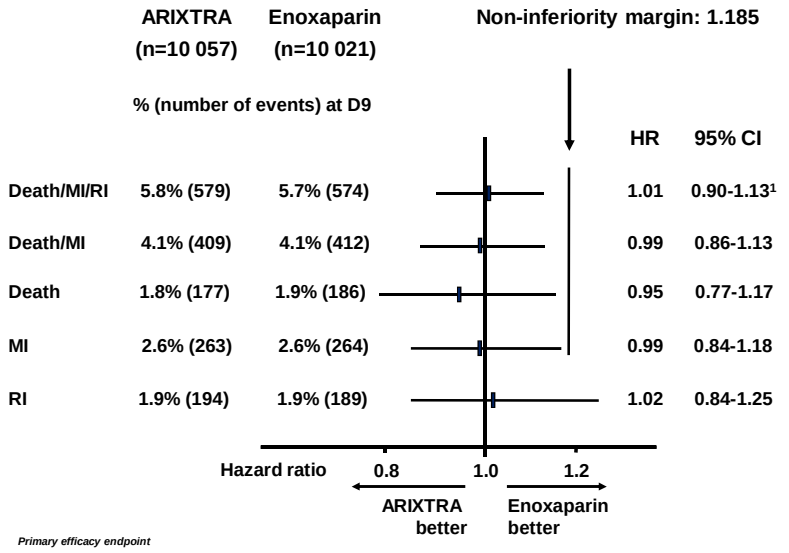
Efficacy results

NB: 90 % of the patients were followed up at 90 days and nearly 80% were followed up for 6 months. The outcome in terms of death or survival is known for 99.9% of the patients.

The mean duration of treatment was 5.5 days in the fondaparinux group and 5.2 days in the enoxoparin group.

Primary endpoint

OASIS-5 – Efficacy results at D9

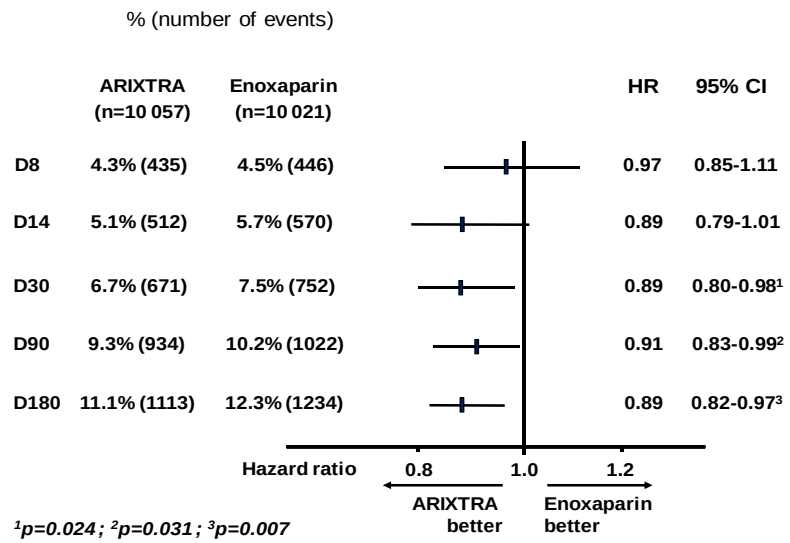


For the composite outcome criteria comprising all-cause death, myocardial infarction (MI) and refractory ischaemia, the non-inferiority of fondaparinux (ARIXTRA 2.5 mg) was demonstrated versus enoxaparin (LOVENOX) (according to the *per protocol* and intention-to-treat analysis) in the 9 days after randomisation.

Secondary endpoints:

- Incidence of the composite endpoint events up to 180 days:

OASIS-5 – Risk of "death/MI/stroke" up to D180



[1]p=0.024 ; [2]p=0.031 ; [3]p=0.007

- On day 30, the incidence of death was 3.5% in the enoxaparin group and 2.9% in the fondaparinux group (relative risk: 0.83; 95% CI: 0.71 - 0.97; p = 0.02). No difference was demonstrated up to day 14 (relative risk: 0.87; 95% CI: 0.72 - **1.04**).
Remarks: the analysis of mortality after D9 must be interpreted with caution, as this was not a primary endpoint but rather a secondary endpoint that was evaluated on four different dates (D9, D30, D90 and D180). The reduction in mortality was not mentioned in the indication (see scientific discussion - EPAR).

- There was no statistically significant difference in the incidence of MI and refractory ischaemia between the groups treated with fondaparinux and enoxaparin.

Net clinical benefit
This was estimated using the following composite endpoints up to D9, D14, D30, D90, D180:
- occurrence of the first event among the combined death/MI/RI/major bleeding endpoint events;
- occurrence of the first event among the combined death/MI/major bleeding endpoint events.

Given the heterogeneity of the evaluated population (with respect to risk of death, risk of bleeding, treatment modalities and exclusion of patients immediately managed by PCI), the interpretation of the results according to these two endpoints is not very relevant.

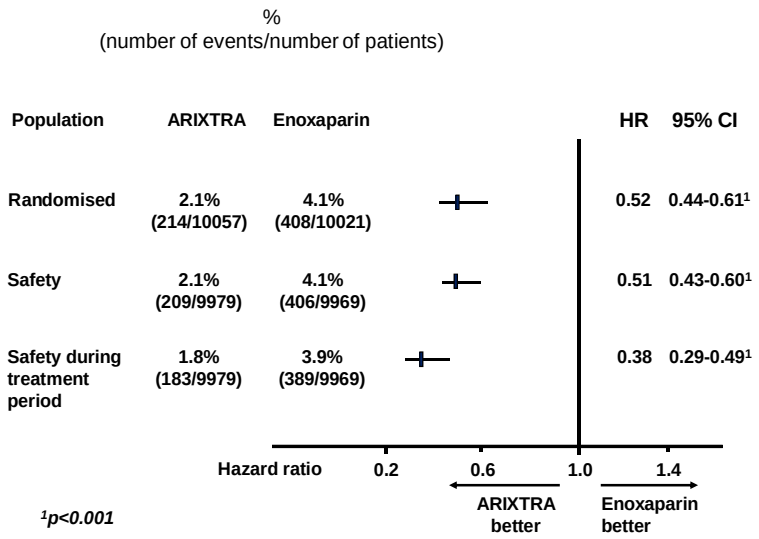
3.2 Adverse events

3.2.1 OASIS-5 study data

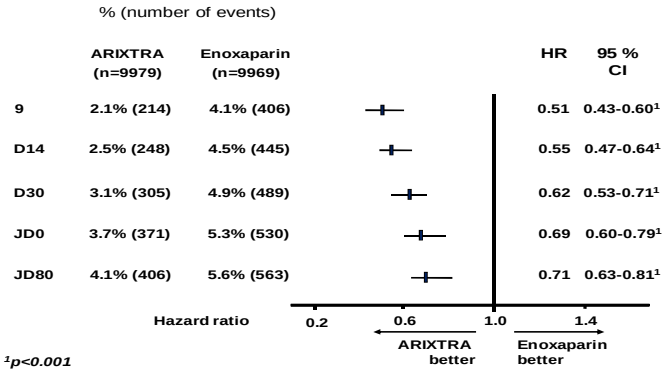
In acute coronary syndromes, 10,057 patients were treated by ARIXTRA for UA or non-ST segment elevation acute coronary syndrome (Non-ST ACS).

Bleeding: By day 9, the incidence of major bleeding events was 2.1% with fondaparinux and 4.1% with enoxaparin (relative risk: 0.52; 95% CI: 0.44 - 0.61; p < 0.001).

OASIS-5 – Risk of major bleeding events at D9



OASIS-5 – Risk of major bleeding events up to D180
(tolerance population)



Remarks

The risk of bleeding was higher in patients who underwent invasive treatment. In this study, over 60% of patients underwent coronary angiography, 34% had PCI and 10% CABG. However, the using radial route instead of the femoral route may reduce the risk of bleeding. It is therefore justifiable to consider this when interpreting these results. In OASIS-5, radial access was used in approximately 20% of patients undergoing PCI. There was no difference in the incidence of primary endpoint events per arterial approach (7.7% for the femoral approach versus 7.1% for the radial approach). However, the incidence of major bleeding events by D9 effectively dropped when a radial approach was used, from 3.5% for the femoral approach to 1.6% for the radial approach (p<0.003).

Incidence of bleeding events per arterial approach (GSK data):
- Femoral approach: 4.8% with enoxaparin versus 2.3% with fondaparinux (HR: 0.48; 95% CI: 0.37-0.62). Reduction in favour of ARIXTRA 2.5 mg.
- Radial approach (20% of the study population**)**: 2.4% with enoxaparin versus 0.9% with fondaparinux (HR: 0.36: 95% CI: 0.11-1.16): no difference between ARIXTRA 2.5 mg and LOVENOX.

Guiding catheter thrombus

- More angioplasty coronary complications were observed with fondaparinux.
- Clinical studies demonstrated a low but increased risk of guiding catheter thrombus in patients receiving fondaparinux for anticoagulation during PCI compared with the control group. For non-primary PCI in UA/NSTEMI patients, the incidences were 1.0% vs. 0.3% respectively for fondaparinux vs. enoxaparin, whereas they were 1.2% vs. 0% respectively for fondaparinux vs. the control group for primary PCI in STEMI patients.

The protocol was amended so that investigators could prescribe IV UFH before or within one hour of angioplasty to replace fondaparinux 2.5 mg. It is difficult to interpret the impact of this treatment regimen when performing angioplasty as there are few comparative clinical data available. Hence, GSK should conduct a post-MA study (PASS Study) to establish the efficacy and tolerance of this strategy.

According to the SPC data on the administration of fondaparinux in the event of percutaneous coronary interventions (PCI/angioplasty):
- There is a risk of guiding catheter thrombus: in UA/NSTEMI patients with life threatening conditions that require urgent revascularisation, the use of fondaparinux prior to and during coronary angioplasty is not recommended.
- In patients undergoing non-primary angioplasty, the use of fondaparinux as the sole anticoagulant during PCI is not recommended. Therefore, UFH should be used in accordance with local practices.

There are limited data on the use of UFH during non-primary PCI in patients treated with fondaparinux:

- In those patients who underwent non-primary PCI 6-24 hours after the last dose of fondaparinux, the median UFH dose was 8,000 IU and the incidence of major bleeding was 2% (2/98).
- In those patients who underwent non-primary PCI < 6 hours after the last dose of fondaparinux, the median UFH dose was 5,000 IU and the incidence of major bleeding was 4.1% (2/49).

Risk of heparin-induced thrombocytopenia [3]

The issue of HIT occurrence has little relevance during treatment of Non-ST ACS to the extent that, on the one hand the recommended duration of anticoagulant treatment with fondaparinux is limited to 8 days, which reduces the risk and, on the other hand for secondary angioplasty, a UFH (which has a higher HIT risk than fondaparinux) should be prescribed (to avoid coronary complications).

3.3 Conclusion

The OASIS-5 study was a randomised double-blind non-inferiority study of nearly 20,000 patients with unstable angina or non-ST segment elevation MI (UA/NSTEMI). It evaluated the non-inferiority of two anticoagulants: fondaparinux 2.5 mg SC once daily versus enoxaparin 1 mg/kg SC twice daily. The average age of patients was 67 and approximately 60% were at least 65. Approximately 40% and 17% of patients had mild (50 ml/min ≤ creatinine clearance < 80 ml/min) or moderate (30 ml/min ≤ creatinine clearance < 50 ml/min) renal insufficiency respectively. In these patients, the enoxaparin dosage was lowered whereas that of fondaparinux 2.5 mg remained unchanged.

The OASIS-5 study population is therefore a population at moderate to high risk of ischaemic complications eligible for early invasive management (within 72 hours).

In the case of angioplasty, the patients received an adjuvant treatment, either IV fondaparinux or IV UFH (enoxaparin patients). After an amendment to the protocol, certain patients in the fondaparinux group received UFH instead of fondaparinux because of the unexpected occurrence of thrombotic complications; this strategy has not been validated and is undergoing evaluation (post-MA).

3 Fondaparinux does not bind with platelet factor 4 and does not cross-react with sera from patients with type II heparin-induced thrombocytopenia (HIT). At the 2.5 mg dose, fondaparinux does not modify the results of routine coagulation tests, such as activated partial thromboplastin time (APTT), activated clotting time (ACT) or prothrombin time (PT)/International Normalised Ratio (INR) in plasma, or the bleeding time or fibrinolytic activity. Fondaparinux does not cross-react with and sera from patients with heparin-induced thrombocytopenia. The efficacy and tolerance of fondaparinux have not been formally studied in patients with type II HIT.

The endpoint was a composite endpoint comprising all-cause death, myocardial infarction (MI) and refractory ischaemia in the 9 days after randomisation. Of the fondaparinux patient group, 5.8% had an event by Day 9 compared to 5.7% of those treated with enoxaparin (relative risk 1.01; 95% CI: 0.90 - 1.13; p value – one-sided non-inferiority = 0.003). The non-inferiority of ARIXTRA 2.5 mg versus enoxaparin (LOVENOX) was established.

No conclusions about the impact of fondaparinux on mortality (secondary endpoint) could be drawn from the study results.
The differences in MI and refractory ischaemia incidence between the fondaparinux- and enoxaparin-treated groups were not statistically significant.

The incidence of major bleeding events by day 9 was 2.1% with fondaparinux and 4.1% with enoxaparin (relative risk: 0.52; 95% CI: 0.44 - 0.61; $p < 0.001$). The risk of bleeding varied according to whether or not an invasive strategy was used, as well according to which arterial approach was used in the case of angioplasty.

The efficacy and tolerance results (major bleeding events) were concordant in predefined sub-groups such as elderly patients, renal insufficiency patients, and patients receiving concomitant platelet aggregation inhibitors (aspirin, thienopyridines or GP IIb/IIIa inhibitors). However, in the sub-group of patients treated with fondaparinux or enoxaparin who were undergoing angioplasty (nearly 1/3 of the patients evaluated in OASIS-5), 8.8% and 8.2% respectively died, had an MI or experienced refractory ischaemia in the 9 days after randomisation (relative risk: 1.08; 95% CI: 0.92 - 1.27). The incidence of major bleeding events by day 9 was 2.2 % with fondaparinux and 5.0 % with enoxaparin (relative risk: 0.43; 95% CI: 0.33 - 0.57). The interpretation of the results for this sub-group prompted the registration authorities to exclude patients undergoing angioplasty within 120 minutes from the indication of ARIXTRA 2.5 mg. This exclusion only pertained to patients requiring emergency reperfusion in order to avoid excluding the possibility of prescribing ARIXTRA 2.5 mg in patients requiring reperfusion during the 72 hours preceding this possible intervention in the catheterisation laboratory (see “scientific discussion”, EPAR).

It is not certain that the OASIS-5 study results can be transposed to a target population of patients in France.
According to the ARIXTRA 2.5 mg MA, only patients not eligible for immediate angioplasty, i.e., those at low risk, may be considered (by extrapolation) able to receive ARIXTRA. However, in this specific population, the non-inferiority of ARIXTRA versus enoxaparin was not clearly established.
This population is not easily identifiable *a posteriori* in the OASIS-5 study insofar as most of the included patients had moderate to severe disease. In addition, the population should be identified *a priori* in daily practice.

Overall, and despite the questions raised by the analysis of the results of the OASIS-5 study, fondaparinux (ARIXTRA 2.5 mg) can be considered an alternative to enoxaparin in non-ST segment elevation acute coronary syndrome patients for whom invasive management is not indicated. In these patients, the possible loss of efficacy (since superiority versus enoxaparin was not established) may be offset by a reduction in bleeding risk, including for those patients with mild to moderate renal insufficiency.
In the most seriously ill patients, and given the results of the OASIS-6 study in patients with myocardial infarction (ST ACS), the Committee is not convinced that fondaparinux 2.5 mg should be used as first-line treatment.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

In the extension of indication to *"treatment of unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI) in patients for whom urgent (< 120 min) invasive management (percutaneous coronary intervention: PCI) is not indicated"*:

4.1 Actual Benefit

All acute coronary syndromes (STE and non-STE) require management by a specialised team. The immediate severity of non-ST segment elevation coronary syndromes (unstable angina, non-ST-elevation myocardial infarction) depends on the patient's clinical condition: stable or unstable, short-term risk of death or not, risk factors. This determines patient management. There are two possible treatment modalities: medical treatment alone or, in certain patients, an invasive strategy with coronary angiography followed by revascularisation through angioplasty (PCI) or aortocoronary artery bypass grafting (CABG). The invasive strategy is performed within 120 minutes (relatively rare situation) or within 24 to 72 hours, since although there is an acute risk of complications, the condition is not immediately life threatening.

Anticoagulants are recommended in combination with platelet aggregation inhibitors in these patients. Several anticoagulants have been evaluated: unfractionated heparin (UFH), enoxaparin (LOVENOX), bivalirudin (ANGIOX) and fondaparinux (ARIXTRA 2.5 mg).
ARIXTRA 2.5 mg is indicated in patients who do not require emergency invasive management (within 120 min) with a percutaneous coronary intervention (PCI). In this situation, ARIXTRA is a drug of first choice.

Impact on public health

Ischaemic heart disease is a major public health burden. The burden of non-ST segment elevation acute coronary syndromes (unstable angina or non-ST segment elevation myocardial infarction [MI]) ineligible for an invasive strategy (PCI*) is considered to be substantial.

The improvement of secondary prevention of MI and unstable angina (in these clinical settings) still constitutes a public health need.

According to the data obtained during the OASIS 5 study versus LOVENOX (non-inferiority in terms of efficacy, reduced risk of bleeding in the absence of angioplasty, uncertain risk of bleeding for angioplasty, small number of ARIXTRA-treated patients receiving a UFH for angioplasty), this proprietary medicinal product is not expected to have an additional impact in terms of morbidity and mortality compared to the existing therapies (LOVENOX).

Furthermore, there is no guarantee that the results of the OASIS 5 study can be extrapolated to clinical practice in France for the following reasons:

- This was an international study (global data) that does not necessarily reflect French practices: there were differences in patient profile, emergency healthcare, and time to treatment initiation, and there more angioplasty procedures using the radial approach).
- There are still unknown factors regarding how this product is tolerated by thrombolysed patients needing to undergo secondary angioplasty (a clinical situation requiring complex anticoagulant strategy).

The ARIXTRA proprietary drug therefore will not provide an additional response to an identified public health need.

Consequently, given the current state of knowledge and the other therapies available at this time, the ARIXTRA proprietary drug has no expected public health benefit in this indication.

The efficacy/tolerance ratio of fondaparinux (ARIXTRA 2.5 mg) is high in patients not treated with angioplasty, i.e., when patients are being treated medically (evaluator's proposal) until the decision between an invasive or a conservative strategy has been made, i.e., as long as angioplasty is not yet been performed.

Conclusion: under these conditions, the actual benefit of ARIXTRA 2.5 mg is substantial.

4.2 Improvement in actual benefit in the indication extension (Non-ST ACS)

ARIXTRA 2.5 mg does not improve actual benefit (IAB V) in the treatment of non-ST segment acute coronary syndromes (Non-ST ACS) compared with current treatments. The non-inferiority of fondaparinux (ARIXTRA 2.5 mg) versus enoxaparin was demonstrated in patients for whom invasive management is indicated.

4.3 Therapeutic use of ARIXTRA 2.5 mg in the treatment strategy for non-ST elevation acute coronary syndrome

Three clinical situations can be identified:
- The patient's clinical condition is immediately life threatening, so the emergency use of an invasive strategy (within 120 minutes) is justified.
- The patient's clinical condition is not immediately life threatening, though there is an acute risk for complications. In this case, an invasive strategy (coronary angiography and possibly revascularisation) can be delayed for up to 72 hours after this diagnosis.
- The patient's clinical condition does not require the use of an invasive strategy.

Given the clinical data of the OASIS-5 study and the wording of the MA, ARIXTRA 2.5 mg may be prescribed in a non-urgent setting for as long as the decision between an early invasive strategy and a conservative strategy has not been made. The issue of the clinical benefit of fondaparinux (ARIXTRA 2.5 mg) in patients requiring delayed (up to 24, 48 or 72 hours, depending on guidelines) coronary reperfusion may nevertheless be raised since there is only limited evidence for recommending fondaparinux in the case of primary or secondary angioplasty: is it effective versus another anticoagulant? What about coronary complications and guiding catheter thrombus with the need to combine an UFH although no evaluation of the relevance of this strategy has been made?
In practice, the assessment of the role and benefit of fondaparinux (ARIXTRA 2.5 mg) in the management of Non-ST segment elevation ACS is different for the European (2007) and American (2007) clinical recommendations - see appendices 1 and 2.

The Committee notes that compared to enoxaparin at a curative dose instead of another anticoagulant (UFH, bivalirudin), ARIXTRA at preventive doses (2.5 mg) causes fewer serious bleeding events and may reduce bleeding-related mortality when no decision has been made to perform coronary angiography (followed by angioplasty). However, the OASIS-5 study does not clearly document this point.

4.4 Target population in the indication extension (UA/NSTEMI)

The target population is defined as patients treated:

- for stable angina who are at an acute risk (UA) and require only medical treatment
- for non-ST segment elevation MI (NSTEMI in with emergency management <120 min) for whom an invasive strategy (percutaneous coronary intervention: PCI) is not indicated.

Estimated target population

The ARIXTRA 2.5 mg target population of was estimated using:

- an analysis of public and private PMSI (French Medicalised Information System Programme) 2006 databases to evaluate the annual number of patients with acute coronary syndrome;
- an analysis of current practices for managing patients with acute coronary syndrome in France using data in the FAST-MI registry.

According to the PMSI database (2006), a primary or associated diagnosis of unstable angina was made for 112,763 hospital stays and non-Q-wave myocardial infarction for 15,186 stays for a total of 127,950 hospital stays.
These two diagnostic categories are now grouped together under the term “non-ST elevation acute coronary syndrome (ACS)” (or “UA/NSTEMI”).

According to HAS (French National Health Authority) guidelines (May 2007):
- Unstable situations are rare and involve under 5% of patients: i.e., nearly 6,400 patients.
- “For patients at high-risk, it is recommended to perform coronary angiography with or without ad hoc revascularisation within 48h”…. “the other patients….are considered to be patients at low risk and..... will undergo complementary non-invasive testing”.
However, according to the FAST-MI registry (1), 78.3% of non-ST+ ACS patients underwent coronary angiography.
- The group of “stable patients at acute risk” defined by the HAS can be described as the entire population undergoing coronary angiography, i.e. 95,170 patients.
- The group of “stable patients not at acute risk” defined by the HAS can be described as patients not undergoing coronary angiography, i.e., 26,380 patients.
- Using the current data, is impossible to define the number of subjects who shift from a situation “with no acute risk” to a situation “at acute risk”.
The ARIXTRA 2.5 mg target population is estimated to be no more than 95,170 patients.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines for use by hospitals and various public services in the extension of indication "*treatment of unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI) in patients for whom urgent (< 120 min) invasive management (percutaneous coronary intervention: PCI) is not indicated*".

Recommendations of the European Society of Cardiology (ESC 2007) concerning use of anticoagulants in patients with UA/NSTEMI

Recommendations	Grades
Anticoagulants must be used in combination with platelet aggregation inhibitors in all patients	**I-A**
The choice of anticoagulant agent must take into account both the risk of ischaemic events and the risk of bleeding	**I-B**
Several anticoagulants are available: UFH, LMWH, fondaparinux and bivalirudin. The choice depends on the initial strategy (urgent invasive, early invasive or conservative)	**I-B**
In an urgent invasive strategy (<120 minutes), treatment must be immediately started with one of the following agents:	**I-C**
• UFH	**IIa-B**
• Enoxaparin	**I-B**
• Bivalirudin	
In a non-urgent situation, as long as a decision between an early invasive or conservative strategy is pending	
• Fondaparinux is recommended on the basis of the most favourable efficacy/tolerance profile	**I-A**
• Enoxaparin with a less favourable efficacy/tolerance profile than fondaparinux should be used only if the bleeding risk is low	IIa-B
• Since the efficacy/tolerance profile of LMWH (other than enoxaparin) or UFH relative to fondaparinux is unknown, these anticoagulants cannot be recommended over fondaparinux	**IIa-B**
• During percutaneous coronary intervention (PCI) procedures, the initial anticoagulant should also be maintained during the procedure regardless of whether this treatment is:	
- UFH	**I-C**
- enoxaparin	**IIa-B**
- bivalirudin	**I-B**
whereas an additional standard UFH dose (50 to 100 U/kg bolus) is necessary in the case of fondaparinux	**IIa-C**
After a PCI procedure	
• Anticoagulation can be stopped within 24 hours of the invasive procedure	**IIa-C**
• In a conservative strategy, fondaparinux, enoxaparin, or other LMWHs can be maintained until hospital discharge	**I-B**

Class I*: Evidence and/or general agreement that a given treatment is beneficial, useful and effective;*
Class II: *Conflicting evidence and/or a divergence of opinions on the usefulness/efficacy of a given treatment or procedure;* ***Class IIa****: Weight of evidence/opinion is in favour of usefulness/efficacy;* ***Level of evidence A****: Data derived from multiple randomised clinical trials or meta-analyses;* ***Level of evidence B****: Data derived from a single randomised clinical trial or large non-randomised studies;*
Level of evidence C*: Consensus of expert opinion and/or small studies, retrospective studies or registries*

Joint recommendations of the American College of Cardiology and the American Heart Association (ACC/AHA 2007) concerning the use of anticoagulants in UA/NSTEMI patients

Recommendations	Grade
Class 1 recommendations	
• Anticoagulant therapy should be added to antiplatelet therapy in UA/NSTEMI patients as soon as possible after presentation	**I-A**
• For patients in whom an invasive strategy is selected, regimens with established efficacy are	
- UFH and enoxaparin	**I-A**
- and fondaparinux and bivalirudin	**I-B**
• For patients in whom a conservative strategy is selected, regimens with established efficacy are	
- UFH and enoxaparin	**I-A**
- and fondaparinux	**I-B**
• In patients in whom a conservative strategy is selected and who have an increased risk of bleeding, fondaparinux is preferable	**I-B**
• If an initial conservative strategy is selected and no subsequent features appear that would necessitate diagnostic angiography (recurrent symptoms/ischemia, HF, or serious arrhythmias), a stress test should be performed. If, after stress testing, the patient is classified as at low risk, continue UFH for 48 h or administer enoxaparin or fondaparinux for the duration of hospitalisation, or up to 8 days	**I-A**
• If coronary artery bypass grafting (CABG) is selected post-angiography, the instructions noted below should be followed:	
- Continue UFH	**I-B**
- stop enoxaparin 12-24 H before CABG and replace it by UFH according to local practice	**I-B**
- stop fondaparinux 24 h before CABG and replace it by UFH according to local practice	**I-B**
• If PCI is indicated after coronary angiography, the anticoagulants must be stopped after PCI in uncomplicated cases	**I-B**
• For patients in whom medical therapy is selected after coronary angiography and in whom no significant coronary lesion is found, anticoagulant therapy should be administered at the discretion of the clinician	**I-C**
• For patients in whom medical therapy is selected as a post-angiography management strategy and in whom significant coronary lesions are found, the following approach is recommended depending on the drug given before angiography	
- Continue UFH IV for at least 48 h or until discharge from hospital	**I-A**
- Continue enoxaparin until discharge from hospital, or for up to 8 d,	**I-A**
- Continue fondaparinux until discharge from hospital, or for up to 8 d	**I-B**
- Either discontinue bivalirudin or continue at a dose of 0.25 mg per kg per h at the physician's discretion,	**I-B**
• In patients in whom a conservative strategy is selected and who do not undergo stress testing, continue UFH for 48 h or administer enoxaparin or fondaparinux until discharge from hospital, or for up to 8 d, and then discontinue anticoagulant therapy	**I-A**
Class IIa recommendations	
• If an initial conservative strategy is selected, enoxaparin or fondaparinux should be preferred to UFH, except if CABG is planned in 24 hours	**IIa-B**

Class I: *Benefit >>> risk; procedure/treatment should be performed/administered;*
Class IIa*: Benefit >> risk; additional studies with focused objectives needed; it is reasonable to perform procedure/administer treatment;*
Grade I-A*: recommendation that procedure/treatment is useful/effective – data from several randomised trials or meta-analyses;*
Grade I-B*: recommendation that procedure/treatment is useful/effective - data from a single randomised trial or several non-randomised studies;*
Grade I-C: *recommendation that procedure/treatment is useful/effective – either expert opinion or case studies or standard-of-care.*